Occupational Exposures and Health Outcomes among Minnesota Taconite Mining Workers

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Elizabeth Melita Allen

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Bruce H. Alexander, Ph.D., Advisor

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Chapter 1:

Introduction and background

Taconite mining in Minnesota

The iron mining industry in Minnesota began in the late 1800s with the discovery of hematite in northeastern Minnesota, within what is now known as the Mesabi Iron Range. Hematite, a high-grade ore, was excavated from the iron formation and shipped directly to steel mills. However, the high-grade ore became less abundant following heavy demand for its use in World War II. In the 1950s, with hematite reserves depleted, the mining and processing of low grade taconite ore began (1). In order for taconite to be commercially useful, its iron must be concentrated. This is done through an extensive process developed in the 1940s by Dr. E.W. Davis of the University of Minnesota and a team of mining engineers (1). Taconite rock is excavated from open pit mines with explosives. The rock is then crushed into a fine powder, and the iron is extracted through magnetic separation and reformed into a more concentrated pellet. The unwanted minerals, or tailings, are slurried with water and transferred to a disposal site. The final product is a fired pellet with an average iron concentration of approximately 65%, and shipped for use in steel production (2). Today, the mining industry in Minnesota produces roughly 40 million tons of high grade iron ore annually, approximately 75% of the total US iron ore production (2). The industry is essential to Minnesota's economy making a $3 billion economic impact and providing thousands of jobs (3).

Taconite mining exposures

The Mesabi Iron Range, located in northeastern Minnesota, is a narrow belt approximately three miles wide and 120 miles long, consisting of iron-rich sedimentary rocks. The mineralogy of the Mesabi Iron Range changes from east to west and is broken

into four distinct mineralogical zones (4). All zones have deposits of taconite along with quartz and iron silicates, but vary in the type of EMP (5). The eastern part of the range, known as zone 4, contains iron-rich amphibole EMPs, which is believed to be less than 1% fibrous (6). The western part of the range, known as zone 1 includes approximately two thirds of the entire Mesabi Iron Range and contains almost exclusively non-asbestiform EMPs. Zones 2 and 3 are considered transitional zones and contain some amphiboles. The primary exposure in taconite operations if of non-asbestiform cleavage fragments however, due to the mineralogical differences in the zones, workers in each zone may be exposed to different types of mineral particles.

Asbestos and silica

Various types of asbestos can differ chemically, but structurally they are all similar in that they are highly fibrous silicate minerals that are crystallized in an asbestiform habit, causing them to separate into long, thin, strong, flexible fibers (7-8). Asbestos also tends to have very large aspect ratios, generally >20:1 for fibers > 5µm in length (8). In contrast, non-asbestiform mineral fibers have aspect ratios as small as >3:1, but usually have widths much larger than asbestiform fibers of the same length. Common non-asbestiform analogs of asbestos may share the same chemical composition but they do not share the same crystal structure. Cleavage fragments, or fragments of EMPs that have broken along a cleavage plane, lack the tensile strength and flexibility of asbestos (8).

Asbestos has been well established as risk factors for lung cancer. The asbestos lung cancer relationship was first documented in the 1950s when the earliest studies of

asbestos miners were published (9). It is now known that asbestos fibers are related to bronchogenic carcinomas including squamous cell carcinomas, small- and large-cell carcinoma, adenocarcinomas, and mesothelioma. The tumors have a very long latency of up to 20 or 30 years and may appear even after inhalation of an extremely low asbestos concentration (10). Identifying population based rates of asbestos-related lung cancer is complicated by the numerous etiologies of lung cancer. However, the projected number of asbestos-caused lung cancer deaths in the United States between 1980 and 2009 was estimated to range from 55,100 (11) to 76,700 (12).

Historically, the association between silica and lung cancer has been debated but recent occupational studies have provided evidence supporting the risk of lung cancer after silica exposure (13). In 1996, the International Agency for Research on Cancer (IARC) concluded that respirable silica was carcinogenic in occupational settings despite the lack of good-quality datasets available to quantitatively evaluate the relationship. Since then, a number of individual studies as well as meta-analyses have been published examining the relationship between silica exposure and lung cancer (14). A recent quantitative risk assessment done by NIOSH predicted an excess lifetime risk of lung cancer mortality of 19/1000 white male workers exposed to respirable silica for 45 years at the current OSHA standard (13). As a result of the growing body of evidence, in 2012 the IARC reconfirmed the classification of silica as a carcinogen with the lung as the target organ (15).

Though exposure to asbestos minerals is known to cause lung cancer and mesothelioma, the health consequences of non-asbestiform EMPs and cleavage fragments

has never been widely studied or understood. To our knowledge, no single study has provided an extensive assessment of the relationship between non-asbestiform EMPs and adverse health effects.

Previous studies

The first study of the health of taconite miners was published in 1983 (16). Study investigators followed a cohort of 5,751 men employed at Reserve Mining Company from 1952 to 1976. There were a total of 298 deaths in the cohort compared to an expected 344 deaths with fewer deaths than expected due to respiratory cancers (15 observed vs. 18 expected, SMR = 0.84, 95% CI: 0.47-1.38). Another study of Minnesota taconite miners was reported by Cooper et al. (17-18). Investigators studied mortality through 1988 in a cohort of 3,431 male workers from Erie and Minntac mines between 1959 and 1977. Total observed deaths were fewer than expected when compared to both Unites States and Minnesota death rates. There were 65 observed deaths from respiratory cancers in the cohort as compared to an expected 87 (SMR = 0.97, 95% CI: 0.75-1.23). The investigators reported no significantly elevated SMRs for any cause of death among the taconite workers. These two mortality analyses are the only studies to date that have attempted to assess the health of Minnesota taconite miners. Though these first studies did not identify and increased risk of mortality, there were limited by very small sample sizes and relatively short follow-up.

Several occupational studies have been conducted that evaluate the health risk to workers exposed to non-asbestiform EMPs in other occupational settings. These include studies of talc miners in upstate New York and Homestake gold miners in South Dakota.

A 2002 study of talc miners in New York followed 809 men between 1950 and 1989 (19) and identified 31 lung cancers as compared to an expected 13 (SMR = 2.32, 95% CI: 1.57-3.29). Mortality experience of workers in this same study population had been studied previously with similar results (20-21). Stille and Tabershaw identified 10 lung cancer deaths in a cohort of 655 workers (SMR = 1.57, 95% CI: 0.75-2.87) (20). Lamm et al. reported 12 lung cancer deaths among 705 miners (SMR = 2.40, 95% CI: 1.24-4.19) (21). Collectively, these studies suggest a weak association between dust exposure and lung cancer. The authors argued that the excess in lung cancer may not be related to talc ore dust; rather it might be explained by a relatively high smoking rate in the population (18). However, it is unlikely that confounding by smoking accounts fully for the observed lung cancer excess (22).

The first study of the health of gold miners in South Dakota was published in 1976 (23). Gillam et al. reported in a study of 440 Homestake gold miners employed for at least 5 years by 1960 an excess in mortality from all causes (71 observed vs. 53 expected) and respiratory cancer (10 observed vs. 2.7 expected) when compared to death rates in South Dakota (23). In another study of Homestake gold miners, investigators followed 1,321 men employed for at least 21 years by 1973 (24). There were a total of 631 deaths in the cohort compared to an expected 550 and 17 deaths from respiratory cancer compared to an expected 16.5. A third study published in 1986 followed 3,328 miners employed for at least one year between 1940 and 1964. Mortality follow-up through 1977 identified 861 deaths compared to an expected 769. After 15 years latency, there were 41 deaths due to lung cancer compared to 40 expected deaths (25). A follow-

up of this cohort was updated in 1995 and identified 115 deaths from lung cancer (SMR = 1.13, 95% CI: 0.94-1.36) (26).

The results of these studies have been interpreted in various ways. In an overall assessment of this literature, Williams et al. concluded that these studies provide "no convincing evidence of increased risk of lung cancer or mesothelioma among individuals exposed to non-asbestos amphiboles in mining and milling of taconite ore, gold ore, or talc (27)." In a similar evaluation of the literature, Gamble and Gibbs noted that there does "not appear to be cleavage fragment-related increases in lung cancer or mesothelioma risk in the studies (7)," but the authors note that there is a gap in knowledge concerning the health effects of exposure to non-asbestiform EMPs. Studies of well-defined occupational cohorts would be helpful (7). *In vitro* assessments have suggested that non-asbestiform mineral particles and cleavage fragments are less potent than asbestiform (8). Some animal studies have suggested that fiber dimension, and not composition, is the major determinant of carcinogenicity for mineral fibers (22). NIOSH has expressed that literature is inconclusive (22). Non-asbestiform EMPs are included in NIOSH recommended exposure limits due to technical limitations of routine EMP assessments and uncertainty about the potential toxicity of non-asbestiform fibers. What is clear is that the literature is sparse and lacking in well-defined exposed populations (7, 22, 27). There remains a need to determine conclusively whether non-asbestiform EMPs that are chemically similar to asbestos, but with different physical forms are also capable of causing disease (22). These mineral particles are present in taconite mining

operations, the predominant exposure being non-asbestiform cleavage fragments, making Minnesota taconite minors an important population for research.

Taconite workers health study

In the early 1980s, the University of Minnesota, School of Public Health, with the support of the Iron Range Resources and Rehabilitation Board, created the Mineral Resources Health Assessment Program (MRHAP). Its goals were to develop expertise concerning hazards of the mining and processing of minerals in Minnesota and to research health effects of mining and mineral processing. Investigators assembled a database of 68,737 individuals from employment records of the seven mines in operation in 1983, US Steel Corporation, Hanna Mining Company, Pickands-Mather and Company, Reserve Mining Company, Eveleth Taconite Company, Inland Steel Company, and Jones and Laughlin Corporation. Resources were not available at the time to complete the project.

In 2008, the University of Minnesota launched the Taconite Workers Health Study (TWHS) (28). The objective was to update the health assessment of the cohort of 68,737 miners collected by MRHAP in 1983 and conduct research projects to help determine the extent to which occupational exposures in the taconite industry affect the health of workers with specific emphasis on respiratory diseases. The TWHS has five main components: 1) An occupational exposure assessment looking at the nature of exposures in the taconite mines, 2) a mortality and cancer study to examine causes of death and cancer rates among taconite workers as compared to the Minnesota population, 3) case control analyses to assess occupational risk factors associated with the

development of mesothelioma and lung cancer, 4) a respiratory health survey of taconite workers and spouses to determine the prevalence of non-malignant respiratory effects associated with taconite industry exposures, and 5) an environmental study of airborne particulates to evaluate the emissions from taconite mining. Work on this study was carried out over five years with efforts from a team of University of Minnesota researchers, graduate students, staff members, and outside advisory board members.

Research objectives

This dissertation is focused on two components of the overall Taconite Workers Health Study, the mortality and cancer study, and the lung cancer case control study. The goal of this research is to characterize the overall health of taconite mining industry workers in Minnesota and to identify the exposure risk of developing lung cancer. This is done first with an overall mortality and cancer outcome assessment and then a more focused lung cancer exposure risk assessment. There are three research aims to this thesis. Each aim is addressed in a chapter within the dissertation.

Specific aim 1

Determine the all cause and specific causes of death among employees in the taconite mining industry in Minnesota. Chapter 2 is a mortality study of taconite workers. Mortality rates of workers with at least one year of employment in the industry prior to 1983 are compared to mortality rates in the general Minnesota population. The purpose of this analysis is to provide a general assessment of risk of fatal diseases in this population. The hypothesis of this study is that mortality from respiratory disease including lung cancer and mesothelioma are higher among taconite mining workers than

among the general population and those who have worked in the industry for longer periods of time have higher mortality rates of lung cancer and mesothelioma.

Specific Aim 2

Examine cancer incidence among taconite workers and determine which cancers are more common in the Minnesota mining population. Determine which lung cancer histological subtype is most common among taconite workers. Chapter 3 is a cancer incidence study in which cancer rates of workers are compared to cancer rates in the general Minnesota population. The purpose of this study is to take a closer look at the health of taconite miners and identify the risk of malignant disease. The hypothesis of this study is taconite workers have different patterns of cancer incidence than the general population due to occupational exposure and lifestyle characteristics.

Specific Aim 3

Examine the association between duration of taconite employment, exposure to EMPs, and exposure to respirable silica, and the risk of lung cancer with a specific look at histological subtype. Chapter 4 describes a nested case-control study in which all lung cancer cases identified within a taconite mining worker population are compared to matched controls to evaluate exposure risks. The hypothesis of this study is risk of lung cancer increases with increasing exposures and risk differs by histological subtype.

Significance

The Taconite Workers Health Study is the first large scale effort to study the potential health hazards of exposures in the taconite mining industry. As part of the TWHS, this dissertation consists of three analyses that characterize the health of taconite

workers and examine whether the risk of developing lung disease is associated with occupational exposures in taconite mining, an important question for Minnesota taconite miners.

Not only will this research answer questions concerning the health risks of Minnesota taconite miners, but it will also help answer important questions in mineral particle research. Exposure risk of non-asbestiform EMPs and cleavage fragments has not been extensively studied and is not understood. This study population is one of the few whose primary exposure potential is to non-asbestiform cleavage fragments, a much needed area of research.

The present-day exposure assessment is the most comprehensive in the taconite industry. This is the first study that combines current and past exposures, work history records, and health data in such a large historical cohort of taconite miners. The results of this project will provide insight into questions regarding EMP risk, and help understand potential health risks within Minnesota's taconite mining industry. Ultimately, this work can be the basis of further study of environmental and occupational exposures of non-asbestiform EMPs, inform new risk assessments, and develop new policies for EMP exposure limits that effectively protect workers' health.

REFERENCES

1. Berndt ME, Brice WC. The origins of public concern with taconite and human health: Reserve Mining and the asbestos case. *Regul Toxicol and Pharmacol* 2008;52(S1):S31-S39.
2. Iron Range Resources and Rehabilitation Board. Explore Minnesota: Iron Ore March 2014. Available at: http://mn.gov/irrrb/images/2014%2520Explore%2520IRON%2520ORE.pdf. Accessed April 30, 2014.
3. Iron Mining Association of Minnesota. Mining Industry. Available at: http://www.taconite.org/mining-industry. Accessed April 30, 2014.
4. McSwiggin PL, Morey GB. Overview of the mineralogy of the Biwabik Iron Formation, Mesabi Iron Range, northern Minnesota. *Regul Toxicol and Pharmacol* 2008;52(S1):S11-S25.
5. Jirsa MA, Miller JD, Morey GB. Geology of the Biwabik Iron Formation and Duluth Complex. *Regul Toxicol and Pharmacol* 2008;52(S1):S5-S10.
6. Wilson R, McConnell EE, Ross M, et al. Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. *Regul Toxicol and Pharmacol 2008;52(S1): S232-S245.*
7. Gamble JF, Gibbs GW. Evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regul Toxicol Pharmacol* 2007;52(S1):S154-S186.

8. Mossman BT. Assessment of the pathogenic potential of asbestos vs. nonasbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. *Regul Toxicol Pharmacol* 2008;52(S1):S200-3.
9. Doll R. Mortality from lung cancer in asbestos workers. *Br J Ind Med*, 1955; 12(2):81 – 86.
10. Pacella A, Andreozzi GB, Fournier J, et al. Iron topochemistry and surface reactivity of amphibole asbestos: relations with in vitro toxicity. *Anal Bioanal Chem*, 2012; 402:871 – 881.
11. Walker AM, Loughlin JE, Friedlander ER, et al. Projections of asbestos-related disease, 1980 – 2009. *J Occup Med*, 1983; 25:409 – 425.
12. Lilienfeld DE, Mandel JS, Coin P, et al. Projection of asbestos related diseases in the United States, 1985 – 2009. I. cancer. *Br J Ind Med*, 1988; 45:86 – 106.
13. Department of Health and Human Services, National Institute for Occupational Safety and Health. Silica, lung cancer, and respiratory disease quantitative risk. A project from the first 10 years of NORA: High Impact, Publication No. 2011-120.
14. Sogl M, Taeger D, Pallapies D, et al. Quantitatie relationship between silica exposure and lung cancer mortality in German uranium miners, 1946 – 2003. *Br J Cancer*, 2012; 107: 1188 – 1194.
15. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 100C, Arsenic, Metals, Fibres, and Dust. International Agency for Research on Cancer: Lyon, 2012.

16. Higgins IT, Glassman JH, Oh MS, et al. Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol* 1983;118(5):710-9.
17. Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. *J Occup Med* 1988;30(6):506-511.
18. Cooper WC, Wong O, Trent LS, et al. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med* 1992;34(12):1173-1180.
19. Honda Y, Beall C, Delzell E, et al. Mortality among Workers at a Talc Mining and Milling Facility. *Ann Occup Hyg* 2002;46(7):575–585.
20. Still WT, Tabershaw IR. The mortality experience of upstate New York talc workers. *J Occup Med,* 1982; 24(6), 480-484.
21. Lamm SH, Levine MS, Starr JA, Tirey SL. Analysis of excess lung cancer risk in short-term employees. *Am J Epidemiol,* 1988;127(6), 1202-1209.
22. Department of Health and Human Services, National Institute for Occupational Safety and Health. Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research, 2011: Publication No. 2011-159.
23. Gillam JD, Dement JM, Lemen RA, et al. Mortality Patterns Among Hard Rock Gold Miners Exposed to an Asbestiform Mineral. *Ann N Y Acad Sci* 1976;336–344.
24. McDonald JC, Gibbs GW, Liddel FDK, et al. Mortality after long exposure to cummingtonite-grunerite. *Am Rev Respir Dis,* 1978;118:271-277.

25. Brown DP, Kaplan SD, Zumwalde RD et al. Retrospective cohort mortality study of underground gold mine workers. In: *Silica, Silicosis, and Cancer*, 1986;335-350.
26. Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of followup. *Am J Ind Med* 1995;27:217-229.
27. Williams C, Dell L, Adams R, et al. State-of-the-science assessment of non-asbestos amphibole exposure: Is there a cancer risk? *Environ Geochem Health* 2013;35:357-377.
28. University of Minnesota. *Taconite workers health study* 2013. Available from: http://taconiteworkers.umn.edu/

Chapter 2:

Mortality experience among Minnesota taconite mining industry workers

STUDY OVERVIEW

***Objective**:* To evaluate the mortality experience of Minnesota taconite mining industry workers.

Methods: Mortality was evaluated between 1960 and 2010 in a cohort of Minnesota taconite mining workers employed by any of the seven companies in operation in 1983. Standardized mortality ratios (SMR) were estimated by comparing observed deaths in the cohort with expected frequencies in the Minnesota population. Standardized rate ratios (SRR) were estimated using an internal analysis to compare mortality by employment duration.

***Results**:* The cohort included 31,067 workers with at least one year of documented employment. Among those, there were 9,094 deaths, of which 949 were from lung cancer, and 30 from mesothelioma. Mortality from all causes was greater than expected in the Minnesota population (SMR = 1.04, 95% CI: 1.02-1.04). Mortality from lung cancer and mesothelioma was higher than expected with SMRs of 1.16 for lung cancer (95% CI: 1.09-1.23) and 2.77 for mesothelioma (95% CI: 1.87-3.96). Other elevated SMRs included those for cardiovascular disease (SMR = 1.10, 95% CI: 1.06-1.14), specifically for hypertensive heart disease (SMR = 1.81, 95% CI: 1.39-2.33) and ischemic heart disease (SMR = 1.11, 95% CI: 1.07-1.16). Results of the SRR analysis did not show variation in risk by duration of employment.

***Conclusions**:* This study provides evidence that taconite workers may be at increased risk for mortality from lung cancer, mesothelioma, and some cardiovascular disease.

Occupational exposures during taconite mining operations may be associated with these increased risks, but non-occupational exposures may also be important contributors.

BACKGROUND AND SIGNIFICANCE

The iron mining industry in Minnesota began in the late 1800s with the discovery of hematite in northeastern Minnesota, within what is now known as the Mesabi Iron Range. Hematite, a high-grade ore, was excavated from the iron formation and shipped directly to steel mills. However, the high-grade ore became less abundant following heavy demand for its use in World War II. In the 1950s, with hematite reserves depleted, the mining and processing of low grade taconite ore began (1). Since then, the taconite mining industry in Minnesota has become the largest supplier of iron ore to the steel industry of the United States (2).

Mining and processing of taconite iron ore results in potential exposure to non-asbestiform amphibole and non-amphibole elongate mineral particles (EMPs), respirable silica, quartz and dust, and cleavage fragments (3). The term 'EMP' refers to any mineral particle with a minimum aspect ratio of 3:1 that is of inhalable size. Cleavage fragments are fractured mineral EMPs created during the crushing and fracturing process (4).

The Mesabi Iron Range is approximately 2.5 miles wide and 122 miles long and is divided into four mineralogical zones (5). All zones have deposits of taconite along with quartz and iron silicates, but vary in the type of EMP (6). The ore body in the eastern range, known as zone 4, contains iron-rich amphibole EMPs (primarily cummingtonite-grunerite), which is believed to be less than 1% fibrous (7). The western end of the range, zone 1, contains almost exclusively non-asbestiform EMPs, primarily of quartz hematite, siderite, chamosite, and greenalite (6, 8). Zone 2 is considered a transitional zone with some amphiboles appearing (5). One mine operates in zone 4, one

mine that is no longer in operation is located in zone 2, the remaining five mines are located in zone 1 which is roughly the western most two thirds of the entire Mesabi Iron Range. There is another mineralogical zone, zone 3, however there are no mines located in this zone. The primary exposure in taconite operations is of non-asbestiform cleavage fragments however, due to the mineralogical differences in the eastern versus western zones, workers in the two zones may be exposed to different types of mineral particles (3). There is an ongoing debate regarding these exposures and the health of miners which includes (1) whether the amphibole minerals mined in the eastern part of the iron range are a threat to human health and (2) whether exposure to non-asbestiform minerals, including cleavage fragments, poses any risk to human health (4, 9-12).

The history of public concern of the health of taconite miners and residents near the mining and processing facilities began in the early 1970s when EMPs, determined to be primarily grunerite, possibly including some asbestiform grunerite, were found in Duluth's drinking water supply as a result of taconite tailings that were disposed of into Lake Superior (8, 13). This prompted studies of the potential health effects from ingestion of Duluth water which did not show increased risk of malignant tumors in either laboratory animals or human populations (14-15). The earliest studies of the health of taconite miners were carried out in the early 1980s. The first study (16) focused on a group of miners from Reserve Mining Company. The authors reported no increased risk of respiratory cancers among the 5,751 miners. Later studies were conducted in 1988 with an update in 1992 (17-18) and similarly did not report an excess mortality among the 3,431 workers from Erie and Minntac mines. In 1997 the Minnesota Department of

Health Cancer Surveillance System reported a 73% excess in cases of mesothelioma among men in the northeastern region of Minnesota between 1988 and 1996 as compared to the rest of the state (19). This resurrected the concern over whether exposures from taconite mining and processing pose a threat to the health of the workers.

To address these lingering uncertainties regarding the health consequences of taconite mining, we conducted a mortality study of workers from multiple mines to characterize the overall health of the Minnesota taconite worker population.

METHODS

Study population

The occupational cohort for this analysis was enumerated in the early 1980s as part of the Mineral Resources Health Assessment Program (MRHAP). The program was developed by the University of Minnesota, School of Public Health, with the support of the Iron Range Resources and Rehabilitation Board. This was done as part of an effort to further research on health effects of mining and mineral processing. Investigators assembled a database of 68,737 individuals from employment records of the seven mines in operation in 1983, US Steel Corporation, Hanna Mining Company, Pickands-Mather and Company, Reserve Mining Company, Eveleth Taconite Company, Inland Steel Company, and Jones and Laughlin Corporation.

In 2008, the University of Minnesota launched the Taconite Workers Health Study (TWHS). The current mortality analysis was one component of the overall TWHS with an objective to update the health assessment of the cohort of 68,737 miners collected by MRHAP in 1983. The cohort included both taconite workers and those who had

worked in the earlier hematite mining operations. To focus the study on workers most likely to have been working after taconite mining began in the 1950s, the cohort used in this analysis was limited to those born in 1920 or later, leaving 46,170 individuals. Of these, 1,927 were excluded, including 477 whose only record on file was an application with no further evidence of employment, 679 whose records were insufficient for vital status follow-up, and 539 for whom employment information was improbable, e.g. began working at age fourteen or younger. Those who died before reference mortality rates were available (before 1960, n=232), were also excluded leaving 44,243 workers. To focus on workers with more stable employment in the taconite industry, this analysis was restricted to workers with at least one year of documented employment giving a study population of 31,067 workers. This exclusion removed not only workers who did not stay in the industry, but also summer workers, often students who only worked a few months.

Vital status ascertainment

The mortality analyses covered the period from 1960 (when complete reference mortality rates were available) through 2010. The vital status of cohort members as of December 31, 2010 was ascertained through several sources including the Social Security Administration (SSA), the National Death Index (NDI), Minnesota Department of Health, and other state health departments. Social security numbers and names of all cohort members were sent to the SSA and were returned with a vital status of *deceased*, *alive*, or *unknown*, with the state of death and date of death identified for decedents. Cohort members who died in Minnesota or whose state of death was unknown were sent

to the Minnesota Department of Health to ascertain causes of death. NDI, established in 1979, is a national death registry designed to facilitate health investigations. For those who died outside of Minnesota in the year 1979 or later, causes of death were obtained from NDI Plus. For individuals who died before 1979, death certificates were obtained from the state health department from the state in which the individual died. Additional tracing was done on those whose vital status was unknown and, if found to be deceased, their death certificates were obtained. Underlying and contributing causes of death were coded to the International Classification of Disease (ICD) version current at the year of death. The ICD codes were obtained directly from the Minnesota Department of Health and the NDI. All other death certificates were reviewed and coded by a nosologist.

Individuals who were identified as deceased but whose death certificates were not found were classified as 'Presumed Dead'. The date of death provided by the SSA was recorded as the vital status date and the cause of death was classified as 'Unknown.' Individuals identified as 'Unknown' by the SSA were traced via a commercial tracing vendor that uses credit bureau address updates. For those who were found to have had recent address activity, their vital status was recorded as 'Presumed Alive' with a vital status date as the most recent date recorded from the web tracing tools. The vital status date for the remaining individuals with an unknown vital status was their last date of employment.

Given the size of the cohort, detailed abstraction of all work histories in the cohort was not feasible, and duration of employment was the primary exposure measure of interest. For this analysis, work records of cohort members were reviewed with the first

and last dates of employment abstracted as well as the last date of activity on the work record. In 4.5% of the data, the work records contained start dates but were missing end dates. In this case, the last date of activity was used as the end date to calculate duration of employment. For roughly 92% of the study population, we also had location (zone 1, 2, or 4) of employment.

Data analysis

The mortality rate of the cohort was compared with that of the Minnesota population to estimate standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) adjusted for sex, and five-year age and calendar period. Person-time at risk was accrued from the first date of employment until the date of death or the end of the follow-up period (December 31, 2010). The expected number of deaths was calculated by applying age, calendar time, and cause-specific mortality rates of the Minnesota population to the person-year observations of the study population. SMRs were obtained by computing the ratio of the observed-to-expected number of deaths for the overall mortality and specific causes of death. In addition to overall SMRs, workers with any evidence of employment in zones 1, 2, and 4 were grouped and SMRs for mesothelioma and lung cancer were estimated for each zone.

To further explore summary results for selected causes of death from the SMR analysis, an internal analysis of mesothelioma, lung cancer, hypertensive heart disease, and ischemic heart disease by duration of employment was undertaken. Mesothelioma was captured under ICD-10 code C45, lung cancer was captured under ICD-7 code 162, ICD-8 code 162, ICD-9 code 162, and ICD-10 codes C33 and C34, hypertensive heart

disease was captured under ICD-7 codes 440-443, ICD-8 codes 400.1, 400.9, 402, and 404, ICD-9 codes 402 and 404, and ICD-10 codes I11 and I13, and ischemic heart disease was captured under ICD-7 code 420, ICD-8 codes 410-414, ICD-9 codes 410-414 and 429.2, and ICD-10 codes I20, I21, I22, I24, I25, I51.3, and I51.6. Exposure categories were grouped by duration of employment into four exposure categories (1 year, 2-5 years, 6-14 years, and 15+ years). Those who worked 2-5 years were considered most representative of taconite workers with low but stable employment; those who worked less than two years were thought to be either transient workers or individuals whose work records were incomplete. Therefore, the 2-5 year exposure group, representing 35% of the study cohort, was used as the reference. Standardized Rate Ratios (SRRs) were computed by standardizing to the age and sex distribution of the total study population. Taylor-series based 95% confidence intervals were calculated for each specific SRR. All SMRs and SRRs were calculated using the Life Table Analysis System (LTAS) 3.0 software (20).

RESULTS

This cohort of 31,067 taconite workers with at least one year of documented employment was predominantly male (93%), contributed 1,152,966 person-years of observation, and experienced 9,094 deaths. Their mean and median durations of employment were 9.4 and 6 years respectively. Table 2-1 shows demographic information of the entire cohort and for those with selected causes of death.

Table 2-1. Characteristics of taconite workers with selected causes of death

	Selected Cause of Death								TOTAL COHORT	
	Mesothelioma		Lung Cancer		Hypertensive heart disease		Ischemic heart disease			
	N	%	N	%	N	%	N	%	N	%
DURATION OF EMPLOYMENT (years)										
1	4	13.33	123	12.96	6	9.68	241	11.03	**4353**	**14.01**
2-5	8	26.67	250	26.34	14	22.58	576	26.36	**10839**	**34.89**
6-14	6	20.00	239	25.18	18	29.03	545	24.94	**9072**	**29.20**
15+	12	40.00	337	35.51	24	38.71	823	37.67	**6803**	**21.90**
SEX										
Male	30	100.0	915	96.42	58	93.55	2143	98.08	**28860**	**92.90**
Female	.	.	34	3.58	4	6.45	42	1.92	**2202**	**7.09**
Unknown	.	.	.	.	.	.	.	.	**5**	**0.02**
AGE AT HIRE										
< 20	12	40.00	247	26.03	15	24.19	628	28.74	**11635**	**37.45**
20-29	14	46.67	494	52.05	34	54.84	1163	53.23	**15962**	**51.38**
30-39	4	13.33	165	17.39	10	16.13	312	14.28	**2851**	**9.18**
40+	.	.	43	4.53	3	4.84	82	3.75	**619**	**1.99**
DECADE OF HIRE										
< 1950	6	20.00	289	30.45	20	32.26	799	36.57	**4557**	**14.67**
1950 to 1959	17	56.67	442	46.58	21	33.87	954	43.66	**9072**	**29.20**
1960 to 1969	6	20.00	143	15.07	14	22.58	272	12.45	**6897**	**22.20**
1970 to 1979	1	3.33	72	7.59	6	9.68	157	7.19	**10332**	**33.26**
> 1980	.	.	3	0.32	1	1.61	3	0.14	**209**	**0.67**
VITAL STATUS										
ALIVE									**20814**	**67.00**
DEAD	30	100.0	949	100.0	62	100.0	2185	100.0	**8952**	**28.82**
PRESUMED ALIVE									**1157**	**3.72**
PRESUMED DEAD									**144**	**0.46**
TOTAL	30	100.0	949	100.0	62	100.0	2185	100.0	**31067**	**100.0**

The mortality rates from all causes (SMR = 1.04, 95% CI: 1.02 – 1.06) and all cancers (SMR = 1.04, 95% CI: 1.00 – 1.08) were higher than the Minnesota population. Among specific cancers, mortality rates for lung cancer (SMR = 1.16, 95% CI: 1.09 – 1.24) and mesothelioma (SMR = 2.77, 95% CI: 1.87 – 3.96) were significantly higher than expected. The mortality rate for cardiovascular disease was also elevated (SMR =

1.10, 95% CI: 1.06 – 1.14), specifically for hypertensive heart disease (SMR = 1.81, 95% CI: 1.39 – 2.33) and ischemic heart disease (SMR = 1.11, 95% CI: 1.07 – 1.16). Table 2-2 shows selected SMRs for the taconite workers cohort. Only one death each for asbestosis and silicosis was observed.

Table 2-2. Selected SMRs for Minnesota taconite workers with ≥ 1 year employment*

Underlying Cause of Death	Observed	Expected	SMR	95% CI
All Causes	9,094	8,764.69	1.04	1.02-1.06
All Cancers	2,710	2,609.86	1.04	1.00-1.08
Respiratory	981	846.74	1.16	1.09-1.23
Larynx	26	23.84	1.09	0.71-1.60
Trachea, bronchus, lung	949	815.67	1.16	1.09-1.24
Pleura	1	1.81	0.55	0.01-3.08
Mesothelioma	30	10.82	2.77	1.87-3.96
Heart diseases	2,676	2,435.81	1.10	1.06-1.14
Hypertensive heart disease	62	34.17	1.81	1.39-2.33
Ischemic heart disease	2,185	1,964.93	1.11	1.07-1.16
Cerebrovascular disease	391	384.30	1.02	0.92-1.12
Hypertension w/o heart disease	35	52.80	0.66	0.46-0.92
Respiratory Diseases	582	621.19	0.94	0.86-1.02
COPD	363	369.89	0.98	0.88-1.09
Asbestosis	1	2.90	0.35	0.01-1.92
Silicosis	1	1.09	0.91	0.02-5.09
Transportation injuries	339	329.15	1.03	0.92-1.15
Other injury	239	221.75	1.08	0.95-1.22
Violence	289	258.41	1.12	0.99-1.26

*adjusted for age, calendar period, and sex

The mortality rates were elevated for both mesothelioma and lung cancer in all three zones of the iron range. Among the 20,282 workers who ever worked in zone 1, the SMRs for mesothelioma and lung cancer were 1.85 (95% CI: 0.98 – 3.16) and 1.18 (95%

CI: 1.09 – 1.27) respectively. Among the 5,580 workers who ever worked in zone 2, the SMRs for mesothelioma and lung cancer were 7.38 (95% CI: 4.30 – 11.82) and 1.43 (95% CI: 1.26 – 1.63) respectively. Among the 6,501 workers who ever worked in zone 4, the SMRs for mesothelioma and lung cancer were 3.17 (95% CI: 1.37 – 6.25) and 1.23 (95% CI: 1.07 – 1.40) respectively.

The internal analysis of mesothelioma, lung cancer, hypertensive heart disease, and ischemic heart disease by duration of employment showed elevated but imprecise SRRs when comparing those with 6-14 years, and 15 + years to those with 2-5 documented work years for hypertensive heart disease. There was no significant elevation in SRRs for mesothelioma, ischemic heart disease, and lung cancer (Table 2-3).

Table 2-3. Standardized rate ratios by duration of employment*

Employment Duration (years)	Cause of Death							
	Mesothelioma		Lung Cancer		Hypertensive heart disease		Ischemic heart disease	
	Obs	SRR (95% CI)	Obs	SRR (95% CI)	Obs	SRR (95% CI)	Obs	SRR (95% CI)
1	4	1.14 (0.34, 3.81)	123	1.01 (0.81, 1.26)	6	0.90 (0.34, 2.41)	241	0.88 (0.76, 1.03)
2-5 (ref)	8	1.0	250	1.0	14	1.0	576	1.0
6-14	6	0.77 (0.26, 2.25)	239	1.01 (0.85, 1.21)	18	1.29 (0.63, 2.63)	545	0.99 (0.88, 1.11)
15+	12	1.08 (0.44, 2.67)	337	0.94 (0.79, 1.13)	24	1.84 (0.82, 4.11)	823	0.98 (0.88, 1.10)

*adjusted for age, calendar period, and sex

DISCUSSION

In this study of Minnesota taconite iron ore miners, an overall higher than expected mortality rate from all-causes was observed among taconite workers. Specifically, elevated causes of death from both respiratory cancers (including lung cancer and mesothelioma) and cardiovascular disease (including hypertensive heart disease and ischemic heart disease) were identified. These rates were elevated in all three

zones of the iron range for both mesothelioma and lung cancer. An internal analysis comparing the association between duration of employment and these causes of death did not show a statistically significant elevation in risk for any duration of employment category for mesothelioma, lung cancer, hypertensive heart disease and ischemic heart disease mortality.

Studies of the morbidity and mortality of miners were first carried out in the early 1980s. Higgins et al. (16) followed a cohort of 5,751 men employed at Reserve Mining Company from 1952 to 1976. The study showed no increases in observed respiratory cancers compared to both the United States and Minnesota. Cooper et al. (17-18) studied mortality through 1988 in a cohort of 3,431 male workers from Erie and Minntac mines between 1959 and 1977. Total observed deaths were fewer than expected when compared to both Unites States and Minnesota death rates. The investigators reported no significantly elevated SMRs for any cause of death. Though these first studies of the health of taconite miners did not show increased risk of mortality, it is important to note that mesothelioma was not captured systematically in mortality registries until 1999 when the ICD version 10 was introduced giving mesothelioma a unique ICD code. Additionally, the follow-up times were not long enough to capture many of the potential cases given the relatively long latency period which for mesothelioma, is estimated to have a median duration of 32 years (21). Aside from these two studies that followed a small number of workers over a relatively short amount of time, there has been no comprehensive look at the heath of taconite miners across the entire Mesabi iron range.

Several occupational studies have been conducted that evaluate the health risk to workers exposed to non-asbestiform EMPs in other occupational settings. These include studies of talc miners in upstate New York and Homestake gold miners in South Dakota. In a 2002 mortality study of talc miners, Honda et al. reported an excess in mortality from all cancers, lung cancer, ischemic heart disease, and non-malignant respiratory disease (22). A 2012 follow-up commentary argued that talc ore exposure also increases the risk of mesothelioma, (11) though that conclusion has been debated (12). Though the authors argue the lack of an exposure-response relationship indicates the lung cancer excess may not be related to talc ore dust; rather it might be explained by a relatively high smoking rate in the population (22), it is unlikely that confounding by smoking accounts fully for the lung cancer excess observed in the study (4). The results of these studies have been argued further as the composition of industrial-grade talc has been redefined. Industrial-grade talc deposits are a complex mixture of mineral particles that vary substantially and may rarely include asbestos fibers (23). Price (23) argues that elevated rates of mesothelioma found in New York talc miners are a result of previous occupational exposure to commercial asbestos. Several studies of miners at the Homestake gold mine in South Dakota were done in the 1970s and 1980s (24-26). An excess of respiratory cancer was reported in the earliest study (24), and a small excess of lung cancer was reported in the studies by McDonald et al. and Steenland & Brown (25-26). The results of these studies suggest a weak association between dust exposure and lung cancer and like the studies of talc miners, no dose-response relationship was observed (4). The

studies of New York talc miners and Homestake gold miners cannot definitively conclude whether exposure to non-asbestiform minerals poses any risk to human health.

The elevated risk of lung cancer and mesothelioma as a result of exposure to asbestiform EMPs is well documented in the literature (4, 27-29). However, risk of exposure to non-asbestiform ampbibole and non-amphibole EMPs as found in taconite mining operations, is not understood and evidence of their toxicity is inconclusive (4). Our results indicate an increased risk for mesothelioma and lung cancer among taconite workers with at least one year of employment, but no exposure-response association for duration of employment was detected. Mortality from cardiovascular disease, specifically hypertensive heart disease and ischemic heart disease were also increased. Major risk factors for the development of heart disease include hypertension, diabetes, and cholesterol. Lifestyle factors, such as smoking, physical activity, and diet also play a role in disease risk. This study result suggests that lifestyle factors likely contribute to disease burden in this working population. However, occupational risk cannot be ruled out entirely. Other workplace factors, such as stress, noise, vibration, extreme temperature, and shift work, may also affect cardiovascular disease risk (30-31). Additionally, environmental factors, such as particulate air pollution, have also been shown to increase the risk of cardiovascular events from short and long-term exposure (32-36) and elevated cardiovascular mortality has been identified in other working cohorts (37). Thus, a combination of workplace and lifestyle factors may be contributing to the excess in cardiovascular disease in this taconite workers cohort.

The following limitations should be considered when interpreting the results of this analysis. Instead of specific exposure measurements for this analysis, duration of employment in the taconite mining industry was meant a as proxy for exposure averaged across all jobs and locations on the range. Our estimate of employment duration was measured as the last date of employment minus the start date. This crude measure of employment duration does not take into account any gaps in work history which could result in employment duration misclassification. Individuals who appear to have worked more than 15 years may have a much shorter cumulative work history when considering gaps in employment. We did not have access to information on some confounding variables, most notably smoking status which is a major risk factor for both lung cancer and cardiovascular disease. Though we could not adjust for smoking in this analysis, it is possible that smoking explains at least some of this excess risk in lung cancer mortality especially given that working cohorts typically have higher smoking rates than the general population and because of the high attributable risk for smoking (38). Smoking however, is not a risk factor for mesothelioma, thus the high mortality ratio of mesothelioma suggests that there may be occupational exposures to account for some of the increased risk of these diseases.

The risk of mesothelioma may also be underestimated as the specific ICD code for this disease was not available until 1999, thus earlier cases were misclassified as another disease. The lower percentage of mesothelioma cases, as compared to other causes of death (Table 2-1) who were hired prior to 1950, the earliest exposed, may represent this misclassification. These undercounted mesotheliomas may have had more

hematite exposure or exposure to the taconite processes in their earlier work. However, identifying other potential mesothelioma cases using previously used rubrics (39) would not change the interpretation that taconite workers have elevated rates of mesothelioma. It is also important to note that the cases were identified as primary causes of death and do not capture incident cases or contributing causes of death and therefore do not accurately reflect the total disease burden in the cohort.

Although the SMR for mesothelioma was elevated, the internal analysis did not identify an association by duration of employment. One possible explanation of this is if the elevated risk of mesothelioma is related to work in the taconite industry, that risk may not be a function of time, rather a function of specific exposures while performing certain job tasks. Likewise, the internal analysis did not show an increased risk of lung cancer, hypertensive heart disease, and ischemic heart disease by duration of employment suggesting that other lifestyle factors are potentially contributing to the elevated SMRs. These results could also have been affected by the crude employment duration measure resulting of misclassification of time worked.

The analysis by zone was a cursory examination of the risk across the iron range, since it evaluated any work in a zone. It does not allow for comparison of risk between zones but only suggests the risk of mesothelioma and lung cancer is elevated with employment in each zone of the iron range. We limited the analysis to iron mining workers who were born in 1920 or later and who had at least one year of documented employment. Restricting the cohort further to those born in 1930 or later (excluding an additional 8,504 workers) in order to potentially better focus on taconite mining did not

substantially change the results and interpretation of this study (lung cancer SMR = 1.15, 95% CI: 1.04 – 1.27, mesothelioma SMR = 3.59, 95% CI: 2.16 – 5.60). Examination of the entire cohort of 44,243 individuals, including those with less than one year of documented employment, likewise did not substantially change the results and interpretation of this study (lung cancer SMR = 1.20, 95% CI: 1.14 – 1.27, mesothelioma SMR = 2.89, 95% CI: 2.11 – 3.87).

This study has some notable strengths including the large size and long follow-up of the cohort and the high proportion of workers whose vital status was ascertained. Vital status was found on 98% of the eligible cohort and few workers (4%) were excluded from the analysis due to data quality problems. Additionally, this study captured mortality from mesothelioma; early mortality studies of taconite workers were unable to evaluate mesothelioma until 1999 when ICD-10 became available. This study allowed us to characterize the mortality of the entire Minnesota mining population as compared to the rest of Minnesota, as well as capture information specific to where miners worked by zone which has not been done before. The analysis identifies a need for future studies with more refined exposure estimates to evaluate the extent to which mining related exposures specifically contribute to disease burden and will be the next step in our evaluation of the health of taconite mining workers.

CONCLUSION

In summary, this analysis suggests taconite workers may be at increased risk for mortality from some cancers and cardiovascular diseases. Duration of employment did not appear to be associated with the mortality risk. However, based on the limited way

exposure potential was evaluated, we cannot say for sure what the role of actual work place exposures play in the disease excess. Additional investigation is warranted.

REFERENCES

1. Berndt ME, Brice WC. The origins of public concern with taconite and human health: Reserve Mining and the asbestos case. *Regul Toxicol and Pharmacol* 2008;52(S1):S31-S39.
2. Minnesota Department of Natural Resources. Digging in MN minerals: Taconite 2011 (Retrieved August 22, 2011). Available from: http://www.dnr.state.mn.us/education/geology/digging/mining.html
3. Hwang J, Gurumurthy R, Raynor P, et al. Comprehensive Assessment of Exposures to Elongate Mineral Particles in the Taconite Mining Industry. *Ann Occup Hyg* 2013;doi:10.1093.
4. Department of Health and Human Services, National Institute for Occupational Safety and Health. Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research, 2011: Publication No. 2011-159.
5. McSwiggin PL, Morey GB. Overview of the mineralogy of the Biwabik Iron Formation, Mesabi Iron Range, northern Minnesota. *Regul Toxicol and Pharmacol* 2008;52(S1):S11-S25.
6. Jirsa MA, Miller JD, Morey GB. Geology of the Biwabik Iron Formation and Duluth Complex. *Regul Toxicol and Pharmacol* 2008;52(S1):S5-S10.
7. Wilson R, McConnell EE, Ross M, et al. Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. *Regul Toxicol and Pharmacol 2008;52(S1): S232-S245.*

8. Langer AM, Maggiore CM, Nicholson WJ, et al. The contamination of Lake Superior with amphibole gangue minerals. *Ann NY Acad Sci* 1979;330:549-572.
9. Williams C, Dell L, Adams R, et al. State-of-the-science assessment of non-asbestos amphibole exposure: Is there a cancer risk? *Environ Geochem Health* 2013;35:357-377.
10. Yang H-Y, Shie R-H, Chen P-C. Carving of non-asbestiform tremolite and the risk of lung cancer: a follow-up mortality study in a historical nephrite processing cohort. *Occup Environ Med* 2013;70:852-857.
11. Finkelstein MM. Malignant Mesothelioma Incidence Among Talc Miners and Millers in New York State. *Am J Ind Med* 2012;868(April):863–868.
12. Nolan RP, Gamble JF, Gibbs GW. Letter to the editor on commentary: malignant mesothelioma incidence among talc miners and millers in New York state by M M Finkelstein. *Am J Ind Med* 2013;56(9):1116-8.
13. Gamble JF, Gibbs GW. An evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regul Toxicol and Pharmacol* 2008;52(S1):S154-S186.
14. Hilding AC, Hilding DA, Larson DM, et al. Biological effects of ingested amosite asbestos, taconite tailings, diatomaceous earth and Lake Superior water in rats. *Arch Environ Health* 1981;36:298-303.
15. Levy BS, Sigurdson E, Mandel J, et al. Investigating possible effects of asbestos in city water: surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. *Am J Epidemiol* 1976;103:362-368.

16. Higgins IT, Glassman JH, Oh MS, et al. Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol* 1983;118(5):710-9.
17. Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. *J Occup Med* 1988;30(6):506-511.
18. Cooper WC, Wong O, Trent LS, et al. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med* 1992;34(12):1173-1180.
19. Minnesota Cancer Surveillance System Epidemiology Report. Cancer incidence Rates in Northeastern Minnesota. Minnesota Department of Health, 1999.
20. Centers for Disease Control and Prevention. Life Table Analysis System 2013. Available from: www.cdc.gov/niosh/ltas.
21. Lanphear BP, Buncher CR. Laten period for malignant mesothelioma of occupational origin. *J Occup Med* 1992;34:718-721.
22. Honda Y, Beall C, Delzell E, et al. Mortality among Workers at a Talc Mining and Milling Facility. *Ann Occup Hyg* 2002;46(7):575–585.
23. Price B. Industrial-grade talc exposure and the risk of mesothelioma. *Crit Rev Toxicol* 2010;40(6):513-530.
24. Gillam JD, Dement JM, Lemen RA, et al. Mortality Patterns Among Hard Rock Gold Miners Exposed to an Asbestiform Mineral. *Ann N Y Acad Sci* 1976;336–344.

25. McDonald JC, Gibbs GW, Liddel FDK, et al. Mortality after long exposure to cummingtonite-grunerite. *Am Rev Respir Dis* 1978;118:271-277.
26. Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of followup. *Am J Ind Med* 1995;27:217-229.
27. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996;9(9):1932–1942.
28. Robinson BWS, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005;366(9483):397–408.
29. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. *Ann Cardiothorac Surg* 2012;1(4):491–6.
30. Kawachi I, Colditz GA, Stampfer MJ, et al. Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 1995;92:3178-3182.
31. Price AE. Heart disease and work. *Heart* 2004;90:1077-1084.
32. Brook RD, Rajagopalan S, Pope CA, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010;121:2331-2378.
33. Dockery DW, Pope CA, Xu X, et al. An Association between Air Pollution and Mortality in Six U.S. Cities. *N Engl J Med* 1993;329:1753-1759.
34. Miller KA, Siscovick DS, Sheppard L, et al. Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women. *N Engl J Med* 2007;356:447-458.

35. Pope CA III, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71–77.
36. Bhatnagar A. Environmental cardiology: studying mechanistic links between pollution and heart disease. *Cir Res* 2006;99:692-705.
37. Gallagher LG, Ray RM, Li W, et al. Occupational exposures and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Am J Ind Med* 2012;55(11):991-999.
38. Centers for Disease Control and Prevention. Current cigarette smoking prevalence among working adults-United States 2004-2009. *MMWR Morb Mortal Wkly Rep* 2011;60(38):1305-1309.
39. Sullivan PA. Vermiculite, Respiratory Disease, and Asbestos Exposure in Libby, Montana: Update of a Cohort Mortality Study. *Environ Health perspect* 2007;115(4):579-585.

Chapter 3:

Cancer incidence among Minnesota taconite mining industry workers

STUDY OVERVIEW

Objective: To evaluate cancer morbidity among Minnesota Taconite mining industry workers.

Methods: Cancer morbidity between 1988 and 2010 was evaluated in a cohort of 40,720 Minnesota taconite mining workers employed between 1930 and 1983. Standardized incidence ratios (SIRs) with 95% confidence intervals (CI) were determined by comparing observed numbers of incident cancers with frequencies in the Minnesota Cancer Surveillance System. SIRs for lung cancer by histological subtypes were also estimated. SIRs were adjusted to account for out-of-state migration and a bias factor was estimated to adjust smoking related cancers.

Results: A total of 5,700 cancers were identified in the study cohort including 51 mesotheliomas and 973 lung cancers. After adjusting for out-of-state migration, the SIR for lung cancer and mesothelioma were 1.3 (95% CI: 1.2-1.4) and 2.4 (95% CI: 1.8-3.2) respectively. Other elevated cancers included stomach (SIR = 1.4, 95% CI: 1.1-1.6), laryngeal (SIR = 1.4, 95% CI: 1.1-1.7), and bladder (SIR = 1.1, 95% CI: 1.0-1.2). Among the lung cancers, SIRs for adenocarcinoma (SIR = 1.2, 95% CI: 1.1-1.4), squamous cell (SIR = 1.3, 95% CI: 1.2-1.5) non-specified (SIR = 1.6, 95% CI: 1.4-1.8), and other (SIR = 1.4, 95% CI: 1.1-1.8) were elevated. Adjusting with a bias factor for smoking attenuated the lung cancer SIR (SIR = 1.1, 95% CI: 1.0-1.1).

Conclusions*:* Taconite workers have an increased risk for certain cancers. Adjustment for smoking attenuates but does not eliminate the risk of lung cancer in this population. Lifestyle and work-related factors may play an important role in elevated morbidity. The

extent to which mining-related exposures contribute to disease burden is being further investigated.

BACKGROUND AND SIGNIFICANCE

Full scale taconite mining began in northeastern Minnesota in the 1950s along the 120 mile long Mesabi Iron Range. This open pit mining is a multi-stage process that involves blasting rock with dynamite, crushing the rock down to a fine powder, magnetically extracting the iron, and reforming the more concentrated product into iron ore pellets. This process generates a significant amount of dust that results in potential exposure to long and short non-asbestiform amphibole and non-amphibole elongate mineral particles (EMPs), respirable silica, quartz, and cleavage fragments (1). Several studies have examined the risk of exposure to non-asbestiform EMPs (2-7), but the toxicity of these exposures is uncertain (8). A limited number of animal studies in this field have provided evidence to suggest that non-asbestiform amphiboles might pose different risks than asbestos (9-11), but that risk remains unclear (8).

Elevated age-adjusted rates of mesothelioma have been reported in northeastern Minnesota counties in proximity to where taconite is mined (12). This apparent increase in cases has been concerning to the mining communities. Despite community-wide health concerns and the lack of knowledge of these potential health effects, there is limited health research related to taconite mining industry workers. Several small-scale mortality studies conducted in the early 1980s and 1990s produced null findings (13-15). A larger mortality study in the population used for this analysis found an excess of death from lung cancer and mesothelioma. In this study, we examine incident cancers in a taconite workers cohort.

METHODS

Study population

The study cohort was enumerated in the early 1980s as part of the Mineral Resources Health Assessment Program (MRHAP). The program was developed by the University of Minnesota, School of Public Health, along with the Iron Range Resources and Rehabilitation Board. Its goals were to develop expertise concerning hazards of the mining and processing of minerals in Minnesota and to research health effects of mining and mineral processing. Investigators assembled a database of 68,737 individuals who had ever worked in one of the 7 mines in operation in 1983, US Steel Corporation, Hanna Mining Company, Pickands-Mather and Company, Reserve Mining Company, Eveleth Taconite Company, Inland Steel Company, and Jones and Laughlin Corporation. Work history information was collected through 1983, though some individuals worked beyond this point.

In 2008, the University of Minnesota launched the Taconite Workers Health Study (TWHS) (16). One objective of the TWHS was to update the health assessment of the cohort of 68,737 miners collected by MRHAP in 1983. The cohort included both taconite workers and those who had also worked in the earlier hematite mining operations. In order to capture workers who were most likely to have been working after taconite mining began in the 1950s, the cohort was limited to those born in 1920 or later, reducing the cohort size to 46,170 individuals. An additional 1,691 were excluded including 477 whose only record on file was an application with no further evidence of employment, 679 whose vital status remained unknown after follow-up, and 535 for whom employment information was improbable, e.g. began working at age fourteen or

younger. For this analysis of cancer incidence, the cohort was further restricted to individuals living to at least 1988 when the Minnesota Cancer Surveillance System would capture the incident cases, which eliminated 3,759 workers who were deceased before 1988. The final study cohort included 40,720 individuals.

Cancer incidence

To identify incident cancers, the cohort was linked to the Minnesota Cancer Surveillance System (MCSS). The MCSS is Minnesota's statewide, population-based cancer registry that collects histological information of newly diagnosed cancers on all Minnesota residents. The system was established in 1988 by state statute as a mandatory reporting system to monitor cancers in Minnesota, inform health professionals, answer the public's questions, and promote cancer research. Cancer incidence including date of diagnosis, cancer site, and histology were obtained for cohort members matched to the MCSS.

Data analysis

The cancer morbidity analyses covered the period from 1988 (when the Minnesota Cancer Surveillance System began collecting data) through 2010. The cancer rate of the cohort was compared with that of the Minnesota population to estimate standardized cancer incidence ratios (SIRs) and 95% confidence intervals (CIs) adjusted for sex, and five-year age and calendar period. Person-time at risk was accrued from January 1, 1988 until cancer diagnosis date, date of death, or the end of the follow-up period (December 31, 2010). For individuals with more than one diagnosis of the same cancer, they were followed only to the date of first diagnosis. The expected number of

cancers was calculated by applying age, calendar time, and sex specific cancer rates of the Minnesota population to the person-year observations of the study population. SIRs were obtained by computing the ratio of the observed-to-expected number of cancers. Selected cancers of interest were mesothelioma, lung, esophageal, kidney, laryngeal, liver and bile duct, oral, pancreatic, stomach, and bladder cancers. These cancers were of interest to study investigators because of their association with asbestos exposure (8, 17-18). All SIRs were computed using STATA 12.1 software.

We further explored lung cancer incidence by histological type. Lung cancer in the study and reference populations were grouped into one of five subtypes: adenocarcinoma, squamous cell, small cell, other/rare (including large cell), and non-specified carcinomas. The International Classification of Diseases for Oncology (ICD-O) histology code groupings were determined by study investigators. These groupings can be found in Appendix Table 3-A. Standardized incidence ratios and 95% CIs were estimated for each of the five lung cancer histological subtypes.

Accurate estimation of cancer incidence rates in the study population requires individuals to remain in the state of Minnesota, and thus under MCSS surveillance. In order to adjust for potential migration, out-of-state deaths were used as an estimate of out-of-state migration by age group in the study population. As part of the Taconite Workers Health Study, the cohort was followed up for mortality with state of death identified for decedents. Details of the mortality follow-up have been described elsewhere (19). The proportion of in-state deaths by age group was used as an estimate

of the proportion of workers who stayed in Minnesota. Person-years were adjusted by age-group accordingly.

No information on tobacco smoking was available for cohort members however, because some of the cancers of interest (lung, oral, laryngeal, and bladder) are strongly associated with smoking (20-21), a bias factor for smoking was calculated to adjust the SIRs for smoking related cancers. A subset of 1,313 taconite mining industry workers participated in a cross-sectional survey where data collection included a questionnaire with smoking history. This subset analysis was one part of the overall TWHS and details of this study can be found elsewhere (22). The smoking prevalence in this subset of workers was used as an estimate of the smoking prevalence in the target population. Minnesota smoking data from the Behavioral Risk Factor Surveillance System (BRFSS) (23) was weighted by the sex and age distribution of the questionnaire participants and used as an estimate of the smoking prevalence for the reference population. Questionnaire data were summarized into ever and never smokers. Among the 1,313 current and former taconite workers, 38.2% reported never having smoked. After weighting the BRFSS smoking data to the age and sex distribution of the questionnaire respondents, 50.1% of Minnesotans fell into the never smoked category. Cancer rates in smokers versus non-smokers obtained from World Health Organization (WHO) estimates for lung cancer was 10, for oral cancer, 27, for laryngeal cancer, 12, and for bladder cancer, 3 (20). These data were used in the following formulas, adapted from Steenland & Greenland, 2004, to estimate a bias factor (24):

$$I_+ = I_0(C_x)(S_1) + I_0(1 - S_1)$$

$$I_- = I_0(C_x)(S_0) + I_0(1 - S_0)$$

Where: I_+ = cancer incidence rate in study population
I_- = cancer incidence rate in Minnesota
S_1 = smoking prevalence in study population
S_0 = smoking prevalence in Minnesota
I_0 = cancer rate in non-smokers
C_x = cancer rate in smokers versus non-smokers

A bias factor for smoking was estimated with I_+/I_- and smoking related cancers were divided by this bias factor to adjust for potential differences in smoking between the study and reference populations. Using the smoking prevalence estimates in the study population, the Minnesota general population, and the cancer rates among smokers versus non-smokers, the bias factor for four of the smoking related cancers (lung, laryngeal, oral, and bladder cancers) was estimated.

RESULTS

This cohort of Minnesota taconite mining industry workers was predominantly male (93%) with an average work history of 6.5 years. Among the 40,720 workers, 5,700 cancers were identified by MCSS (5408 for men and 292 for women). Of those, 973 lung cancers and 51 mesotheliomas were identified.

After adjusting for age, sex, calendar period, and out-of-state migration, the cohort members experienced elevated rates of mesothelioma (SIR = 2.4, 95% CI: 1.8-3.2), lung (SIR = 1.3, 95% CI: 1.2-1.4), laryngeal (SIR = 1.4, 95% CI: 1.1-1.7), stomach (SIR = 1.4, 95% CI: 1.1-1.6), and bladder (SIR = 1.1, 95% CI: 1.0-1.2) cancers. SIRs and 95% CIs for selected cancers of interest are summarized in table 3-1.

Table 3-1. Selected SIRs for Minnesota Taconite Workers

Cancer	Observed	Expected	SIR[a]	95% CI
Mesothelioma	51	21.1	2.4	1.8-3.2
Lung	973	750.9	1.3	1.2-1.4
Esophagus	87	76.9	1.1	0.9-1.4
Kidney	170	178.2	1.0	0.8-1.1
Larynx	94	68.6	1.4	1.1-1.7
Liver & bile duct	52	49.4	1.1	0.8-1.4
Oral	172	162.5	1.1	0.9-1.2
Pancreas	120	105.9	1.1	0.9-1.4
Stomach	105	77.7	1.4	1.1-1.6
Bladder	363	338.5	1.1	1.0-1.2

a Adjusted for age, sex, calendar period, and out-of-state migration

A closer look at lung cancer by histological subtypes showed that among the 973 incident lung cancers, 313 were adenocarcinomas, 260 were squamous cell carcinomas, 138 were small cell carcinomas, 201 were non-specified lung cancers, and 61 were other or rare types of lung cancer. SIRs were elevated for adenocarcinoma (SIR = 1.2, 95% CI: 1.1-1.4), squamous cell (SIR = 1.3, 95% CI: 1.2-1.5), non-specified (SIR = 1.6, 95% CI: 1.3-1.8), and rare cancers (SIR = 1.3, 95% CI: 1.0-1.7) after adjusting for age, sex, calendar period, and out-of-state migration. Table 3-2 shows SIRs for lung cancer by histological subtype.

Table 3-2. SIRs for lung cancer by histological subtype

Lung cancer histological subtype	**N**	**SIR[a]**
Adenocarcinoma	313	1.2 (1.1, 1.4)
Squamous cell	260	1.3 (1.2, 1.5)
Small Cell	138	1.1 (1.0, 1.3)
Non-specified	201	1.6 (1.3, 1.8)
Rare/other (including large cell)	61	1.3 (1.0, 1.7)
Total	973	1.3 (1.2, 1.4)

a Adjusted for age, sex, calendar period, and out-of-state migration

The estimated bias factors for lung, laryngeal, oral, and bladder cancers were 1.2, 1.2, 1.2, and 1.1 respectively. The bias factor for lung cancer (1.2) was similar to the one estimated in the adapted example (1.18) from Steenland & Greenland, 2004 (24). After adjustment using the smoking bias factor, the SIR for lung cancer was attenuated but remained above what would be expected in the Minnesota population (SIR = 1.1, 95% CI: 1.0-1.2). The rates of laryngeal, oral, and bladder cancers were as expected in the Minnesota population after the bias factor adjustment (laryngeal SIR = 1.1, 95% CI: 0.9-1.4, oral SIR = 0.9, 95% CI: 0.7-1.0, bladder SIR = 1.0, 95% CI: 0.9-1.1). Though the effect of smoking on lung cancer risk by histological subtype varies, squamous and small cell carcinomas are found to be the most strongly associated with smoking (25). The same sensitivity analysis was applied to squamous and small cell carcinomas. The SIRs were attenuated to what would be expected in the Minnesota population for both squamous (SIR = 1.1, 95% CI: 0.9-1.2) and small cell carcinoma (SIR = 0.9, 95% CI: 0.8-1.1). SIRs with adjustments for smoking are summarized in table 3-3.

Table 3-3. SIRs for smoking related cancers before and after bias factor adjustment for smoking.

Cancer	SIR[a]	95% CI	Smoking adjusted SIR[b]	95% CI
Lung	1.3	1.2-1.4	1.1	1.0-1.2
Squamous cell	1.3	1.2-1.5	1.1	0.9-1.2
Small cell	1.1	1.0-1.3	0.9	0.8-1.1
Larynx	1.4	1.1-1.7	1.1	0.9-1.4
Oral	1.1	0.9-1.2	0.9	0.7-1.0
Bladder	1.1	1.0-1.2	1.0	0.9-1.1

a Adjusted for age, sex, calendar period, and out-of-state migration
b Bias factor for lung, laryngeal, oral and bladder cancers = 1.2, 1.2, 1.2, and 1.1 respectively

DISCUSSION

In this analysis of cancer incidence among Minnesota taconite mining industry workers, there were higher than expected rates of certain cancers as compared to the general Minnesota population, specifically for mesothelioma, lung, laryngeal, stomach, and bladder cancers. Each lung cancer by histological subtype showed an increased SIR. A sensitivity analysis to account for differences in smoking rates between the study and reference populations attenuated the association between laryngeal, bladder, and oral cancers substantially as well as squamous cell and small cell carcinomas of the lung. However, even after smoking bias adjustment, the overall lung cancer SIR remained elevated. In total, these data support an elevated SIR for those cancers that have historically had the strongest relationship to asbestos and EMP exposure. These observations are in a population of workers exposed to a variety of mineral dusts including asbestiform and non-asbestiform elongate mineral particles.

The strong association between asbestos exposure and mesothelioma and lung cancer is well documented (8, 26-28) however, the toxicity of their non-asbestiform analogs is not understood. Results from recent studies have suggested that exposure to non-asbestiform EMPs does not have high potential for disease (11, 29-30) however, NIOSH has specifically identified non-asbestiform EMPs as a needed area of research (8). Non-asbestiform EMPs are included in NIOSH recommended exposure limits due to technical limitations of routine EMP assessments and uncertainty about the potential toxicity of non-asbestiform fibers. For example, the inconclusive evidence in epidemiological studies of New York talc miners (2) and Homestake gold miners (5-7), and evidence from animal studies suggesting that fiber dimension, and not composition, is the major determinant of carcinogenicity for mineral fibers. There remains a need to determine conclusively whether non-asbestiform amphibole mineral particles that are chemically similar to asbestos, but with different physical forms that are also capable of causing disease (8). These mineral particles, including low-levels of non-asbestiform mineral particles, are present in taconite mining operations. Additionally, the predominant exposure potential during the mining and processing of taconite is of short mineral particles, less than five microns in length (1). These short mineral particles are currently not included in NIOSH regulatory standards (8, 31) and have not been studied to the extent that regulated particles have been (32).

We observed elevated SIRs for all types of lung cancer. Small-cell lung cancer is rarely observed in never-smokers (33) while adenocarcinoma is the predominant histological type in never-smokers (33-34). Moreover, adenocarcinoma has been shown

to be the most common histological subtype in asbestos-exposed individuals (35-36). The results of our study show that of the 973 lung cancers identified in the study cohort, 138 were small-cell and 313 were adenocarcinoma. The smoking adjusted results suggest that smoking habit does not account for all of the lung cancer excess in this population. Occupational exposures may also contribute to the elevation in cancer incidence.

The earliest studies of taconite mining exposures focused on ingestion exposure and showed no association between cancers and EMP ingestion (37-38). These were followed by mortality assessments in specific mining companies (13-15). Though these mortality studies did not show a significant excess in respiratory cancers, they had small study populations, short follow-up periods and thus limited statistical power. In 2007, the Minnesota Department of Health reported a 73% excess in cases of mesothelioma for men in northeastern Minnesota between 1988 and 1996 (39), consistent with the elevated SIR reported here. The cause of this excess remains unknown.

The few studies of other occupational cohorts who experience exposures to non-asbestiform mineral particles have been inconclusive. Talc miners in upstate New York and gold miners in South Dakota experience potential exposures to non-asbestiform EMPs. The studies of talc miners reported an excess in mortality from all cancers, lung cancer, ischemic heart disease, and non-malignant repiratory disease, however a lack of exposure-response relationship was seen (2-4). Studies of the Homestake gold mine in South Dakota published in the 1970s and 1980s reported an excess of respiratory cancer and a small excess of lung cancer (5-7) with no observed dose-response relationship,

suggesting a weak association between dust exposure and lung cancer. Due to the limitations of these epidemiology studies, NIOSH has concluded that the findings provide inconclusive evidence regarding the health effects associated with exposures to non-asbestiform EMPs (8). This analysis provided evidence of a possible association between non-asbestiform exposures and cancer.

Some limitations should be considered when interpreting the results of this analysis. Utilizing the Minnesota state cancer registry data requires cohort members to remain in Minnesota in order to capture newly diagnosed cancers. Because it was not feasible to identify if an individual was diagnosed with cancer outside of Minnesota before the end of follow up, adjustments in person-years were required to correct for potential underestimation of SIRs. This study used out-of-state deaths by age group as an estimate of the proportion of individuals in each age group who left Minnesota. We also did not have information on lifestyle factors, most importantly smoking history, a known risk factor for several of the cancers of interest. Differences in smoking in our study cohort and reference population were likely given the documented higher rates of smoking in working cohorts (40). We were able to address this issue with a sensitivity analysis which estimated smoking rates of the study population using data from a smaller study of Minnesota taconite workers. However, there are potential limitations with using this subset of miners as an estimate of smoking habits in our study population. There is potential selection bias of those who participated in the subset analysis by smoking status. We do not know if our study population is representative of the smoking habits of the entire taconite cohort. Additionally, those who participated in the subset analysis were

alive in 2010 and thus may have very different smoking habits than their historic counterparts due to generational differences in smoking patterns. However, because smoking habits for the reference population were taken from BRFSS 2010 data, the relative differences in smoking between the two groups were taken at the same time. We assumed that population smoking rates changed at the same rate as cohort smoking rates and thus the bias factor analysis accounted for this relative difference in smoking between the two groups and adjusted the SIRs accordingly. The sensitivity analysis also required knowing the cancer rate is smokers versus non-smokers. This estimation can vary among different sources (20, 24) however changing this variable in the bias factor calculation did not substantially change the results of the sensitivity analysis.

One of the main strengths of this study is the large size of the cohort. The study population included all taconite mining industry workers with any work experience across the entire Minnesota Iron Range with very few workers (4%) excluded from the analysis due to data quality problems. Having mortality data including state of death for the study population allowed for an estimation of out-of-state migration which can be challenging for other cancer incidence studies of this nature.

CONCLUSION

In summary, this analysis suggests that Minnesota taconite mining industry workers are at risk for development of mesothelioma, lung cancer, and other cancers. The elevated risk of lung and other cancers may be due entirely to elevated smoking and other unmeasured confounders among the workers. However, because confounding variables were not measured and workplace exposure measurements were not evaluated

in this analysis, we cannot say for sure if actual work place exposures contribute to that excess in cancer incidence. A detailed examination of taconite workplace exposures is warranted.

REFERENCES

1. Hwang J, Gurumurthy R, Raynor P, et al. Comprehensive Assessment of Exposures to Elongate Mineral Particles in the Taconite Mining Industry. *Ann Occup Hyg* 2013;doi:10.1093.
2. Honda Y, Beall C, Delzell E, et al. Mortality among Workers at a Talc Mining and Milling Facility. *Ann Occup Hyg* 2002;46(7):575–585.
3. Finkelstein MM. Malignant Mesothelioma Incidence Among Talc Miners and Millers in New York State. *Am J Ind Med* 2012;868(April):863–868.
4. Nolan RP, Gammble JF, Gibbs GW. Letter to the editor on commentary: malignant mesothelioma incidence among talc miners and millers in New York state by M M Finkelstein. *Am J Ind Med* 2013;56(9):1116-8.
5. Gillam JD, Dement JM, Lemen RA, et al. Mortality Patterns Among Hard Rock Gold Miners Exposed to an Asbestiform Mineral. *Ann N Y Acad Sci* 1976;336–344.
6. McDonald JC, Gibbs GW, Liddel FDK, et al. Mortality after long exposure to cummingtonite-grunerite. *Am Rev Respir Dis* 1978;118:271-277.
7. Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of followup. *Am J Ind Med* 1995;27:217-229.
8. Department of Health and Human Services, National Institute for Occupational Safety and Health. Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research, 2011: Publication No. 2011-159.

9. Davis JM, Addison J, McIntosh C, et al. Variations in the carcinogenicity of tremolite dust samples of differing morphology. *Ann NY Acad Sci* 1991;643:473-490.
10. Mossman B, Sesko A. In vitro assays to predict the pathogenicity of mineral fibers. *Toxicology* 1990;60:53-61.
11. Mossman BT. Assessment of the pathogenic potential of asbestos vs. nonasbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. *Regul Toxicol Pharmacol* 2008;52(S1):S200-3.
12. National Institute for Occupational Safety and Health. Malignant mesothelioma: Counties with highest age-adjusted death rates (per million population), U.S. residents age 15 and over, 2000-2004. Work-Related Lung Disease (WoRLD) Surveillance Report Update, 2008: http://www2.cdc.gov/drds/WorldReportData/FigureTableDetails.asp?FigureTableID=901&GroupRefNumber=T07-10, accessed January 17, 2014.
13. Higgins IT, Glassman JH, Oh MS, et al. Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol* 1983;118(5):710-9.
14. Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. *J Occup Med* 1988;30(6):506-511.
15. Cooper WC, Wong O, Trent LS, et al. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med* 1992;34(12):1173-1180.

16. University of Minnesota. *Taconite workers health study* 2013. Available from: http://taconiteworkers.umn.edu/

17. National Toxicology Program. Asbestos. In: *Report on Carcinogens. Twelfth Edition*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 2011.

18. Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Asbestos*. September 2001. Retrieved January 28, 2014, from: http://www.atsdr.cdc.gov/toxprofiles/tp61.pdf.

19. Allen E, Alexander B, MacLehose R, et al. Mortality Experience Among Minnesota Taconite Mining Industry Workers, *Occupational and Environmental Medicine*, *accepted April 2014, awaiting citation.*

20. World Health Organization. Tobacco Free Initiative 2014. Available from: http://www.who.int/tobacco/research/cancer/en/.

21. Secretan B, Straif K, Baan R, et al. A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *The Lancet Oncol* 2009;10:1022-4.

22. Odo NU, Majdel JH, Perlman DM, et al. Estimates of restrictive ventilator defect in the mining industry. Considerations for epidemiological investigations: a cross-sectional study. BMJ Open 2013; *3:e002561 doi:10.1136/bmjopen-2013-00256.*

23. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System 2013. Available from: http://www.cdc.gov/brfss/data_tools.htm.

24. Steenland K, Greenland S. Monte Carlo Sensitivity Analysis and Bayesian Analysis of Smoking as an Unmeasured Confounder in a Study of Silica and Lung Cancer. *Am J Epidemiol* 2004;160:384-392.

25. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer* 2001 Feb-Mar;31(2-3):139-48.

26. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996;9(9):1932–1942.

27. Robinson BWS, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005;366(9483):397–408.

28. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. *Ann Cardiothorac Surg* 2012;1(4):491–6.

29. Berry G, Gibbs GW. An overview of the risk of lung cancer in relation to exposure to asbestos and of taconite miners. *Regul Toxicol Pharmacol* 2008;52(S1):S218-22.

30. Gamble JF, Gibbs GW. Evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regul Toxicol Pharmacol* 2007;52(S1):S154-S186.

31. Occupational Safety and Health Association. OSHA Standards 1910.1001 Asbestos. Available at

https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9995. Accessed J.

32. Aust AE, Cook PM, Dodson RF. Morphological and chemical mechanisms of elongate mineral particle toxicities. *J Toxicol Environ Health B Crit Rev* 2011;14:40-75.
33. Pallis AG, Syrigos KN. Lung cancer in never smokers: disease charateristics and risk factors. *Crit Rev Oncol Hematol* 2013 Dec;88(3):494-503 .
34. Toh CK, Gao F, Lim WT, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *Journal of Clinical Oncology* 2006;24:2245-51.
35. Raffn E, Lynge E, Korsgaard B. Incidence of lung cancer by histological type among asbestos cement workers in Denmark. *Br J Ind Med* 1993 January;50(1):85-89.
36. de Klerk, NH, Musk AW, Eccles J et al. Exposure to crocidolite and the incidence of different histological types of lung cancer. *Occup Environ Med* 1996;53:157-159.
37. Hilding AC, Hilding DA, Larson DM, et al. Biological effects of ingested amosite asbestos, taconite tailings, diatomaceous earth and Lake Superior water in rats. *Arch Environ Health* 1981;36:298-303.
38. Levy BS, Sigurdson E, Mandel J, et al. Investigating possible effects of asbestos in city water: surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. *Am J Epidemiol* 1976;103:362-368.

39. Minnesota Cancer Surveillance System Epidemiology Report. Cancer incidence Rates in Northeastern Minnesota. Minnesota Department of Health, 1999.

40. Centers for Disease Control and Prevention. Current cigarette smoking prevalence among working adults-United States 2004-2009. *MMWR Morb Mortal Wkly Rep* 2011;60(38):1305-1309.

APPENDIX 3-1

Table 3-A. Lung cancer major histology groupings

Histology	ICD-O code	count
ADENOCARCINOMA		313
Acinic Cell Adenocarcinoma	85503	1
Adenocarcinoma NOS	81403	263
Bronchiolo-Alveolar Adenocarcinoma	82503	23
Bronchiolo-Alveolar Mucinous	82533	1
Bronchiolo-Alveolar non-mucinous	82523	4
Mixed Cell Adenocarcinoma	83233	1
Mucin Producing Adenocarcinoma	84813	11
Clear Cell Adenocarcinoma	83103	1
Mucinous Adenocarcinoma	84803	5
Papillary Adenocarcinoma NOS	82603	3
SMALL CELL CARCINOMA		139
Combined Small Cell Carcinoma	80453	2
Intermediate Cell Small Cell Carcinoma	80443	5
Neuroendocrine Carcinoma	82463	9
Oat Cell Carcinoma	80423	4
Small Cell Tumor	80023	1
Small Cell Carcinoma NOS	80413	118
SQUAMOUS CELL CARCINOMA		258
Basaloid Squamous Cell Carcinoma	80833	1
Squamous Cell Carcinoma Spindle Cell	80743	1
Squamous Cell Carcinoma Keratinizing	80713	9
Squamous Cell Carcinoma Non- Keratinizing	80723	10
Squamous Cell Carcinoma	80703	237
NON-SPECIFIED		202
Neoplasm Malignant	80003	19
Non-Small Cell Carcinoma	80463	97
Carcinoma NOS	80103	68
Undifferentiated Carcinoma	80203	11
Carcinoid Tumor	82403	4
Atypical Carcinoid Tumor	82493	1
Tumor cells Malignant	80013	2
RARE/OTHER		61
Anaplastic Carcinoma	80213	2
Spindle Cell Carcinoma	80323	1
Large Cell Carcinoma NOS	80123	38
Large Cell Carcinoma Rhabdoid phenotype	80143	1
Adenosquamous Carcinoma	85603	12
Fibrous Histiocytoma	88303	1
Large Cell Neuroendocrine Carcinoma	80133	5
Sarcoma NOS	88003	1

Chapter 4:

Lung cancer risk among Minnesota taconite mining workers

STUDY OVERVIEW

Objective: To examine the association between employment duration, elongate mineral particle (EMP) exposure, and silica exposure in the taconite mining industry and the risk of lung cancer.

Methods: We conducted a nested case control study of lung cancer within a cohort of Minnesota taconite iron mining workers employed by any of the seven mining companies in operation in 1983. Lung cancer cases were identified by vital records and cancer registry data through 2010. Two age-matched controls were selected from risk sets of cohort members alive and lung cancer free at the time of case diagnosis. Calendar time specific exposure estimates were made for every job and used to estimate workers cumulative exposures. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. Lung cancer risk was evaluated by total time worked, and cumulative EMP and silica exposure modeled continuously and by quartile.

Results: A total of 1,706 cases and 3,381 controls were included in the analysis. After adjusting for work in hematite mining, asbestos exposure, and sex, the OR for total duration of employment was 1.00 (95% CI: 0.96-1.01). The ORs for total exposure were 0.94 (95% CI: 0.89-1.01) for EMPs and 1.22 (95% CI: 0.81-1.83) for silica. The risk of lung cancer did not appear to change with increasing exposure when examined by quartiles.

Conclusions: This study suggests that taconite mining exposures do not increase the risk for the development of lung cancer.

BACKGROUND AND SIGNIFICANCE

Taconite mining is an open pit multi-stage process that involves blasting rock with explosives, crushing it down to a fine powder, magnetically extracting iron, and reforming a more concentrated product into high-grade iron ore pellets, the process of which can result in a dusty environment. The mining and processing of taconite iron ore results in potential exposure to non-asbestiform amphibole and non-amphibole elongate mineral particles (EMPs), respirable silica, and cleavage fragments (1). The term 'EMP' refers to any mineral particle with a minimum aspect ratio of 3:1 that is of inhalable size. Cleavage fragments are fractured mineral EMPs created during the crushing and fracturing process (2).

The Mesabi Iron Range, located in northeastern Minnesota, is a narrow belt approximately three miles wide and 120 miles long, consisting of iron-rich sedimentary rocks. The mineralogy of the Mesabi Iron Range changes from east to west and is broken into four distinct mineralogical zones (3). All zones have deposits of taconite along with quartz and iron silicates, but vary in the type of EMP (4). The eastern part of the range, known as zone 4, contains iron-rich amphibole EMPs, which is believed to be less than 1% fibrous (5). The western part of the range, known as zone 1 includes approximately two thirds of the entire Mesabi Iron Range and contains almost exclusively non-asbestiform EMPs. Zone 2 is considered a transitional zone and contains some amphiboles. Another mineralogical zone, zone 3 is also considered a transitional zone, however there are no mines located in that zone. The primary exposure in taconite operations is non-asbestiform cleavage fragments however, due to the mineralogical

differences in the zones, workers in each zone may be exposed to different types of mineral particles.

The causal relationship between exposure to fibers from asbestos minerals and lung cancer is well documented (2, 6-8) however, evidence from epidemiological studies of workers exposed to non-asbestiform EMPs is inconclusive. Since 1990, non-asbestiform EMPs have been included within the NIOSH recommended exposure limits of asbestiform EMPs due to the inconclusive findings of epidemiological studies (2). These include studies of talc miners in upstate New York (9-11), and gold miners in South Dakota (12-14). Historically, the association between silica and lung cancer has been debated but recent occupational studies have provided evidence supporting the risk of lung cancer after silica exposure (15). In 1996, the International Agency for Research on Cancer concluded that respirable silica was carcinogenic in occupational settings despite the lack of good-quality datasets available to quantitatively evaluate the relationship (16).

Health risks associated with taconite mining have been a concern to the public for several decades, but few studies have evaluated the health of miners in Minnesota. In 1983, a mortality analysis of 5,751 miners showed no increase in risk of respiratory cancer (17). A similar mortality analysis of 3,431 workers published in 1988 and 1992, likewise did not report an excess of mortality for any cause of death (18-19). These early studies had small study populations, focused on single mining companies, and had relatively short follow-up periods and thus limited power. However, a recent comprehensive mortality analysis found elevated lung cancer mortality among taconite

mining workers (20). No mortality study to date has evaluated the association between quantitative exposure level and cancer risk.

The purpose of this study is to address uncertainties regarding the health consequences of taconite mining by examining the association between employment duration, EMP exposure, and silica exposure in the taconite mining industry and the risk of lung cancer. This study also provides a unique opportunity to examine some of the key questions surrounding risk associated with exposure to non-asbestiform EMP exposure.

METHODS

Study population and follow-up

This was a nested case-control study of lung cancer within a cohort of Minnesota taconite iron mining workers and part of the Taconite Workers Health Study conducted by the University of Minnesota (21). The original cohort was enumerated in 1983 by the University of Minnesota and included 68,737 individuals with any employment in the mining industry. The earliest records were found to have sparse work history information, unreliable data for vital records linkages and early workers would have spent a majority of their working life in hematite mining. In order to restrict the cohort to those thought to have the most complete records and focus on employment in taconite, the study cohort was limited to those born in 1920 or later leaving 46,170 individuals.

Lung cancer cases were identified by mortality records and cancer registry data through 2010. The vital status and causes of death of cohort member were ascertained through several sources including the Social Security Administration, the National Death

Index (NDI), Minnesota Department of Health, and other state health departments. The Minnesota Department of Health provided causes of death for those who died within the state. For those who died outside of Minnesota in 1979 or later, causes of death were obtained from NDI Plus. For those who died prior to 1979 when NDI was established, death certificates were obtained from state health departments. Underlying causes of death were coded to the International Classification of Disease (ICD) version current at the year of death. The ICD codes were obtained directly from the Minnesota Department of Health and the NDI. All other death certificates were reviewed and coded by a nosologist.

To identify incident cancers, the cohort was linked to the Minnesota Cancer Surveillance System (MCSS). The MCSS was established in 1988 and is Minnesota's statewide, population-based cancer registry that collects histological information of newly diagnosed cancers on all Minnesota residents by state statute. Incident cancers including date of diagnosis, cancer site and histology were obtained for cohort members matched to the MCSS.

Selection of cases and controls

In this nested case-control study, all lung cancer cases identified via death record or MCSS were included. Two controls for each case were selected using an incidence density sampling protocol. Eligible controls were selected from risk-sets for each case by age (year of birth +/- five years) and alive and without a lung cancer diagnosis on the date of death or date of diagnosis of their index case.

Exposure assessment

An exposure data matrix was developed using work history records and quantitative, time-specific exposure estimates for each job and department to generate cumulative exposure metrics for each worker. Exposures for controls were truncated at the date of diagnosis or death of the matched case. Details of the exposure assessment and historical reconstruction are provided elsewhere (1) and summarized below.

A comprehensive database of mining industry job titles was assembled and grouped by title, tasks, locations and procedures. The jobs were condensed into 181 standardized job titles and further grouped into 28 similarly exposed groups (SEGs). The SEGs were used to systematically capture work history records and link estimates of exposure to EMPs and respirable silica for the exposure data matrix. Quantitative exposure estimates were derived from an exposure reconstruction that incorporated data from a comprehensive exposure characterization conducted as part of the Taconite Workers Health Study and historical industrial hygiene monitoring data collected by Mine Safety and Health Administration (MSHA) and the mining companies (1).

For the Taconite Workers Health Study exposure characterization, personal exposure measures were collected for all SEGs in all operating mines in the Mesabi Iron Range in 2010. Several workers per SEG were selected for sampling and each participant wore a personal air-sampling pump for approximately six hours of a work shift on three separate occasions. The filter samples were analyzed for EMPs by phase contrast microscopy which identifies all EMPs longer than 5 μm, with a diameter of 0.25 μm and with an aspect ratio ≥ 3. Respirable silica was analyzed using NIOSH 7500

Crystalline silica X-ray diffraction. The results from the samples were used to calculate a single time-weighted average concentration for the shift for each participant.

Historical exposures data were obtained from the Mine Data Retrieval System maintained by MSHA and the internal databases of two currently operating taconite mining companies. Available personal exposure data were used to create the historical reconstruction. Historical and current EMP and respirable silica data were combined into a master database to estimate an SEG specific exposure. Annual average exposures were estimated for each combinations of SEG, year, and mine using a time-varying linear regression model. The final exposure matrix included seven mines, 28 SEGs, and 56 years between 1955 and 2010. Five of the mines are located in zone 1, one mine is located in zone 4, and one mine that is no longer in operation is located in zone 2.

Company work records were abstracted to collect job title, mine, and dates of employment. Job titles were standardized and placed into one of the original 28 SEGs. Additional SEGs were created at the department level for jobs that had insufficient description to classify into a specific SEG. Jobs with no specific information about where or what the individual did was classified into a missing/unknown SEG. Exposure levels for department level SEGs were based on the average of other SEGs in that department. Exposures for the missing/unknown SEG were an average of all SEGs within that mine. Employment history was combined with the exposure matrix to estimate a cumulative exposure for each worker. Each SEG had an EMP and silica concentration that differed by company and year. This concentration was multiplied by the length of time spent working in the SEG and then summed to give a cumulative EMP

exposure for each workers measured in (EMP/cc)-years and a cumulative silica exposure measured in (mg/m^3)-years.

Many of the workers had employment history in the mining industry before taconite mining began in the 50s and 60s. The transition from hematite to taconite mining occurred at different times for the seven different companies. Historical data on mining operations and yearly taconite production totals was used to determine the year in which taconite mining began for each company. Any jobs held prior to that year were assigned to a hematite SEG for which EMP and silica exposure estimates were not available.

It is possible that commercial asbestos was used throughout the mines for maintenance and building and therefore a potential additional exposure to some of the workers. Each SEG was evaluated to determine whether it involved potential exposure to commercial asbestos. A high or low commercial asbestos score was assigned based on the likelihood and frequency of exposure for that SEG. These scores were reviewed by industrial hygiene experts within the taconite industry. Time spent in an SEG with a high probability of exposure to commercial asbestos was used as a covariate in the models.

Data analysis

Conditional logistic regression estimated the odds ratios (OR) and 95% confidence intervals (CI) for the association between taconite mining exposures and the development of lung cancer. In the final models, ORs were adjusted for sex, hematite mining exposure (measured in years), and potential commercial asbestos exposure (measured in years). Taconite mining exposure was characterized by both employment

duration and cumulative EMP and silica exposure. Employment duration and EMP exposure was examined in an overall and zone specific analysis divided into years worked or EMP exposure in each zone of the iron range (zone 1, 2, or 4). Both EMPs and silica exposure were modeled by quartile and by continuous exposure.

The histological subtype of lung cancer was available for the cases identified by MCSS. Separate analyses were done for each of five major histological subtype: squamous cell, adenocarcinoma, small cell, non-specified, and other/rare carcinomas.

All statistical analyses were conducted using SAS 9.2.

RESULTS

Follow-up of the 46,170 workers identified 1,725 cases corresponding to 3,450 controls. After work history abstraction, 3 cases along with their 6 corresponding controls, and 4 additional controls were excluded due to poor data quality, e.g. conflicting dates of birth in different records. Another 16 cases and their 32 corresponding controls along with an additional 27 controls were excluded whose only record on file was an application with no further evidence of employment in the mining industry. The final analysis included 1,706 lung cancer cases and 3,381 controls. Of the 1,706 cases, 309 were identified only through MCSS, 723 were identified only through death certificates, and 674 cases were identified by both MCSS and death certificates.

The general characteristics of the study population are presented in Table 4-1. The study population was mostly male (96% of cases and 94% of controls). The mean duration of employment in taconite mining of the cases and controls were 7.7 and 8.5 years respectively. The total cumulative exposure of EMPs and silica was higher in the

controls than in the cases (1.7 (EMP/cc)-years and 0.31 (mg/m^3)-years for controls and 1.5 (EMP/cc)-years and 0.28 (mg/m^3)-years for cases). Total employment duration and cumulative EMP exposure was greatest in zone 4 for both cases and controls. The shop mobile department had the greatest employment duration for both cases and controls followed by the mining department.

Table 4-1. Characteristics of cases and controls

	CASES (N=1706)	CONTROLS (N=3381)
	N (%)	**N (%)**
Sex		
Male	1637 (95.96)	3183 (94.14)
Female	69 (4.04)	198 (5.86)
Ore type		
Taconite only	668 (39.16)	1239 (36.67)
Hematite only	738 (43.26)	1530 (45.28)
Taconite & hematite	300 (17.58)	610 (18.05)
Ever worked by zone		
Zone 1	347 (20.34)	642 (18.99)
Zone 2	366 (21.45)	618 (18.28)
Zone 4	327 (19.17)	699 (20.67)
	Mean	**Mean**
Years of employment		
Taconite	7.67	8.52
Hematite	3.57	3.67
Years of taconite employment by zone		
Zone 1	7.38	7.60
Zone 2	5.41	7.11
Zone 4	8.81	9.27
(EMP/cc)-years		
Total	1.478	1.679
Zone 1	0.520	0.521
Zone 2	1.173	1.537
Zone 4	2.509	2.605
Silica (mg/m^3)-years		
Total	0.281	0.307
Years of employment by department		
Mining	1.28	1.36
Crushing	0.16	0.20
Concentrating	0.20	0.22
Pelletizing	0.25	0.24
Shop mobile	2.59	2.98
Shop stationary	0.68	0.71
Office	0.30	0.65
Missing/unknown	0.48	0.46
General mine	0.69	0.47
General plant	0.38	0.44
General shop	0.68	0.79

Total duration of employment in taconite mining did not appear to increase the risk of lung cancer (OR = 0.99, 95% CI: 0.96-1.01). The ORs for total exposure were 0.95 (95% CI: 0.89-1.01) for EMPs and 1.22 (95% CI: 0.81-1.83) for silica. A decrease in ORs with increasing exposure was observed across quartiles for EMP and silica exposure however, none of the quartiles exhibited a significant increase in risk. As compared to quartile 1 exposure levels, those with no taconite exposure showed a decrease in risk of lung cancer (EMP OR = 0.81, 95% CI: 0.67-0.98; silica OR = 0.81, 95% CI: 0.68-0.98). Odds ratios and 95% CIs for the analysis by employment duration, total exposure, and exposure quartiles can be found in table 4-2.

Table 4-2. Risk of lung cancer by employment duration, cumulative EMP, and cumulative silica exposure

	OR	95% CI
Employment duration		
Taconite years[a]	0.99	0.96-1.01
Hematite years[b]	0.99	0.98-1.01
Duration by Department[c]		
Mining	0.99	0.97-1.01
Crushing	0.96	0.88-1.05
Concentrating	0.99	0.93-1.06
Pelletizing	1.02	0.97-1.07
Shop Mobile	0.99	0.98-1.01
Shop Stationary	1.01	0.98-1.05
Office	0.95	0.92-0.99
Total Exposure		
(EMP/cc)-years[a]	0.95	0.89-1.01
Silica (mg/m^3)-years[d]	1.22	0.81-1.83
(EMP/cc)-years quartiles[e]		
Q1	1	
Q2	1.00	0.79-1.25
Q3	0.98	0.77-1.24
Q4	0.82	0.57-1.19
Unexposed[f]	0.81	0.67-0.98
Silica (mg/m^3)-years quartiles[g]		
Q1	1	
Q2	1.04	0.84-1.29
Q3	0.95	0.74-1.22
Q4	0.97	0.70-1.35
Unexposed[f]	0.81	0.68-0.98

a Adjusted for hematite exposure, silica exposure, asbestos exposure, and sex
b Adjusted for taconite exposure, silica exposure, asbestos exposure, and sex
c Adjusted for years in unknown SEGs, hematite, general mine, general plant, general shop, sex, and asbestos
d Adjusted for taconite exposure, hematite exposure, asbestos exposure, and sex
e Lower cut point for Q1-4 = 0, 0.1298, 0.4527, and 2.353 (EMP/cc)-years
f Worked only in hematite production and did not have taconite exposure
g Lower cut point for Q1-4 = 0, 0.0373, 0.2064, 0.5189 (mg/m^3)-years

The risk of lung cancer did not appear to change in any particular zone of the iron range by employment duration or cumulative EMP exposure. Results of the analysis by zone can be found in table 4-3.

Table 4-3. Risk of lung cancer by employment duration and cumulative EMP exposure in each zone of the iron range

	OR	95% CI
Taconite years by zone[a]		
Zone 1	1.01	0.97-1.04
Zone 2	0.99	0.96-1.02
Zone 4	0.99	0.96-1.01
(EMP/cc)-years by zone[a]		
Zone 1	1.00	0.87-1.16
Zone 2	0.94	0.85-1.02
Zone 4	0.95	0.89-1.01

a adjusted for hematite exposure, silica exposure, asbestos exposure, exposure in other zones, and sex

A total of 973 lung cancer cases were identified by MCSS and were included in the sub analysis by histological subtype. No significant association was found with EMP or silica quartiles for squamous cell, adenocarcinoma, small cell, non-specified, or other carcinomas of the lung. ORs were greatest for squamous cell and non-specified carcinoma however, all confidence intervals crossed 1. Results of the analysis by histological subtype can be found in table 4-4.

Table 4-4. Risk of major histological subtypes of lung cancer by cumulative EMP and silica exposure

	Odds Ratios (95% CIs)				
	Squamous N=258	**Adeno N=313**	**Small cell N=139**	**Non-specified N=202**	**Other N=61**
(EMP/cc)-years (quartiles)[a]					
Unexposed[c]	0.65 (0.40-1.06)	0.78 (0.50-1.22)	0.77 (0.37-1.60)	0.93 (0.53-1.64)	0.89 (0.33-2.43)
Q1	1	1	1	1	1
Q2	1.03 (0.58-1.82)	0.92 (0.55-1.53)	0.99 (0.46-2.14)	0.96 (0.49-1.90)	0.47 (0.13-1.67)
Q3	1.20 (0.66-2.20)	0.79 (0.46-1.36)	0.93 (0.41-2.06)	0.91 (0.47-1.74)	1.01 (0.33-3.07)
Q4	1.04 (0.42-2.58)	0.54 (0.23-1.30)	1.07 (0.31-3.70)	1.44 (0.56-3.72)	0.11 (0.01-1.04)
Silica (mg/m^3)-years (quartiles)[b]					
unexposed†	0.67 (0.41-1.08)	0.78 (0.51-1.19)	0.64 (0.30-1.34)	1.06 (0.59-1.91)	1.24 (0.44-3.49)
Q1	1	1	1	1	1
Q2	1.11 (0.64-1.95)	0.92 (0.57-1.48)	0.76 (0.36-1.60)	1.15 (0.62-2.16)	2.10 (0.73-6.05)
Q3	1.25 (0.71-2.18)	0.96 (0.59-1.56)	0.71 (0.32-1.57)	1.57 (0.79-3.10)	0.99 (0.22-4.47)
Q4	1.28 (0.73-2.24)	0.96 (0.58-1.59)	0.98 (0.43-2.25)	1.72 (0.88-3.36)	1.90 (0.62-5.83)

a Adjusted for hematite exposure, silica exposure, asbestos exposure, and sex
b Adjusted for hematite exposure, EMP exposure, asbestos exposure, and sex
c Worked only in hematite production and did not have taconite exposure

DISCUSSION

In this study of the association between lung cancer and Minnesota taconite industry exposures, no increased risk in the development of lung cancer was observed. Employment duration did not increase the risk of lung cancer. Cumulative EMP and silica exposure likewise did not increase the risk of lung cancer when examined by both total exposure and exposure quartiles. Due to geological differences in the rock between zones of the iron range, a zone specific analysis was conducted to evaluate whether or not

risk of lung cancer differed by the unique exposure potential in each zone. The zone specific analysis did not show substantial differences in risk for each zone, nor did the risk of lung cancer increase with exposure in any particular zone of the iron range when examined by employment duration and EMP exposure. Adenocarcinoma has been shown to be the most common histological subtype of lung cancer in asbestos-exposed individuals (22-23). This would suggest that if non-asbestiform EMPs did have a carcinogenic affect, it might vary by histological subtype. However, an analysis by histological subtype did not show any increase in risk for any of the five major subtypes, adenocarcinoma, small cell, squamous cell, non-specified, and other or rare carcinomas of the lung. This was true for both EMP and silica exposure quartiles.

Previous analyses from the Taconite Workers Health Study showed an excess in mortality (20) and cancer incidence in this taconite workers cohort. Specifically, standardized mortality ratios and standardized incidence ratios were estimated comparing the all cause and cause specific mortality and cancer rates in the overall cohort to the Minnesota population. Mortality was elevated for mesothelioma (SMR = 2.8, 95% CI: 1.9-4.0) lung cancer (SMR = 1.2, 95% CI: 1.1-1.2) and cardiovascular disease (SMR = 1.1, 95% CI: 1.1-1.1). Cancer incidence was elevated for mesothelioma (SIR = 2.4, 95% CI: 1.8-3.2) and lung cancer (SIR = 1.3, 95% CI: 1.2-1.4). Results from the current analysis suggest that the increase in risk for certain cancers and cardiovascular disease in this study population may be due largely to non-occupational exposures including lifestyle factors.

Lung cancer can have a relatively long latency period before diagnosis. Given that the work history records were collected in 1983 and follow-up continued through 2010, much of the study population (those diagnosed after 1993) had at least a 10 year lag built into the data analysis. However, 28% of the cases were diagnosed before 1993. The analyses were repeated using both a 10 and 20 year lag but the study results and interpretations did not change substantially.

Various types of asbestos can differ chemically, but structurally they are all similar in that they are highly fibrous silicate minerals that are crystallized in an asbestiform habit, causing them to separate into long, thin, strong, flexible fibers (24-25). Asbestos also tends to have very large aspect ratios, generally >20:1 for fibers > 5µm in length (24). In contrast, non-asbestiform EMPs have aspect ratios >3:1 and have widths much larger than asbestos fibers of the same length. Common non-asbestiform analogs of asbestos may share the same chemical composition but they do not share the same crystal structure. Cleavage fragments, or fragments of EMPs that have broken along a cleavage plane, lack the tensile strength and flexibility of asbestos (24). The health consequences of cleavage fragments have never been widely studied (25).

The strong association between asbestos exposure and lung cancer is well documented (2, 6-8) however, the toxicity of non-asbestiform EMPs is not understood. *In vitro* assessment of non-asbestiform EMPs and cleavage fragments have suggested that non-asbestiform EMPs and cleavage fragments are less potent than asbestiform (24), but epidemiology studies have been inconclusive. NIOSH has specifically identified non-asbestiform EMPs as a needed area of research (2). Non-asbestiform EMPs are included

in NIOSH recommended exposure limits due to technical limitations of routine exposure assessments and uncertainty about the potential toxicity of non-asbestiform EMPs. Research focused on exposure to non-asbestiform EMPs has consisted largely of mortality studies within a few mining industries. Previous studies of New York talc miners (9) and South Dakota gold miners (12-14) have shown inconclusive evidence of an association between non-asbestiform EMPs and malignant lung disease. Results from some animal studies have suggested that fiber dimension, and not composition, is the major determinant of carcinogenicity for mineral fibers (2). There remains a need to determine whether non-asbestiform EMPs that are chemically similar to asbestos, but with different physical forms are also capable of causing disease (2). These mineral particles are present in taconite mining and processing operations, the predominant exposure being non-asbestiform cleavage fragments, making Minnesota taconite miners an important population for research. This study provides evidence to suggest that exposure to non-asbestiform EMPs is not a major risk factor for development of lung cancer.

Some limitations should be considered when interpreting the results of this analysis, the greatest of which are the major areas of potential exposure misclassification. Despite an exhaustive effort to identify all available exposure data, measurements were extremely sparse for some time periods and some SEGs. The exposure reconstruction relied on imputation and regression modeling to estimate some historical exposure levels. Assumptions that influenced large categories of exposure estimates, for example, the

assumption that exposures could be extrapolated linearly, may have caused systematic misclassification of exposure for certain time periods.

Incorrect assignment of SEGs based on work records is another potential area for exposure misclassification. Details in individual work records varied greatly including level of detail in job titles and dates of employment. Though standardization of job titles was done to the greatest extent possible, in many cases there was not enough information in the work record to assign specific SEGs. In these cases general SEGs that averaged exposures across mines were used. Quality of work records varied by mine, therefore SEG misclassification may have occurred in specific mines. This could have masked any significant finding by zone.

Smoking is a major risk factor for lung cancer. However, to be a confounder for an internal exposure response analysis, smoking must be differentially distributed by level of exposure. Though we did not have smoking information for the study population there were data available on the smoking habits from a survey of 1,313 current and former taconite workers conducted in 2010 as part of the Taconite Workers Health Study. Roughly 75% of these individuals were in the cohort from which the cases and controls were identified. We used these data to indirectly examine the association between smoking and EMP exposure as a means to assess the potential for confounding due to smoking.

The SEG based exposure algorithms were applied to the reported work histories from the 2010 survey study. Cumulative exposure and work history was compared by smoking status. Potential for confounding by age was evaluated by stratifying workers

into age groups. Cumulative EMP exposures of survey participants by smoking category and age are shown in the appendix (Table 4-A). Among the 1,313 workers who participated in the 2010 survey sub study, younger workers (< 60 years of age) were less likely to be ever smokers and also had less cumulative EMP exposure than older workers. However, the older participants in the survey were largely retirees with very long work histories, thus higher cumulative exposures. The majority of the study population (98%) was over the age of 60 in 2010 and thus the older survey participants are most representative of the study population. For the older survey participants, exposure did not vary appreciably by smoking status, and the small variation suggests slightly higher exposures among smokers. This evidence suggests it is unlikely that differential smoking habit in the study population is the reason for a lack of association between the exposures and lung cancer. In fact, the direction of potential confounding would be to overestimate a risk with taconite work exposures and lung cancer. Further, the association between EMP exposure and lung cancer remained the same when the potential confounding was reduced by restricting the analysis to older workers (≥ 60 years of age). Models were repeated using logistic regression and adjusted for age in addition to all other covariates (appendix Table 4-B).

There are notable limitations to using the survey population to examine EMP exposure by smoking and age. The survey participants had greater cumulative exposure levels than the study population, they had to be alive in 2010 and were therefore younger and potentially healthier than the study population, and they were subject to selection bias as we relied on volunteers for participation. Despite these limitations, the survey

participants are the best comparison group for identifying smoking variation among exposure levels.

Exposure to commercial asbestos is another known cause of lung cancer and was used regularly in the early and mid part of the century. It is likely that commercial asbestos was used in the building and maintenance of taconite plants however there is limited information on its use and no quantitative data on asbestos type or exposure level. This analysis accounted for commercial asbestos by relying on industrial hygiene experts to identify the probability of exposure in each SEG and final models included years of work in an SEG with a high probability of asbestos exposure. Without a quantitative measure of commercial asbestos exposure, our estimate has potential for misclassification. For asbestos exposure to have confounded an association between taconite mining exposures and lung cancer, the lower exposure workers would have to have had high levels of asbestos exposure. However, asbestos probability was assigned based on job descriptions, not exposure assessment. It is unlikely that systematic misclassification occurred for only lower or higher exposed workers.

This study has some notable strengths. The large study population provided enough statistical power to examine the exposure disease relationship in various ways. The 2010 exposure assessment was the most comprehensive assessment in the taconite mining industry. All mines in operation, departments, and SEGs were represented in the assessment and direct measurements of EMPs were used for the analysis. The cohort from which the cases were identified was thorough and included all taconite miners ever employed by seven mining companies up to 1983. Use of both mortality records and

Minnesota cancer surveillance allowed us to capture a near complete set of lung cancer cases in the cohort. Work history information came directly from mining company records and did not rely upon individual workers, eliminating the possibility of recall bias. The case control design allowed for comprehensive examination of lung cancer risk that has not been possible in previous mortality studies of workers exposure to non-asbestiform EMPs.

CONCLUSION

This study provides evidence to suggest that exposure to non-asbestiform EMPs is not a major risk factor for development of lung cancer. Limitations in the exposure assessment should be considered carefully when interpreting the results of this study.

REFERENCES

1. Hwang J, Gurumurthy R, Raynor P, et al. Comprehensive Assessment of Exposures to Elongate Mineral Particles in the Taconite Mining Industry. *Ann Occup Hyg* 2013;doi:10.1093.
2. Department of Health and Human Services, National Institute for Occupational Safety and Health. Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research, 2011: Publication No. 2011-159.
3. McSwiggin PL, Morey GB. Overview of the mineralogy of the Biwabik Iron Formation, Mesabi Iron Range, northern Minnesota. *Regul Toxicol and Pharmacol* 2008;52(S1):S11-S25.
4. Jirsa MA, Miller JD, Morey GB. Geology of the Biwabik Iron Formation and Duluth Complex. *Regul Toxicol and Pharmacol* 2008;52(S1):S5-S10.
5. Wilson R, McConnell EE, Ross M, et al. Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. *Regul Toxicol and Pharmacol 2008;52(S1): S232-S245.*
6. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996;9(9):1932–1942.
7. Robinson BWS, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005;366(9483):397–408.
8. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. *Ann Cardiothorac Surg* 2012;1(4):491–6.

9. Honda Y, Beall C, Delzell E, et al. Mortality among Workers at a Talc Mining and Milling Facility. *Ann Occup Hyg* 2002;46(7):575–585.
10. Finkelstein MM. Malignant Mesothelioma Incidence Among Talc Miners and Millers in New York State. *Am J Ind Med* 2012;868(April):863–868.
11. Nolan RP, Gamble JF, Gibbs GW. Letter to the editor on commentary: malignant mesothelioma incidence among talc miners and millers in New York state by M M Finkelstein. *Am J Ind Med* 2013;56(9):1116-8.
12. Gillam JD, Dement JM, Lemen RA, et al. Mortality Patterns Among Hard Rock Gold Miners Exposed to an Asbestiform Mineral. *Ann N Y Acad Sci* 1976;336–344.
13. McDonald JC, Gibbs GW, Liddel FDK, et al. Mortality after long exposure to cummingtonite-grunerite. *Am Rev Respir Dis* 1978;118:271-277.
14. Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of followup. *Am J Ind Med* 1995;27:217-229.
15. Department of Health and Human Services, National Institute for Occupational Safety and Health. Silica, lung cancer, and respiratory disease quantitative risk. A project from the first 10 years of NORA: High Impact, Publication No. 2011-120.
16. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 100C, Arsenic, Metals, Fibres, and Dust. International Agency for Research on Cancer: Lyon, 2012.

17. Higgins IT, Glassman JH, Oh MS, et al. Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol* 1983;118(5):710-9.
18. Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. *J Occup Med* 1988;30(6):506-511.
19. Cooper WC, Wong O, Trent LS, et al. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med* 1992;34(12):1173-1180.
20. Allen EM, Alexander BH, MacLehose RF, Ramachandran G, Mandel JH. Mortality Experience among Minnesota Taconite Mining Industry Workers. *Occup Environ Med,* accepted for publication April 2014, awaiting citation.
21. University of Minnesota. *Taconite workers health study* 2013. Available from: http://taconiteworkers.umn.edu/
22. de Klerk, NH, Musk AW, Eccles J et al. Exposure to crocidolite and the incidence of different histological types of lung cancer. *Occup Environ Med* 1996;53:157-159.
23. Raffn E, Lynge E, Korsgaard B. Incidence of lung cancer by histological type among asbestos cement workers in Denmark. *Br J Ind Med* 1993 January;50(1):85-89.
24. Mossman BT. Assessment of the pathogenic potential of asbestos vs. nonasbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. *Regul Toxicol Pharmacol* 2008;52(S1):S200-3.

25. Gamble JF, Gibbs GW. Evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regul Toxicol Pharmacol* 2007;52(S1):S154-S186.

APPENDIX 4-1

Table 4-A. Cumulative EMP exposure by smoking and age for workers who participated in a 2010 survey analysis

Age (years)	Current smoker	Former Smoker	Never smoker	Total
< 50	N=24 (13%)	N=42 (23%)	N=115 (64%)	N=181
Cumulative EMP (mean)	1.05	1.22	0.89	0.98
50-59	N=69 (17%)	N=158 (40%)	N=169 (43%)	N=396
Cumulative EMP (mean)	2.18	2.43	1.85	2.14
60-69	N=40 (12%)	N=214 (62%)	N=90 (26%)	N=344
Cumulative EMP (mean)	3.58	3.39	3.42	3.42
70+	N=9 (3%)	N=167 (63%)	N=89 (34%)	N=265
Cumulative EMP (mean)	4.73	5.12	4.78	4.99

Table 4-B. Comparison of ORs of full study population and study population excluding workers < 60 years of age

	Full study population		Younger workers removed[a]	
	OR	95% CI	OR	95% CI
Employment duration				
Taconite years[b]	0.99	0.96-1.01	0.99	0.96-1.01
Hematite years[c]	0.99	0.98-1.01	0.99	0.98-1.01
Total Exposure (EMP/cc)-years[b]	0.95	0.89-1.01	0.95	0.89-1.01
(EMP/cc)-years quartiles				
Q1	1		1	
Q2	1.0	0.79-1.25	1.01	0.80-1.28
Q3	0.98	0.77-1.24	0.93	0.73-1.18
Q4	0.82	0.57-1.19	0.82	0.57-1.19
unexposed	0.81	0.67-0.98	0.80	0.66-0.97

a Adjusted for age in addition to covariates in full study population models
b Adjusted for hematite exposure, silica exposure, asbestos exposure, and sex
c Adjusted for taconite exposure, silica exposure, asbestos exposure, and sex

Chapter 5:

Conclusions

OVERALL CONCLUSIONS

The purpose of this research was to characterize the overall health of Minnesota taconite mining workers with a specific focus on lung disease and evaluate the association between occupational exposure and lung cancer risk. The mortality and cancer incidence studies focused on evaluating the overall health of taconite miners. Both studies identified an increased risk of mortality and incidence of certain diseases when compared to what would be expected in the general Minnesota population. Specifically, taconite workers have an increased risk in mortality from mesothelioma, lung cancer, and heart disease. This study did not use specific exposure measurements so we can only speculate as to why workers might have a greater risk of mortality from these diseases. The only known cause of mesothelioma is asbestos exposure. It is possible that taconite workers also had greater lifetime exposure to asbestos than the general population either in other occupational settings or in commercially used asbestos within the mining industry. Alternatively, exposure to non-asbestiform EMPs and cleavage fragments that are present in taconite mining operations is a risk factor for developing mesothelioma. This result warrants further investigation, but was not part of the scope of this dissertation. Both lung cancer and heart disease have multiple etiologies. Most notably, lifestyle factors such as smoking habit, alcohol consumption, diet, and physical activity contribute to the risk of disease development. However, asbestos exposure is a major risk factor for the development of lung cancer and airborne particulate matter increases the risk of cardiovascular disease. It is possible that exposure to non-asbestiform EMPs and cleavage fragments contribute to this increase in risk.

However, without a specific exposure measurement, we cannot say for sure whether occupational exposures within the taconite mining industry contribute to disease burden or if taconite workers have different lifestyle practices than the general population that increase their risk of these diseases.

Results of the cancer incidence analysis confirmed that taconite workers are at a greater risk of developing mesothelioma and lung cancer and the analysis additionally identified elevated rates of laryngeal, stomach, and bladder cancers. A specific look at lung cancer histology showed that risk of developing lung cancer is elevated for all major histological subtypes. In this analysis, we attempted to make a crude adjustment for smoking for the smoking-related cancers. Using a reasonable estimate of the difference in smoking rates between the taconite workers and the general Minnesota population, we found that the apparent increase in risk disappeared. This adjustment was based on estimated smoking rates as we did not have smoking data on the study population, however it suggests that smoking may play a major role in the disease burden in this population.

The final part of this dissertation was to determine if the increase in risk of lung cancer mortality and incidence may be related to exposures present in taconite mining operations. This was done with a lung cancer case control study in which time spent working and cumulative exposures were evaluated. Results of this analysis suggested that workers do not have a greater risk of developing lung cancer with longer durations of employment or with increasing cumulative exposure levels. Again, we did not have smoking data on this population but smoking estimates were used to examine the

possibility of confounding and indicated that smoking did not confound this null result. This suggests that the elevated risk in lung cancer mortality and incidence identified in the previous analyses are not related to occupational exposures present in taconite mining operations. Due to major limitation in the exposure calculations, exposure misclassification is the greatest potential for bias of these results. Though this analysis suggests that non-asbestiform EMP exposure does not increase the risk of lung cancer, this should be considered as one piece of a greater collection of studies. This study alone does not prove that non-asbestiform EMPs and cleavage fragments pose little threat to health, but rather it contributes to the growing body of evidence that suggests so. Further studies of occupational cohorts with well-defined exposure calculations to non-asbestiform EMPs and cleavage fragments would help determine the exposure-disease association.

With this research, we are able to address long-standing concerns of the health of Minnesota taconite mining workers as well as address uncertainties regarding non-asbestiform EMP and cleavage fragment exposure. The elevated mortality and cancer incidence suggests that this population may benefit from health promotion campaigns. We hope that this research will be a basis for further study of non-asbestiform exposure risk, inform new risk assessments, and provide a foundation to help protect workers' health.

BIBLIOGRAPHY

Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Asbestos*. September 2001. Retrieved January 28, 2014, from: http://www.atsdr.cdc.gov/toxprofiles/tp61.pdf.

Allen EM, Alexander BH, MacLehose RF, Ramachandran G, Mandel JH. Mortality Experience among Minnesota Taconite Mining Industry Workers. *Occup Environ Med,* accepted for publication April 2014, awaiting citation.

Aust AE, Cook PM, Dodson RF. Morphological and chemical mechanisms of elongate mineral particle toxicities. *J Toxicol Environ Health B Crit Rev* 2011;14:40-75.

Berndt ME, Brice WC. The origins of public concern with taconite and human health: Reserve Mining and the asbestos case. *Regul Toxicol and Pharmacol* 2008;52(S1):S31-S39.

Berry G, Gibbs GW. An overview of the risk of lung cancer in relation to exposure to asbestos and of taconite miners. *Regul Toxicol Pharmacol* 2008;52(S1):S218-22.

Bhatnagar A. Environmental cardiology: studying mechanistic links between pollution and heart disease. *Cir Res* 2006;99:692-705.

Brook RD, Rajagopalan S, Pope CA, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010;121:2331-2378.

Brown DP, Kaplan SD, Zumwalde RD et al. Retrospective cohort mortality study of underground gold mine workers. In: *Silica, Silicosis, and Cancer*, 1986;335-350.

Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System 2013. Available from: http://www.cdc.gov/brfss/data_tools.htm.

Centers for Disease Control and Prevention. Current cigarette smoking prevalence among working adults-United States 2004-2009. *MMWR Morb Mortal Wkly Rep* 2011;60(38):1305-1309.

Centers for Disease Control and Prevention. Life Table Analysis System 2013. Available from: www.cdc.gov/niosh/ltas.

Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. *J Occup Med* 1988;30(6):506-511.

Cooper WC, Wong O, Trent LS, et al. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med* 1992;34(12):1173-1180.

Davis JM, Addison J, McIntosh C, et al. Variations in the carcinogenicity of tremolite dust samples of differing morphology. *Ann NY Acad Sci* 1991;643:473-490.

Dockery DW, Pope CA, Xu X, et al. An Association between Air Pollution and Mortality in Six U.S. Cities. *N Engl J Med* 1993;329:1753-1759.

Department of Health and Human Services, National Institute for Occupational Safety and Health. Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research, 2011: Publication No. 2011-159.

Department of Health and Human Services, National Institute for Occupational Safety and Health. Silica, lung cancer, and respiratory disease quantitative risk. A project from the first 10 years of NORA: High Impact, Publication No. 2011-120.

Doll R. Mortality from lung cancer in asbestos workers. *Br J Ind Med*, 1955; 12(2):81 – 86.

Finkelstein MM. Malignant Mesothelioma Incidence Among Talc Miners and Millers in New York State. *Am J Ind Med* 2012;868(April):863–868.

Gallagher LG, Ray RM, Li W, et al. Occupational exposures and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Am J Ind Med* 2012;55(11):991-999.

Gamble JF, Gibbs GW. Evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regul Toxicol Pharmacol* 2007;52(S1):S154-S186.

Gillam JD, Dement JM, Lemen RA, et al. Mortality Patterns Among Hard Rock Gold Miners Exposed to an Asbestiform Mineral. *Ann N Y Acad Sci* 1976;336–344.

Higgins IT, Glassman JH, Oh MS, et al. Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol* 1983;118(5):710-9.

Hilding AC, Hilding DA, Larson DM, et al. Biological effects of ingested amosite asbestos, taconite tailings, diatomaceous earth and Lake Superior water in rats. *Arch Environ Health* 1981;36:298-303.

Honda Y, Beall C, Delzell E, et al. Mortality among Workers at a Talc Mining and Milling Facility. *Ann Occup Hyg* 2002;46(7):575–585.

Hwang J, Gurumurthy R, Raynor P, et al. Comprehensive Assessment of Exposures to Elongate Mineral Particles in the Taconite Mining Industry. *Ann Occup Hyg* 2013;doi:10.1093.

International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 100C, Arsenic, Metals, Fibres, and Dust. International Agency for Research on Cancer: Lyon, 2012.

Iron Mining Association of Minnesota. Mining Industry. Available at: http://www.taconite.org/mining-industry. Accessed April 30, 2014.

Iron Range Resources and Rehabilitation Board. Explore Minnesota: Iron Ore March 2014. Available at: http://mn.gov/irrrb/images/2014%2520Explore%2520IRON%2520ORE.pdf. Accessed April 30, 2014.

Jirsa MA, Miller JD, Morey GB. Geology of the Biwabik Iron Formation and Duluth Complex. *Regul Toxicol and Pharmacol* 2008;52(S1):S5-S10.

Kawachi I, Colditz GA, Stampfer MJ, et al. Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 1995;92:3178-3182.

Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer* 2001 Feb-Mar;31(2-3):139-48.

de Klerk, NH, Musk AW, Eccles J et al. Exposure to crocidolite and the incidence of different histological types of lung cancer. *Occup Environ Med* 1996;53:157-159.

Lamm SH, Levine MS, Starr JA, Tirey SL. Analysis of excess lung cancer risk in short-term employees. *Am J Epidemiol,* 1988;127(6), 1202-1209.

Langer AM, Maggiore CM, Nicholson WJ, et al. The contamination of Lake Superior with amphibole gangue minerals. *Ann NY Acad Sci* 1979;330:549-572.

Lanphear BP, Buncher CR. Laten period for malignant mesothelioma of occupational origin. *J Occup Med* 1992;34:718-721.

Levy BS, Sigurdson E, Mandel J, et al. Investigating possible effects of asbestos in city water: surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. *Am J Epidemiol* 1976;103:362-368.

Lilienfeld DE, Mandel JS, Coin P, et al. Projection of asbestos related diseases in the United States, 1985 – 2009. I. cancer. *Br J Ind Med*, 1988; 45:86 – 106.

McDonald JC, Gibbs GW, Liddel FDK, et al. Mortality after long exposure to cummingtonite-grunerite. *Am Rev Respir Dis* 1978;118:271-277.

McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996;9(9):1932–1942.

McSwiggin PL, Morey GB. Overview of the mineralogy of the Biwabik Iron Formation, Mesabi Iron Range, northern Minnesota. *Regul Toxicol and Pharmacol* 2008;52(S1):S11-S25.

Miller KA, Siscovick DS, Sheppard L, et al. Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women. *N Engl J Med* 2007;356:447-458.

Minnesota Cancer Surveillance System Epidemiology Report. Cancer incidence Rates in Northeastern Minnesota. Minnesota Department of Health, 1999.

Minnesota Department of Natural Resources. Digging in MN minerals: Taconite 2011 (Retrieved August 22, 2011). Available from: http://www.dnr.state.mn.us/education/geology/digging/mining.html

Mossman B, Sesko A. In vitro assays to predict the pathogenicity of mineral fibers. *Toxicology* 1990;60:53-61.

Mossman BT. Assessment of the pathogenic potential of asbestos vs. nonasbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. *Regul Toxicol Pharmacol* 2008;52(S1):S200-3.

National Institute for Occupational Safety and Health. Malignant mesothelioma: Counties with highest age-adjusted death rates (per million population), U.S. residents age 15 and over, 2000-2004. Work-Related Lung Disease (WoRLD) Surveilllance Report Update, 2008: http://www2.cdc.gov/drds/WorldReportData/FigureTableDetails.asp?FigureTableID=901&GroupRefNumber=T07-10, accessed January 17, 2014.

National Institute of Occupational Safety and Health (NIOSH). Silica, lung cancer, and respiratory disease quantitative risk. A project from the first 10 years of NORA: High Impact. DHHS (NIOSH) Publication No. 2011-120.

National Toxicology Program. Asbestos. In: *Report on Carcinogens. Twelfth Edition*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 2011.

Nolan RP, Gamble JF, Gibbs GW. Letter to the editor on commentary: malignant mesothelioma incidence among talc miners and millers in New York state by M M Finkelstein. *Am J Ind Med* 2013;56(9):1116-8.

Odo NU, Majdel JH, Perlman DM, et al. Estimates of restrictive ventilator defect in the mining industry. Considerations for epidemiological investigations: a cross-sectional study. BMJ Open 2013; *3:e002561 doi:10.1136/bmjopen-2013-00256.*

Occupational Safety and Health Association. OSHA Standards 1910.1001 Asbestos. Available at https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9995. Accessed J.

Pacella A, Andreozzi GB, Fournier J, et al. Iron topochemistry and surface reactivity of amphibole asbestos: relations with in vitro toxicity. *Anal Bioanal Chem*, 2012; 402:871 – 881.

Pallis AG, Syrigos KN. Lung cancer in never smokers: disease charateristics and risk factors. *Crit Rev Oncol Hematol* 2013 Dec;88(3):494-503 .

Pope CA III, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71–77.

Price AE. Heart disease and work. *Heart* 2004;90:1077-1084.

Price B. Industrial-grade talc exposure and the risk of mesothelioma. *Crit Rev Toxicol* 2010;40(6):513-530.

Raffn E, Lynge E, Korsgaard B. Incidence of lung cancer by histological type among asbestos cement workers in Denmark. *Br J Ind Med* 1993 January;50(1):85-89.

Robinson BWS, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005;366(9483):397–408.

Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. *Ann Cardiothorac Surg* 2012;1(4):491–6.

Secretan B, Straif K, Baan R, et al. A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *The Lancet Oncol* 2009;10:1022-4.

Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of followup. *Am J Ind Med* 1995;27:217-229.

Steenland K, Greenland S. Monte Carlo Sensitivity Analysis and Bayesian Analysis of Smoking as an Unmeasured Confounder in a Study of Silica and Lung Cancer. *Am J Epidemiol* 2004;160:384-392.

Sogl M, Taeger D, Pallapies D, Bruning T, Dufey F, Schnelzer M, Straif K, Walsh L, Kreuzer M. Quantitatie relationship between silica exposure and lung cancer mortality in German uranium miners, 1946 – 2003. British Journal of Cancer, 2012; 107: 1188 – 1194.

Still WT, Tabershaw IR. The mortality experience of upstate New York talc workers. *J Occup Med,* 1982; 24(6), 480-484.

Sullivan PA. Vermiculite, Respiratory Disease, and Asbestos Exposure in Libby, Montana: Update of a Cohort Mortality Study. *Environ Health perspect* 2007;115(4):579-585.

Toh CK, Gao F, Lim WT, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *Journal of Clinical Oncology* 2006;24:2245-51.

University of Minnesota. *Taconite workers health study* 2013. Available from: http://taconiteworkers.umn.edu/

Walker AM, Loughlin JE, Friedlander ER, et al. Projections of asbestos-related disease, 1980 – 2009. *J Occup Med*, 1983; 25:409 – 425.

Williams C, Dell L, Adams R, et al. State-of-the-science assessment of non-asbestos amphibole exposure: Is there a cancer risk? *Environ Geochem Health* 2013;35:357-377.

Wilson R, McConnell EE, Ross M, et al. Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. *Regul Toxicol and Pharmacol 2008;52(S1): S232-S245.*

World Health Organization. Tobacco Free Initiative 2014. Available from: http://www.who.int/tobacco/research/cancer/en/.

Yang H-Y, Shie R-H, Chen P-C. Carving of non-asbestiform tremolite and the risk of lung cancer: a follow-up mortality study in a historical nephrite processing cohort. *Occup Environ Med* 2013;70:852-857.