

**ASBESTOS EXPOSURE AND INCIDENCE OF DISEASE AMONG A GROUP OF FORMER
CHRYSTILE ASBESTOS MINERS AND MILLERS FROM BAIE VERTE, NL, CANADA**

by

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Abstract

Asbestos is one of the most well-known and extensively studied occupational hazards. Over the past century, the health effects of asbestos exposure have been studied in thousands of books, journal articles, and media publications, from all over the world. Despite the vast amount of knowledge that exists about asbestos there continues to be controversy about the relative health risks associated with its different types, that is, serpentine (chrysotile) and amphibole asbestos fibres. The continued production and use of chrysotile asbestos in many countries around the world, as well as the ongoing exposure of millions of workers globally to asbestos, has kept it a subject of ongoing debate and concern.

Although asbestos is a well-established cause of both malignant and non-malignant disease, a number of recent meta-analyses have sought to estimate the relative risk of diseases related to exposure to each of the different fibre types. The lack of epidemiological studies with good quality exposure assessments, particularly in the mining/milling industry, as well as the lack of retrospective exposure assessments for most cohorts, has led to an over-reliance on studies of a single population of chrysotile-only exposed cohorts: the Québec chrysotile miners/millers cohort. These studies, however, have been criticized as being heavily influenced by the asbestos industry.

This thesis, which consists of an introductory chapter, three interrelated studies, and a concluding chapter, presents data on an under-studied cohort of chrysotile miners/millers from Baie Verte, Newfoundland and Labrador (NL), Canada. The first study will describe the development of a job exposure matrix (JEM) that was used to perform a retrospective exposure assessment for former workers of the mine/mill. The second study is an

epidemiological assessment of a sub-group of the overall cohort of former employees who voluntarily joined the Baie Verte Miners Registry, an exposure/disease registry that was established to aid in the compensation process for former workers who have, or will, develop asbestos-related diseases. The third study outlines the process of enumerating the remainder of the cohort from historical union records (i.e., those who did not join the Baie Verte Miners Registry) and the epidemiological analysis of this group and of the two groups combined. Taken as a whole, this thesis demonstrates the good quality of the retrospective exposure assessment that has been conducted on this group of former asbestos workers and it supports the position that chrysotile asbestos is a cause of malignant mesothelioma. It also confirms the increased risk of asbestosis, as well as cancer of the lung, larynx, esophageal, and colorectum, in workers who were exposed to chrysotile asbestos. This cohort of chrysotile miners/millers is, therefore, a useful addition to the literature for estimating the relative potency of the different asbestos fibre types.

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Philip, my son Nicholas, and daughter Olivia, and is in memory of our daughter, Sommer (2008).

Co-Authorship Declaration

This thesis incorporates work performed by the author as part of an earlier contract between SafetyNet, the occupational health and safety research centre of Memorial University (MUN), and the Workplace Health Safety and Compensation Commission (WHSCC) to develop the Baie Verte Miners Registry. I was retained by SafetyNet, in consultation with other key members of the project team (Paul Demers, John Oudyk and Stephen Bornstein), to design and conduct a retrospective exposure assessment for the former employees of the Baie Verte mine who joined the Baie Verte Miners' Registry, as well as an epidemiological analysis of the incidence and relative risk of asbestos-related diseases in that cohort. This work was incorporated as a key component into the final report for the Baie Verte project (<http://www.bvminers.ca/>). My work for the project was then updated and expanded as part of my thesis. In the Baie Verte report and in this thesis, the key ideas, experimental designs, data analysis and interpretation, were performed by the author using data provided by the Baie Verte team and with advice and supervision of three members of that team, Stephen Bornstein, Paul Demers and John Oudyk. The additional work required for this thesis (i.e., locating the union files, identifying the second cohort, applying the job-exposure matrix to them, designing and performing the epidemiological analysis and integration of that that analysis with that of the original cohort) was designed and performed by the author with input from these three plus from Dr. Peter Wang who joined the other three as members of my supervisory team.

List of Abbreviations

AIHA - American Industrial Hygiene Association

ANOVA - Analysis of Variance

BVMR - Baie Verte Miners' Registry

CI - Confidence Interval

COPD - Chronic Obstructive Pulmonary Disease

EPA - Environmental Protection Agency (United States)

GSD - Geometric Standard Deviation

IARC - International Agency for Research on Cancer

ICD - International Classification of Diseases

IOM - Institute Of Medicine

f/ml - Fibres per Millilitre (of air)

f/ml-yrs - Fibres per Millilitre (of air), per person years at risk

JEM - Job Exposure Matrix

MCP - Medical Care Plan (Newfoundland and Labrador)

mg/m³ - milligrams per cubic meter (of air)

mg/m³-yrs - milligrams per cubic meter (of air) per person years at risk

mppcf - millions of particles per cubic feet (of air)

mppcf-years - millions of particles per cubic feet (of air), per person years at risk

MUN - Memorial University of Newfoundland

NIOSH - National Institute for Occupational Safety and Health (United States)

NL - Newfoundland and Labrador

NLCHI - Newfoundland and Labrador Centre for Health Information

PYAR - Person-Years At Risk

RR- Rate Ratio or Relative Risk

SEG - Similar Exposure Group

SMR - Standardized Mortality Rate

SIR - Standardized Incidence Rate

USW - United Steelworkers Union

WHSCC - Workers' Health Safety and Compensation Commission (Newfoundland and Labrador)

Chapter 1: Background and objectives.

1.0 A brief history of asbestos, the "Magic Mineral". the epidemiology of asbestos-related diseases and the ongoing controversy.

The word "asbestos" is derived from the ancient Greek word for "inextinguishable" or "unquenchable"¹. It is the commercial term used to describe a group of naturally occurring mineral silicate fibres from the serpentine and amphibole families. This includes chrysotile, which is the only serpentine mineral, and the five amphibole minerals - actinolite, tremolite, anthophyllite, crocidolite and amosite² (Table 1-1). Asbestos was commonly known as the "magic mineral" and was used in a large number of commercial and industrial applications because of its extraordinary physical and chemical properties. Its high tensile strength and flexibility; its resistance to heat, chemical and biological degradation; and its thermal, electrical and acoustical insulation properties have made it the perfect ingredient for more than three thousand commercial and industrial products, such as thermal and electrical insulation, roofing materials, friction products, cement products, flooring, textiles and many more³. However, the economic and commercial benefits of asbestos have been outweighed by the devastating health effects that have come to be associated with the "magic" fibres, thereby leading to the widespread discontinuation of its use.

Modern industrial use of asbestos began with the mining/milling of chrysotile in Canada, South Africa and the USSR in the late 19th century^{4,5}. Growth in the production and consumption of asbestos continued for decades with approximately 5 million metric tons mined as early as 1930 and a peak in the mid-1970s of an estimated 5.09 million metric

tons per year⁶. Top producers of asbestos, both historically and recently, have included Canada, the former Soviet Union, South Africa, China, Kazakhstan, Brazil and Zimbabwe, with Canada topping the list in the first half of the 20th century and the former Soviet Union and China being the dominant producers in the second half⁷. According to the U.S. Geological Survey, annual world production in 2011 was just over 2 million tonnes with Russia being the primary producer, followed by China, Brazil, Kazakhstan, Canada and India⁸. In the peak years, developed countries, including Northern and Western Europe, Australia, Canada, Germany, and the USA, were also the highest consumers of asbestos. However, the gradual recognition of the association between asbestos exposure and the occurrence of serious health consequences led to increasing restrictions on its use in many countries around the world. The use of amphibole asbestos was, for the most part, discontinued in the 1970s and the use of serpentine asbestos in building materials was phased out in the early to mid-1980s. In 1997, France implemented a complete ban on all asbestos use, which was followed by bans in the other members of the European Union as well as in a number of other countries around the world⁹. Currently, a complete ban on asbestos is in place in 55 countries¹⁰. While these bans and restrictions led to a reduction in the worldwide production of asbestos, consumption in developing countries and in countries with little or no regulations for the use of asbestos remains heavy. In 2003, China was the leading consumer of asbestos, followed by Russia, India, Kazakhstan, Ukraine, Thailand, Brazil and Iran, collectively accounting for 82% of the world's asbestos consumption¹¹.

Table 1-1: Geological occurrence of asbestos fibres.

	Chrysotile [1001-29-5] ^a	Amosite [19172-73-5]	Crocidolite [12001-28-4]	Tremolite [14567-73-8]
Mineral Species	chrysotile	cummingtonite-grunerite	riebeckite	tremolite
Structure	as veins in serpentine and mass fiber deposits	lamellar, coarse to fine, fibrous and asbestiform	fibrous in ironstones	long, prismatic, and fibrous aggregates
Origin	alteration and metamorphism of basic igneous rocks rich in magnesium silicates	metamorphic	regional metamorphism	metamorphic
Essential Composition	hydrous silicates of magnesia	hydroxy silicate of Fe and Mg	hydroxy silicate of Na, Mg, and Fe	hydroxy silicate of Ca and Mg

^a Chemical Abstract Service Registry numbers in square brackets

1.1 Asbestos and Human Health

The health effects of the "magic mineral" were first suspected in the early 1900s in England. Its association with fibrosis of the lungs was recognized in the 1930s when the death of a textile worker was reported in the medical literature as being attributed to asbestos exposure¹². It wasn't until the 1950s that researchers firmly established the causal relationship between asbestos fibres and lung cancer in a cohort of asbestos workers¹³, and it was only in the 1960s that mesothelioma was accepted as being due to asbestos exposure in a group of South African miners¹⁴. Since then, a large amount of research has been conducted into the health effects of asbestos exposure making asbestos the most important and most studied occupational hazard of the past century. A large majority of the epidemiological studies have involved groups of occupationally exposed workers in a variety of industries, including the mining and milling of asbestos, the manufacture of textiles, insulation work and construction. In addition to asbestosis, lung

cancer and mesothelioma, asbestos exposure has also been shown to cause a number of other non-malignant and malignant diseases, including pleural plaques, pleural effusion, laryngeal and ovarian cancers, and possibly cancers of the gastrointestinal tract^{5,6,15,16}.

Despite the dramatic reduction in the production and use of asbestos in the past thirty years, the number of cases of asbestos-related diseases continues to rise today and this trend is expected to persist in the coming decades. For instance, recent data demonstrate a dramatic rise in the number of fatal occupational cancers being compensated in Canada, primarily cancers associated with asbestos¹⁷. From 1997 to 2010, approximately 70% of the accepted claims for occupational cancer deaths in Canada were attributable to asbestos-related cancers, with the number of claims for mesothelioma and asbestos-related lung cancer combined accounting for 87.3% of all compensated claims. This increase in asbestos-related diseases has been demonstrated in other countries and largely reflects the sustained period over which hundreds of thousands of workers were exposed to asbestos in primary and/or secondary industries (e.g., mining/milling, manufacturing of asbestos products, and installation of asbestos products) during the asbestos era, as well as the long latency period associated with the development of asbestos-related diseases, which can be as long as 40 years after first exposure¹⁸.

In addition to the rising number of new cases of asbestos-related diseases in former asbestos workers, a number of other factors make this carcinogen an ongoing concern. Although there are severe restrictions in place on asbestos usage in many countries, exposure is still a major issue. Globally, it is estimated that there are 125 million people who continue to be occupationally exposed to asbestos and that 107,000 deaths annually

can be attributed to asbestos-related diseases due to workplace exposure¹⁹. Many of these workers are in developing countries where asbestos is still being used in manufacturing industries, primarily the fabrication of friction and cement products, and in construction. The lack of technology to control the levels of asbestos in the workplace, the lack of surveillance mechanisms for identifying exposures and early detection of disease, and inadequate legislation to govern occupational health and safety, all impose challenges for the prevention of asbestos-related disease in these countries¹⁰. Therefore, the burden of asbestos-related diseases in these societies will likely mimic that of the developed world's experience in the previous half century. In developed countries buildings that were built during the asbestos era still contain a large amount of asbestos-containing materials, such as fireproofing, thermal insulation products, surfacing materials and flooring. Exposure of workers and building occupants can occur during renovation, demolition, and maintenance activities in these buildings. For instance, in Canada, it is estimated that there are 152 000 people, primarily men, who are currently exposed to asbestos in their workplace²⁰. The largest exposed group is in the construction sector, where exposure occurs because of poor control measures during renovation, refurbishing and demolition projects in older buildings that contain asbestos-containing materials²⁰. This is also true for workers who perform building maintenance activities, as well as tradespeople such as plumbers, electricians, carpenters, roofers and painters, who are exposed by inadvertently disturbing asbestos-containing building materials^{21,22}. In addition, the asbestos abatement industry, which was formed in the 1980s to remove asbestos-containing materials from older buildings, employs workers who are exposed to asbestos on a regular basis and the health consequences of these exposures is still not known²⁰. Thus, asbestos exposure remains an

important occupational hazard all over the world and continues to place a large number of people at risk of developing asbestos-related diseases in the future.

Finally, the controversy regarding the relative potency of the various types of asbestos fibres, and the political issues associated with Canadian chrysotile, have played an important role in making asbestos an ongoing subject of scientific research. Although all types of asbestos have been established as being causally associated with the development of asbestosis, lung cancer, and mesothelioma, there is experimental and epidemiological evidence to suggest that there may be differences in the ability of chrysotile and amphibole asbestos fibres to induce disease, notably mesothelioma²³⁻²⁶. The amount of research devoted to understanding the relative carcinogenic potency of the different asbestos fibre types has increased substantially over the past thirty years¹⁰. During this time, numerous studies have been published claiming considerably higher disease risk in workers exposed to amphibole asbestos, or to a mixture of fibre types, relative to workers exposed predominantly to chrysotile asbestos. This distinction has important public health implications because virtually all of the world's current asbestos production and consumption is chrysotile, and the majority of asbestos-containing products in older buildings is chrysotile. As a result, past, as well as current, exposures have primarily involved chrysotile fibres. Furthermore, a worldwide ban on all forms of asbestos has not yet been implemented, with chrysotile remaining the only type of asbestos not included in the Rotterdam Convention's^a list of Prior Informed Consent products, primarily because of

^a The Rotterdam Convention (formally, the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade) is a multilateral treaty to promote shared responsibilities and cooperative efforts among Parties in the international trade of certain hazardous chemicals. The convention promotes open exchange of information and helps to ensure that governments have the information they need about hazardous chemicals for assessing risks and taking informed decisions

opposition by the major asbestos producing countries, notably Canada (until 2012) and Russia. As a result of the debate over chrysotile much effort is still being devoted to understanding the health risks associated with the different fibre types.

Adding to the controversy regarding the relative toxicity of chrysotile asbestos is the lack of epidemiological studies on chrysotile-only exposed cohorts with high-quality exposure assessments. This is especially true of the chrysotile mining/milling industry. Consequently, there has been a reliance on the data from the few cohorts, largely in Quebec, for which adequate information exists. The following sections of this chapter will provide a literature review of the epidemiology of asbestos-related diseases, followed by an in-depth review of the chrysotile controversy and what the current study contributes to it.

1.2 Epidemiology of Asbestos-Related Diseases

1.21 Measurements of Exposure

An important criterion for the establishment of causation in epidemiology is the exposure-response relationship, that is, the change in health outcome caused by differing levels of exposure to a contaminant of interest²⁷. In order to demonstrate the presence of an exposure-response relationship researchers must be able to quantify the amount of contaminant that subjects are exposed to. In the case of asbestos, a number of sampling and analytical methods have been utilized over the years to measure the amount of asbestos in the air. These measurements have been used in correlation with disease occurrence in order to demonstrate the association between asbestos exposure and

on chemical imports. Signatory nations can decide whether to allow or ban the importation of chemicals listed in the treaty, and exporting countries are obliged to make sure that producers within their jurisdiction comply (<http://www.pic.int>).

disease. Accordingly, descriptions of asbestos exposure in the literature use a variety of units. Prior to the 1970s, the most commonly used approach was the midjet impinger method which was introduced in the 1930s. It measured particles of airborne dust without discriminating between dust and actual asbestos fibres. This method expressed the concentration of dust as millions of particles per cubic foot (mppcf) of air. In the 1960s and 1970s, the membrane filter method was introduced. In this approach, a known volume of air is drawn over a filter assembly and the numbers of fibres deposited on the filter that are greater than 5µm in length and have a length-to-width ratio of at least 3:1 are counted using phase contrast microscopy. The concentration of asbestos fibres is expressed as the number of fibres per millilitre (f/ml) of air and this method is still the standard method for asbestos fibre sampling. Another approach that is sometimes used is gravimetric analysis which measures the mass of dust collected on a filter and is expressed in milligrams per cubic meter of air (mg/m³). This method also does not discriminate between dust particles and fibres.

These measures of asbestos exposure are used in epidemiological studies to estimate individual subjects' cumulative asbestos exposure. Cumulative asbestos exposure is the total amount of asbestos a person has been exposed to over his/her working lifetime. It is calculated using his/her work history and estimates of exposure for each job and for each time period worked. Cumulative asbestos exposure is expressed as f/ml-years or mppcf-yrs and is used to estimate the risk of asbestos-related disease in epidemiological studies. In the following sections, discussions of various studies will refer to one or another of these differing units to describe asbestos exposure, depending on the time period in which the

study was done. The limitations associated with the different methodologies for measuring asbestos exposure will be discussed in Chapter 3.

1.22 Asbestosis

The most studied of the non-malignant lung diseases caused by asbestos exposure is asbestosis. Asbestosis is a form of pneumoconiosis and is defined as a diffuse interstitial fibrosis of the lungs caused by inhalation of high concentrations of asbestos dust. It generally involves a long latency period with symptoms usually manifesting themselves 20 or more years after initial exposure, although very high exposures can lead to quicker progression of the disease^{28,29}. People with asbestosis are at an increased risk of developing asbestos-related lung cancer, although asbestosis need not be present for lung cancer to develop³⁰⁻³².

Many studies have reported the association between asbestos fibres and fibrosis of the lungs. The first case of asbestosis causing death was described in 1924 by Cooke ¹². The death of English textile worker Nellie Kershaw from pulmonary asbestosis was the first published account of death attributed to occupational asbestos exposure. Her death led to an inquest that was influential in the development of asbestos regulations in Britain in the early 1930s³³. In 1930, the first epidemiological study of textile workers exposed to asbestos established an association between asbestos exposure and lung disease³⁴. This was followed by numerous reports and studies that observed the association between asbestos exposure and fibrosis of the lungs.

In 1939, a study of 541 asbestos factory workers in North Carolina reported an exposure-response relationship between exposure and fibrosis of the lung. In this study, both

exposure and duration of work at the factory were shown to be associated with a consistent and regular increase in the number of workers showing clinical signs of asbestotic lung changes. The proportion of workers in the lowest exposure category (i.e., less than 4.9 mppcf and 5 to 10 years work in the industry) who showed signs of asbestosis was 5%. In comparison, 68% of workers with exposures of 5 to 10 mppcf and more than 10 years in the industry, and 58% of those with exposures of more than 10 mppcf and more than 10 years in the industry, showed signs of asbestosis³⁵. In 1965, a large group of asbestos insulation workers from the US were studied. 10.4% of those with less than 10 years in the industry had chest abnormalities on radiographs consistent with asbestosis. This proportion increased dramatically with increasing duration of work, to 44.1%, 72.8%, 87.1% and 94.2% of workers showing signs of asbestosis with 10-19, 20-29, 30-39 and >40 years of work, respectively³⁶. Over the years, the relationship between increasing asbestos exposure and the development of asbestosis has been confirmed in virtually all groups of asbestos-exposed workers in all industries studied. Minimum cumulative exposure levels that have been associated with radiographic, histologic, spirometric, or clinical signs of lung fibrosis in groups of chronically exposed workers vary from study to study, and include:

- 38 f/ml-yrs in British asbestos textile factory workers³⁷;
- 62 f/ml-yrs in Indian cement workers³⁸;
- 30 f/ml-yrs in British Columbia chrysotile miners and millers³⁹;
- 10-30 f/ml-yrs in Swedish asbestos cement workers^{40,41};
- 70 f/ml-yrs in South African crocidolite and amosite miners⁴²;
- 15 f/ml-yrs in autopsied cases of deceased crocidolite miners and millers⁴³; and
- 10-20 f/ml-yrs in deceased textile workers from South Carolina⁴⁴.

It has also been suggested that a lifetime risk of 2/1000 exists at cumulative exposures as low as 4.5 f/ml-yrs⁴⁵.

Asbestosis mortality has also been extensively studied in occupationally exposed groups of asbestos workers. Although pneumoconioses have never been reliably recorded on death certificates, significantly increased mortality rates associated with asbestosis, or other non-malignant respiratory diseases, have been reported in almost all groups of occupationally exposed workers, with cumulative exposure estimates ranging from 32 to 1,271 f/ml-yrs^{46,47,48,49}. In a study of South Carolina textile workers a Standardized Mortality Ratio (SMR^b) of 2.32 was observed for pneumoconiosis and other respiratory diseases in workers with less than 3 f/ml-yrs, and the SMR increased to 27.2 for workers with more than 150 f/ml-yrs⁵⁰. In a large cohort of Québec miners/millers, pneumoconiosis-related mortality increased from 0.23 to 2.7 cases per 1000 person-years^c for those with cumulative exposures less than 100 mppcf-years and 300 mppcf-years, respectively⁵¹. In the most recent follow up of a cohort of Australian miners/millers who were exposed to amphibole asbestos, the SMR for pneumoconioses was estimated to be between 15.5 and 27.5⁵², with an exposure-response relationship similar to that demonstrated previously⁵³.

^b The **Standardized Mortality Ratio (SMR)**, or the **Standardized Incidence Ratio (SIR)**, is the ratio of the sum of the observed cases (incident deaths or incident diseases) in the exposed population, relative to the sum of the expected numbers in the exposed population, where the expected numbers are based on rates in the reference population (Checkoway, H., Pearce, N., and Kriebel, D. (2004) "Research Methods in Occupational Epidemiology", 2nd edition, Oxford University Press Inc.)

^c **Person-time** is an estimate of the actual time-at risk in years, months, or days, that all persons contributed to a study. In certain studies, people are followed for different lengths of time, as some will remain disease-free longer than others. A subject is eligible to contribute person-time to the study only so long as he or she remains disease-free and, therefore, still at risk of developing the disease of interest. By knowing the number of new cases of disease and the person-time-at-risk contributed to the study, an investigator can calculate the incidence rate of the disease, or how quickly people are acquiring the disease. In epidemiological studies, risk is often described for different levels of cumulative asbestos exposure, which is reported as the concentration of asbestos exposure per unit of person-time (e.g., f/ml-years).

⁵⁵. Furthermore, very recent studies of the health status of chrysotile miners/millers from China have also demonstrated increased mortality from non-malignant respiratory diseases in workers exposed to asbestos as compared to the general Chinese population, with SMRs of 9.62 for asbestosis⁵⁶, and 3.53 for non-malignant respiratory diseases⁵⁷. A clear exposure-response relationship was shown for non-malignant respiratory diseases in all groups of exposed Chinese chrysotile miners/millers, with increasing relative risks (RR) observed from 1.55 in the lowest cumulative exposure group (<20 f/ml-yrs), to 1.55 (≥ 20 f/ml-yrs), 4.26 (≥ 100 f/ml-yrs), and 9.36 in the highest exposed group (≥ 450 f/ml-yrs)⁵⁸. In this study, the age-adjusted mortality rate from non-malignant respiratory diseases in the most heavily exposed group was nearly 10 times that of the least exposed group. Together, these studies demonstrate that, regardless of the industry or fibre type, the association between asbestos exposure and asbestosis has been unquestionably established.

Because asbestos exposure has declined dramatically in the past 20-30 years, a decline in the number of asbestosis cases would also have been expected, but this has not been the case. In the USA, according to the Centre for Disease Control and Prevention, the number of reported asbestosis cases has actually increased almost 20-fold over the past decades from 77 cases in 1968 to 1,493 in 2000, with the annual mortality rate also increasing from 0.54 to 6.88 per million people⁵⁹. This same trend is also seen in Australia, where amphibole asbestos was mined/milled from 1937 to 1966. In that country, the asbestosis mortality rate increased three-fold from 1979 to 2002⁶⁰. In a publication on asbestosis surveillance in British Columbia, Canada, the authors demonstrated a 30% increase in new asbestosis cases from 1992 to 2004 with an overall incidence rate of 2.82 per 100,000 people⁶¹. In

developed countries, the increase in asbestosis incidence and mortality rates is related to the large number of people exposed to asbestos years ago combined with the long latency period associated with this disease. However, because asbestos is still being produced and used in a number of countries around the world an epidemic of asbestos-related disorders, including asbestosis, is expected in the coming decades⁶².

1.23 Lung Cancer

Cancer of the lung is the most common form of cancer in humans and is reported to be the leading cause of cancer death worldwide⁶³. The relationship between exposure to asbestos and lung cancer risk has been studied for many years and asbestos is uniformly accepted as being causal in the induction of lung cancer. An increased risk of asbestos-related lung cancer is considered to be linearly related to cumulative asbestos exposure and is associated with a latency period of approximately 15 to 20 years or more. While lung cancer is known to have a number of environmental causes, the best known being cigarette smoking to which approximately 90% of all lung cancers are attributed, it is estimated that approximately 4-12% of lung cancers are due to asbestos exposure⁶⁴. Simultaneous exposure to cigarette smoke and asbestos is considered to have a synergistic effect whereby the risk of lung cancer in people exposed to both agents is greater than the risk of lung cancer in people exposed to either of these agents alone. This relationship often complicates the analysis of the association between asbestos exposure and lung cancer in groups in which smoking is prevalent.

The first indication of an association between asbestos exposure and lung cancer was in the 1930s with reports of cases of lung cancer in workers with asbestosis^{64,65}. It wasn't until

1955 that the link between asbestos exposure and lung cancer was scientifically established with the publication of a retrospective study of a cohort of asbestos textile workers in which an increase in lung cancer mortality was observed as compared to the general population¹³. This has been followed by numerous epidemiological studies validating the association between an increased risk of lung cancer and asbestos exposure in all industries examined, including:

- asbestos insulation union members from Canada and the USA (RR=4.35)²²;
- a cohort of workers at a pipe insulation plant in the USA (RR=2.77)⁶⁷;
- textile workers in Italy (RR=2.82)⁶⁸;
- textile workers in South Carolina, USA (RR=1.95)⁵⁰ and North Carolina, USA (RR=1.96)⁶⁹;
- asbestos cement factory workers in Denmark (RR=1.63)⁷⁰;
- automotive friction products workers in Canada (RR=1.40)⁷¹;
- asbestos factory workers in China (RR=4.2)⁷²;
- Australian crocidolite miners (SMR=1.52)⁵²;
- Québec chrysotile miners/millers (SMR=1.37)⁷³;
- vermiculite miners in Libby Montana, USA (SMR=1.7)⁷⁴;
- South African miners (SMR=1.72)⁷⁵;
- plumbers and pipe fitters in Canada (RR=1.27)⁷⁶; and
- workers in the ship repair, refitting and construction industry in Italy (RR=1.77)⁷⁷.

In many of these studies, an exposure-response relationship between asbestos exposure and lung cancer has also been demonstrated. For example, in the South Carolina textile

cohort, the SMR for lung cancer increased steadily from 1.5 for workers with less than 15 f/ml-yrs cumulative exposure to 1.81, 3.41, and 5.68, for workers in the 15 - 60, 60 - 120, and >120 f/ml-yrs groups⁵⁰. A 37-year longitudinal study at a Chinese asbestos products manufacturing plant that examined the mortality patterns of male workers reported an overall relative risk of lung cancer of 3.31, however, this was increased to 3.49 in workers with "medium level" exposure, and 6.01 in highly exposed workers⁷⁸. This same trend has been shown in the cohort of vermiculite miners from Libby, Montana⁷⁴ who were exposed to a mixture of non-commercial asbestiform fibres, often referred to as 'Libby amphibole'⁷⁹, which is similar to asbestos fibres and includes approximately 84% winchite, 11% richterite and 6% tremolite. In this study an increase in the risk of lung cancer was observed across all categories of cumulative exposure, with SMRs of 1.5, 1.6, 1.8, and 1.9, for the cumulative exposure categories 1 to 4.49, 4.5 to 22.9, 23.0 to 99.0, and ≥ 100 f/ml-yrs. Numerous epidemiological studies of asbestos workers in a wide range of industries have observed a strong association between asbestos exposure and lung cancer risk, as well as a positive exposure-response relationship with increasing cumulative asbestos exposure.

Because asbestos-related lung cancer is morphologically and histologically similar to lung cancer with other etiological origins (i.e., smoking, ionizing radiation, or other pollutants), and because of the high incidence of lung cancer in the general population due to cigarette smoking, it is difficult to estimate the current magnitude and future burden of asbestos-related lung cancer. Most publications focus on mesothelioma (since 80-90% of all mesotheliomas are caused by asbestos exposure) and asbestosis (a disease that, by definition, is caused only by asbestos exposure)^{80,81} as markers of asbestos exposure and

use these to produce projections of asbestos-related lung cancer burden. Generally it is thought that there are two lung cancers (or more) for every mesothelioma case diagnosed¹⁰. Others, however, have estimated an average of 0.7 lung cancers (ranging from 0.5 to 1.0) for every mesothelioma death in crocidolite cohorts, 6.1 (ranging from 3.6 to 10.5) for chrysotile, 4.0 (ranging from 2.8 to 5.9) for amosite, and 1.9 (ranging from 1.4 to 2.6) for mixed fibre cohorts⁸¹. Thus, asbestos-related lung cancers are likely to remain an important component of the total burden of lung cancer deaths in the future as part of the legacy of past occupational asbestos exposure and the continuing exposure of many workers to asbestos in today's workplaces.

Another difficulty in the estimation of the current and future burden of asbestos-related lung cancer is the lack of understanding of the risk associated with low asbestos exposure. In most developed countries it is unlikely that individuals are currently exposed to the high levels of asbestos that were studied in the past because of improvements in industrial hygiene in workplaces and because of the decline in the direct handling of raw asbestos after the 1970s. A recent study used flexible meta-regression techniques to calculate risk estimates of lung cancer at low asbestos exposures⁸². This study reported relative risks for lung cancer to be as high as 1.027 (95% CI: 1.020 – 1.034) at 4 f/ml-yrs cumulative exposure, and 1.30 (95% CI: 1.215 – 1.392) at 40 f/ml-yrs. The authors claim that these data suggest that the increase in relative risk of lung cancer due to low cumulative asbestos exposure may be larger than originally thought and, consequently, that a larger fraction of lung cancer incidence may be attributable to relatively low cumulative exposure levels. This could have important public health implications in developed countries where low cumulative exposure is common.

1.24 Mesothelioma

Mesothelioma is a very rare malignancy that originates in the mesothelial cells of the pleural and peritoneal tissues. It is a rapidly fatal cancer with a latency period of 30 or more years and is associated with an average survival time of 9 to 12 months after diagnosis¹⁸. The primary risk factor for mesothelioma is asbestos exposure with an attributable fraction estimated at 85-90%⁸³. Asbestos exposure causing mesothelioma usually occurs in an occupational setting, although domestic and environmental mesotheliomas (that is, among family members of asbestos workers or persons living in proximity to asbestos production or manufacturing facilities) have been known to occur⁶. Other etiological associations that have been suggested for mesothelioma include; (1) ionizing radiation exposure for the treatment of other cancers such as breast cancer and Hodgkin's' disease; (2) the simian-virus 40 (SV40), which originated from a polio vaccine in the 1950s and 60s, and for which the data indicates a co-carcinogenic effect between asbestos and the virus; (3) and other asbestiform fibres that are not considered "asbestos" because they have not been commercially exploited, such as winchite, richterite and erionite, for which the data have been suggestive of a causal association.^{6,18,84} Furthermore, although smoking is known to have a synergistic effect on the induction of asbestos-related lung cancer, tobacco smoke does not have any relation to the development of mesothelioma, presumably because the carcinogens from tobacco smoke are probably deposited in the lung tissue before the fibres are translocated to the mesothelial tissue.^{18,85} Despite the interest in other etiological agents, asbestos exposure remains the primary risk factor for the induction of mesothelioma in the general population.

The first evidence of mesothelioma being causally linked to asbestos exposure was reported by Wagner and his colleagues in 1960 in South Africa's Northwest Cape Province where asbestos had been mined for decades¹⁴. Wagner reported 33 cases of mesothelioma, 23 in people who worked in the crocidolite mines and 10 in others who lived in the area. This study was the first published account demonstrating a causal association between asbestos exposure and mesothelioma. Since then, cases of mesothelioma have been reported in almost all studies of asbestos-exposed populations regardless of the type of asbestos used or the industry involved. This includes: 173 cases in a cohort of asbestos insulation workers from Canada and the USA³³; 4 cases in workers from a pipe insulation plant in Texas, USA⁶⁷; 37 cases in a cohort of Italian textile workers⁶⁸; 3 and 4 cases in the South Carolina and North Carolina textile workers, respectively^{50,69}; 10 cases in a Danish cement factory⁸⁶; 11 cases in workers from a friction products plant in Derbyshire, UK⁸⁷; 85 cases in asbestos factory workers in East London, UK⁸⁸; 8 cases in plumbers and pipefitters in Ontario, Canada⁷⁶; 316 in male miners/millers from Wittenoon Australia⁸⁹; 38 cases in Québec miners/millers⁷³; 16 in South African miners/millers⁷⁵; 14 in Italian miners/millers⁹⁰; and 6 in vermiculite miners/millers from Libby Montana, USA⁷⁴.

Because of the rarity of mesothelioma, even a small number of cases in an exposed population is significant. The rarity of the disease has also made it very difficult to study the exposure-response relationship between exposure and disease development. Mesotheliomas have been found in workers exposed for brief durations and those exposed for many years, suggesting that there is no evidence of a threshold below which there is no risk of mesothelioma⁹¹. However, recent data from the Australian miners/millers cohort suggest that the mesothelioma rate in this group is dose-related, with 5 times more

mesotheliomas observed in the group with the highest cumulative exposure (>50 f/ml-yrs) than in the group with the lowest (<10 f/ml-yrs)⁸⁹. The authors of this study also report that the majority of peritoneal mesotheliomas (37%) occurred in the group with the highest cumulative exposure, thus supporting the claim, originally made over 40 years ago, that peritoneal tumors are associated with heavier exposures than pleural mesotheliomas⁹².

As with other asbestos-related diseases, the number of cases of mesothelioma continues to rise despite the fact that the use of asbestos has declined dramatically over the past 30 years. This is owing to the large number of people exposed in the 1960s and 1970s and to the long latency period of the disease. It has been estimated that, worldwide, nearly 43,000 people die of mesothelioma every year⁹³. The number of Canadian men diagnosed with mesothelioma has been steadily increasing over the past 20 years from 153 cases in 1984 to 344 cases in 2003, with the annual incidence rate increasing from 14 to 21 per 1 million population²². Mesothelioma incidence varies from country to country with the highest annual crude incidence rates (approximately 30 cases per 1 million people) in Australia, Great Britain and Belgium, which generally corresponds to areas where, historically, asbestos production and usage has been the highest⁹⁴. Except in the USA, where incidence data suggest a plateau and subsequent decline in new cases since 2000-2005, current predictions suggest that peak mesothelioma incidence in developed countries hasn't occurred yet⁹⁵. For instance, in 2008, there were 661 cases of mesothelioma diagnosed in Australia, with an annual incidence rate of 29 cases/1 million population. It is predicted that the mesothelioma incidence will peak in that country between 2014 and 2021. In the UK, the annual incidence rate was also 29 cases per 1 million population in 2009 with the

peak expected between 2011 and 2015. In that country, a five-fold increase in the number of cases has been observed since 1980. This same trend is reported for Italy, where the incidence rate is approximately 24 cases/1 million population with a peak in mesothelioma incidence predicted to occur between 2015 and 2024. In Japan, the peak is not expected to occur until the period between 2027-2060 with 66,000 cases predicted between 2003 and 2050⁹⁵. This is largely due to the fact that asbestos consumption has been high in Japan since 1980, so that the latency period for mesothelioma is not expected to be realized until later this century⁹⁴.

Current worldwide estimates of mesothelioma incidence are likely underestimates because it is thought that there is one case of mesothelioma missed for every four to five recorded⁹⁶. It has been suggested that this may be due to diagnostic and coding challenges associated with mesothelioma^{18,22}. This includes the potential misdiagnosis of mesothelioma as lung cancer or stomach cancer, and the fact that, until 1994, there was no separate International Classification of Diseases (ICD) code for mesothelioma. For these reasons, the true burden of the disease is likely much greater than currently thought, even for developed countries where adequate data are available. In some parts of the world, the data on mesothelioma rates are unavailable or insufficient to estimate the current burden of the disease or predict the future trends. In many of these countries, asbestos is still widely consumed so that an outbreak of mesothelioma can be expected to occur in the coming decades and will likely resemble the experience of the many countries that have already experienced, or are still in the midst of, a mesothelioma epidemic.

1.25 Other Cancers

Many occupational epidemiology studies of asbestos-exposed workers have not included a direct analysis of mortality or morbidity caused by cancers of other potentially relevant target sites, since lung cancer and mesothelioma have been the principal areas of research. Cancers that are thought to be potentially associated with asbestos exposure include cancers of the gastrointestinal tract, such as cancer of the larynx, esophagus, stomach, and colorectum, and also ovarian cancer and pharyngeal cancer. The evidence of an association between asbestos exposure and these cancers has been critically examined by both the Institute of Medicine (IOM)¹⁶ and the International Agency for Research on Cancer (IARC)⁶. In 2006, the IOM conducted an evaluation of the available epidemiological and toxicological literature pertaining to the association between asbestos exposure and cancers of the pharynx, larynx, oesophagus, stomach, and colorectum in order to judge whether or not the evidence was sufficient to infer a causal relationship. Furthermore, the IARC working group has recently published a monograph on the carcinogenic properties of asbestos in humans. Both these sources are used here to summarize the evidence of the association between these other cancers and asbestos exposure.

1.25.1 Cancer of the Larynx

Of all the other cancers studied in relation to asbestos exposure, laryngeal cancer has been the most frequently examined in case-control and cohort studies of asbestos-exposed populations with evidence of an exposure-response relationship having been found in both types of studies¹⁶. Elevated relative risks of laryngeal cancer have been found in the following studies: a study of a cohort of insulation workers with an SMR of 1.70³³; a study

of miners/millers in Australia with an elevated SMR of 1.56⁵² and an elevated SIR rate of 1.82⁹⁷; a study of UK textile workers which found increased mortality; an Italian cohort study of miners/millers in which an elevated SMR of 2.67 (95% CI: 1.15 - 5.25) was observed as well as a dose-response relationship between cumulative asbestos exposure and the risk of death from laryngeal cancer, with SMRs ranging from 1.43 in workers with less than 100 f/ml-yrs to 2.22 in workers with exposures of 100 to 400 f/ml-yrs and 3.85 in workers with more than 400 f/ml-yrs⁹⁸. A follow-up of this cohort in 2009 supported the original findings⁹⁹, but in both studies a portion of the increase in risk of laryngeal cancer was attributed to the elevated alcohol consumption in this cohort. Overall, based on all the available epidemiological, toxicological and medical evidence, the IOM committee concluded that a causal association between asbestos exposure and cancer of the larynx had been clearly established¹⁶ and asbestos has been accepted as being causal in the association with laryngeal cancer⁶. This is consistent with the conclusion reached by IARC.

1.25.2 Cancer of the Ovary

Most occupational epidemiologic studies of asbestos-exposed workers involve male subjects, since males have been the predominant sex in industrial work places. There have, however, been a few studies that have involved females. The IARC working group has conducted a review of the available literature on female asbestos-exposed populations and has concluded that a causal association is evident between asbestos exposure and cancer of the ovary. The studies considered in that review included cohort mortality studies that showed a strong positive association between heavy asbestos exposure and ovarian cancer. For instance, groups of female factory workers who manufactured gas masks in the UK

were studied, and elevated SMRs of 2.75, 1.48, and 2.13 were reported for ovarian cancer^{100,101}. Also, a group of women employed in an asbestos textile plant in Italy was studied and an elevated SMR of 2.61 was reported, with an increase in SMR with length of employment⁶⁸. Other studies examined by the IARC working group included: cohorts of women and girls who have been environmentally exposed to asbestos in Australia; former workers of an asbestos cement factory in Italy; former workers of an asbestos-board insulation manufacturing plant in London; and female pulp and paper workers in Norway⁶. The conclusion of the IARC working group was that a causal association between asbestos exposure and ovarian cancer has been clearly established, based on a number of strongly positive cohort studies of women with heavy occupational exposure and supported by other epidemiological evidence that also indicates a positive relationship. This conclusion is also consistent with laboratory findings indicating that asbestos fibres can accumulate in the ovaries of women with household exposure to asbestos¹⁰² or through occupational exposure, presumably through distribution of fibres via the lymphatic system¹⁰³.

1.25.3 Cancers of the Pharynx, Stomach, Colorectum and Esophagus

For cancers of the pharynx, stomach and colorectum, the IOM committee concluded that the evidence is suggestive but not sufficient to infer a causal relationship between asbestos exposure and cancer at these sites. Positive associations were found between asbestos exposure and pharyngeal cancer based on the fairly consistent findings in the studies considered. The IOM also conducted a meta-analysis using the data from the published cohort and case-control studies considered in its review. They reported summary relative risks, for pharyngeal cancer, in people with "any" exposure to asbestos of 1.44 (95% CI

1.04-2.00) from the cohort studies, and 1.5 (95% CI 1.1-1.7) from the case-control studies. While smoking and alcohol consumption are the main risk factors for pharyngeal cancer, the association with asbestos exposure was apparent in several studies when these risk factors were considered¹⁶.

The same conclusions were drawn for cancer of the stomach for which positive associations were observed in several cohorts with heavy exposure to asbestos, as was a positive exposure-response relationship between cumulative asbestos exposure and stomach cancer mortality. For instance, a three-fold increase in mortality for stomach cancer was observed in a cohort of US insulation workers¹⁰⁴ as well as a positive exposure-response relationship with increasing duration of exposure. Similar findings were reported for miners/millers in Québec, and for several other cohorts⁷³. Furthermore, two large and well performed meta-analyses were noted as being supportive of the positive association between asbestos exposure and stomach cancer^{105,106}, as well as meta-analyses conducted by the IOM of the cohort and case-control studies considered¹⁶.

IARC also found evidence of a positive association between asbestos exposure and cancer of the colorectum, as well as an exposure-response relationship in populations with prolonged heavy exposure. This conclusion was based on the data from several cohort studies, for instance, the cohort of American insulation workers which demonstrated an excess of mortality due to colorectal cancer with increasing duration of work: an SMR of 0 was observed for workers with less than 20 years' work, but this increased to 3.68 for workers with 20-35 years' work and 2.58 for workers with more than 35 years' work¹⁰⁷. Elevated SMRs have also been reported for other groups of occupationally exposed

workers, including factory workers in Paterson, NJ¹⁰⁸, asbestos cement workers in Sweden¹⁰⁹, asbestos insulation board manufacturing workers from London, UK⁸⁸, and other groups. The positive association between asbestos exposure and cancer of the colorectum is also supported by the positive exposure-response relationships observed between cumulative asbestos exposure and colorectal cancer in several of the cohort studies examined, as well as by a number of well conducted meta-analyses¹⁶.

The available evidence for assessing the potential relationship between asbestos exposure and esophageal cancer was extremely limited and results were inconsistent and difficult to interpret because of the small number of cases. Although several cohort and case-control studies, as well as a number of meta-analyses indicated some association, the IARC committee concluded that the evidence for this type of cancer was suggestive but not conclusive to support a causal relationship.

1.3 The Chrysotile Controversy

All types of asbestos are considered to be carcinogenic by the leading scientific and health authorities, including the National Toxicology Program in the United States⁵, the National Institute of Occupational Safety and Health¹¹⁰, the Environmental Protection Agency¹¹¹, the Agency for Toxic Substances and Disease Registry¹¹², the World Health Organization^{49,113}, and the International Agency for Research on Cancer⁶. In the most recent IARC monograph, all asbestos fibre types are deemed to be causally associated with the development of lung cancer, mesothelioma, laryngeal cancer and ovarian cancer. Despite this, there has been continuing discussion as to whether or not a difference exists in the toxicity between the major fibre types - the amphiboles and the serpentines.

The first observation of a difference between fibre types was made in South Africa in the 1960s, where mesotheliomas were found in people living in the area where crocidolite was processed and in the workers mining and milling the fibres, but not in the chrysotile mining area¹¹⁴. Since then, a large amount of research has been dedicated to understanding the relative toxicity of chrysotile and amphibole asbestos fibres. Much of this research, however, has been funded by the asbestos industry in an attempt to overcome the growing objections to the use of asbestos¹¹⁵. Furthermore, a large portion of this research has been conducted by a limited number of scientists in countries where the chrysotile asbestos industry has had the largest economic and political impact. In Canada, for instance, a group of researchers from McGill University and the Chrysotile Institute (formerly known as the "Asbestos Institute") have been some of the major proponents of the continued "safe" use of chrysotile asbestos¹¹⁶. McDonald and his colleagues have long claimed that chrysotile, unlike amphibole asbestos, presents no danger so long as the proper precautions are taken, and this argument has been used to justify the continued production of asbestos in Canada and its export to the developing world. The published research supporting these ideas has been criticized as being heavily influenced by an industry desperate to save itself from litigation and bankruptcy¹¹⁷. Therefore, the scientific literature surrounding asbestos has a social and political context that has to be taken into account when considering the debate on asbestos fibre type and disease.

1.31 The History of the Chrysotile Controversy

The controversy surrounding chrysotile asbestos has a lengthy history, beginning with the observations of Wagner in the 1960s. These findings had a major impact on the amphibole

asbestos industry, so much so that the production and use of crocidolite and amosite declined dramatically and eventually ceased altogether. As a result, the market demand for chrysotile increased and the focus of the industry shifted towards demonstrating the safety of chrysotile asbestos. Research conducted on the Québec cohort suggested that the health risks in chrysotile miners/millers were minimal compared to the risks found in studies of workers exposed to other types of asbestos¹¹⁵. However, these arguments became problematic when cases of mesothelioma began to appear in the Québec chrysotile miners/millers, as well as in other groups of workers exposed primarily to chrysotile asbestos. In the 1990s, papers published on the Québec cohort reported different patterns of mesothelioma in miners/millers from different mining areas where the tremolite content of the ore was found to be different, therefore claiming that the mesothelioma risk observed amongst exposed miners/millers was caused by the presence of trace amounts (< 0.1%) of amphibole fibres (i.e., tremolite) in the ore rather than by chrysotile. They also suggested that chrysotile asbestos may be less potent than amphiboles in the induction of lung cancer^{118,119}. This eventually became known in the published literature as the "amphibole hypothesis"^{120,121}, and it was largely used to promote claims that chrysotile was safe for use¹¹⁵.

The amphibole hypothesis arose primarily because of two important observations in the 1970s: (1) chrysotile fibres appear to be cleared from the lungs much faster than amphibole fibres (i.e., they are less biopersistent than amphiboles); and (2) several cohorts of chrysotile-exposed workers were reported to have lower (albeit still elevated) rates of lung cancer and mesothelioma than groups with amphibole or mixed fibre exposures. Despite the fact that numerous studies of chrysotile-only exposed cohorts, toxicological and

mechanistic studies, review articles, and meta-analyses have successfully refuted the arguments of the amphibole hypothesis and clearly demonstrated the relationship between chrysotile asbestos and mesothelioma^{23-26,50,64,121-128}, a few proponents of the safety of chrysotile remain^{119,129}. Furthermore, although there is general consensus among most scientists and health agencies that chrysotile asbestos is a major risk factor for lung cancer, mesothelioma and non-malignant respiratory disease, the controversy has not yet been resolved but has, rather, subtly switched to the issue of the relative toxicity of the different fibre types.

1.32 The Lung Cancer Debate

The ongoing debate regarding the potency of chrysotile asbestos in causing lung cancer stems primarily from inconsistencies in the estimates of risk among exposed cohorts of workers. A number of meta-analyses, using data from published cohort studies of asbestos-exposed workers in a number of industries, have estimated the relative potencies (excess risk per unit of exposure) of the different fibre types for lung cancer. Hodgson and Darnton²³ estimated the relative potency of chrysotile versus amphibole fibres to be in the range of 1:10 to 1:50, with a best estimate of excess lung cancer risk of 0.1% per f/ml-yr in chrysotile exposed cohorts and up to a maximum of 0.5%. In contrast, the estimate of excess risk for amosite and crocidolite cohorts was approximately 1% and 5% per f/ml-yr, respectively. Berman and Crump²⁶ also estimated chrysotile to be of lower potency than the amphiboles with ratios ranging from 1:6 and 1:60, depending upon the fibre dimensions considered. More recently, a study by van der Bij et al. examined the exposure-response relationship between asbestos exposure and lung cancer risk at low cumulative

exposures and reported smaller potency differences between the fibre types than those of Berman and Crump and of Hodgson and Darnton. They reported only a three- to four-fold difference in excess risk between amphibole asbestos and chrysotile asbestos, with an excess risk for chrysotile of 1.006 (95% CI: 0.848 – 1.194) at 4 f/ml-yrs cumulative asbestos exposure, and 1.064 (95% CI: 0.873 – 1.297) at 40 f/ml-yrs cumulative exposure. In comparison, the estimate of excess risk for amphibole asbestos was 1.022 (95% CI: 0.568 – 1.837) at 4 f/ml-yrs, and 1.232 (95% CI: 0.687 – 2.209) at 40 f/ml-yrs 1.232⁸². One of the major reasons for the inconsistency amongst the results of the various meta-analyses is the large discrepancies in reported risk between the various chrysotile exposed cohorts - most notably, the large disparity between the slope of the exposure-response relationship reported in studies of the Québec miners' cohort^{51,130,131} and that reported in studies of the South Carolina textile workers' cohort^{50,132,133}.

The Québec chrysotile miners/millers cohort has been studied since 1966 and analyses of their mortality have been published at various follow-up times. In the 1980 follow-up¹³⁰ and the 1994 follow-up¹³⁴, elevated SMRs for lung cancer were reported in this group of 1.25 and 1.39, respectively, for men 20 or more years after first employment. The 1994 study also examined the exposure-response relationship between cumulative asbestos exposure and lung cancer. In the three highest exposed groups they found the risk of lung cancer to be 1.5 (33-400 mppcf-yrs), 1.65 (400-1000 mppcf-yrs) and 3.04 (> 1000 mppcf-years). However, the authors found that in the group of workers exposed to less than 300 mppcf-years (which they equate to 1000 f/ml-yrs) there was no increase in lung cancer risk, thus claiming exposure to lower levels of chrysotile asbestos to be safe.

On the other hand, in the South Carolina textile worker cohort, the risk of lung cancer has been reported as being much higher. This cohort has been studied since the early 1970s with multiple follow-ups since then. Elevated SMRs for lung cancer have been reported at each follow-up, the most recent being in 2007 with an SMR of 1.95⁵⁰. A positive exposure-response relationship with cumulative asbestos exposure has also been consistently demonstrated, with relative risks increasing in each cumulative exposure group, with SMRs of 1.55, 1.34, 1.52, 1.81, 3.41 and 5.68, in the < 1.5, 1.5 to 5, 5 to 15, 15 to 60, 60 to 120 and > 120 f/ml-yrs groups, respectively. It is important to note that the primary type of asbestos used in the South Carolina textile plant was Québec chrysotile.

Of all the epidemiological studies evaluating the risk of lung cancer due to chrysotile asbestos exposure, these two cohorts have produced both the lowest rates (the Québec cohort) and the highest rates (the South Carolina cohort) of asbestos-induced lung cancer. The estimated potency factors (i.e., the excess risk per unit of exposure) for these groups has been reported as being more than 60 times higher for the South Carolina textile cohort (1.8 per f/ml-yrs) than for the Québec miners/millers cohort (0.029 per f/ml-yrs)²⁶. The discrepancy in lung cancer potency between these two cohorts has been one of the main reasons why the debate regarding the relative toxicity of chrysotile asbestos for lung cancer has persisted.

Recent studies published on other chrysotile cohorts have begun to shed new light on the association between chrysotile asbestos and lung cancer. For example, a cohort of North Carolina textile workers has recently been studied by the authors of the South Carolina cohort study⁶⁹. They found the overall SMR for lung cancer to be 1.96, with a strong

exposure-response relationship with both employment duration and cumulative asbestos exposure. Lung cancer SMRs increased steadily with increasing employment duration, from 1.82, 1.86, 2.06, 2.34, to 2.50 for the <1, 1-5, 5-10, 10-20 and >20 years groups. Lung cancer SMRs also increased steadily with increasing cumulative asbestos exposure, from 1.0, 1.50, 1.12, to 1.78, for the <11.5, 11.5-34.8, 34.8-152.7 f/ml-yrs groups. Furthermore, there have been a number of recently published studies on cohorts of chrysotile-exposed workers in China. A 37-year longitudinal study of male workers from an asbestos manufacturing plant in China that produced various asbestos products using chrysotile fibres only, examined lung cancer mortality and reported an overall age- and smoking-adjusted relative risk of lung cancer of 3.31. Although individual cumulative exposures could not be estimated because of the lack of exposure data, a clear exposure-response pattern was demonstrated with the hazard ratio increasing from 1.94 in the low exposure group (i.e., office workers and those in well-ventilated areas), to 3.49 and 6.01 in the medium and high exposure groups (i.e., workers in poorly ventilated areas and raw material/textile sections)⁷⁸. Furthermore, studies of Chinese chrysotile asbestos miners/millers have yielded results that contradict those of the Québec cohort with respect to lung cancer risk. In a study of 1,932 chrysotile asbestos miners/millers in China¹³⁵, a significant exposure-response relationship was observed with the probability of lung cancer incidence increasing with levels of cumulative dust exposure, from 6.58/10,000 for exposures of less than 2000 mg/m³-years, to 91.72/10 000 and 141.02/10 000, for greater than 2000 - 3000 mg/m³-years, and > 3000 mg/m³-years, respectively. Finally, another study of 1,539 male chrysotile miners/millers from China has also demonstrated an elevated risk of lung cancer, with an overall SMR of 3.59 that differed between the two

groups identified, with the exposed group of "miners/millers" having an SMR of 4.71 as compared to the internal control group (i.e., administrative workers) whose SMR was only 1.20⁵⁷. In that study however, quantitative estimates of subjects' cumulative asbestos exposure were not reported. Overall, the results emerging from the Chinese cohorts differ markedly from the Quebec results and strongly support the position that chrysotile asbestos exposure is a major risk factor for lung cancer.

Taken together, these analyses of the epidemiological data for chrysotile-only exposed cohorts clearly demonstrates a strong association between lung cancer and chrysotile asbestos despite the heterogeneity among the cohorts, which has proved to be the greatest challenge in determining an overall estimate of risk of lung cancer for chrysotile asbestos. While the precise reason for the differences between the cohorts is unknown, a number of explanations have been proposed. For example, one of the first reasons suggested for the large lung cancer risk in the South Carolina textile cohort was that co-exposure to mineral oils led to an overestimate of risk. However, a nested case-control study demonstrated the persistence of the elevated risk when co-exposure to mineral oil was held constant thus indicating that this theory is not tenable^{50,121,136}. Other possible explanations include differences in fibre size distribution between the different industries (i.e., mining/milling operations and textile operations)^{25,137-139}, and errors in the exposure assessment process and quality of study design^{140,141}.

Fibre size has been hypothesized as being a factor in the toxicity of asbestos since Stanton first proposed it in 1981¹⁴². It has been suggested that the biological processes of retention, degradation and clearance are different depending on fibre size, in that short

thick fibres are more easily cleared from the lung through the process of phagocytosis, whereas long thin fibres are more persistent^{137,142}. It has also been suggested that this difference in fibre size is an explanation for the different outcomes in the Québec miners/millers as compared to the South Carolina textile cohorts^{23,25,26,69,143} since longer, thinner fibres are thought to be the primary exposure in textile manufacturing as compared to shorter thicker fibres in the mining/milling industry¹³⁷. Risk estimates for lung cancer are similar among the cohorts in the textile industry both with pure chrysotile and with mixed fibres, and these are generally higher than the estimates for the mining/milling or asbestos products industries^{23,121}. In fact, reasonably good agreement in lung cancer potency has been shown among the chrysotile mining cohorts (i.e., the Québec miners/millers and the Italian miners/millers)^{98,132}, and among the various textile cohorts (i.e., South Carolina, Pennsylvania, Rochdale textile cohorts)^{132,144,145} further lending support to the idea that industry type (and the differences in fibre size distribution) may be a major factor in the difference in lung cancer potencies^{23,121,137}. For instance, in the Italian cohort of chrysotile miners/millers the overall risk of lung cancer mortality was estimated in 1990 at 1.10⁹⁸ and, although this increased to 1.27 in a follow-up study in 2009, it remained statistically insignificant⁹⁹. The analysis of cumulative exposure and lung cancer mortality risk found an SMR of 0.83 for cumulative exposures of less than 100 fibre-years (i.e., f/ml-yrs), rising to 1.57 for 100 - 400 fibre-years, and 1.37 for exposures of more than 400 fibre-years. The authors of these studies attribute the modest relationship with lung cancer to a number of potential factors, such as limitations associated with the exposure assessment, the exclusion of contract workers from the study, concurrent diagnosis of other causes of death (e.g., chronic obstructive pulmonary disease and asbestosis), the

healthy/unhealthy worker effect, and differences in smoking habits between the cohort and the general population⁹⁹. Lung cancer potency estimates for the Italian cohort have been between 0.03% expected lung cancers per f/ml-yr and 0.051%, which is similar to the Québec estimates of 0.06 and 0.029^{23,26}.

In the textile industry, the potency estimates for the North Carolina textile cohort are fairly consistent with that of the South Carolina cohort. Although smaller (1.38% excess risk per f/ml-yr for the North Carolina cohort, as compared to 4.6% excess risk per f/ml-yr for the South Carolina cohort) they are both much higher than the potency estimates for the Québec and Italian miners/millers cohorts^{23,26,69,121}. Furthermore, the fibre size theory has been supported in recent years by additional research conducted on historical samples collected in the South Carolina and North Carolina textile plants where it has been shown that longer thinner fibres are associated with higher lung cancer rates than shorter thicker fibres^{69,138,139,146-148}.

Another possible explanation for the heterogeneity in the slope of the exposure-response relationship between chrysotile exposure and lung cancer risk among the various cohorts is the quality of the exposure assessment¹⁴⁰. A recent study by Lenters et al. evaluated several aspects of the exposure assessment process of numerous studies (including the Québec and South Carolina cohorts) in relation to its effect on estimates of lung cancer potency. They concluded that the inclusion of studies with higher quality exposure assessments (i.e., well-documented exposure assessments, larger differences between cumulative exposure groups, greater coverage of the exposure history by exposure measurement data, and more complete job histories) led to higher potency estimates for

chrysotile asbestos than studies without these characteristics, noting that the South Carolina textile cohort has both the highest lung cancer potency estimates and the one of the highest quality exposure assessments in the literature. They also concluded that the lower potency estimates in the studies considered to be of poorer quality were thought to be related to exposure misclassification and thus an attenuation of the slope of the exposure-response relationship. For instance, the Quebec miners/millers study, which has one of the lowest potency factors, was described as suffering from numerous limitations including insufficient job history information and undocumented movement of workers¹⁴⁰. Therefore, the authors conclude that the quality of the exposure assessment process accounts for part of the disparity in lung cancer potency factors between the various studies and that combining only higher quality studies yields higher meta-estimates of lung cancer risk per unit of exposure than does including all available studies. While the authors also recognize that fibre-size distribution may play a role in the variation of risk among the cohorts, they claim that the findings regarding the effect of the exposure assessment process casts doubt on the conclusion that the epidemiological evidence strongly supports a difference in lung cancer potency between the different fibre types.

In conclusion, the heterogeneity in the exposure-response relationship among the cohorts exposed only to chrysotile is difficult to resolve, although fibre size and exposure assessment quality seem to account for at least some of this heterogeneity. However, the possibility that chrysotile may be as potent, or nearly as potent, for causing lung cancer as amphibole asbestos, still exists and this has led organizations such as the ACGIH, NIOSH, OSHA and other standard setting groups to set equal exposure limits for all the fibre types.

1.33 *The Mesothelioma Debate*

Cases of mesothelioma have been observed in almost all studies of asbestos-exposed populations around the world and the association between asbestos exposure and this rare malignancy is undisputed. However, there are remaining uncertainties about the relative potency of the different asbestos fibre types for mesothelioma. Despite the lingering claims by a few scientists that chrysotile asbestos is not a cause of mesothelioma^{119,129}, the consensus in the scientific community is that chrysotile is capable of causing mesothelioma but it is likely not as potent as the amphibole fibres, especially crocidolite^{4,5,15,23,25,26,124}. This is supported by epidemiological studies that have reported far more mesotheliomas in cohorts of workers exposed predominantly to amphibole asbestos or to a mixture of asbestos types, as compared to those exposed to chrysotile only. For example, in the most recent follow-up of the large cohort of crocidolite miners from Australia, 329 deaths (316 men and 13 women) due to mesothelioma (pleural and peritoneal) have been reported amongst the almost 7,000 members of this cohort, giving a proportionate mortality of 10% for men, and 8% for women⁸⁹. Furthermore, in workers exposed to amosite asbestos in a New Jersey insulation manufacturing factory, 2.9% of deaths were attributed to mesothelioma¹⁰⁸. Another group of insulation applicators from the US and Canada experienced 458 mesotheliomas, accounting for 10% of all deaths³³.

In contrast, chrysotile-exposed cohorts have experienced considerably less mortality due to mesothelioma than amphibole workers. For example, there have only been 38 mesotheliomas reported amongst the 11,000 workers in the Québec chrysotile miners' cohort, giving a proportionate mortality of 0.47%⁷³. In the chrysotile mining cohort from

Italy five mesotheliomas have been reported among 1056 men⁹⁹, equating to a proportionate mortality ratio of 0.85% for this group. A cohort of chrysotile textile workers in South Carolina had three mesotheliomas out of 1,961 deaths (0.15%)⁵⁰ while 4 mesotheliomas were found in a similar cohort of workers in North Carolina⁶⁹ also accounting for 0.15% of the total deaths⁶⁹. Taken together, these studies support the notion that chrysotile asbestos is capable of causing mesothelioma, but that it may not be as potent as amphibole asbestos.

Meta-analyses that have attempted to quantify the difference between the fibre types for mesothelioma causation have assigned varying potency factors to chrysotile and amphibole asbestos. The hypothesized fibre potency gradient in mesothelioma causation for South African crocidolite and other amphiboles as compared to chrysotile fibres, ranges from 500:1, to 200:1, to 10:1 and 1:1¹²⁸. Hodgson and Darnton²³ concluded that the quantified risk for mesothelioma at the cumulative exposure levels reported in the reviewed cohorts presented a reasonably coherent representation in which the risk of mesothelioma for the three principal types of commercially used asbestos was in the order of 1:100:500 for chrysotile, amosite and crocidolite, respectively. That is, amosite and crocidolite were considered to be 100 and 500 times more potent in causing mesothelioma than chrysotile. Berman and Crump²⁶ also estimated potency factors for the differing asbestos types. They reported that the hypothesis that chrysotile and amphibole forms of asbestos are equally potent was strongly rejected and that the hypothesis that chrysotile potency was zero could not be rejected. The best estimates for the relative potency of chrysotile ranged from 0 to 1/200th that of amphibole fibres. However, the recent discovery of additional cases of mesotheliomas in workers from the chrysotile mine/mill in Italy has drawn attention to the

fact that the risk of mesothelioma previously calculated for this group was seriously underestimated⁹⁰. Mirabelli et al. discovered nine cases of mesothelioma among workers who were active in the mine in addition to the five cases reported by Pira^{90,99}, which would result in an increased proportionate mortality ratio of approximately 2.37%. Therefore, the potency of chrysotile asbestos appears to be higher than previously estimated and has since been estimated as 14:1 for amosite compared to chrysotile, and 54:1 for crocidolite compared to chrysotile^{6,24}.

1.4 The Baie Verte Chrysotile Asbestos Mine/Mill and Registry

1.41 The History of the Baie Verte Asbestos Mine/Mill

The town of Baie Verte is located on the Northeast coast of the province of Newfoundland and Labrador (NL), on the Baie Verte Peninsula in White Bay (Figure 1-1). The Baie Verte asbestos deposit was discovered in 1955 and exploratory drilling took place until 1957. In 1959, a small test plant was constructed and became active. In 1963, Advocate Mines, a division of the Johns-Manville Company, began open-pit mining of the chrysotile asbestos deposit. The mine closed in 1980 but was reopened in 1982 by Transpacific Asbestos Limited, which operated it until 1989. In 1990, it was reopened for a third and final time under the name Baie Verte Mines Limited and closed again in 1994¹⁴⁹. The major markets for the Baie Verte chrysotile mine/mill were in Western Europe and South America.

The milling process at Baie Verte utilized dry methods until approximately 1989 at which time wet processing methods were introduced¹⁵⁰. In dry mining/milling operations, the ore is blasted or drilled from the open pit and then crushed to a nominal size, dried, and stored until milled. Fibre extraction then occurs through a series of crushing operations

followed by vacuum aspiration of the ore running on a vibrating screen. In wet milling operations, the asbestos is dispersed in water and not dried until after the final separation process is complete. This method is supposedly advantageous for dust control and the separation of mineral contaminants from the fibre product¹⁵¹.

During the years when the mine was operating, a number of control measures were gradually put in place to reduce dust levels. For example, dust collectors were fitted onto the drills in the pit, jute bags were replaced by reinforced plastic film bags, a vacuum dryer was installed in the crusher/dryer building, a laundry facility, change rooms and a car wash were built, and improvements were made to the ventilation system inside the mill². In 1964, an air sampling program was introduced to measure the dust levels in various areas around the mine/mill using the midget impinger method. Regular air monitoring was done by company, union and government representatives. In 1975, the method of air sampling changed to the membrane filter method which measured fibre concentrations rather than dust concentrations.

In 1976, Dr. Irving Selikoff, a world-renowned specialist in occupational disease, was commissioned by the provincial government to conduct a clinical study of the workforce of the Baie Verte mine/mill. In his report in 1977, Dr. Selikoff identified respiratory changes consistent with asbestos-related disease in approximately 10% of the Baie Verte workers (485 examined). On the basis of these findings, a number of recommendations were made to reduce dust levels and worker exposure, and for the development of a registry of the Baie Verte employees in order to monitor the health status of these workers¹⁵². Although a

number of the recommended changes were put into place, including the improved hygiene methods described above, the registry was not developed until 2008.

Figure 1-1: Map of Newfoundland indicating geographical location of the community of Baie Verte.



1.42 The Baie Verte Miners' Registry

The Baie Verte Miners' Registry (BVMR) was established in 2008 by the Workplace Health and Safety Compensation and Commission (WHSCC), the United Steelworkers' Union (USW), and the Baie Verte Peninsula Miners' Association, in partnership with the Safety Net

research centre of Memorial University of Newfoundland (MUN). One of the major objectives of the registry was to gather information on asbestos-related disease among former employees. According to the BVMR website (<http://www.bvminers.ca>), the primary purpose of the registry was to facilitate the process of applying for compensation, for former workers and their families, by having all the appropriate documentation stored in a comprehensive and confidential database. Also, the data collected by the registry was to be used to help evaluate the health effects of working with chrysotile asbestos.

The BVMR is a voluntary registry in which former employees of the mine were to make initial contact with the project team and subsequently complete consent forms in order to be enrolled. The BVMR contains the following types of information on each registrant:

- Demographic and contact information;
- Vital status;
- Health status;
- Relevant medical history, including diagnosis of all asbestos-related diseases and other cancers, as well as clinical respiratory data;
- Workers' compensation claim information;
- Detailed work history information;
- Estimated duration and intensity of exposure to asbestos;
- Non-occupational risk factors such as smoking and alcohol consumption;

As of April 2011, the BVMR contained 1003 consented subjects, of whom 810 were alive and 193 were deceased (having been registered by their authorized next of kin). Information on demographics, work history, and smoking and alcohol usage was gathered

from “Health and Employment” questionnaires administered to employees and/or next of kin” using, among other questions, standardized questions on respiratory health taken from the American Thoracic Society’s Adult Questionnaire. Work history information was obtained from company records as well as miners’ medical files and workers’ compensation files, when available. In order to produce estimates of exposure, air sampling data was compiled by the author of this thesis from historical company, union and government records and used by her to develop a job exposure matrix (JEM) for the project team. The JEM is described in further detail in Chapter 2.

The health information in the BVMR was collected from a number of sources. Hospitals records were obtained from institutions visited by registrants (as listed on their questionnaires) and for which signed consent forms for release of medical information had been received. The WHSCC also provided compensation claim files for any registrant who had made an asbestos-related claim. The BVMR also contains self-reported disease diagnoses for registrants who filled out the health and employment questionnaire and medical information obtained from their regular miner’s medical examinations stored at the local hospital (the Baie Verte Health Centre).

Data linkage to secondary data sources was also attempted for registrants, through the Newfoundland and Labrador Centre for Health Information (NLCHI), in order to obtain information on health status for as many registrants as possible. The province’s Clinical Database Management System contains demographic, clinical and administrative data collected at hospitals when patients are discharged from inpatient and surgical day services. This database captures information regarding hospitalization for both NL

residents and for non-residents receiving care in the province. When the Registry was constructed, the period for which these electronic data were available was 1992 to 2008. The Cancer and Chronic Disease Research Database contains linked records from the Newfoundland and Labrador Chronic Disease Surveillance System and the Oncology Patient Information System, for which data are provided by the provincial Cancer Treatment and Research Foundation. This dataset covered the years 1995 to 2007 and only those registrants residing in NL at the time of their diagnosis and treatment.

Information on cause(s) of death was obtained through data linkage to the provincial mortality system held by NLCHI. The provincial mortality system contains demographic, administrative and clinical data for deaths of both residents and non-residents that occur in NL. This dataset was used to link each registrant's name, date of birth and/or MCP (Medical Care Plan) number (which is a unique number assigned to each resident covered under the provincial medical care program) to determine vital status and when applicable, cause(s) of death as listed on death certificates. The years available for this dataset were 1991-2009. This data linkage was also available only for registrants who died while residing in NL. Additional and more detailed information on the development of the registry can be found in the official BVMR report¹⁵⁰.

The BVMR report provides detailed information on the development of the registry, as well as an overview of the data that were collected as part of registration, such as self-reported respiratory symptoms, and tobacco and alcohol consumption, all of which were obtained from the health and employment questionnaire. The report also provides information on the development of the job exposure matrix (which was performed by the author as part of

her role as a member of the BVMR project team) and the findings and an epidemiological evaluation of the asbestos-related diseases found in the registrants of the BVMR. The development of the BVMR and this thesis were approved by the Memorial University Human Research Ethics Authority.

1.5 Current Thesis

As a member of the BVMR project team, the author developed the JEM and conducted the exposure assessments as described in detail in Chapter 2 of this document. The author also performed the epidemiological analysis of disease incidence in the registrants of the BVMR, as discussed in the official report for the BVMR¹⁵⁰. For the current thesis, however, important changes were made to the methodology used in the epidemiological analysis and these are discussed in Chapter 3 of the thesis. Because the Registry contains data only on the former employees who voluntarily registered for the BVMR efforts were made by the author to obtain information on the remainder of the former workers of the Baie Verte asbestos mine, that is, people who did not register in the BVMR. This work was separate from the activities related to the construction of the BVMR and is described in detail in Chapter 4 of this thesis.

1.6 Conclusion

It is clear from the epidemiological evidence that all types of asbestos are capable of causing asbestosis, lung cancer, malignant mesothelioma, and other cancers. Although chrysotile may be less potent in this regard than the amphibole types, given the widespread use and continuing exposure to chrysotile in many countries around the world and the projections of a continuing epidemic of mesothelioma, a complete ban on the

production and use of chrysotile asbestos is warranted. However, proponents of chrysotile have succeeded in keeping it off the Rotterdam Convention's list of toxic substances, partly because of the continuing assertion that chrysotile can be used safely, thereby allowing the production and use of chrysotile to continue. One reason for the ongoing debate regarding the relative potency of the different fibre types is the lack of chrysotile exposed cohorts with quality exposure assessments that can be used in the risk assessment process. This is especially true of the chrysotile mining/milling industry since there have only been two cohorts of miners/millers used in the meta-analyses conducted by both Hodgson and Darnton²³ and Berman and Crump²⁶ - The Québec Miners/Millers and the Italian Miners/Millers. This has led to a reliance on the Québec data, since it is the only one of these two studies to have published a quantitative exposure assessment, and this has limited the ability of researchers to accurately assign potency estimates for chrysotile asbestos. Therefore, new studies from the chrysotile mining/milling industry, with high quality exposure assessments, are greatly needed to contribute to the debate on the relative potency of chrysotile asbestos and to aid in the risk assessment process, especially for exposure to lower levels of asbestos that are more typical of current workplaces. This thesis analyzes the results of one such study - the Baie Verte Chrysotile Miners and Millers. This cohort provides an opportunity to move away from the heavy reliance on the Quebec and Italian cohorts which, until now, have been on only sources of data on chrysotile-exposed miners and millers.

1.7 Study Objectives

The aim of the current research is to conduct a formal epidemiological analysis of the data collected by the BVMR that starts with the results generated for the BVMR report but goes well beyond it. This thesis will examine the relationship between chrysotile asbestos exposure and the occurrence of asbestos-related diseases in the group of former chrysotile miners/millers from Baie Verte, Newfoundland, Canada, both those who joined the Registry and those who did not. Because of the concern relating to the ongoing production and use of chrysotile asbestos in developing countries, the continued exposure of workers to asbestos in buildings, and the controversy in the scientific literature relating to the relative potency of the different fibre types, the results of this thesis can make a significant contribution to the literature on chrysotile asbestos toxicity in the mining/milling industry. Specifically, the objectives of this research are:

- 1) To report on the development of a quantitative JEM using historical air sampling records in order to conduct a retrospective exposure assessment for the cohort of former chrysotile miners/millers from Baie Verte, Newfoundland. The JEM has been used to estimate cumulative asbestos exposure for former workers for whom detailed work histories are available (i.e., those who are registered in the BVMR). The methodology used to develop the quantitative job exposure matrix will be described and will be compared to similar exposure assessments in the literature, specifically that of the other chrysotile mining/milling cohorts (i.e., the Québec chrysotile miners' cohort and the Italian chrysotile miners' cohort).

2) To evaluate the risk of asbestos-related disease in the cohort of former Baie Verte chrysotile miners/millers who registered with the BVMR, by comparing the incidence rates of asbestos-related diseases in this group to the rates of those diseases in the Canadian and Newfoundland populations. This research will also evaluate the exposure-response relationship between chrysotile asbestos exposure and the risk of developing asbestosis, lung cancer and colorectal cancer.

3) To enumerate the former workforce of asbestos miners/millers from Baie Verte, Newfoundland, from historical union records, which include both the registrants of the BVMR and those former workers who did not register in the BVMR. An epidemiological study was conducted on the larger group to assess the full health impact of the Baie Verte chrysotile asbestos mine/mill and to compare the results of the combined cohort study to the results of the registry-based study.

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Chapter 2.0: A retrospective exposure assessment for former chrysotile asbestos miners and millers from Baie Verte, NL.

2.0 Abstract

Introduction: The epidemiologic literature contains very few cohort studies of chrysotile asbestos miners/millers that include high-quality retrospective exposure assessments. This has limited the ability of meta-analyses to decipher the large differences between the risk of lung cancer reported by the various chrysotile-only cohort studies¹⁻³.

Objective: As part of the creation of the Baie Verte Miners' Registry (Baie Verte, NL, Canada) a two-dimensional job exposure matrix (JEM) was developed for the purpose of estimating asbestos exposures for former chrysotile asbestos miners/millers. The industrial hygiene data used in the creation of the JEM were first analyzed to assess their reliability for use in a retrospective exposure assessment.

Methods: To develop the JEM, two sources of industrial hygiene data were used that covered the years 1963-1994. For the 1963-1975 period, a report containing summary data (i.e., quarterly average fibre concentrations, f/ml) was used to calculate yearly average fibre levels for similar exposure groups (SEGs). For the 1976-1994 period, the results of approximately 7,000 airborne asbestos samples were used to calculate mean asbestos concentrations. These raw data (1976-1994) were evaluated to determine the goodness-of-fit to the lognormal distribution for each SEG. Also, personal sampling data from a government report from the summer of 1980 and data from the 1991-1994 time period were used to assess the between- and within-worker proportion of the total variance. Once the data was deemed to be sufficiently reliable, it was then used to design and implement a

job exposure matrix (JEM) which was linked to individual registrants' work histories to calculate cumulative asbestos exposure for each registrant.

Results: Mean exposures peaked in 1967-68 and then gradually decreased over time. Prior to 1976, exposures were greatest in the Pit, whereas in later years the highest exposures were in the Mill. The distribution for most SEGs (82.6%) could adequately be described as fitting a log-normal distribution although variability within SEGs often exceeded (55%) a geometric standard deviation (GSD) of 2.5. Furthermore, the between-worker portion of the total variance exceeded 20% in half of the job titles for which information was available.

Discussion: Overall, the data used to create similar exposure groups in the development of the JEM were deemed to be of adequate quality for estimating cumulative asbestos exposures for the former employees of the Baie Verte asbestos mine/mill. The variability between workers in the same job was often high and is an important factor to be considered when using estimates of cumulative asbestos exposure to adjudicate compensation claims. The exposures experienced in this cohort are comparable overall to those of other chrysotile asbestos miners/millers cohorts, specifically the Italian and Québec cohorts.

2.1 Introduction

It is well recognized that exposure to all forms of asbestos is associated with the development of a number of malignant and non-malignant diseases, most notably asbestosis, mesothelioma, and cancers of the lung⁴. Positive associations have also been observed between asbestos exposure and cancers of the pharynx, stomach and colorectum⁵. However, there is continuing debate regarding the relative potency of the various types of asbestos (i.e., chrysotile as opposed to amphibole asbestos fibres) in the causation of lung cancer and mesothelioma. To address this debate, a number of meta-analyses^{1-3,6} have attempted to elucidate the potency factors, for lung cancer and mesothelioma, associated with exposure to the different forms of asbestos fibres. Data from epidemiological studies of workers exposed primarily to crocidolite, amosite, chrysotile, or to mixed fibres, in various asbestos industries (i.e., textile, mining/milling, friction products, cement products and insulation) have been used in these risk assessments. However, in order to assess the relationship between chrysotile asbestos exposure and disease risk, these studies have relied mainly on the quantitative exposure assessment of a single cohort, the Quebec miners' cohort⁷. This has limited the evaluation of the risk of asbestos-related diseases in workers exposed to chrysotile asbestos only, especially with respect to industry type.

Generally, there has been an overall lack of studies on chrysotile miners/millers with the existing literature consisting primarily of studies of the Québec cohort, of an Italian cohort, and more recently of a Chinese cohort of chrysotile miners/millers⁸⁻¹¹. Furthermore, the published reports on these studies do not contain sufficient information to be able to

evaluate the quality of the data used in the exposure assessment process and to draw conclusions regarding the reliability of the resulting exposure estimates that are often used for epidemiologic or compensation purposes.

The aim of this study is to describe the exposure patterns of a group of former chrysotile miners/millers, from Baie Verte, Newfoundland, Canada. It will also describe the methods used for reconstructing historical exposures, that is the development of a job exposure matrix (JEM) for this group of workers, taking into account job tasks, control measures and process changes, and will use a number of statistical techniques to evaluate the quality of the data used to develop the exposure estimates.

2.2 Materials and Methods

2.21 Baie Verte Miners Registry

The chrysotile asbestos mine/mill in Baie Verte Newfoundland, Canada, began its activities in the mid-late 1950s and started commercial operations in 1963. Production of asbestos continued for 31 years until the mine's final closure in 1994. In 2008, the Baie Verte Miners' Registry (BVMR) was established as a joint effort between the provincial Workplace Health, Safety and Compensation Commission, Memorial University of Newfoundland, and the United Steelworkers Union of Canada. The purpose of the BVMR was to enroll as many of the former employees of the Baie Verte asbestos mine as possible and to gather information regarding their vital status, employment history, medical history, and current health status, in order to assist them and the provincial workers' compensation board in the compensation process. One of the key elements of the BVMR was to perform a retrospective exposure assessment using historical industrial hygiene data obtained from

government, company and union records in order to estimate each subject's cumulative asbestos exposure. The details of the BVMR are described elsewhere¹².

2.22 Exposure Assessment

In order to estimate individual cumulative asbestos exposure, average asbestos concentrations for each job title and time period had to be calculated. This was done using a two-dimensional Job Exposure Matrix (JEM)^d which was developed to provide quantitative estimates of average fibre concentrations by job title and time period (Table 2-1). The methods used to develop the JEM and to assess each registrant's exposure generally followed the standard approach as proposed by Seixas and Checkoway¹³ as well as the Environmental Protection Agency's (EPA) "Guidelines for Statistical Analysis of Occupational Exposure Data"¹⁴.

Table 2-1: Excerpt of the JEM (f/ml by job title and year) for 4 of the 52 Similar Exposure Groups (SEGs).

Job Title	Job Code	1963-1966	1967-1968	1969-1971	1972-1974	1975	1976-1979	1980-1984	1985-1989	1990-1994
Primary Crusher Operator	M-01	26.5	56.5	21.5	14.5	4.0	1.93	0.45	0.45	0.45
Primary Crusher Attendant/Helper	M-02	26.5	56.5	21.5	14.5	4.0	2.90	1.09	1.09	1.09
Secondary Crusher Operator	M-10	26.5	56.5	21.5	14.5	4.0	1.42	1.42	1.42	1.42
Dryer Operator	M-11	26.5	56.5	21.5	14.5	4.0	2.18	1.19	1.88	1.88
Etc.										

^d A **job exposure matrix (JEM)** is a tool used to assess exposure to potential health hazards in occupational epidemiology studies. The JEM comprises different levels of exposure to workplace hazards (e.g., asbestos) for specific job titles and provides a systematic means of converting coded occupational data (i.e. job titles) into groupings of possible exposures, precluding the need to assess each individual's exposure in detail. Kauppinen, T.P., Mutanen, P.O., and Seitsamo, J.T. (1992). "Magnitude of misclassification bias when using a job-exposure matrix." **Scan J Work** 18(2): 105-112.

The BVMR's exposure assessment utilized two separate sources of industrial hygiene data. One source of data was from a study done at the mine in the early 1980s¹⁵ that used industrial hygiene samples collected by company and union representatives from 1966 to 1975 using the historical midjet impinger method as well as a smaller number of samples that were collected from 1975 to 1980 using the membrane filter method¹⁶. The other source contained the results of airborne asbestos samples that were collected at the worksite from 1976-1994 using the National Institute for Occupational Safety and Health (NIOSH 7400) membrane filter method¹⁷. These sources will be described below. Detailed employment history was obtained for each registrant as part of the BVMR and used in conjunction with the JEM to calculate estimates of cumulative asbestos exposure.

2.23 Industrial Hygiene Data: 1976-1994

Data for the time period 1976-1994 were obtained from monthly lists of routine air sampling results that were provided to the author by the national office of the United Steel Workers (USW) of Canada. Data from approximately 7,000 personal and stationary samples^e collected by the company, union and government were extracted, entered into a spreadsheet, and reviewed for quality. The data were organized according to the job title and job code of the individual wearing the sampling device, the department of the mine/mill where that individual worked, the year the sample was collected, and any other pertinent information contained in these records. All air sampling done in the years 1976-1994 was collected using the membrane filter method in which sampling was typically

^e Personal samples are collected using a portable sampling pump and collection media that are attached to a worker's shirt or jacket collar and collects a sample of air from the worker's breathing zone. The sample result is representative of that individual's exposure. A stationary sample, on the other hand, is collected in a general area where work is taking place and represents the concentration of a contaminant in that area (i.e., source emission).

performed at a flow rate of 2 L/min for one to two hours. Fibre counting was done according to NIOSH analytical method 7400.

In addition, personal sampling data (n = 900) from an intensive four-month government study carried out in 1980¹⁸ as well as personal sampling data from company records for the years 1991-1994, were used to estimate the between-worker and within-worker components of variance for various job titles. These datasets contained repeated samples for multiple identified workers, allowing for the calculation of the components of variance in the exposure data using ANOVA techniques.

2.24 *Similar Exposure Groups*

Similar exposure groups (SEGs) are commonly used in the occupational exposure assessment process (and thus, in JEMs) to predict the exposure of groups of workers to the agent being studied rather than having to try to produce estimates for every individual. SEGs are defined as groups of workers having the same general exposure profile because of the similarity of the nature and frequency of the tasks they perform, the material and processes with which they work and the similarity of the way they perform those tasks¹⁹. In this study, SEGs were defined according to job title and department and were used to define one of the axes of the JEM (see Table 2-1). The other axis of the JEM was time period which is an important factor because of airborne asbestos concentrations decreased over time as various control measures were implemented.

SEGs were developed by grouping sampling data by the job codes found in the union's records which specified both the department and the job title for which the sample was taken. This was used to construct the vertical axis of the JEM. Sampling data were also

coded according to the year in which the sample was taken. Yearly average asbestos concentrations were calculated for each department and were examined graphically to identify groups of consecutive years that appeared to be similar in terms of exposure. These were then grouped into “year categories” which comprised the horizontal axis of the JEM. This grouping of years was supported by an evaluation of the timeline of changes relating to technology and control measures introduced to the mine/mill processes (Table 2-2), that was developed from interviews with former employees as well as from historical records detailing technological changes, control measures, and production changes. It was also supported by comparing the departmental yearly averages using a one-way ANOVA to ascertain the adequacy of the assigned year categories as predictors of exposure. Nine “year categories” were defined covering the years 1963-1994.

Table 2-2: Process changes and control measures at the Baie Verte asbestos mine/mill.

Year	Control Measures
1964	Drills used in Pit fitted with dust collectors.
1970	Jute bags replaced with reinforced plastic film bags in packaging area; vacuum system installed in crusher/dryer building system.
1972	Installation of ventilation in secondary crusher/dryer building to bring in outside air.
1973	Dust masks made available to all workers.
1975	Vacuum tables set up in mill for screen repair, and at the dock for pallet repair.
1976	Replacement of dust control equipment on paddle trammels; water added to tailings conveyor system to reduce dust emissions.
1978-1980	14 week worker strike; baghouse in secondary crusher/dryer building completed; automatic bag opener and refeed system installed in packaging area; car wash introduced; mobile lunch rooms; pressurized cabs for tractor operators; dedusters added to tailings system to recover fibres lost to tailings; mine dry constructed with showers, double lockers and a change house; dust control system added to dry rock storage building.
1988	Construction of wet mill begins.
1990-1994	Wet methods used in processing of tailings.

Personal samples were available for almost all the job titles found at the mine/mill and were used rather than stationary samples in the assignment of exposure estimates for the SEGs as they are more representative of worker exposure. The only exception was the “Stevedore” job title for which stationary data were used since no personal samples were available. The lack of personal samples for this job title is likely due to the fact that stevedores were, for many of the years that the mine/mill was in operation, employees of an outside contracting company rather than of the mine and were not members of the union. Other job titles for which little or no sampling data were obtained (i.e., no personal samples or relevant stationary samples) were grouped with job titles that were deemed similar in terms of their physical location within the workplace and the tasks that were performed, according to the detailed job descriptions found in the records provided by the union. For example, there were only four personal samples available for “Utility Painter”; therefore, this job title was grouped with “Labourer” since these jobs were similar with respect to their mobility in and around the mill site.

To create the SEGs, the data for job titles that were considered to be similar were evaluated using independent sample t-tests to statistically compare average exposures by year category to ensure the adequacy of each grouping. For example, the exposure for the job titles “Blaster” and “Blaster Helper” was not significantly different in year category 6 (‘Blaster’ mean = 0.44 f/ml; ‘Blaster Helper’ mean = 0.84 f/ml; $p = 0.37$), or in year category 7 (‘Blaster’ mean = 0.25 f/ml; ‘Blaster Helper’ mean = 0.35 f/ml; $p = 0.42$) or in year category 8 (‘Blaster’ mean = 0.17 f/ml; ‘Blaster Helper’ mean = 0.24 f/ml; $p = 0.17$). Accordingly, they were combined. Also, some job titles were sub-divided according to the

area within the department where the samples were collected. For example, “Forklift Operator” was separated into two SEGs - “Mill Forklift Operator” and “Warehouse Forklift Operator.” Independent sample t-tests were also used to compare the mean asbestos concentrations in adjacent year categories within SEGs and when the means were not significantly different the adjacent year categories were combined.

Finally, departmental exposure estimates were calculated in order to assign exposure values for subjects whose work history records indicated the department worked but did not specify a particular job title. In this case, average concentrations were calculated for each year category and were listed in the JEM as “Unknown” job title within each department. A brief description of the departments can be found in Table 2-3.

Table 2-3: Departments, process descriptions and number of SEGs at the Baie Verte Asbestos mine/mill.

Department	No. Personal Samples	No. SEGs	Description
Mill (M)	2778	23	Primary and secondary crushing of ore; drying of crushed material and storage while awaiting processing, screening, and packaging; workers exposed to dust in ambient air in all areas of the mill.
Pit (P)	445	12	Open pit mine; ore blasted from bench and transported with shovels and loaders; workers exposed to dust in ambient air from drilling and tailings.
Erection & Repair (E&R)	1118	12	Maintenance of vehicles, garage, cleaning of vehicles; workers exposed to dust in ambient air and from vehicles.
Employee Relations (EmpRel)	73	1	Laundry services and janitorial services; this department was located in a separate building; workers exposed to dust on clothes during laundry duties and in ambient air.
Office Services (OS)	41	1	Stores; located in E&R building, kept parts and materials needed for operation; exposed to dust in ambient air
Quality Control (QC)	289	2	Testing fibre grades; laboratory located in mill; workers exposed to dust in handling and collecting of raw material and in ambient air.
Office	29	1	Office employees, located in various offices around mill, pit and E&R; workers exposed dust in ambient air
Total	4773	52	

The resulting JEM contained SEGs along the vertical axis and calendar period (year categories) along the horizontal axis. 52 SEGs were created encompassing seven departments within the mine/mill complex and nine year categories, resulting in 468 cells in the JEM. The JEM was entered into an SPSS syntax file and linked to the work history records of each registrant through the job code and year category fields. A time-weighted estimate of exposure was calculated based on the job code and year category found in each record of an subject's work history. The exposure estimates for all the work history records for each person were then summed generating a cumulative exposure estimate for each person based on his/her specific job history.

2.25 Industrial Hygiene Data: 1963-1975

Industrial hygiene samples taken in the 1960s and 70s by company and government sources were done using the midget impinger method. Edstrom describes, in an unpublished study (1981), how these data were collected and analysed¹⁵. He also describes the different conversion factors that were developed for various areas of the mine/mill complex^f in order to convert dust and fibre measurements, using the midget impinger method, to fibre counts (f/ml) for each location^{15, 16}. Unfortunately, the raw data used by Edstrom for the 1963-1975 time period could not be located. However, the average quarterly asbestos concentrations calculated for various locations in the mine/mill complex were obtained from Edstrom's 1981 report¹⁵ and were used to estimate exposures for this study. According to that report, stationary samples were used to calculate average fibre concentrations in numerous areas of the mine/mill in conjunction with estimates of

^f The areas of the mine/mill complex included: the pit, crusher, dryer, screens, refining (trommels), bagging, erection and repair, warehouse, quality control, tailings cabin, and other (lunchroom, offices, car wash).

the amount of time workers in each job title spent in these various areas. This information was then used to calculate an area/time specific estimate of exposure for the different job titles for each quarter-year from 1963 through 1975. These quarterly averages were used in the current study to calculate yearly averages for the period from 1963 to 1975.

2.26 Data Analysis

To validate the grouping of exposure data into SEGs, the lognormal distribution model was used²⁰. In this model, it is presumed that the underlying distribution for workplace exposure data is the lognormal distribution. This assumption was verified for each SEG using the raw data from 1976-1994 and the statistical tool created by the American Industrial Hygiene Association (AIHA) for the evaluation of occupational exposure data (IHStat™)²⁰, as well as SPSS. Log-transformed data for each SEG were analyzed for goodness of fit to the log-normal distribution using both the Kolmogorov-Smirnov and the Shapiro-Wilk tests of normality. Cumulative probability plots and frequency histograms were generated and were used to visually inspect the data for log-normality. Descriptive statistics, including arithmetic means (calculated by the Minimum Variance Unbiased Estimate), geometric standard deviations (GSD), and Land's Exact 95% confidence intervals were generated for each SEG for each year category.

For SEGs that were found to have a bimodal distribution^g (through examination of the frequency histogram) non-parametric measures were used to estimate exposure rather than the arithmetic mean. Sensitivity analyses were conducted to determine the hypothetical difference in cumulative exposure estimates for workers in these job titles,

^g A bimodal distribution is a continuous probability distribution with two different modes that appear as distinct peaks in the probability density function.

depending on which of the two exposure scenarios was used to assign a value to the JEM. Also, the data from both the 1981 government report¹⁸ and the 1991-1994 documents were used to apportion the between-worker and within-worker variance using the ANOVA methods outlined by the publication “Testing compliance with occupational exposure limits for airborne substances”²¹.

For the years 1976-1980, data were available from both of the sources of industrial hygiene data described earlier. These overlapping data were used to analyze the relationship between the two datasets in an attempt to evaluate the reliability of the summary data that were used to estimate the earlier exposures (1963-1975). A linear regression model was used on the paired yearly averages (1976-1980) from the two datasets to calculate the slope and intercept of the regression line. We also calculated the coefficient of determination (R^2) to ascertain the proportion of variability in the data that is accounted for by the linear regression model.

2.3 Results

2.31 SEGs

The total number of SEGs was 52. The data for most SEGs ($n=43$) could be adequately described as fitting a lognormal distribution while a small number of exposure groups ($n=6$) fit a normal distribution. Geometric standard deviations (GSD) ranged from 1.74 (“Forklift Operator-Warehouse”) to 5.61 (“Senior Tester”), with 45% of the GSDs falling below 2.5, 35% between 2.5 and 3.0, 16% between 3.0 and 4.0, and 4% over 4.0. The vast majority of the GSDs in the Mill (92%) were below 3.0, while the Pit had 35% of its GSDs between 3.0 and 4.0, indicating more variation in exposure within SEGs in the Pit than in

the Mill. This may be due to the effect of weather on the dust levels in the Pit or to the variability of the amount of asbestos in the ore.

Sample size was also used to evaluate the quality of the cells in the JEM based on criteria described in the EPA document¹⁴ and the AIHA document¹⁹. These documents suggest that six random measurements is the minimum required to judge the exposure acceptability of a SEG, 10 measurements will provide a reasonable approximation of the exposure distribution, and at least 30 measurements are needed to conduct rigorous goodness-of-fit testing. Cells with less than six samples for an SEG (i.e., for each time period, or cell of the JEM) were considered to be “poor” quality, 6-10 samples “fair”, 11-29 samples “good” and cells with more than 30 samples were considered to be “very good”¹⁹. That is, if an SEG had more than 30 samples for a specific time period, then that cell in the JEM would be considered to be of “very good quality” from a statistical perspective. On the other hand, if there were fewer than 6 samples available, the data in this JEM cell would be considered to be of “poor” quality.

Overall, a large proportion (89.8%) of the cells in the JEM was found to qualify as “good” or “very good” quality (Table 2-4), whereas only 1% of all cells would be considered “poor” quality. Also, there were only minimal differences across departments with respect to the percentage of cells that fell into the “good” and “very good” categories, ranging from 77.7% (QC) to 95.8% (E&R).

Table 2-4: Evaluation of the quality of the cells in the JEM for each department of the Baie Verte asbestos mine/mill complex.

Department	≤ 6 samples/cell “Poor”	> 6 and ≤ 10 samples/cell “Fair”	> 10 and ≤ 30 samples/cell “Good”	> 30 samples/cell “Very Good”	Total # of Cells
Mill	---	4 (8.2%)	14 (28.6%)	31 (63.3%)	49
E&R	---	1 (4.2%)	11 (45.8%)	12 (50.0%)	24
Pit	1 (6.35%)	2 (12.5%)	8 (50.0%)	5 (31.35%)	16
QC, OS & EmpRel	---	2 (22.2%)	4 (44.4%)	3 (33.3%)	9
Overall	1 (1.0%)	9 (9.2%)	37 (37.8%)	51 (52.0%)	98

Three job titles (“Primary Crusher Attendant”, “Service Truck Driver”, and Dry Rock Storage Attendant”) were found to be represented by a bimodal distribution, rather than a lognormal or normal distribution, for at least one of the defined year categories. For example, Figure 2-1 shows the frequency distribution for “Primary Crusher Attendant”. The data for this group was split into its two frequency distributions and analyzed separately. As shown in Table 2-5, the values that would be assigned to the cell of the JEM vary considerably depending on which of the two frequency distributions is used. If the lower peak is used, the value in the JEM would be 0.08 f/ml. This would mean that a person who spent 10 years during this time period working as a Primary Crusher Attendant would be assigned a cumulative asbestos exposure of 0.8 fibre-years/ml (i.e., 0.08 f/ml X 10 years = 0.8 f/ml-yrs). On the other hand, if we assign the value associated with the second peak (1.31 f/ml), the same person would be given a cumulative exposure of 13.1 fibre-years/ml, which is over 16 times greater than if we used the mean of the lower peak. In this case, taking into consideration the number of samples associated with each distribution (8 versus 12) and the exposure estimates for the year categories

immediately before and after the time period in question, the higher peak was used to assign the value to the JEM. The same assumptions were made for the “Service Truck Driver” and “Dry Rock Storage Attendant” SEGs for which the lower peaks also contained small sample sizes ($n=6$ and $n=4$, respectively).

Figure 2-1: Frequency distribution and cumulative probability plot for “Primary Crusher Attendant”, for the years 1980-1984, showing bimodality of the frequency distribution.

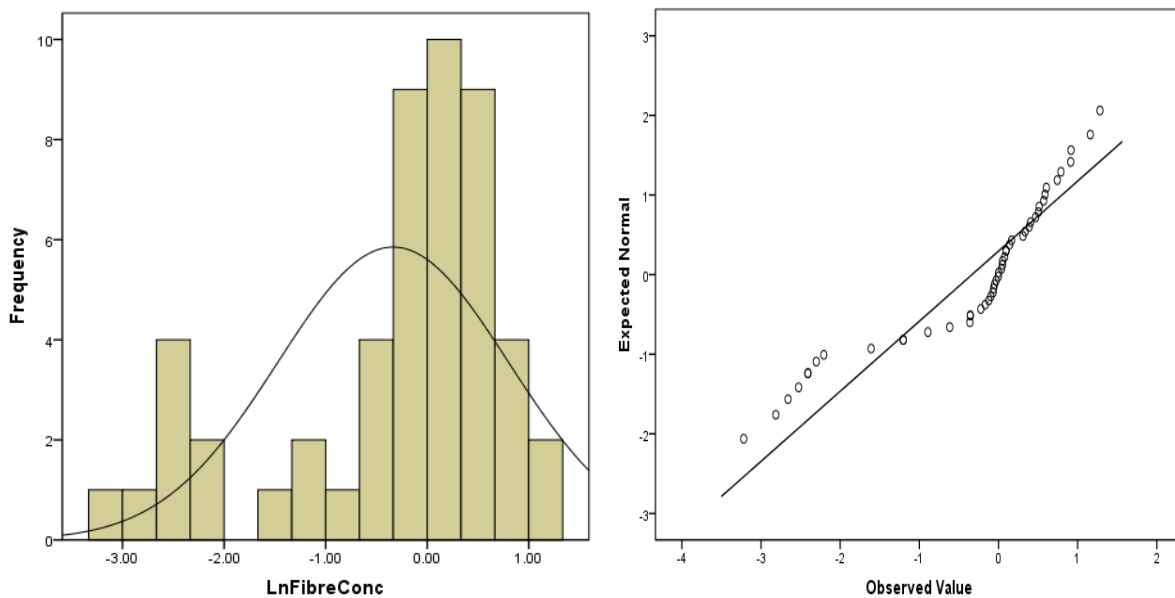


Table 2-5: Descriptive statistics for the two frequency distributions of Primary Crusher Attendant for the year category 6.

Statistic	Peak 1 (n=8)	Peak 2 (n=42)
Mean (f/ml)	0.08 (0.07 – 0.10)	1.31 (1.12 – 1.58)
Log Normal	Yes	Yes
GM	0.08	1.09
GSD	1.39	1.83
95 th Percentile	0.13	2.96
Median	0.09	1.07
Mode	0.09	1.00 - 1.50
JEM value (f/ml)	0.08	1.31

2.32 Exposure: 1963-1975

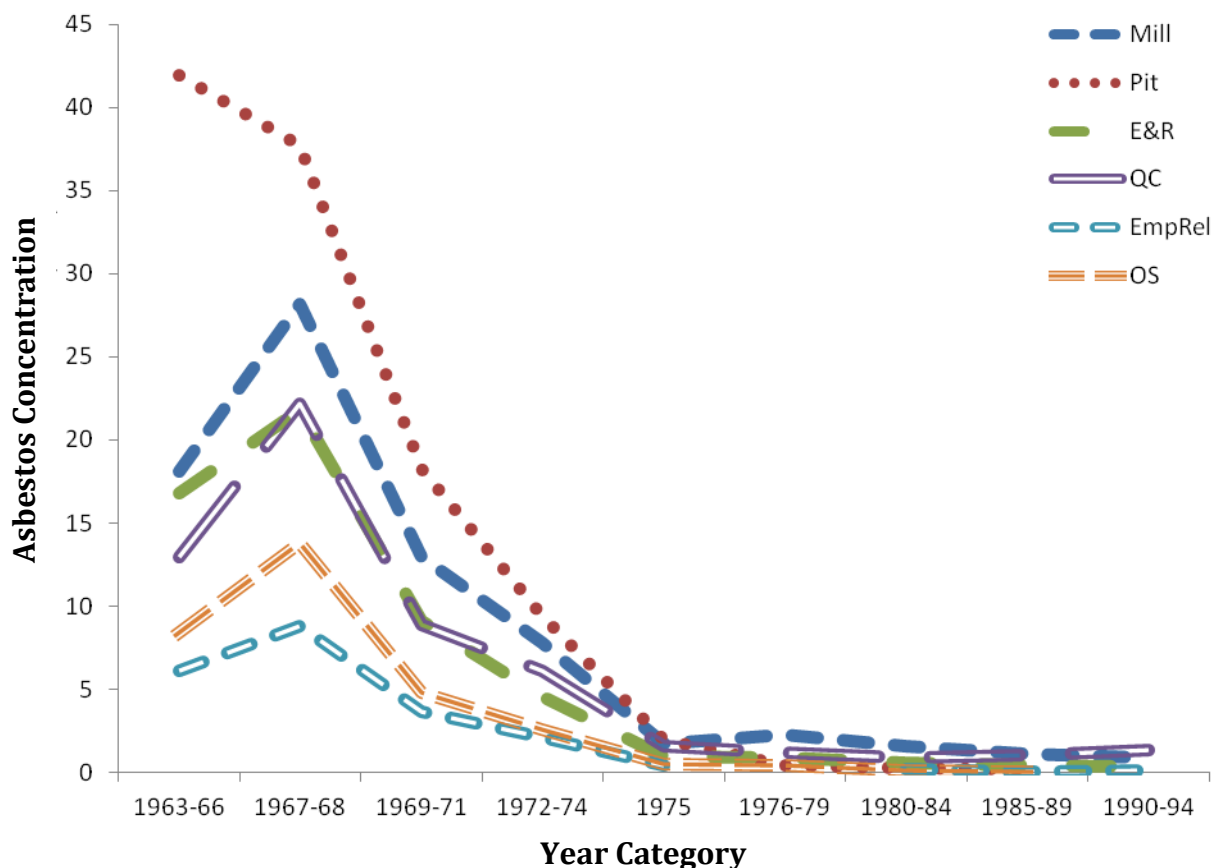
According to the data that were extracted from the 1981 Edstrom report, the highest exposures in the 1963-1975 time period were for the jobs “Shuttle Operator”, “Primary Crusher Operator”, “Dryer Operator”, “Secondary Crusher Operator” and “Dry Rock Storage Attendant”. All of these jobs were located in the mill. These jobs had an average exposure of 66.55 f/ml at their peak in 1968. Overall, exposure during these years was highest in the Pit (Table 2-6) and lowest in the Employee Relations department. Exposures in all departments peaked during 1967-1968 and gradually decreased over time (Figure 2-2). This pattern can be attributed to the refinement of the process and increased production in the early years, followed by the implementation of control measures (Table 2-2) in the mine/mill in the later years, particularly in the wake of the Selikoff report and the strike, which combined to reduce the airborne concentrations of asbestos fibres.

Table 2-6: Average fibre concentration (f/ml) by department for all year categories.

Dept	1963-66*	1967-68*	1969-71*	1972-74*	1975*	1976-79	1980-84	1985-90	1991-94
Mill	18.13	28.17	12.94	7.83	1.76	2.24 (1.90-2.58)	1.55 (1.45-1.65)	1.11 (1.04-1.19)	0.89 (0.77-1.02)
Pit	41.90	37.74	18.29	9.40	1.93	0.43 (0.32-0.54)	0.28 (0.23-0.33)	0.23 (0.17-0.29)	---
E&R	16.81	21.80	9.12	4.55	0.94	0.85 (0.63-1.08)	0.59 (0.50-0.68)	0.46 (0.40-0.52)	0.37 (0.31-0.45)
QC	12.99	22.19	8.87	6.12	1.56	1.17 (0.65-1.69)	0.91 (0.68-1.15)	1.03 (0.73-1.33)	1.32 (0.45-2.19)
Emp Rel	6.12	8.81	3.69	2.15	0.44	---	0.16 (0.08-0.23)	0.06 (0.04-0.08)	0.09 (0.06-0.12)
OS	8.45	13.81	4.78	2.60	0.50	0.46 (0.16-0.76)	0.14 (0.07-0.21)	0.04 (0.02-0.06)	---

* 95% confidence intervals are not given for the years 1963-1975 since raw data were not available.

Figure 2-2: Yearly average concentration of asbestos fibres, 1963-1994, in the various departments of the Baie Verte mine/mill complex.

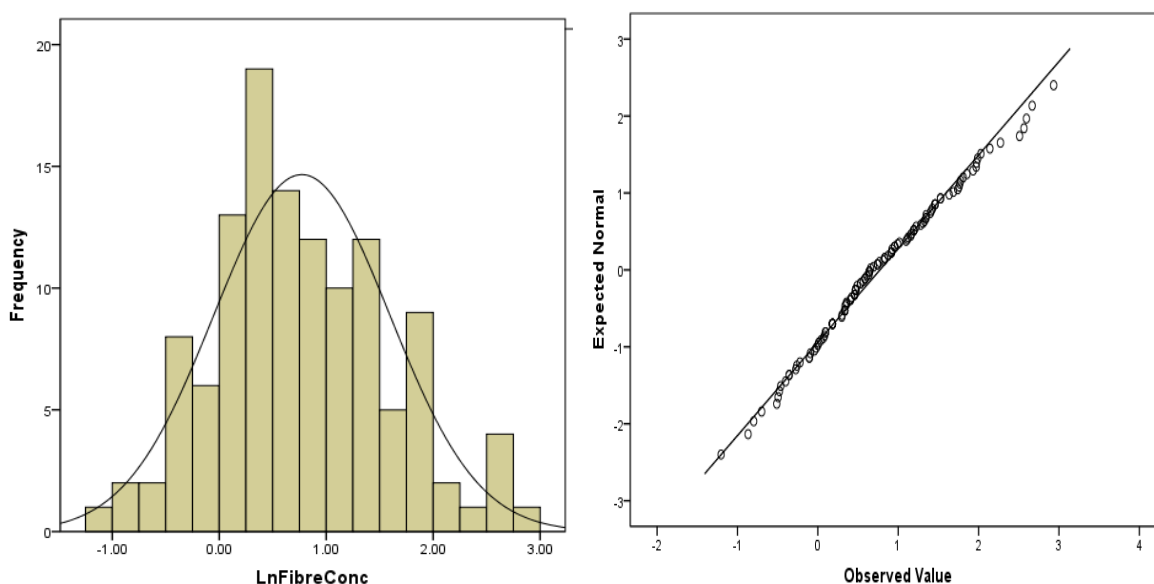


2.33 Exposure: 1976-1994

Generally, exposures decreased over time in all departments of the mine/mill complex (Figure 2-2) and airborne concentrations of asbestos varied considerably between SEGs and departments over the entire period (Table 2-6). The SEG with the highest exposures during the 1976-1994 time period was “Dry Rock Storage Attendant” with an overall average exposure of 3.19 f/ml, and a maximum exposure of 18.8 f/ml in 1980. This job was responsible for regulating the flow of ore between the dry rock storage area (where ore was stored after it had been dried) and the mill. The average yearly concentration of

asbestos fibres for this SEG ranged from 7.45 f/ml in 1976 to 1.76 f/ml in 1990. Figure 3 shows the frequency distribution and cumulative probability plot of the log-transformed data for “Dry Rock Storage Attendant”. These graphs demonstrate the goodness-of-fit of the log-transformed data to the lognormal distribution. The lowest exposed job during the time period 1976-1994 was “Backhoe Operator” in the Pit department. The average exposure for this SEG was 0.08 f/ml with a maximum of 0.26 f/ml in 1982. The exposure for this SEG did not change much over the years, with an average exposure of 0.05 f/ml in 1982 and 0.065 f/ml in 1990.

Figure 2-3: Frequency distribution and cumulative probability plot for "Dry Rock Storage Attendant", for the years 1980-1984, demonstrating the goodness-of-fit to the lognormal distribution.



2.34 Components of Variance

The analysis of the between- and within-worker variance was used to evaluate the reliability of the use of job titles in the creation of the SEGs by comparing the exposure

variability of individual workers with the exposure variability of an overall SEG. Groups with less than 20% between-worker variability are considered to be adequately representative of the exposure experienced by all members of that particular group, and so the value assigned to the JEM is considered to be appropriate for all workers within that SEG¹⁹. On the other hand, SEGs with more than 20% between worker variability can be indicative of dissimilar exposures amongst members of that group (e.g., one or more workers' exposure is significantly higher or lower than the rest of the group) and the value assigned to the JEM will likely underestimate some workers' exposure and overestimate that of others.

Overall, the SEGs in the Mill department were the most consistent, with 11 of the 20 SEGs analyzed having less than 20% between worker-variability while the remaining nine SEGs ranged from 21% ("Dry Rock Storage Attendant") to 74% ("Janitor"). In the E&R department seven of 13 SEGs had less than 20%, with the others ranging from 27% ("Mechanic") to 99% ("Mobile Equipment Operator"). On the other hand, only two of seven jobs in the Pit satisfy this criterion with the remaining five SEGs ranging between 31% ("Shovel/Loader Operator") and 84% (Labourer"). This is consistent with the fact that most of the SEGs in the Mill department had GSDs < 3.0 (92%), while 35% of SEGs in the Pit department had GSDs > 3 thus indicating more variation.

The high between-worker variance found for some SEGs may be explained in some cases by the small number of samples available for analysis (i.e., a small number of workers in the SEG and/or few repeated samples per person). For example, "Mobile Equipment Operator" in the E&R department, which had 99% between-worker variance, had repeated

samples for only two people, and one of those people had only two samples and the other had four samples. In other cases, the SEG contained jobs that were very mobile within the mine/mill complex (e.g. “Labourer” in the Pit) and, therefore, exposures would have varied considerably between workers depending on where within the complex they were working when a sample was collected. Furthermore, the amount of between-worker variance was significantly different in the two datasets used (1980 versus 1990s) for some SEGs. For instance, the percentage of between-worker variance was 67% for “Plant Millwright” in the 1980 data but was found to be 0% in the 1990 data. This may be explained by the fact that the 1980 dataset included multiple intra-shift samples that were carried out over the duration of a shift (and therefore likely to be more representative of true exposure), whereas the 1990 data consisted of sample results that were only one to two hours in duration and did not cover a full shift.

Overall, the use of job titles to create SEGs and, thus, for the estimation of individual exposures, appears to be appropriate for most job titles at the Baie Verte mine/mill. However, for those SEGs for which the between-worker variance was greater than 20%, care should be taken, especially for the purposes of adjudicating compensation claims, since the value in the JEM may not be representative of the exposure of everyone in that group.

2.35 Correlation between the two data sources (1976-1980)

Using a linear statistical model to evaluate the degree of agreement between the two industrial hygiene data sources used in this study (i.e., for the five years when there was overlap of the two), we found that the intercept of the regression line was not

significantly different from zero and was therefore dropped from the regression model. The inclusion of an intercept did not make a significant difference in the amount of variance explained by the model as demonstrated by values of the coefficient of determination (R^2) (Table 2-7). In this table, the variable x defines exposure estimates as calculated using the earlier dataset (1963-1980) and y defines the data derived from the later dataset (1976-1994). The regression equations show that Edstrom's exposure estimates are consistently lower than that of the later dataset. For example, overall the later estimates are 1.91 times higher than that of the estimates derived from Edstrom's data. In the Mill department the later exposure estimates are almost twice that of Edstrom's while in the Pit they are only 1.24 times the earlier values. In each of the departments, except the Mill, the 95% confidence intervals around the mean value did not include 0. However, in the Mill, the confidence intervals around the individual predicted values did include 0 and, therefore, when using these values in a JEM to estimate individuals' exposure values, the individual predicted values may be more appropriate.

Table 2-7: Regression equations by department with and without the intercept.

Department	Equation (with intercept)	R^2 (without intercept)	Equation (without intercept)	R^2 (with intercept)
Overall	$y=1.86x + 0.04$	0.38	$y=1.91x$	0.38
Mill	$y=1.63x + 0.41$	0.29	$y=1.99x$	0.27
E&R	$y=1.16x + 0.20$	0.32	$y=1.47x$	0.36
Pit	$y=1.07x + 0.07$	0.12	$y=1.24x$	0.12

2.4 Discussion

The development of the Baie Verte Miners' Registry has made possible the investigation of the exposures experienced by the former workers of the Baie Verte chrysotile mine/mill that operated from 1963 to 1994. The development of the JEM was one of the first steps required in the retrospective exposure assessment and was instrumental in the estimation of cumulative asbestos exposures for the BVMR.

It is important to examine the reliability of the exposure estimates used in a JEM as a way of considering the possible sources of bias in the data and the potential for exposure misclassification. To assess the quality of such estimates, three factors based on criteria established by recognized organizations^{14,19,20}, were used in this study, to ascertain whether the estimates are of high enough quality to be reliable. The factors considered were: the number of samples used to compute the means for each cell in the JEM; the goodness-of-fit of the exposure distributions of the SEGs to the lognormal distribution; and the proportion of between-worker variability in the SEGs. From the point of view of sample size, we found that 89% of the cells in the JEM had a sufficient number of samples to be considered either "good" or "very good" quality to make a reasonable judgement of the exposure distributions of the SEGs. As for the goodness-of-fit testing, we were able to ascertain that job title was an appropriate grouping mechanism for the creation of SEGs. This was true for almost all of the SEGs with the exception of a few whose frequency distributions were found to be bimodal (i.e., "Primary Crusher Attendant", Service Truck Driver", and "Dry Rock Storage Attendant"). In these cases the upper peak was used to assign an estimate to the JEM, which therefore represents a reasonable worst case scenario

for these SEGs. Finally, by evaluating the descriptive statistics for each SEG (i.e., measures of variation - GSD), and by assessing the components of variance (within- and between-worker components of variance) we have a better understanding of the limitations of the exposure data for certain SEGs and/or for some of the departments (i.e., the Pit) where exposures were more variable. These limitations must be considered when estimates of individuals' cumulative exposure are used to adjudicate compensation claims because exposures may have varied significantly in certain jobs and/or departments (e.g., "Senior Tester", GSD = 5.61). The potential misclassification of individuals with respect to exposure may, as we will see in Chapter 3, also affect the results of an epidemiological study on this group of former asbestos workers.

For the period prior to 1976, we have not been able to provide an equally rigorous evaluation of the quality of the exposure estimates because we were unable to obtain the original raw sampling data. However, using a limited amount of overlapping data from the 1976-1980 period, we found that the mean exposure levels estimated by Edstrom were consistently lower than those in the 1976-1994 dataset. It is possible that Edstrom underestimated the exposure values, at least for the period prior to the mid-1970s when exposures in the mine/mill complex began to drop. The difference seen between the two data sets for 1976-1980 may be partially accounted for by the fact that Edstrom used stationary samples to estimate exposure while the later dataset consisted of personal samples which are more representative of actual worker exposure. This is most likely to be an issue in cases where asbestos fibres are actually being disturbed (e.g., bagging of asbestos fibres) because the concentration of asbestos fibres in the breathing zone of the worker may be much higher than what is captured by a stationary sampling device.

However, the reverse may also be true if a stationary sample is placed in an area where high levels of asbestos are found but where workers did not actually work. In this case, these samples would overestimate workers' exposure.

Another limitation of the Edstrom dataset is that it was developed using conversion factors to convert measurements of total airborne dust particles and fibres (reported in mppcf and mfpcf, respectively, and measured with the midget impinger method) into airborne fibre measurements (reported in f/ml). This conversion is common in epidemiological studies of asbestos that utilize historical industrial hygiene data and can introduce systematic bias into a study because of the uncertainty associated with the conversion factor(s). This approach may lead to exposure misclassification and can bias the results of an exposure-response analysis towards the null hypothesis thus masking the true effect of asbestos exposure on the health outcome²². This type of bias is especially profound in studies that utilize a general conversion factor for all areas of the workplace. Edstrom, however, developed area-specific conversion factors for the Baie Verte mine/mill, thus reducing the amount of uncertainty associated with the conversion process. Furthermore, because cumulative exposure is calculated in the same manner for both diseased and non-diseased subjects, any exposure misclassification due to underestimation of exposure in the earlier time period would be non-differential in nature and would tend to bias the results of an epidemiological study of exposure-response towards the null hypothesis.

A further potential limitation of occupational exposure data is the bias that may be introduced by the sampling strategy employed by the person or group conducting the sampling. For example, the sampling strategy used by union, worker, or government

representatives might be to capture the worst-case exposure scenarios. Therefore, results of this type of sampling may overestimate the true exposure. On the other hand, sampling conducted by a company representative might seek to capture best-case scenarios and this may underestimate true exposure. In the current study, sampling data retrieved from the union records contained data from all three sources (i.e., company, union, and government) and are, therefore, likely to have captured all possible exposure scenarios, thus reducing the overall amount of bias involved.

If we compare the exposures calculated in the present study for the early years of the mine's operation to those reported in the literature for other chrysotile mining/milling cohorts, we find that our estimates fall somewhere in the middle. Rubino²³ reported on the exposures of a chrysotile mining cohort from Balangero, Italy. Table 2-8 presents average exposures for both the Italian and the Baie Verte cohorts for two periods, 1961-1970 and 1971-1975. This table shows that, for the drilling and crushing processes, the exposures in the Balangero study are lower for both time periods than our data while the reverse is true for the bagging process. For the fibre separation processes, the estimates are very similar.

Table 2-8: Comparison of mean exposure levels from this study to the Italian mill (taken from Rubino, 1979).

Area (Years)	Balangero (f/ml)	Baie Verte (f/ml)
Drilling (1961-70)	14	37
Drilling (1971-75)	5	8
Crushing (1961-70)	14	31
Crushing (1971-75)	3	12
Bagging (1961-70)	20	11
Bagging (1971-75)	6	5
Fibre Separation (1961-70)	21	22
Fibre Separation (1971-75)	8	7

On the other hand, a different pattern can be seen when we compare our data to those of the Québec chrysotile mills. The exposure levels reported by Nicholson²⁴ (Table 2-9) in all areas of five Québec mills were much higher than the levels found by the present study for the same time period (1973-1975). Gibbs²⁵ also reported on exposure levels in the general mill air for the “worst”, “best” and “average” of the Québec mills (Table 2-9). In 1972, exposure levels reported for the Baie Verte mine/mill fall somewhere between the levels found in Québec for the “best” and for the “average” mills, and in 1973 and 1974, the Baie Verte levels are in line with those of the “average” Québec mill. However, the levels found in Baie Verte in the later years (1975-77) are closer to those for the “best” mills in Québec.

Table 2-9: Comparison of mean exposure levels in Baie Verte to levels in five Québec mills reported by Nicholson (1979) and Gibbs (1979).

Area (Years)	Québec (f/ml) lowest to highest (Nicholson, 1979)	Baie Verte (f/ml)	Year	Québec (f/ml) “average mill” (“worst”-“best”) (Gibbs, 1979)	Baie Verte (f/ml)
QC Lab (1973-75)	9 - 20	4.9	1972	24 (3.5 ^a)	7.5
Crushing (1973-75)	26	11.7	1973	9 (3 - 50)	8.0
Dryer (1973-75)	36	11.7	1974	8 (2 - 29)	8.0
Bagging (1973-75)	9 - 16	4.5	1975	7 (1.5 - 9.0)	1.7
Shops (1973-75)	10	2.1	1976	3.5 (1.5 - 4.0)	1.2
General Mill Air (1973-75)	9 - 35	5.9	1977	2 (1 - 2)	0.9

^a “best” mill; no data given for the “worst” mill for 1972

These comparisons suggest that our exposure estimates lie somewhere between those of the Italian chrysotile miners and those of the Québec chrysotile miners. However, if the

pre-1976 estimates in our study are, as we have suggested, underestimates, then it is possible that the Baie Verte exposures for the earlier years were actually similar to those found in Québec during the same time period.

In conclusion, the current study is one of a small number of retrospective exposure assessments involving chrysotile asbestos miners/millers. This study demonstrates that exposures were very high (i.e., ranging from an average of 6 to 42 f/ml) in all areas of the Baie Verte chrysotile mine and mill in the early years of operation and gradually decreased over time. Our ability to analyze the quality of the available data, at least for the 1976-1994 period, allows us to be quite confident about the reliability of the estimates used in the JEM for those years and in the resulting estimates of cumulative asbestos exposure. However, the potential for exposure misclassification, resulting from the uncertainty associated with the conversion of historical midjet impinger results to fibre concentrations in the earlier data, and the lack of availability of the raw sampling data with which to accurately quantify this uncertainty must be kept in mind when using the results for epidemiological studies on this group of workers. This also applies to the use of estimates of individual cumulative asbestos exposure for the adjudication of compensation claims. While the exposure estimates are comparable to other similar chrysotile mining/milling cohorts in the epidemiological literature, future research into the sources of bias from the earlier industrial hygiene dataset would be useful in order to quantify the potential exposure misclassification.

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Chapter 3.0: Incidence of asbestos-related disease in former chrysotile asbestos miners/millers from Baie Verte, NL – Part I

3.0 Abstract

Introduction: The literature contains very few chrysotile asbestos miners/millers cohorts with high-quality retrospective exposure assessments. This has limited the ability of meta-analyses to decipher the large difference in the risk of lung cancer reported among the small number of chrysotile-only cohorts.

Objective: The aim of the current study is to help fill this gap by evaluating the risk of asbestos-related cancers with cumulative exposure to chrysotile asbestos in a group of former chrysotile miners/millers from Baie Verte, Newfoundland, Canada.

Methods: Most of the registrants (n=950) of the Baie Verte Miners' Registry (BVMR) were included in the current study. The BVMR provided demographic, health, vital status, and work history information for a group of former workers of the mine/mill. The National Institute for Occupational Health and Safety (NIOSH) lifetable analysis system was used to calculate 5-year age and calendar period person-years distributions which were then used to estimate the expected number of cancers using both Canadian and Newfoundland and Labrador (NL) incidence rates. Standardized incidence ratios (SIR) were calculated for cancer of the lung, larynx, stomach, esophagus, pharynx and colorectum. A Poisson regression model was used to evaluate the exposure-response relationship between lung cancer and cumulative asbestos exposure, time since first exposure, and duration of exposure.

Results: Excess cases of lung cancer (SIR = 1.38, 95% CI = 1.00-1.87) and colorectal cancer (SIR = 1.47, 95% CI = 1.08-1.96) were observed relative to the NL population. The number of cases of laryngeal cancer was also elevated when the Canada incidence rates were used as the reference population (SIR = 2.35, 95% CI = 1.03-4.63). There were two cases of mesothelioma observed in this group and 40 cases of asbestosis. A strong exposure-response relationship was demonstrated between asbestosis and cumulative asbestos exposure, time since first exposure, and exposure duration. The exposure-response relationship with lung cancer showed an elevated risk in the highest cumulative exposure group (RR = 1.25) only and an increase in risk with time since first exposure. There was also an exposure-response relationship demonstrated between colorectal cancer and both cumulative exposure and time since first exposure.

Discussion: This study lends further support to the assertion that chrysotile asbestos is associated with the development of asbestosis, lung cancer, and mesothelioma, as well as other cancers such as colorectal, laryngeal and esophageal cancer. However, further follow-up is needed to fully assess the impact of asbestos-related disease in this group of former chrysotile miners/millers.

3.1 Introduction

Asbestos is well recognized as a cause of both malignant and non-malignant diseases. Exposure to asbestos fibres has been firmly established as causal in the development of asbestosis, mesothelioma, and lung cancer, and more recently of cancer of the larynx and ovary^{1,2}. Positive associations have also been recognized between asbestos exposure and cancer of the pharynx, stomach and colorectum^{2,3}. However, there is a continuing debate regarding the relative potency of the various types of asbestos (i.e., chrysotile as opposed to amphibole asbestos fibres) with regard to the risk of lung cancer and mesothelioma. The arguments used to support the claim that chrysotile asbestos is less potent than the amphibole forms have been primarily based on studies that suggested that the greater biopersistence (i.e., longer half-life) of amphibole fibres in human lung tissue is related to the carcinogenic process⁴. In an attempt to keep the chrysotile asbestos industry alive after the recognition of the health effects of asbestos exposure in the 1950s and 1960s, these studies were used to support claims that amphibole asbestos, but not chrysotile, was responsible for lung cancer and mesothelioma in exposed workers. Despite the fact that these theories have been widely rejected,^{2,4-6} the industry and government bodies from several asbestos-producing countries continue to insist that chrysotile can be used safely. These claims create an important public health policy issue primarily because of the increasing use of asbestos in developing countries and because of the ongoing resistance by numerous producing countries to the inclusion of chrysotile asbestos in the Rotterdam Convention's list of chemicals requiring prior informed consent.

All types of asbestos are considered to be carcinogenic by the leading scientific and health authorities, including the World Health Organization's International Program on Chemical Safety⁷, the National Toxicology Program (USA)⁸, the National Institute of Occupational Safety and Health (USA)⁹, the United States Environmental Protection Agency¹⁰, the Agency for Toxic Substances and Disease Registry (USA)¹¹, the World Health Organization¹², and the International Agency for Research on Cancer (IARC)². Regardless, much effort has been made to decipher the relative risk associated with the different fibre types. Meta-analyses have attempted to elucidate the relative potency of the different forms of asbestos for both lung cancer and mesothelioma¹³⁻¹⁶. These studies have estimated the lung cancer risk to differ by a factor ranging from 6 to 60 for amphibole asbestos as compared to chrysotile. More recently, a study examining the exposure-response relationship between asbestos exposure and lung cancer risk at low cumulative exposures reported only a three- to four-fold difference in excess risk between amphiboles and chrysotile asbestos¹⁷. The large difference in these claims about relative potency factors for lung cancer has been attributed to the heterogeneity that exists in the slope of the exposure-response relationship for lung cancer among chrysotile-only exposed cohorts, most notably the Québec chrysotile miners/millers¹⁸ and the textile workers from South Carolina^{19,20}. These two cohorts have produced both the lowest rates (the Québec cohort) and the highest rates (the South Carolina cohort) of asbestos-induced lung cancer with the estimated potency factors (i.e., the excess risk per unit of exposure) reported as being more than 60 times higher for the South Carolina textile cohort (1.8 per f/ml-yrs) than for the Québec miners/millers cohort (0.029 per f/ml-yrs)²¹. The reason for this substantial difference between these two cohorts remains unknown, although fibre-size distribution has been the predominant area

of investigation in recent years. It has been proposed that long, thin fibres (which make up the majority of the inhalable fibres in the textile industry) are thought to be more carcinogenic than short, thick fibres (which are associated with mining/milling processes), and that this may partially account for the observed differences between these two cohorts^{15,22,23}. Another potential explanation for the heterogeneity is the variation in the quality of the exposure assessments in these studies, with higher quality exposure assessments being associated with higher estimates of risk ²⁴. Therefore, it is evident that fibre type is likely not the only factor contributing to the difference in lung cancer risk in the epidemiological data. Furthermore, while the heterogeneity between these two cohorts might never be fully resolved, most experts accept that chrysotile is a potent lung carcinogen.

Another topic of considerable controversy is the relationship between exposure to the different types of asbestos fibres and mesothelioma risk. Although there is no question that exposure to all types of asbestos can cause mesothelioma, there is evidence to suggest that chrysotile asbestos is less potent than the other fibre types². While mesotheliomas have been observed in all studies of chrysotile-exposed workers from all industry types, the meta-analyses referred to above report that the risk is lower for chrysotile than for amphiboles although there is disagreement about how large the difference is. Hodgson & Darnton¹⁴ have estimated the relative potency factors for chrysotile to be 1/100th that of amosite and 1/500th that of crocidolite, while Berman & Crump's estimates fall somewhere between zero and 1/200th that of the amphiboles¹⁵. However, newer studies have suggested that the risk of mesothelioma from chrysotile exposure is higher than previously thought^{5,25}, which has led to a reduction in the estimated ratio of potency factors for

mesothelioma to 1:14 for chrysotile versus amosite and 1:54 for chrysotile versus crocidolite²⁶.

Because of the continuing controversy surrounding the potency of chrysotile asbestos and the overall lack of chrysotile-only cohorts, particularly of miners/millers, the aim of this study is to introduce a new cohort of chrysotile asbestos miners/millers from Newfoundland, Canada and: (1) to examine the incidence of asbestos-related diseases in this group of miners/millers as it compares to the reference population(s); and (2) to evaluate the exposure-response relationship between exposure to chrysotile asbestos and lung cancer, pulmonary fibrotic disease (asbestosis), and colorectal cancer using a quantitative, retrospective exposure assessment that has been developed for this group (chapter 2).

3.2 Methods

3.21 Study Population

This study is a retrospective cohort study on former workers of the Baie Verte chrysotile asbestos mine/mill, located in Baie Verte, NL, which began production in 1963 and operated for 31 years until it closed in 1994. In 2008, an employee registry (the Baie Verte Miners' Registry (BVMR)) was established as an exposure/disease registry for former employees of the mine/mill²⁷. The primary purpose of the registry was to aid in the compensation process for workers who had developed asbestos-related diseases and it contains information on each registrant's vital status, employment history, medical history and current health status. While the exact number of former employees is not known it has been estimated that approximately 2400-2800 people worked at the mine/mill during its

operating time²⁷. However, this estimate includes seasonal, transient and contract workers. Based on union records only, the number of former workers who were employed directly by the mine/mill is in the vicinity of 1900.

The membership of the BVMR consists of former workers who were employed directly by one or more of the companies that operated the mine/mill (i.e., unionized employees, non-unionized management and staff); or by an external stevedoring company until the late 1970s at which time they became unionized company employees; or by other external companies who did various types of contractual work on the site. For the purposes of the present study, the following exclusion criteria were applied: (1) registrants for whom no work history records were available and whose employment could not be verified through union records; (2) registrants who were not directly employed at the mine/mill during its operating years; and (3) registrants whose work at the mine/mill was with outside contractors only (other than the stevedoring companies) and for whom an estimate of time worked or cumulative exposure could not be calculated.

3.22 Health Information

The BVMR contained information on disease diagnoses which was obtained from the provincial cancer registry and mortality database, and from hospital records, miners' medical examination records, and/or workers compensation files. Because of the time lapse between the development of the BVMR and the collection of data for this thesis, updated linkage data was obtained from the provincial cancer registry and mortality database and was the primary source of health information for the current study. Data on disease diagnoses was then collected from the other records in the BVMR which was also

the primary source of health information for non-residents of NL since data linkage was only available for NL residents. The specific diseases of interest included mesothelioma, cancers of the lung, and larynx, asbestosis, pulmonary fibrosis, interstitial pulmonary fibrosis, pneumoconiosis, pleural fibrosis, and rounded atelectasis. Cancers of the gastrointestinal tract were also recorded, including cancer of the stomach, colon, rectum and esophagus, as well as cancer of the pharynx. Only primary cancers were considered in the current study. Diagnoses of asbestosis, pneumoconiosis, pulmonary fibrosis, and interstitial pulmonary fibrosis are grouped together in the current study as asbestosis.

3.23 Work Histories

Individual work history records in the BVMR were obtained from company personnel files which listed the beginning and ending dates in each job, as well as job titles and job codes. These records were available for approximately 80% of the registrants and were derived from company personnel files that were provided by the provincial Workplace Health, Safety and Compensation Commission (WHSCC) for all consenting registrants. When available, this information was used to construct subjects' work history in preference to information provided by registrants in response to a questionnaire administered as part of the registration process, as it was considered to be more accurate. These records were not available for all registrants, and in some cases only partial records existed, especially for the 1991-1994 years. Accordingly, the data from the personnel files were supplemented by other sources including miners' medical examination files from the local hospital and self-reported or proxy-reported work history. Seniority lists containing the names of employee and their employee number were also provided by the United Steelworkers (USW). This

was convenient because employee numbers were assigned consecutively according to the year/date of hire and this allowed an approximate date of first exposure to be assigned for subjects whose work history records were not complete.

3.24 *Exposure Assessment*

A department, job title and calendar-year specific Job Exposure Matrix (JEM) was constructed by the author for the BVMR and was used both in the final report for the Registry and in the current study to calculate cumulative asbestos exposure. The JEM is a tool used to assign values of exposure intensity to a person's employment history for each job on which they worked at the mine/mill and for the specific amount of time they worked in that job. It is a two-dimensional matrix table with job titles on one axis and time periods on the other. The cells within the table contain average exposure values for each job title at each period of time as derived from an analysis of air sampling data collected in the mine/mill during its operation.

The JEM was linked with each subject's detailed work history from the BVMR using unique identifiers for each job code and time period, in order to calculate each registrant's cumulative asbestos exposure (f/ml-yrs). A full description of the development of the JEM can be found in Chapter 2. Briefly, the data from over 7,000 personal and stationary samples were extracted from monthly lists of routine air sampling results, done by the company, union or government, and provided by the USW. These air samples were taken at the mine/mill during the period from 1976 to 1994 and were based on the membrane filter method in which sampling was typically performed at a flow rate of 2 L/min for an average of one to two hours. Fibre counting on these samples was done according to NIOSH

analytical method 7400²⁸. The results from these air samples were used to calculate average exposure values (fibre concentrations) which make up the cells of the JEM. These average fibre concentrations were generated for each job title for which air sampling data was available and for groups of years that were deemed similar with respect to exposure, based on information collected regarding changes in the mine/mill processes.

For exposures prior to 1976, data from an earlier study on this group of workers conducted by H. Edstrom for the WHSCC²⁹ provided exposure estimates for the years 1963 through 1975. Quarterly dust concentrations (mppcf) for each job title were converted by Dr. Edstrom into fibre concentrations (f/ml) based on conversion factors that were developed for the different areas of the mine/mill and estimates of the proportion of the working time that people in these jobs spent in each of these areas³⁰. Annual average fibre concentrations for each group of job titles were then calculated and assigned to time periods with similar exposures³⁰.

3.25 Statistical Analysis

The NIOSH life table analysis system^{31,32} was used to calculate the person-years at risk (PYAR) accumulated by each subject. PYAR is the amount of time each person was at risk of acquiring the disease of interest and it began accumulating on the date first exposed and ended at the earliest of the date of diagnosis of the disease of interest, or the date of death, or the date last observed, or the end of the study period (Dec 31st, 2010). The PYAR distribution, which was summarized across subjects and stratified according to five-year age and calendar-year periods, was used to calculate the expected number of cancers using the corresponding incidence rates for the reference population(s).

Both Canadian and NL cancer incidence rates (males, 5-year age and calendar year stratified) were obtained from the Public Health Agency of Canada for the period from 1969 to 2010, and were used in the present analysis. For years when incidence rates were not available (i.e., 1955-1968) the rates from adjacent years were used. Standardized Incidence Ratios (SIR^h) and the corresponding 95% confidence intervals were calculated using the OpenEpi software³³ for the diseases of interest. Because of the small numbers of women in this group (n=21) and the small number of cancer cases (n=1) among them, data analysis was limited to the male population. There were no incidence data available from the general population(s) for either asbestosis or mesothelioma, and therefore SIRs were not calculated for these diseases. However, in an unexposed population there would be no cases of either mesothelioma or asbestosis expected since asbestos is the only well-established cause of these diseases.

3.26 Exposure-Response Analysis

Poisson regression was used to estimate the exposure-response relationship of lung cancer, asbestosis and colorectal cancer with various indicators of exposure using an internal analysis of the cohort (i.e., the lowest exposed group was used as the reference group) while controlling for the effects of age and calendar year. Rate ratios (RR) were estimated for each cumulative exposure category, each time-since- first- exposure category, and each duration-of-time-worked category, relative to the lowest group, and adjusted for

^h A **Standardized Incidence Ratio (SIR)** is used to determine if the occurrence of cancer in a study population is higher or lower than expected, given the population and age distribution for that group. The SIR is obtained by dividing the observed number of cases of cancer in the study group by the “expected” number of cases, that is, the number of cases that would expected to occur in that group if the disease rate in the reference population (usually the province or country) applied.

age (<60, 60-69, 70-79 and >80) and calendar period (1955-1989, 1990-2010). The estimated RRs for the effect of exposure X was estimated as $e^{\beta X}$, where β is the regression coefficient for exposure X, and 95% confidence intervals (CI) were estimated from the standard error of β using a normal approximation. Measures of exposure used in this analysis included: cumulative asbestos exposure – (< 4 f/ml-yrs, 4 - 25 f/ml-yrs, 25 - 100 f/ml-yrs, 100 - 200 f/ml-yrs, and > 200 f/ml-yrs); time since first exposure – ($0 \leq 20$ years, $20 \leq 30$ years, $30 \leq 40$ years, and > 40 years); and duration of exposure – (< 1 year, 1 - 5 years, 5 - 10 years, 10 - 20 years, and > 20 years). Cumulative exposure categories and time since first exposure categories were determined based on similar studies in the literature. Calendar year periods were determined based on the availability of data from the cancer registry and mortality databases. Detailed work histories were not available for 26 registrants and they were not included in the exposure-response analysis of cumulative asbestos exposure. They were, however, included in the analysis of time since first exposure and duration of exposure.

3.3 Results

The BVMR included a total of 1003 registrants of whom 53 were excluded from the present study. There were no employment records located for 32 registrants; 7 did not work at the mine/mill; and 14 were employees of external contractors (Figure 3-1). This left 950 subjects in the current study. Females (n=21) were excluded from the statistical analysis but are included in the demographic data shown in Table 3-1. The 929 male subjects, who worked at the mine/mill for at least one day, beginning no earlier than Jan 1, 1957, were included in the statistical analysis.

Figure 3-1: Flowchart indicating the inclusion and exclusion criteria applied to the Baie Verte Miners' Registry Registrants and the resulting subjects included in current study.

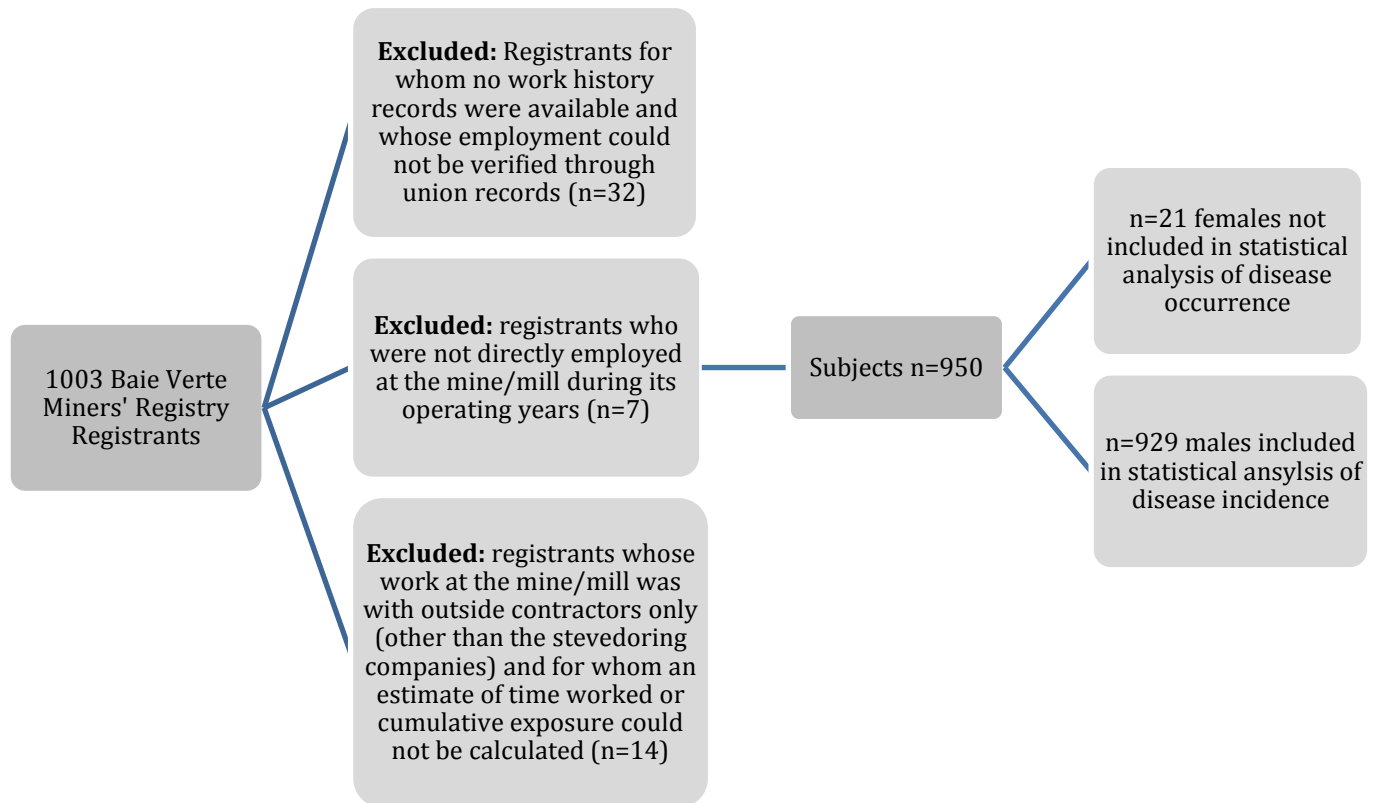


Table 3-1 provides a summary of the demographic characteristics of the subjects. The majority were male (97.8%) and were alive at the end of the study period (80.9%). Overall, this group of study subjects could be considered a fairly young group with the average age of the living being 64 years old and the youngest subject being 38 years old at last follow up. Approximately 50% of the subjects began working at the mine/mill in the early years when the exposure levels were very high (i.e., the 1960s or earlier), while only 8.9% of them began work after the second company took over operations (i.e., after 1980) and by

which time exposure levels had dropped substantially. Most of the people in this study group worked at the mine/mill for a considerable period, on average 10.4 years. 45.4% of subjects worked at the mine/mill for more than 10 years and 16.2% worked there for more than 20 years. Cumulative exposures in this group ranged from 0.001 f/ml-yrs, for two registrants who each worked for only 5 days starting in 1990, to 375 f/ml-yrs, for a registrant who started working at the mine/mill in 1963 and who continued for 31 years. The average cumulative exposure in this group was 72.33 f/ml-yrs.

3.31 Disease Incidence

Two cases of mesothelioma, both of the pleura, were observed in this group and were documented in both the BVMR and in the cancer registry/mortality linkage data. One of these cases was among the 53 subjects excluded from the present study because the subject's employment history could not be verified. The other case was a person who began work at the mine/mill in the early 1970s and continued working there for over 12 years, accumulating 28 f/ml-yrs of cumulative asbestos exposure. The diagnosis of mesothelioma was made 34 years after first exposure. There also was one case of peritoneal cancer listed in the BVMR but it was not identified as a mesothelioma.

A cumulative total of 31,970 PYAR were experienced by this group between Jan 1st, 1957 and Dec 31st, 2010. 171 cancers were observed (not including non-melanoma skin cancers), 110 of which were found in the cancer registry and/or mortality database, while the remaining 61 cases were found in the other files of the BVMR.

When the age-standardized incidence rates for NL were used as the reference group there was no significant increase in the number of total cancers in this group (Table 3-2) with a total of 166.71 expected giving an SIR of 1.03. However, an examination of disease-specific morbidity showed that there was a significant increase in risk for both lung cancer (SIR = 1.38, 95% CIs 1.00-1.88) and colorectal cancer (SIR = 1.47, 95% CIs 1.07 - 1.97) and there was an elevated risk of laryngeal and esophageal cancer found (SIR = 2.16 and 1.49, respectively). Twenty-one of the 39 cases of lung cancer observed were found in the cancer registry and/or mortality data and the remaining eighteen were found in the medical files in the BVMR. There were 28.2 cases expected giving an elevated SIR of 1.38 (95% CI 1.00-1.88). A significant excess of colorectal cancers were experienced by this group relative to the NL population. Of the 43 colorectal cancers observed 24 cases were obtained from the cancer registry/mortality database and the other 19 came from the BVMR. There were 29.28 cases expected based on NL incidence rates, resulting in a significant SIR of 1.47 (95% CIs 1.07–1.97). There were 7 cases of laryngeal cancer found (all of which were documented in both the registry and the cancer registry/mortality database) and 3.24 cases expected giving an elevated SIR of 2.16 (95% CIs 0.87 - 4.45). Finally, there were three cases of esophageal cancer observed which were all found in both the BVMR and the linkage data and 2 cases expected giving an SIR of 1.49.

Table 3-1: Descriptive data for the current group of study subjects from the BVMR

	No. of Registrants	Percentage
Sex		
Male	929	97.8%
Female	21	2.2%
	950	
Vital Status¹		
Alive	769	80.9%
Deceased	181	19.1%
Average Age (years, range)¹		
Living	64.25 (S.D. 9.94)	(38 - 91)
At Death	67.14 (S.D. 12.05)	(22 - 91)
Year First Exposed²		
1957-1964	268	28.3%
1965-1969	206	22.0%
1970-1974	196	21.1%
1975-1979	184	19.8%
1980-1984	32	3.8%
1985-1994	43	5.1%
Total	929	100
Time Worked³		
< 3 months	44	4.8
3 months to 1 year	75	8.1
1 to 5 years	201	21.8
5 to 10 years	183	19.9
10 to 20 years	269	29.2
> 20 years	149	16.2
Total	921	100
Cumulative Asbestos Exposure (f/ml-yrs)³		
0 - <1.0	106	11.5
1.0 - 4.0	120	13.0
4.0 - 25.0	223	24.2
25.0 - 100	234	25.4
100 - 200	134	14.5
>200	104	11.3
Total	921	100

1 - As of end of follow up

2 - Includes male subjects only

3 - Includes male subjects only, for whom complete work history information was available

Using Canadian cancer incidence rates as the reference population, there was no significant increase in the number of total cancers in this group (Table 3-2), with a total of 170.58

expected giving an SIR of 1.00 (95% CI 0.86-1.16). A significant excess of colorectal cancers were experienced by this group relative to the Canadian population, with only 22.58 cases expected resulting in a significant SIR of 1.90 (95% CIs 1.39 - 2.55). Other cancers showed elevated risks but were not significant. There were 29.21 cases of lung cancer expected using the Canadian incidence rates giving a slightly elevated SIR of 1.34. This was also true for: cancer of the stomach with an elevated SIR of 1.68; cancer of the stomach (where 3 of the 8 observed stomach cancers were found in the cancer registry/mortality database) with a slightly elevated SIR of 1.68; laryngeal cancer (SIR=2.35); and esophageal cancer (SIR=2.39). There was no increase in pharyngeal cancers found in this group with only four cases identified in the registry as compared to 6.58 and 9 cases expected based on national and provincial incidence rates, respectively.

There were 40 cases of asbestosis observed amongst the study subjects and this included cases that were diagnosed as either “asbestosis”, “pneumoconiosis”, “pulmonary fibrosis”, or “interstitial pulmonary fibrosis”. All these cases were obtained from the BVMR and no cases were found in the mortality database. Because of the lack of incidence rates for mesothelioma and asbestosis in the reference populations, SIRs were not calculated. However, in an unexposed population the number of expected cases of mesothelioma and asbestosis would be close to zero.

Table 3-2: SIRs for various cancers using both the Canadian and NL cancer incidence rates as the reference populations.

Disease	No. Obs	PYAR	Incidence rate per 100 000 PYAR	SIR - Canada		SIR - NL	
				Exp	SIR (95% CI)	Exp	SIR (95% CI)
All Cancers	171	31 970	534.88	170.58	1.00 (0.86 – 1.16)	166.71	1.03 (0.89 – 1.19)
Pharynx	4	31 984	12.51	6.58	0.61 (0.17 – 1.56)	9.00	0.44 (0.12 – 1.13)
Esophagus	3	31 984	9.38	2.39	1.26 (0.26 - 3.68)	2.01	1.49 (0.31 - 4.35)
Stomach	8	31 972	25.02	4.75	1.68 (0.72 - 3.31)	8.16	0.98 (0.42 – 1.93)
Colorectal	43	31 730	135.52	22.56	1.90 (1.39 - 2.55)**	29.28	1.47 (1.07 – 1.97)*
Larynx	7	31 984	21.89	2.98	2.35 (0.94 - 4.84)	3.24	2.16 (0.87 – 4.45)
Lung	39	31 025	125.71	29.21	1.34 (0.96 – 1.82)	28.20	1.38 (1.00 – 1.88)*
Asbestosis	40	30 743	130.11	---	---	---	---

*p<0.05, **p<0.001

3.32 Exposure-Response Relationship

Table 3-3 shows the results of the exposure-response relationship between various measures of exposure and the risk of lung cancer. There was a slight increase in the risk of lung cancer as cumulative exposure increased but only for the group with more than 200 f/ml-yrs cumulative exposure which had a relative risk (RR) of 1.25 (p<0.05) as compared to the lowest exposed group. This analysis is based on 37 of the 39 observed lung cancers since detailed work histories were not available for two of the registrants and, therefore, cumulative asbestos exposures could not be calculated. There was an increase in lung cancer risk observed with time since first exposure (p < 0.0001), with the highest risk in the 30-40 years group (RR=4.50). Workers in the both the 20-30 years group and the > 40 years group had twice the risk of developing lung cancer compared to the 0-20 years group,

with relative risks of 1.97 and 2.14, respectively. The total amount of time worked at the mine/mill was found to be inversely associated with disease risk, with the RR of lung cancer actually decreasing in all groups ($p < 0.05$).

A strong exposure-response relationship was found between asbestosis and all three measures of exposure (Table 3-4). For cumulative exposure, the RR increased in each exposure category, from 1.0 in the < 4 f/ml category, to 8.79 in the >200 f/ml-yrs category ($p < 0.001$). The same trend was true for time since first exposure ($p < 0.0001$), with the highest RR found in the group with 30-40 years since first exposure (RR=5.30). Duration of exposure also demonstrated an exposure-response relationship ($p < 0.0001$) with a steady increase in RR in all groups, up to 4.68 in the >20 years group, and a slight dip in the 5 -10 years duration group (RR=1.96). The highest RR was in the 10-20 years of employment group (RR=6.95).

Table 3-3: Poisson regression analysis of the exposure-response relationship between lung cancer and cumulative asbestos exposure, time-since-first-exposure, and duration-of-exposure.

	# Cases Lung Cancer	PYAR	RR*	95% CI	Trend p value
Cumulative Asbestos Exposure (f/ml-yrs)					< 0.05
< 4	4	6352.09	1.00	---	
4 ≤ 25	7	7720.17	1.01	0.29 – 3.47	
25 ≤ 100	7	8693.66	0.47	0.14 – 1.67	
100 ≤ 200	8	4935.15	0.68	0.20 – 2.33	
> 200	11	3324.34	1.25	0.38 – 4.08	
Duration of Exposure (years)					< 0.05
< 1	5	4191.60	1.00	---	
1 ≤ 5	4	8730.54	0.28	0.07 – 1.03	
5 ≤ 10	6	6869.83	0.38	0.11 – 1.25	
10 ≤ 20	15	8060.53	0.55	0.19 – 1.57	
> 20	7	3172.91	0.30	0.09 – 0.99	
Time Since First Exposure (years)					< 0.0001
0 ≤ 20	6	17368.42	1.00	---	
20 ≤ 30	9	7530.41	1.97	0.58 – 6.89	
30 ≤ 40	18	5345.9	4.50	0.75 – 16.19	
> 40	6	1725.76	2.14	0.33 – 9.67	

*age and calendar year adjusted

A strong exposure-response relationship was also found between colorectal cancer and time since first exposure (Table 3-5). The relative risk increased from 5.18 in the 0-20 years group, to 6.98 in the 20-30 years group, and remained elevated at 6.83 in the >40 years group ($p < 0.0001$). The risk of colorectal cancer was doubled or nearly doubled in all categories of cumulative asbestos exposure, with relative risks of 2.07, 1.83, 1.72, and

2.03 in the 4-25, 25-100, 100-200, and >200 f/ml-yrs groups, although the 95% CIs included 1.0 in each case. There was no apparent increase in risk of colorectal cancer with increasing duration of work, with relative risks of less than 1.0 in each category.

Table 3-4: Poisson regression analysis of the exposure-response relationship between asbestosis and cumulative asbestos exposure, time-since-first-exposure and duration-of-exposure.

	# Cases Asbestosis	PYAR	RR*	95% CI	Trend p value
Cumulative Asbestos Exposure (f/ml-yrs)					< 0.001
< 4	1	6329.76	1.0	---	
4 ≤ 25	7	7659.07	3.84	0.46-31.67	
25 ≤ 100	12	8539.29	4.98	0.62-39.88	
100 ≤ 200	10	4869.63	6.02	0.73-49.72	
> 200	10	3344.77	8.79	1.06-72.84	
Duration of Exposure (years)					<0.0001
< 1	1	4203.63	1.0	---	
1 ≤ 5	6	8633.33	2.65	0.32-22.08	
5 ≤ 10	4	6841.53	1.96	0.22-17.64	
10 ≤ 20	20	7910.66	6.95	0.92-52.59	
> 20	9	3153.39	4.68	0.57-38.63	
Time Since First Exposure (years)					< 0.0001
0 ≤ 20	8	17302.69	1.0	---	
20 ≤ 30	8	7455.90	2.52	0.75-8.41	
30 ≤ 40	16	5363.87	5.30	1.22-23.08	
> 40	8	1666.26	4.41	0.86-22.69	

*age and calendar year adjusted

Table 3-5: Poisson regression analysis of the exposure-response relationship between colorectal cancer (CRC) and cumulative asbestos exposure, time since first exposure and duration of exposure.

	# Cases Colorectal Cancer	PYAR	RR*	95% CI	Trend p value
Cumulative Asbestos Exposure (f/ml-yrs)					0.12
< 4	4	6337.18	1.0	---	
4 ≤ 25	11	7650.96	2.07	0.66-6.52	
25 ≤ 100	13	8635.41	1.83	0.58-5.79	
100 ≤ 200	8	4851.66	1.72	0.49-5.99	
> 200	7	3329.45	2.03	0.56-7.35	
Duration of Exposure (years)					0.09
< 1	5	4100.09	1.0	---	
1 ≤ 5	9	8720.13	0.74	0.25-2.22	
5 ≤ 10	7	6735.43	0.67	0.21-2.13	
10 ≤ 20	16	8031.79	0.99	0.36-2.78	
> 20	6	3127.62	0.47	0.14-1.62	
Time Since First Exposure (years)					< 0.0001
0 ≤ 20	4	17356.36	1.0	---	
20 ≤ 30	13	7475.42	5.18	1.37-19.66	
30 ≤ 40	18	5238.90	6.98	1.57-31.15	
> 40	8	1678.82	6.83	1.31-35.58	

*age and calendar year adjusted

3.4 Discussion

This study of the former workers registered in the BVMR showed a higher than expected number of cases of lung, laryngeal and colorectal cancer relative to the provincial and/or national incidence rates. Depending on the reference group (i.e. NL or Canada) the risks were different with NL rates producing higher risks of lung cancer and esophageal cancer,

and Canadian rates generating higher risks of stomach, laryngeal and colorectal cancer. The difference in the expected number of cancers cases, and hence risk, between the reference groups is not surprising since the incidence rates for many cancers (e.g. colorectal, stomach and larynx) are known to be higher in NL than in the rest of the country. This is thought to be due to both dietary³⁴ and genetic factors³⁵. However, the risk associated with both colorectal and laryngeal cancer was still elevated in this group when compared to the provincial rates, suggesting a positive association that is attributable to asbestos exposure. While the provincial rates may be seen as the more appropriate basis for comparison, it is important to note that they are also less stable than the Canadian incidence rates.

Analysis of exposure-response relationships demonstrated a strong association between asbestosis and increasing cumulative asbestos exposure, time since first exposureⁱ and employment duration. The same trend was true of the exposure-response relationship between lung cancer and time since first exposure, with the risk of lung cancer being over four times higher in the 30-to-40 year category than the 0-to-20 year group. On the other hand, the only elevation in lung cancer risk was observed in the highest cumulative exposure group, that is, employees with more than 200 f/ml-yrs where the relative risk was 1.25. The low number of lung cancer cases in each cumulative exposure category may contribute to the lack of an exposure-response relationship and follow up of this cohort may strengthen this analysis.

ⁱ Increasing risk with time since first exposure is an indication of the latency period of a particular disease. Duration of employment (or exposure) is a common summary measure of exposure to the agent of interest.

A strong exposure-response relationship was also observed between the risk of colorectal cancer and time since first exposure. The risk of colorectal cancer was 5 times greater in workers with 20-30 years since first exposure and almost 7 times greater for workers with more than 30 years since first exposure. Colorectal cancer risk was also observed to be elevated in all categories of cumulative exposure in comparison to the least exposed group.

A reverse association was observed between lung cancer and duration of exposure where the risk actually decreased. Duration of work can be a poor indicator of exposure since it is not reflective of the actual amount of exposure. For instance, workers who began working at the mine/mill in the later years (i.e. after 1975 or 1980) and who continued to work there for 15-20 years would not have had the same amount of cumulative asbestos exposure as someone who began working in the 1960s (who worked for the same amount of time) because the concentration of airborne asbestos fibres decreased dramatically over the years. Therefore, duration of exposure does not always reflect the exposure-response relationship with asbestos-related diseases. Other reasons for this inverse relationship may be incomplete follow-up of cancer cases (that is, cancer cases that were not identified in the cancer registry and/or mortality databases) and potential confounding exposures for workers in the shorter work duration category, such as cigarette smoking. Because the exposure-response relationship between duration of work and asbestosis is clearly evident in the data, it is believed the incomplete follow-up and the presence of confounding variables for lung cancer are more likely to be the cause. Also, there are very few asbestosis cases in workers with less than 1 year total work duration (n=1) as compared to 5 cases of lung cancer in the same category, indicating the potential presence of

confounding in this group. Additional analysis of the exposure-response relationship taking into account the confounding effects of smoking on lung cancer is recommended.

Two pleural mesotheliomas were observed among the registrants of the BVMR but only 1 case was included in this study with a proportionate mortality ratio of 0.6%. This is similar to other groups of chrysotile miners/millers however more cases are likely in the future since the latency period for this disease can range from 20 to 40 years or longer³⁶. The crude incidence rate of asbestosis was 130.11 cases per 100,000 person-years, which is consistent with the South Carolina textile cohort (102.10 cases per 100,000)²⁰, but considerably higher than the Québec miners/millers cohort (84.68 cases per 100,000)³⁷.

A number of limitations of the current study must be taken into consideration. Because the registry was voluntary, it is likely that it under-represents deceased former workers who may not have been registered by their next of kin for a number of possible reasons. For instance, deceased former workers may not have had any living next of kin (e.g., spouse) to register them, or living next of kin (e.g., children) may not have understood that they could register deceased family members or they may have moved away from the region and the province and were not aware of the Registry. They also may not have understood the benefits of registering their deceased relatives, since the primary purpose of the registry was to aid in the compensation process which provides only limited benefits for some next of kin and none for others. Furthermore, because estimates of the total workforce of the Baie Verte mine/mill, as reported by the BVMR, have ranged from approximately 2000 to 2800 former workers²⁷ there are many former workers for whom we do not have health information. Therefore, it is possible that of many of these former workers who are not

registered in the BVMR are deceased, and they may have had asbestos-related diseases. As a matter of fact there is good reason to believe that there are numerous miners' medical files at the Baie Verte hospital for deceased former workers who were not registered in the BVMR. Inclusion of these subjects could make a difference to the results of the epidemiological analysis of this group. If, in fact, the BVMR represents mainly the surviving workers who would be eligible for compensation, this could have diluted the risk estimates reported in this study.

A further limitation of the current study is that the data linkage was limited to provincial databases (i.e., the cancer registry and the mortality database) even though a significant portion (26%) of the registrants live outside of NL. This presents problems in obtaining information on health status, since health information for non-residents was limited to hospital data and only for those hospital records for which consent was received. Even for these hospitals, the data received was limited because some hospitals did not reply to requests for information and others insisted on very stringent conditions and high costs for the provision of data. In addition, it is likely that registrants and/or their next of kin did not provide the registry team with the names of all the hospitals that they had used over the years. It is possible, therefore, that some relevant diagnoses were missed, especially for non-residents and for diseases with poor prognosis such as lung cancer, which might not be adequately captured through the use of hospital data. This may also partially explain the discrepancy between the number of cases obtained from the cancer registry and mortality databases in comparison to the number of cases obtained by the BVMR from other sources, and the weak exposure-response relationship observed in the lung cancer

data. Data linkage to the national cancer database would very likely increase the number of cancer cases in this group.

In addition, the years of coverage of the provincial electronic databases were extremely limited since electronic records were available from the mortality database and the cancer registry starting only in 1991 and 1995, respectively. Deaths and cancer cases that occurred before then would not have been captured through the electronic data linkage, which may also partially explain the difference in the number of cases of disease found between the two types of sources. Therefore, additional research is needed with data linkage to the national cancer registry and mortality databases that might provide much more information on the health outcomes for this group of workers.

Other limitations of the current study may also have had an effect on the findings. For some individuals, no detailed work histories were available in the files provided by the WHSCC and the USW and their work histories were constructed using less reliable sources such as hospital records (miner's medicals) or the responses given by the individual or a proxy to the questionnaires administered as part of the BVMR. Using these types of data for the purposes of calculating exposure may cause exposure misclassification which typically leads to an attenuation of the exposure-response relationship^{38,39}. In addition, an exposure lag was not applied to the individuals' person-years contribution which could also cause a dilution of the observed risk of asbestos-related diseases. Exposure lags are frequently used in the study of exposure-related cancer because it takes into account the long latency period that often exists between exposure and cancer diagnosis⁴⁰. The

unlagged exposure model^j used in this study may have contributed to an attenuation of the rate ratios by including observation time for individuals not yet at risk of asbestos-related disease²⁶. Furthermore, the potential for exposure misclassification because of uncertainty associated with the retrospective exposure assessment, in the early years of the mine/mill (as described in Chapter 2), may have masked the exposure-response relationship, notably between cumulative asbestos exposure and lung cancer because exposure misclassification tends to bias the results of the exposure-response analysis towards the null hypothesis. The use of conversion factors to convert measurements of dust exposure to fibre exposure has been shown to be problematic¹⁶. A comparison of overlapping industrial hygiene data (Chapter 2) from 1975-1980 using the 2 types of exposure measurements (i.e. dust and fibres) show that early exposures (i.e. at least during the period prior to the mid-1970s when exposures in the mine/mill complex began to drop) may have been underestimated in this group. However, the conversion factors used to estimate exposure for this group in the early years were department/area specific which reduce the amount of bias introduced by the conversion process. An examination into the effect of this potential bias should be included in future studies of this group.

Because the follow-up time of the current study (approximately 50 years after the mine/mill began operations in 1957) is relatively short and because of the long latency period associated with the development of asbestos-related diseases, it is anticipated that, as more time elapses, additional cases of asbestos-related diseases will occur which, if

^j Exposure lagging is a form of latency analysis and it refers to the exclusion of exposure that occurs during the months or years immediately preceding the outcome. The lagging of exposure information is often done to allow for an induction (latency) period in cumulative exposure-disease analyses and has been shown to have an effect on the slope of the exposure-response relationship²⁵. An unlagged model does not adjust for latency.

included in the analysis, would strengthen the results already observed in the current study. Individuals in the BVMR whose exposure began when the mine/mill opened in the mid-1960s and 1970s have reached the end of the typical latency period for asbestos-related disease only within the past decade or so or have not yet reached it. For others whose exposure began later (e.g. in the 1980s or 1990s), the end of the latency period will be approaching in the period 2010-2030. Approximately 50% of the registrants began work at the mine/mill after the 1970s as is indicated by the fact that more than half of the contributed person-years for this group is in the 0 to 20 years “time since first exposure” category (17,368 PYAR). Therefore, additional follow-up will be needed in the future to fully assess the impact of asbestos-related disease in this group of former asbestos workers.

Despite these limitations, the current study also has some important strengths, including the use of a quantitative retrospective exposure assessment, described in Chapter 3. This is often lacking in many epidemiology studies and is not available for other chrysotile-exposed cohorts such as the Chinese mining/milling cohort. There was also a considerable amount of information available regarding the mining/milling process as well as key informant interviews with former workers that gave insight into the changing environmental conditions of the workplace during the years of operation. Furthermore, this study used incidence data rather than mortality data which is more likely to show associations between asbestos exposure and cancers that are not necessarily or always fatal, such as colorectal cancer. Using incidence data is also likely to identify more asbestosis diagnoses, since these tend to be poorly captured on death certificates, and this is apparent in the exposure-response relationship demonstrated in this study.

Other studies of chrysotile exposed workers have shown results that differ from these findings. In studies of a cohort of Italian chrysotile asbestos miners/millers, there was no increase in lung cancer observed after several follow-ups. The first study found a SMR of 1.06 with only 11 deaths from lung cancer⁴¹. After additional follow-up time, the SMR increased slightly to 1.10⁴² and 1.27²⁵, both of which are lower than what was observed in this study. In the Québec cohort, an increased risk of lung cancer was found with increasing asbestos exposure, but the authors report this effect only in workers exposed to more than 1000 f/ml-yrs^{18,37}. This differs from the current study in that the increase in risk of lung cancer for the registrants of the BVMR is seen at a much lower cumulative exposure, that is, 200 f/ml-yrs. In contrast, other studies such as the South Carolina cohort of textile workers have shown an increase in lung cancer risk at much lower exposures beginning at 100 f/ml-yrs⁴³. More recently, studies of Chinese chrysotile miners/millers have also shown a statistically significant increase in mortality from lung cancer in chrysotile exposed miners/millers, with the authors reporting an SMR of 1.51 in the most recent follow-up⁴⁴. Although this cohort does not have a quantitative exposure assessment with which exposure-response could be confirmed, it lends strong support to the position that that chrysotile mining/milling is a risk factor for lung and other cancers.

In conclusion, the current study shows an increased risk of lung cancer, colorectal cancer, laryngeal cancer and asbestosis associated with chrysotile asbestos exposure in this group of former miners/millers. An elevated risk of lung cancer was demonstrated with the highest levels of cumulative asbestos exposure as well as increasing time since first exposure. Also, a strong exposure-response relationship was found between asbestosis and cumulative exposure to chrysotile asbestos, time since first exposure, and employment

duration. Colorectal cancer risk also appeared to increase with increasing cumulative exposure and a strong relationship was demonstrated with time since first exposure. One pleural mesothelioma was observed in this group lending further support to the fact that chrysotile asbestos can cause mesothelioma. This is the first study done of this group of chrysotile asbestos workers. Although only 20% of the study subjects were deceased, use of incidence data revealed elevated risks of asbestos-related cancers and asbestosis. Subsequent follow-up of this group will very likely identify additional cases of asbestos-related disease and shed further light on the health effects of chrysotile asbestos in the mining/milling industry.

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Chapter 4: Incidence of asbestos-related disease among former chrysotile asbestos miners and millers from Baie Verte, NL – Part II.

4.0 Abstract

Introduction: Chrysotile asbestos exposure is known to cause both malignant and non-malignant disease, but the debate regarding the potency of chrysotile asbestos for lung cancer and mesothelioma is ongoing. In order to contribute to this debate, Part 1 of this study (Chapter 3) examined the incidence of asbestos-related disease due to chrysotile asbestos exposure in a group of former workers of the Baie Verte chrysotile asbestos mine/mill who were enrolled in an exposure/disease registry (i.e. the Baie Verte Miners Registry (BVMR)). Because the BVMR only accounts for approximately 35-50% of the full cohort of former workers, it was determined that the full cohort would need to be enumerated and incidence of disease examined in order to fully understand the health impacts of the Baie Verte asbestos mine/mill.

Objective: The aim of the current study is to enumerate the cohort of former chrysotile asbestos miners/millers from Baie Verte, Newfoundland, and evaluate the risk of asbestos-related cancers in the additional group of workers that were not part of the BVMR (i.e. Non-Registrants), as well as in the combined group of Registrants and Non-Registrants.

Methods: Records were obtained from the Canadian branch of the United Steelworkers Union (USW) and were used to create as comprehensive a list as possible of the former employees of the Baie Verte asbestos mine/mill. From this list, the names and dates of birth of those former workers who were not enrolled in the BVMR ('the Non-Registrants') were selected and submitted to the Newfoundland and Labrador Centre for Health

Information to obtain information on disease diagnosis through linkage to the provincial cancer registry and mortality databases. The NIOSH Lifetable Analysis System was used to calculate 5-year age and calendar period person-years distributions which were employed to estimate the expected number of cancers for these groups using both Canadian and NL incidence rates as the reference populations. Standardized incidence rates were calculated for cancer of the lung, larynx, stomach, and colorectum. A Poisson regression model was used to evaluate the exposure-response relationship between lung cancer and time since first exposure, for both the Non-Registrants and the Combined Cohort consisting of the non-Registrants and the Registrants studied in chapter 3.

Results: Union records identified a total of 1748 former workers of the Baie Verte mine/mill, of whom 864 were included in the BVMR. When the NL cancer incidence rates were used to calculate the expected number of cancers in these Non-Registrants, excess cases of lung cancer (SIR = 1.68) and esophageal cancer (SIR = 1.46) were observed. When the Combined Cohort was examined, the SIRs remained elevated for lung cancer (1.45) and esophageal cancer (1.44). There was also an increase in the number of observed cases of colorectal cancer (SIR = 1.27) and laryngeal cancer (SIR = 1.81). This trend was observed when both the national and provincial referent rates were used. There were no additional cases of mesothelioma found and no cases of asbestosis in the mortality database. A strong exposure-response relationship was found between lung cancer and time since first exposure for both the Non-Registrants and the Combined Cohort. Among the Non-Registrants, the greatest risk was observed in the group with 20-30 years since first exposure (RR = 7.46), while for the Combined Cohort the highest risk was found in the 30-

40 years since first exposure category where the risk was five times higher than the control group.

Discussion: This study was successful in enumerating a large portion of the former workers from the Baie Verte chrysotile asbestos mine/mill that had not been included in the BVMR and to analyze their risk for certain key asbestos-related cancers. The findings lend further support to the position that chrysotile asbestos is associated with the development of asbestosis, lung cancer, mesothelioma, as well as other cancers such as colorectal, laryngeal and esophageal cancer. However, further follow-up is needed to fully assess the impact of asbestos-related disease in this group of former chrysotile miners/millers.

4.1 Introduction

Asbestos is well recognized as a cause of both malignant and non-malignant disease. Exposure to asbestos fibres has been firmly established to be causal in the development of asbestosis, mesothelioma, and lung cancer, as well as cancer of the larynx and ovary^{1,2}. Positive associations have also been recognized between asbestos exposure and cancer of the pharynx, stomach and colorectum^{2,3}. However, there is continuing debate regarding the relative potency of the various types of asbestos (i.e., chrysotile as opposed to amphibole asbestos fibres) in the causation of lung cancer and mesothelioma. Because of the ongoing production, export and use of chrysotile and pressure from the industry and some governments, the debate regarding the relative toxicity of chrysotile asbestos has persisted and remains an important issue for policy makers, especially in countries where production and/or use of chrysotile asbestos is still occurring.

In order to estimate the risk of disease associated with chrysotile asbestos, numerous risk assessments have attempted to decipher the relative potencies of the different asbestos fibre types. However, there have been very few studies of workers who have been exposed to chrysotile asbestos only and this has led to a reliance on data from a small number of cohorts - primarily, the cohort of chrysotile miners/millers from Québec Canada⁴, and the South Carolina textile workers⁵. Other cohorts of chrysotile-only workers include the miners/millers from Italy, and more recently China, these studies lack quantitative exposure assessment data for those cohorts.

Part I of this study (Chapter 3) introduced a new group of chrysotile asbestos miners/millers from NL, Canada. These workers were former employees of the mine/mill

in Baie Verte, NL who joined an exposure/disease registry called the Baie Verte Miners' Registry (BVMR). The creation of this registry included the development of a retrospective quantitative exposure assessment (see Chapter 2) which was used to estimate cumulative exposure for each registrant. Chapter 3 of this thesis reports on the epidemiological analysis of this group of Registrants, which found an elevated risk of cancer of the lung, colorectum, and larynx. There were also two pleural mesotheliomas identified and 40 cases of asbestosis. However, the BVMR Registrants represents only a portion (approximately 34 to 48%) of the total workforce of the Baie Verte asbestos mine/mill. In order to understand the full impact of chrysotile exposure, it was deemed important to identify and study as many of the former employees as possible including those not included in the BVMR.

This chapter will attempt to enumerate as many of the former employees as possible and to determine the incidence of asbestos-related diseases among them, in order to get a more complete representation of the health effects of the chrysotile asbestos mine/mill. The objectives of the current study are: (1) to enumerate the cohort from available union records; (2) to evaluate the risk of asbestos-related cancers in this second group of workers (also known as the "Non-Registrants") as it compares to the group of workers studied in Chapter 3 (the 'Registrants'); (3) to evaluate the risk of asbestos-related cancers using the combined data from both groups (the "Combined Cohort"); and (4) to evaluate the exposure-response relationship between exposure to chrysotile asbestos and lung cancer risk for the 'Non-Registrants and for the Combined Cohort.

4.2 Methods

4.21 *Study Population*

This study was a retrospective cohort study of former workers of the Baie Verte, NL chrysotile asbestos mine/mill. Records were obtained from the Canadian branch of the United Steelworkers Union (USW) and consisted of seniority lists from the three companies that operated the mine/mill, two lists of staff/management and unionized employees (which listed each person's name, date of birth and employee number) and additional 100 personnel files mainly for management employees. These records were used to create as comprehensive a list as possible of the former employees of the mine/mill. Each person's name, date of birth, and other relevant information (e.g. employee number) were abstracted from these records, which provided the identification of 1748 individuals. Approximately half of the identified workers (n = 864) were included in the Registry and 884 were not (i.e., the 'Non-Registrants').

4.22 *Health Information*

The names and dates of birth of the Non-Registrants were first linked to the provincial healthcare insurance database (MCP – Medical Care Plan). This allowed for more efficient linkage to the other databases, including the provincial cancer registry and the provincial mortality database, from which information was sought on all cancer diagnoses and cause(s) of death for deceased "Non-Registrants". Some limited health information, such as death certificates and workers' compensation records, was also found in the union records for a small number of people (n=8) and this information was also used in the current study. Linkage to the MCP database was also used to obtain information on coverage dates

through the use of termination codes. For example, when a person moves out of the province a termination code is assigned to that individual's file to indicate that he/she is no longer covered under the provincial healthcare insurance system. These individuals were considered lost to follow-up and their person-years at risk (PYAR) was truncated at the termination date and this was assigned as their date last observed (i.e., date last known to be alive).

4.23 Work Histories and Exposure Assessment

Detailed work history records were not available in the union files, however the seniority lists contained employee numbers and these were recorded for each Non-Registrant. Employee numbers were used to estimate the year of first exposure since employee numbers were assigned consecutively according to the date of hire.

4.24 Statistical Analysis

The NIOSH life table analysis system^{6,7} was used to calculate the number of PYAR accumulated by each Non-Registrant. PYAR began accumulating on the date first exposed (i.e., the date hired) and ended at the earlier of either the date of diagnosis of the disease of interest, or the date of death, or the date last observed, or the end of the study period (Dec 31, 2010). For persons that were lost to follow up, their contribution to the PYAR was ceased on the date they were last known to be alive (i.e., according the MCP linkage data). The PYAR distribution was stratified according to five-year age and calendar-year periods and was used to calculate the expected number of cancers using the corresponding incidence rates from the Canadian and Newfoundland and Labrador (NL) reference populations.

As was done for the Registrant cohort, both Canadian and NL cancer incidence rates were used to calculate the expected number of cancers in this group. These rates were obtained from the Public Health Agency of Canada, for the years 1969 to 2010. For years when incidence rates were not available (i.e., 1955-1968) the rates from the adjacent (later) years were used. Standardized Incidence Ratios (SIRs) and the corresponding 95% confidence intervals were calculated using the OpenEpi software⁸ for the diseases of interest. As with the cohort of Registrants, because of the low numbers of women in this group and the small number of cancer cases (n=1) in the female portion of this group, data analysis was limited to the male population only.

4.25 Exposure-Response Analysis

Poisson regression was used to estimate the exposure-response relationship between lung cancer and time since first exposure, using an internal analysis of the cohort while controlling for the effects of age and calendar year. Because detailed work histories were not available for the 'Non-Registrants', the exposure-response relationship was restricted to time since first exposure only. Rate ratios (RR) were estimated for each category of time since first exposure (< 20, 20 ≤ 30, 30 ≤ 40, and > 40 years) relative to the lowest group and were adjusted for age (< 60, 60 ≤ 69, 70 ≤ 79 and >80), and calendar period (1955-1984, 1985-2010). The estimated RRs for the effect of exposure X was estimated as $e^{\beta X}$, where β is the regression coefficient for exposure X, and 95% confidence intervals (CI) were estimated from the standard error of β using a normal approximation.

4.3 Results

Of the 884 "Non-Registrants" there were 195 for whom a date of birth was not found and who were thus excluded from the study. There were also six people for whom a year first exposed could not be assigned, and they were also excluded from the study, leaving 683 subjects not included in the analysis of the previous chapter. Table 4-1 is a summary of the demographic characteristics of the 'Non-Registrants', as well as that of the BVMR group (i.e. "Registrants") for comparison purposes. The majority of the 'Non-Registrants' were male (91.7%), with only 57 females (8.3%) in the group. Like the "Registrants", these study subjects could be considered a fairly young group with the average age of the living being 60 and the youngest subject only 32 years old as of last follow up. The average age at death of the deceased members was 68 years with only 13.2% of the subjects known to be deceased.

Table 4-1: Demographic characteristics of the "Non-Registrants" and compared to the "Registrants".

	No. Of "Non-Registrants"	Percentage (%)	No. Of "Registrants"	Percentage (%)	Combined: "Non-Registrants" + "Registrants"	Percentage (%)
Sex						
Male	626	91.7%	929	97.8%	1555	95.2%
Female	57	8.3%	21	2.2%	78	4.8%
Total	683	100%	950	100%	1633	100%
Vital Status						
Alive	593	86.8%	769	80.9%	1362	83.4%
Deceased	90	13.2%	181	19.1%	271	16.6%
Total	683	100%	950	100%	1633	100%
Average Age						
Living	60	32 - 99	64	(38 - 91)	62	32 - 99
At death	68	43 - 92	67	(22 - 91)	67.5	22 - 92
Year First Exposed						
1957-64	137	20.1%	269	28.3%	406	24.9%
1965-69	116	16.8%	209	22.0%	325	19.9%
1970-74	228	33.4%	200	21.1%	428	26.2%
1975-79	172	25.2%	188	19.8%	360	22.0%
1980-84	27	4.0%	36	3.8%	63	3.9%
1985-94	3	0.4%	48	5.1%	51	3.1%
total	683	100%	950	100%	1633	100%

The majority of the "Non-Registrants" (approximately 59%) began working at the mine/mill in the 1970s when exposures were still relatively high, while 37% began in the

early years (i.e. 1960s) when the exposure levels were extremely high. Only 4.4% began work after the second company took over operations (i.e., after 1980) and when exposure levels had dropped off substantially. When compared to the "Registrants", this cohort included a slightly higher proportion of females (8.3% vs 2.2%), and a smaller proportion of deceased (13.2% vs 19.1%) former workers. This group also differed from the "Registrants" with respect to the date of first hire, with only 36.9% of the "Non-Registrants" as compared to 50.3% of the "Registrants having started work before 1969. Furthermore, this group also contains more people (5.1%) who started working in the later years of the operation when exposures were significantly lower (i.e. the late 1980s and early 1990s), as compared to the BVMR group (0.4%). Overall this suggests that this group of study subjects were likely less exposed and younger than the BVMR subjects, and more likely to have left the province when the mine closed.

4.31 Enumeration of the Cohort

An analysis of the union records allowed us to estimate how many people worked at the Baie Verte mine/mill over the years, and therefore, how representative the current study is of the overall cohort. Based on this analysis it would appear that the total number of people who can be identified as having worked for one or more of the three Baie Verte companies was between 2069 and 2213. From 1963 to 1981 the mine/mill operated as Advocate Mines Ltd. The highest employee number found in the union records (i.e. blue-collar workers) for Advocate Mines was 1725. There were also 152 people listed as "staff" (i.e. white collar workers) and 47 people for whom neither an employee number nor a "staff" designation was found. If we assume that the employee numbers were assigned

sequentially this would give an overall estimate of at least 1924 people (1725+152+47) who would have been employed during this period. From the BVMR study (Chapter 3) there were 893 people who began work at the mine/mill during the years 1963-1981, representing 46.4% of the total estimated workforce. The current study found an additional 674 people who began work during this same time period, bringing the coverage of the Advocate Mines Ltd. workforce to approximately 81.4%. However, if these numbers are correct there are an additional 357 people who were employees of Advocate Mines, and who were not captured in the union records. These numbers also do not include many of the stevedores because they were not unionized until the late 1970s or 1980, or other contractual workers who worked at the site.

Baie Verte Mines took over the mine/mill in 1982 and operations continued until 1991. The employee numbering system was restarted at one and the union records show that the highest employee number during this time period was 758. Of these 758 employees, records were found for 614, along with 18 "staff" and 11 people without either an employee number or a "staff" designation. This gives a minimum total of 787 Baie Verte Mines' employees for 643 (81.7%) of whom records were found in the union files. Of the 643 found in the union records, 498 also worked at Advocate Mines, Ltd. while 145 began working at the mine/mill during the period 1982-1991 and are listed as employees of the second company, Baie Verte Mines, only. If these numbers are correct, however, there are still at least another 144 people who worked at Baie Verte Mines but who were not captured in the union records. Therefore, it is harder to determine how representative the subjects in the current study are of the workers from the 1982-1991 time period.

Terra Nova Mines operated from 1991 to 1994, at which time the mine/mill closed permanently. This operation processed fibre from the tailings piles and was much smaller than the previous workforce. The highest employee number found in the union files for Terra Nova Mines was 97 and records for 80 of these were found. However, according to data from the BVMR there were 115 people who worked there during this time period. It is likely that the BVMR also captured staff (i.e., white-collar workers) who were not included on the seniority list found in the union records. All of the 80 people included in the union records for these final years had worked for all three companies and were long-standing employees.

Overall, there were at least 1924 people who worked at the mine/mill from 1963-1981, and an additional 145 who worked there from 1982 to 1991, giving an overall total of 2069 former workers. In addition there were 144 employee numbers that were unaccounted for from the union records and who may or may not have worked at the mine/mill during the earlier years. Records were found for an additional 63 people who did not have an employee number or a seniority date listed. Of these 63 people, 19 were listed as staff and 17 were listed as stevedores. Some or all of these people might be included in the 357 missing people from advocate mines and/or the 144 missing from the Baie Verte Mines list. Therefore, on the basis of the recovered union records, the overall number of people employed by the Baie Verte mine/mill is somewhere between 2069 and 2213.

4.32 Disease Incidence

Amongst the 683 male and female Non-Registrants for whom a date of birth and a year first exposed was found, there were 180 subjects for whom linkage to the NL provincial health

care database (MCP) was unsuccessful. This could be due to a number of reasons such as incorrect date of birth, incorrect spelling of their name, etc. These people were excluded from further analysis since a date last observed could not be determined. As explained above, females (n=57) were also excluded from further analysis because of the lack of cases of diseases. This left 446 subjects for the subsequent analysis.

There were also a large number of subjects (n=192) whose coverage under the MCP system was terminated, for various reasons, and who were therefore considered to be lost to follow-up. For subjects who moved outside of the province (n = 32) their date last observed was assigned as the date of termination, as provided by the linkage data from the MCP database. For subjects whose account had been inactive for a significant period of time (n = 160), the date last observed was assigned as ten years prior to the termination date since the province terminates accounts only when they have been inactive for ten years. In addition, there were termination codes for 55 deceased subjects in which case the date of death was provided and used as date last observed.

The group of Non-Registrants (n=446) remaining in the analysis experienced a total of 11,933 PYAR between Jan 1st, 1957 and Dec 31st, 2010. Observed and expected number of cancers, calculated using both the Canadian, and NL, cancer incidence rates, are given in Table 4-2. Using Canada as the reference population, no excess cancers were found in this group, with 61.58 cancers expected as compared to the 49 that were observed (SIR = 0.80). The number of observed cases of cancers of the colorectum and larynx was on par with what would be expected, with the SIRs for these diseases being very close to unity. The same is true for stomach cancer (SIR = 1.02) and for esophageal and lung cancer, with SIRs

of 1.14 and 1.16, respectively. Using NL as the reference group produced similar results, although the risk of lung cancer increased, with an SIR of 1.68, but the 95% confidence intervals included 1.0.

Table 4-2: SIRs for the "Non-Registrants" using both Canada and NL, as the reference population.

Disease	# Cases	PYAR	Incidence rate per 100 000 PYAR	SIR** - Canada		SIR** - NL	
				Expected	SIR (95% CI)	Expected	SIR (95% CI)
All Cancers	49	11,933	410.6	61.58	0.80 (0.59-1.06)	58.75	0.84 (0.62-1.11)
Esophagus	1	12,056	8.3	0.88	1.14 (0.03-6.35)	0.76	1.32 (0.03-7.35)
Stomach	2	12,075	16.6	1.96	1.02 (0.12-3.68)	3.50	0.57 (0.07-2.06)
Colorectal	8	12,060	66.3	8.73	0.92 (0.40-1.81)	10.85	0.73 (0.31-1.44)
Larynx	1	12,056	8.3	1.16	0.86 (0.02-4.79)	1.17	0.85 (0.02-4.73)
Lung	14	12,067	116.0	12.07	1.16 (0.63-1.95)	8.32	1.68 (0.92-2.82)

*95% CI does not include 1.0

**age and calendar year adjusted

When the Non-Registrants and the "Registrants" considered together as the "Combined Cohort", 220 total cancers were observed which was slightly lower than the number of expected cancers (Table 4-3), using both national and provincial incidence rates. When using the national incidence rates as the reference population there were an excess number of colorectal cancers and stomach cancers observed in this group. There was also an elevated risk of lung cancer and laryngeal cancer, but the confidence intervals included 1.0. When compared to the NL reference population lung cancer risk was significantly

increased (SIR = 1.45) with 53 observed cases versus 36.52 expected. Esophageal cancer, colorectal cancer and laryngeal cancer also had elevated risks.

Table 4-3: SIRs for the Combined Cohort (i.e., “Registrants” and “Non-Registrants”), using both Canada and NL as the reference population.

Disease	# Cases	PYAR	Incidence rate per 100 000 PYAR	SIR** - Canada		SIR** - NL	
				Expected	SIR (95% CI)	Expected	SIR (95% CI)
All Cancers	220	43,903	501.1	232.16	0.95 (0.82-1.09)	225.46	0.98 (0.85-1.13)
Esophagus	4	44,040	9.1	3.27	1.22 (0.33-3.12)	2.77	1.44 (0.39-3.68)
Stomach	10	44,047	22.7	3.71	2.70* (1.30-4.97)	11.66	0.86 (0.41-1.58)
Colorectal	51	43,790	116.5	31.31	1.63 (1.21-2.15)*	40.13	1.27 (0.94-1.68)
Larynx	8	44,040	18.2	4.14	1.93 (0.83-3.80)	4.41	1.81 (0.78-3.57)
Lung	53	43,092	123.0	41.28	1.28 (0.95-1.69)	36.52	1.45 (1.08-1.91)*

* 95% CI does not include 1.0

** age and calendar period adjusted

4.33 Time Since First Exposure

Table 4-4 shows the results of the analysis of the exposure-response relationship between lung cancer risk and time since first exposure for the Non-Registrant group. Time since first exposure was found to be a significant predictor of lung cancer risk ($p < 0.05$) when controlling for the effects of age and calendar period. In the group with 20 to 30 years since first exposure, the lung cancer risk was more than seven times that of the control group (RR = 7.46), and the lung cancer risk in the group with 30 to 40 years since first exposure was almost four times higher (RR = 3.81) than the control group. For the

Combined Cohort, this pattern persisted, with a clear increase in the risk of lung cancer with increasing time since first exposure, such that the risk for workers in the 20 to 30 year group was more than three times that of the control group (RR = 3.18). This increased to RR = 5.08 for the 30 to 40 year group and dropped off to 2.26 for the more than 40 year group.

Table 4-4: Poisson regression analysis of the exposure-response relationship between lung cancer and time since first exposure for the Non-Registrants alone and for the Combined Cohort.

	<i># Cases</i>	<i>PYAR</i>	<i>SIR**</i>	95% CI
Time Since First Exposure - "Non-Registrants" Only				
0 – 20 years	3	7708.75	1.00	---
20 – 30 years	7	2581.32	7.46*	1.50 – 37.18
30 – 40 years	4	1511.87	3.81	0.44 – 33.31
> 40 years	0	265.78	---	---
Time Since First Exposure - "Non-Registrants" + "Registrants"				
0-20 years	9	25 424.94	1.00	---
20-30 years	15	10 229.36	3.18*	1.19 - 8.46
30-40 years	23	6927.31	5.08*	1.45 - 17.75
>40 years	6	2004.30	2.26	0.53 - 9.68

*95% CI does not include 1.0

**age and calendar year adjusted

4.4 Discussion

The current study sought to identify and study the former chrysotile asbestos miners/millers from Baie Verte, who did not join the BVMR. This was done using historical union records and included an evaluation of the health effects of chrysotile asbestos

exposure on this group. This study identified an additional 884 people who worked at the mine/mill but was able to collect information for only about half of them. Overall, it is estimated that approximately 78.9 to 84.5% of the cohort was captured through a combination of the BVMR and the union records. This does not include employees of outside contractors who worked as stevedores during the early Advocate Mines period since these jobs did not become part of the union until the 1980s. However, it does include both unionized workers and some white-collar employees in administrative and managerial positions.

In the Non-Registrant group an increased risk of lung cancer and esophageal cancer was evident but the analysis was based on a small number of cases (14 and 1, respectively) and the confidence intervals included zero. However, when combined with the Registrants (i.e. the Combined Cohort) the risk of lung cancer was significantly increased with an SIR of 1.45 relative to the provincial rates. The risk of stomach and colorectal cancer was also significantly increased with SIRs of 2.70 and 1.63 when compared to the Canadian population. These results are consistent with the epidemiological analysis conducted in chapter 3 (the "Registrants") with the exception of laryngeal cancer which was elevated in the Combined Cohort but not statistically significant when compared to either the provincial or national population. Furthermore, analysis of the exposure-response relationship using an internal comparison group, demonstrated a substantial increase in the risk of lung cancer, for both the Non-Registrants and the Combined Cohort, with increasing time since first exposure. This is also consistent with the results presented in Chapter 3.

This study found fewer total cancers than would be expected in this group as compared to both the national and provincial cancer incidence rates. This may be explained by the fact that this group is still a relatively young cohort with an average age of 62 in the combined group and only 16.6% of the cohort is deceased. Also, many of the cohort members have not yet attained sufficient latency time for cancer development with almost 25% of the former workers having started work in the late 1970s and early 1980s. Accordingly, further follow up of this group will be essential to deciphering the health impact of exposure to chrysotile asbestos in this cohort of former miners/millers.

The incomplete follow up of the "Non-Registrants" with only 446 people of the original 884 included in the statistical analysis is also likely to have affected the results of this study. Because we are missing information for 50% of the study population (i.e., those people for whom a date of birth was not found and those who could not be linked to the provincial MCP database) we very likely are missing more cases of disease. For instance, it is believed that many of the people for whom a date of birth was not found were short-term workers who were hired just before the mine/mill closed in 1981. This is supported by the fact that a "hire/lay off" list and union cards that were found among the records listed the names of a substantial number of workers (n = 92) who were hired at the mine/mill just before its closure in 1981 and whose names were not listed on subsequent Baie Verte Mines' seniority lists. Also, there were 38 marine stevedores for whom a date of birth was not found and who also may have been short-term workers hired sporadically by the company on an as-needed basis.

In order to more accurately enumerate and follow up the full cohort, company personnel files for all the Non-Registrants, which are located at the provincial WHSCC office, should be examined. These records would be extremely useful since they contain the appropriate personal information (i.e. date birth, MCP number and social insurance number) to allow for better data linkage. These files also contain work history records that would permit the calculation of subject cumulative asbestos exposure, as well as duration of exposure. This would allow us to conduct exposure-response analyses similar to that conducted for Registrants of the BVMR whose employee files were provided to the research team by the WHSCC (Chapter 3). Therefore, obtaining the personnel files for the workers who have not registered in the BVMR is imperative for any follow-up study of this cohort in order to assess the full impact of chrysotile asbestos exposure.

Another limitation of the current study is that the electronic versions of both the cancer registry and the provincial mortality database did not begin until the early 1990s. This is significant because many of the workers in the current study and in the BVMR began work in the early 1960s and, with a latency period of 20 or more years for asbestos-related cancers, it is possible that a number of cancer diagnoses and/or deaths occurred during the 1980s but have not been included in our analysis either for the Registrants or for the Non-Registrants. This hypothesis is supported by the fact that eight of the 14 lung cancer cases observed among the "Non-Registrants" were actually found in the union records rather than from the data linkage obtained from the cancer registry and the mortality database. All eight of these cases occurred in the 1980s and were recorded either in death certificates and/or in WHSCC records. Furthermore, union records note seven more lung cancer cases among the Non-Registrants but for which no proof of diagnosis could be found. It is

possible that these cases also occurred prior to the creation of the province's electronic databases.

These additional lung cancers may also be among workers who no longer live in NL. It is believed that many of the people in the current study moved out of the province in the early 1980s when the operation, the town's principal source of employment, closed for the second time. In fact, numerous address cards were found in the union records that listed forwarding addresses for former workers who had moved out of the province during this time. MCP accounts had also been terminated for thirty-two subjects because the holder had left the province. In addition, it is worth noting that for a large number of former employees who were lost to follow up (n=160) their names and dates of birth were linked to the MCP but their accounts had been terminated because they were inactive for a period of at least ten years, most likely because they had left the province. Because of the limitations related to data linkage to the provincial cancer registry and mortality databases and because of the large number of people lost to follow-up because of migration out of the province, the number of cases of asbestos-related cancers in this study is very likely underestimated. Linkage to the national mortality database and to the national cancer registry could help capture disease incidence and/or mortality for at least some of these subjects.

While there were only two pleural mesotheliomas found in the "Registrants" and no additional cases found in the current study, an inquiry into the number of mesotheliomas documented in the NL provincial cancer registry identified 52 diagnosed cases since 1969. It is possible that some of these cases involved workers who were exposed at the only

asbestos mine/mill in the province but that were not included in this study for one or more of the reasons identified above. It is also possible that given the very long latency period that is often associated with mesothelioma additional cases may be observed in this group in years to come.

In conclusion, the current study has demonstrated a positive association between chrysotile asbestos exposure and an increased risk of cancer of the lung, colorectum, and larynx in the combined group of former chrysotile miners/millers. It has also demonstrated an increased risk of lung cancer with increasing time since first exposure. While an analysis of union records has allowed the study of a substantial number of former employees not included in the BVMR, follow-up for many subjects was unsuccessful because electronic linkage to health records was limited to provincial databases only and because of the limited years of coverage of these databases. Further investigation of this cohort is needed using personnel files from the WHSCC. Information from these files would help capture health information on subjects lost to follow up as well as provide work history information and allow for the calculation of cumulative exposure and an analysis of the exposure-response relationship. Also, data linkage to national databases, such as statistics Canada mortality database and the national cancer registry, would likely identify a higher number of deceased persons and cancer cases that were missed in this study.

4.5 References

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Chapter 5: Conclusion

The epidemic of asbestos-related disease that the developed world has experienced over the past fifty or more years has been described as occurring in three "waves". The first wave occurred in workers who were exposed to asbestos from handling raw asbestos fibres. This involved workers in the mining/milling industry, transport workers who handled the bags of raw fibres during loading and transport, and workers who manufactured asbestos-containing products such as friction products, cement products and textiles. The second wave of asbestos-related disease occurred in workers using and installing asbestos-containing products. This included construction workers, ship builders, electrical installers, and boiler makers who were exposed to asbestos while installing, cutting, and manipulating these products, and also insulation workers who applied asbestos-containing fireproofing/insulation in buildings throughout the 1960s and 1970s and who are well known to have experienced a large number of asbestos-related disease, notably mesotheliomas. The third wave is said to have occurred in people who were exposed through secondary use of asbestos-containing products. For example, building renovators and building maintenance personnel who are exposed to asbestos fibres from building products that are disturbed during renovation or maintenance activities as well as workers in the asbestos abatement industry who are exposed to asbestos fibres while removing asbestos-containing materials from buildings.

The majority of the asbestos-related diseases seen today are associated with asbestos exposures that occurred years ago in the primary and secondary asbestos industries and are largely considered to be part of the first and second "waves" of asbestos-related

disease. While these "waves" are, for the most part, past in developed countries, the third wave has only just been recognized in the past decade or so, and is anticipated to continue into the current century because of ongoing exposure to asbestos and the long latency periods involved. In Canada, for instance, it is estimated that there are currently 152 000 workers who are exposed to asbestos in the workplace 88% of whom are in the construction industry¹. Although current exposure levels are generally much lower than that experienced by workers years ago, current workers are still at risk of developing asbestos-related diseases². Workers in the asbestos abatement and remediation industry are exposed to asbestos on a regular basis and their exposures are known to be well above the occupational exposure limits³. Although this industry is highly regulated and control measures are quite strict these workers have been shown to be at an elevated risk of asbestos-related diseases⁴. Other groups who may potentially be exposed to asbestos and thus at risk of developing asbestos-related diseases include people who live close to naturally occurring asbestos deposits or sites that are environmentally contaminated with asbestos fibres (e.g., old mine/mill sites or manufacturing plants that have not been properly decommissioned or remediated). Attention has also focused on the possible exposure of occupants from deteriorating asbestos-containing materials in the buildings where they work or live. The asbestos to which these various groups are currently exposed is primarily chrysotile since 95% of the world's past asbestos production (and 100% of current asbestos production) has been chrysotile and the large majority of asbestos-containing materials in buildings are chrysotile^{5,6}.

Furthermore, these "waves" of asbestos-related disease experienced by the developed world are only beginning to manifest themselves in developing countries where asbestos

continues to be mined and/or used in the production of asbestos-containing products. This is evident from the results of numerous studies that have been conducted in China, one of the current major producers and consumers of chrysotile asbestos, where research has shown that the risk of asbestos-related disease in both mining/milling and asbestos manufacturing industries is of great concern⁷⁻¹³. This is also true of other developing countries, such as India and Indonesia, where the consumption of asbestos has increased over the past 20 to 30 years. The burden of asbestos-related diseases in these countries is anticipated to peak in the coming decades^{14,15}. Because the asbestos market is exclusively chrysotile, chrysotile exposure remains an important public health issue in both developed and developing countries and the controversy regarding the relative toxicity of chrysotile as compared to amphiboles remains a topic of scientific concern.

The reason for the delayed response to the pending epidemic of asbestos-related disease in developing countries is due, in part, to the belief, fostered by industry representatives and some researchers that chrysotile asbestos is, unlike the amphiboles, actually safe. The discovery of the strong association between amphibole asbestos exposure and mesothelioma in the 1960s led asbestos-producing companies and countries to attempt to save the chrysotile industry by promoting the safe use of chrysotile. It has been, and sometimes still is, argued that chrysotile asbestos is less toxic than the amphibole forms, particularly with regard to mesothelioma, and that the exposures required to induce asbestosis and asbestos-related cancers are considerably higher when chrysotile asbestos is the only type of exposure. It is on this basis that the asbestos industry and governments of producing nations (specifically Canada and Russia) have succeeded in preventing the addition of chrysotile asbestos to the Rotterdam Convention's list of chemicals requiring

Prior Informed Consent and have justified the continuing sale and use of the mineral in developing countries¹². In 2006 and 2008, Canada was the only western country to oppose this addition, despite the fact that adding chrysotile to this list would not ban sales or exports of these products but would merely ensure that importing countries are warned about the health hazards related to the product they are importing and would be required to provide prior informed consent to receive them.

Numerous epidemiologic studies, case reports, controlled animal experiments, and toxicological studies refute the assertion that chrysotile is safe¹⁶⁻²³. Recently, the results of recent epidemiological studies in countries such as China also demonstrate that claims regarding the safe use of chrysotile asbestos are not credible. As long as there remains debate in the scientific literature about the relative toxicity of chrysotile as compared to the amphiboles, and as long as there is continuing exposure to chrysotile asbestos, it is likely to never be subject to a complete worldwide ban and the epidemic of asbestos-related diseases will continue. Furthermore, the risk associated with low exposures, which would be representative of building occupants or environmental exposures, is uncertain because the risk assessment process has relied on available epidemiological data that largely represents very high exposure which were typical in workplaces years ago. While researchers have been successful at using existing epidemiological data to estimate the risk of asbestos-related disease at low exposures²⁴⁻²⁸, it is recognized that there are too few studies with exposure assessments of sufficient quality to adequately address the questions of potency. It is also recognized that additional research on the health risks of chrysotile asbestos is required, particularly studies with high quality exposure assessments, to allow risk assessors to model attributable risk with greater confidence^{29,30}. This thesis not only

supports the results of the Chinese studies it also provides the literature with a high quality exposure assessment for chrysotile asbestos that can be used in the risk assessment process.

The research presented in this thesis, along with the Baie Verte Miners' Registry project, provides a major contribution to the discussion on the toxicity of chrysotile asbestos. This thesis reports on a new cohort of former chrysotile miners/millers from Baie Verte, NL, Canada, and has described the retrospective exposure assessment process which was used to conduct an epidemiological analysis of asbestos-related diseases in this group. This analysis demonstrated an increased risk of asbestosis, lung cancer, and mesothelioma, as well as positive associations with cancer of the larynx, stomach, esophagus and colorectum, associated with exposure to chrysotile asbestos in the mining/milling industry. This is consistent with other studies of chrysotile exposed workers in the mining/milling industry, including the recent studies of Chinese miners/millers.

The first study in this thesis (chapter 2) described the methods used to develop the job exposure matrix that was used to perform a retrospective exposure assessment for the group of former workers who joined the BVMR. This exposure assessment demonstrated that exposures at the mine/mill complex were very high in the early years when production first began (i.e., the 1960s and 1970s), decreased over the years as the knowledge of the health effects of asbestos became known and control measures were implemented to reduce exposure. The exposure assessment developed for the BVMR can be, according to the evaluation performed in chapter 2, considered of good quality in comparison to other exposure assessments for asbestos cohorts in the published literature,

because it was developed using best established statistical methods from a large database of quantitative personal exposure measurements. The only other quantitative exposure assessment in the chrysotile mining/milling industry is that of the Québec miners/millers cohort^{31,32}. The studies of the Québec cohort have been criticized as being heavily influenced by the asbestos industry^{33,34} and the quality of its exposure assessments has been called into question^{29,30}. The work done for the BVMR and for this thesis provides a much needed substitute for the studies of the Quebec miners/millers.

In the second study (Chapter 3) an epidemiological analysis demonstrated an increased risk of asbestos-related diseases in the group of workers who registered for the BVMR, specifically, increased risks for cancers of the lung, larynx, esophagus, stomach and colorectum. There were also 40 cases of asbestosis and two mesotheliomas observed in this group. An exposure-response relationship analysis also demonstrated an association between various measures of asbestos exposure and lung cancer, colorectal cancer and asbestosis. This is in keeping with other studies of chrysotile exposed workers, including those in the Chinese mining/milling industry.

The third study (Chapter 4) described the methods used to expand the cohort of former Baie Verte employees using union records to identify and study workers who had not joined the voluntary registry. Although this study was successful at increasing the study population by approximately 50%, a fairly large number of people identified could not be included in the study because of missing information. However, an epidemiological analysis of cancer risk in the remaining group of "Non-Registrants", showed an increased risk of lung cancer which was maintained when the two groups (i.e. "Non-Registrants" and

"Registrants") were combined. There was also an increased risk of colorectal and laryngeal and cancer observed in the combined group. Lung cancer risk was also found to increase with time since first exposure. This study also identified the need for more complete follow up of this group to fully assess the health impact of the Baie Verte Chrysotile mine/mill on these workers.

Overall, this thesis confirms that chrysotile asbestos causes lung cancer, asbestosis, and mesothelioma, as well as colorectal cancer and laryngeal cancer, in a large group of former employees of a chrysotile mine/mill. It supports the fact that the controversy surrounding the potency of chrysotile asbestos relative to the other types of asbestos fibres is one of purely politics and therefore lends to the argument that a complete ban on all types of asbestos, including chrysotile, is warranted. Chrysotile asbestos is clearly a health hazard to those who are exposed to it and since it is the only type of asbestos still being produced and exported around the world immediate action should be taken. As for the Baie Verte Miners' cohort, further research is still needed to fully enumerate the full cohort and more complete follow up, however this preliminary examination of exposure and health outcomes clearly supports the notion that chrysotile asbestos is detrimental to the health of exposed workers and further identifies the need to cease all production and use of chrysotile asbestos worldwide in order to prevent further outbreaks of disease in countries where asbestos continues to be produced and consumed.

5.1 References

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