



Occupational
Cancer
Research
Centre

INVESTIGATION OF MCINTYRE POWDER EXPOSURE AND NEUROLOGICAL OUTCOMES IN THE MINING MASTER FILE COHORT: FINAL REPORT

Submitted to:

The Workplace Safety and Insurance Board of Ontario

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Occupational Cancer Research Centre
Ontario Health (Cancer Care Ontario)



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Acronyms

CI	Confidence Interval
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
HIN	Health Insurance Number
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems 10 th Revision
ICD-9	International Statistical Classification of Diseases 9 th Revision
ICES	Institute for Clinical and Evaluative Sciences
MMF	Mining Master File
MP	McIntyre Powder
MRF	McIntyre Research Foundation
NACRS	National Ambulatory Care Records System
OCRC	Occupational Cancer Research Centre
OHIP	Ontario Health Insurance Plan
RPDB	Registered Persons Database
RR	Incidence rate ratio
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
WSIB	Workplace Safety and Insurance Board

Executive Summary

McIntyre Powder (MP), an aluminum and aluminum oxide powder, was developed by the McIntyre Research Foundation and administered to Ontario miners from 1943 to 1979 as a purported prophylaxis against the development of silicosis. Workers were required to inhale MP, which was dispersed in the air in sealed change rooms, prior to their underground work shifts. The practice was ended when it was determined that it offered no protective effect against silicosis. Concerns were also raised regarding potential neurological health effects among MP-exposed miners.

Aluminum has long been suspected of having a role in the development of neurological diseases, but the results of experimental and human studies are mixed. MP exposure among miners may be different from these other studies because of the particle sizes (often in the nano range) and the brief but very high doses that were delivered. There are very few studies that have examined the risks of neurological diseases among MP-exposed miners, and previous findings are inconclusive. The role of MP in neurological disease risk is at issue because questions have been raised regarding workers' compensation benefits for exposed miners. We sought to evaluate neurological disease risk among miners working in Ontario at the request of Ontario's Workplace Safety and Insurance Board (WSIB). Our study examined risks of Alzheimer's disease, parkinsonism, Parkinson's disease and motor neuron disease in the largest ever cohort of MP-exposed miners.

For this research project the Occupational Cancer Research Centre (OCRC) has completed the following activities:

1. **Assessed the completeness of the electronic version of Mining Master File (MMF)** to ensure that the file contains all available data on miners from existing paper records, and assess whether the WSIB holds a complete set of paper records;
2. **Enhanced the MMF** with additional data on McIntyre Powder from available historical records located at the Occupational Cancer Research Centre (OCRC), WSIB, and Ontario Provincial Archives;
3. **Conducted MMF linkage** to hospital discharge, ambulatory care, and outpatient databases held at the Institute for Clinical and Evaluative Studies (ICES) to identify chronic neurological diseases;
4. **Completed cohort analysis** to compare the risk of neurological disease in miners who have been exposed to MP to the general population of Ontario and, in a separate analysis, to other miners in the cohort with no record of exposure to MP.

Activities 1 and 2 were completed previously and are described in detail in the Interim Report submitted to the WSIB (September 14, 2018¹). Activities 3 and 4 are described in the present report.

The Mining Master File (MMF) is an electronic database of medical exam records from 1928 to 1988 for Ontario mining workers and captures work histories spanning 1890 to 1988. These records contain information for approximately 90,000 Ontario miners regarding the types of mines they worked in, durations of employment, and job classifications. Records also include information about whether and when a miner was exposed to MP, and in which mine they were employed. This study used two methods for classifying miners as exposed or unexposed to MP. The first relied on self-reported MP exposure that was recorded during annual medical exams. The second used information about the years of employment, the mines in which they worked, and their job classification cross-referenced with MP licensing records, government, and health and safety organization records.

¹ Demers PA, Berriault CJ, Zeng X, Arrandale, VH. Investigation of Neurological Outcomes and McIntyre Powder Exposure in the Mining Master File Cohort: Progress Update. Toronto, Canada: Cancer Care Ontario, Sep 14, 2018. pp 15.

MMF records do not contain any information about neurological disease diagnoses. To identify cases of disease, records were linked by the Institute for Clinical and Evaluative Sciences (ICES, Toronto) to diagnostic information in hospitalization (DAD), ambulatory care (NACRS) and physician billing (OHIP Claims) records. Using these data, epidemiologists at the OCRC were able to compare risks of neurological disease among MP-exposed miners to the general population of Ontario, as well as to unexposed miners. Effects of duration of employment, duration of exposure, time since last exposure, and exposure by ore mined (e.g. gold, uranium, nickel or copper) were examined.

Among miners in the MMF that were determined to be eligible for the study cohort, almost 80% were successfully linked to administrative health records. Workers were eligible for study inclusion if they were alive and living in Ontario as of January 1, 1992, and if their records contained sufficient information for linkage and analysis.

This study included 36,826 Ontario miners with 9,548 (25.9%) exposed to MP according to self-reports. Among these MP-exposed workers, 334 were diagnosed with Alzheimer's disease, 364 were diagnosed with parkinsonism, 251 were diagnosed with Parkinson's disease and 20 were diagnosed with motor neuron disease during the 1992-2018 follow-up period. The second method for classifying MP exposure based on years of employment, mine, and job type classified 13,828 workers as exposed.

Miners with MP exposure had a 34% greater incidence rate of Parkinson's disease (RR 1.34, 95% CI 1.14-1.57) and a 19% greater rate of parkinsonism (RR 1.19, 95% CI 1.05-1.36) compared to miners that had never been exposed to MP based on self-report. The increased risk of parkinsonism was due to the excess cases of Parkinson's disease. With the second exposure assessment approach, the risk of Parkinson's disease increased with duration of MP exposure and was highest for workers with more than 10 years of MP exposure. Using the first exposure assessment approach based on self-report, all durations of exposure showed similar elevations of risk for Parkinson's disease. It has been reported that the formulation of MP changed in 1956, with the powder's particle size becoming smaller. Risk of Parkinson's disease was highest among workers that had at least some exposure to the post-1956 MP formulation. No association was observed between MP exposure and risk of Alzheimer's disease or motor neuron disease for any duration of exposure or calendar period of exposure.

MP was administered to workers in Ontario's gold and uranium mines. There were differences in the timing of administration between these mines, with use peaking in gold mines in the early 1960s and peaking in uranium mines a decade later. The risk of Parkinson's disease was highest among MP-exposed gold miners, while no increased risk was observed among gold miners without MP exposure. Additionally, analyses were suggestive of an increased risk among MP-exposed uranium miners, especially for parkinsonism. Given that MP exposure among uranium miners generally occurred more recently than among gold miners, it is possible that associations will become clearer with additional follow-up in the future.

Compared to the general population of Ontario, no excess risk was observed for Parkinson's disease or parkinsonism for miners in general, but those with MP exposure had 27% and 14% increased risks of Parkinson's disease and parkinsonism, respectively. Mining industry workers had 20% increased risk of Alzheimer's disease, and 31% increased risk of motor neuron disease, but this risk was not associated with MP exposure.

This was the single largest study of neurological effects of MP exposure. In contrast with previous studies based on mortality, which often miss neurological diseases not recorded on death certificates, this study captured diagnoses of neurological disease from existing administrative health records. These data sources became available in 1992 and thus diagnoses preceding this date were unavailable for study. Also, while it was of interest to examine the effects of MP on the risk of ALS, these cases could not be identified in the data. However, it has

been reported that approximately 70% of motor neuron disease cases are ALS. If MP was strongly associated with ALS risk, we would have expected to observe an association for motor neuron disease.

This study of Ontario miners found evidence of an association between MP exposure and increased risk of Parkinson's disease, with the highest risk among workers exposed in gold mining. No association was observed for MP exposure and Alzheimer's disease or motor neuron disease, but an overall increased risk in miners compared to the general population was observed. Limitations in available health data sources prevented a large proportion of miners, including almost 2/3rd of miners historically exposed to MP, from being included in our analysis, and follow-up was limited to years after 1992 only. Further study of the causes of neurological disease among miners is warranted.

Background

McIntyre Powder (MP), an aluminum and aluminum oxide powder, was developed by the McIntyre Research Foundation (MRF), based in Ontario, as a purported prophylaxis against the development of silicosis (1-3). It was administered to Ontario gold and uranium miners from 1943 to 1979. The composition of MP was reported to be 85% aluminum oxide and 15% elemental aluminum (4). Workers were required to inhale MP, which was dispersed in the air in sealed change rooms (see Figure 1 for an example), prior to their underground work shifts, for a prescribed 10 minutes at concentrations of 20,000 – 34,000 parts per ml in air (2, 3, 5, 6). Based on historic documents reviewed by the Occupational Cancer Research Centre (OCRC), exposure ranged from 5 to 20 minutes. The practice was ended when it was determined that it offered no protective effect against silicosis. Concerns were also raised regarding potential neurological health effects among MP-exposed miners (7-13). MP was used extensively in Ontario, as well as across Canada in Quebec, British Columbia, and in a small number of mines in Manitoba, the Northwest Territories, Saskatchewan and the Yukon (14). It was also used globally including in foundries and clay and refractory materials plants in the United States (Ohio, Pennsylvania, New York, West Virginia, Missouri, Indiana, Illinois, Michigan, New Jersey, California, Georgia, Maryland, New Hampshire, Oklahoma, Tennessee, and Wisconsin), and mines in Mexico, Chile, Australia, the Belgian Congo, and the United Kingdom (14).

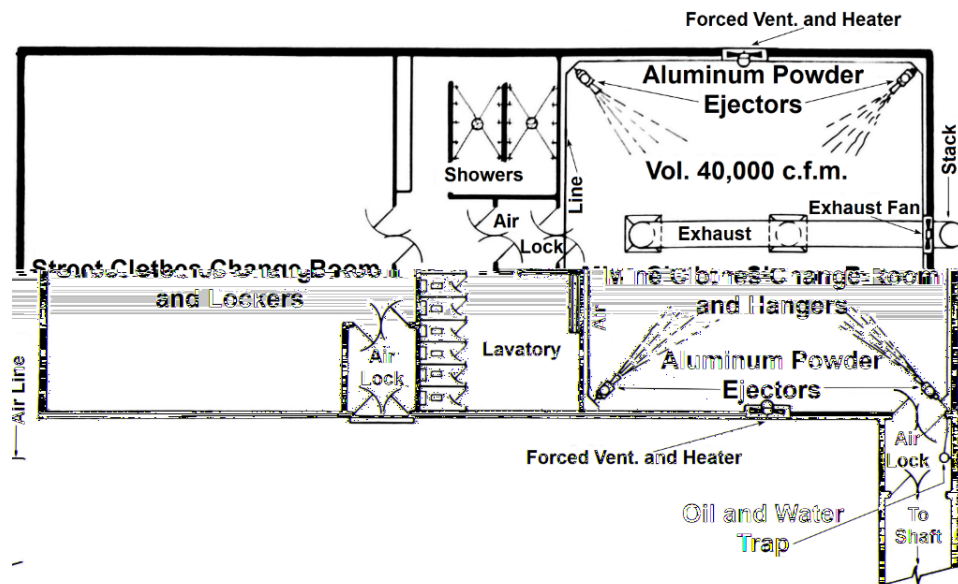


FIGURE 1 ALUMINUM POWDER DISPERSAL IN A MINE DRYHOUSE ADAPTED FROM NEWKIRK ET AL., 1957.

The hypothesis that aluminum was related to neurological disease emerged from observations of elevated aluminum levels in brain tissues of Alzheimer's (15, 16) and Parkinson's disease patients (17, 18). Studies in animal models have also reported pathophysiological changes following aluminum exposure that resemble neurological diseases (19, 20) including Alzheimer's (20-24), Parkinson's (25, 26) and motor neuron disease (27, 28). However, the results of epidemiological studies of aluminum exposure and neurological disease have been inconsistent (29-34). In a meta-analysis of eight cohort and case-control studies, Wang and colleagues (2016) reported that individuals with chronic aluminum exposure were 71% more likely to develop Alzheimer's disease (35). Fewer epidemiological studies have directly explored the relationship between aluminum exposure and Parkinson's disease (29, 36-38) or motor neuron disease (34, 39, 40). While the relationship between aluminum and Alzheimer's disease has been examined in epidemiological studies, hypotheses regarding Parkinson's

disease have centered almost entirely on increased aluminum concentrations observed in the *substantia nigra* of these patients (18) and suggestive evidence regarding pathogenesis of several mechanisms of aluminum-induced neurodegeneration (36). No association was found between aluminum concentration in brain samples and Parkinson's disease in a 36-year multicenter study (16) and a small case-control study of Italian ALS patients did not find an association with aluminum (33, 34).

Occupational studies of aluminum exposure and neurological disease have also had mixed results (32, 41) and mainly used neuropsychological tests or other performance measures as opposed to clinical diagnoses (42, 43). Occupational aluminum exposure can occur in a variety of settings (44), ranging from extraction of aluminum from bauxite (45) to metal refining and industrial use of aluminum products (46). A meta-analysis of occupational exposure to aluminum (47-49) did not find an association with Alzheimer's disease (50). Zayed and colleagues (51) found an elevated risk of Parkinson's disease associated with occupational exposure to a combination of manganese, iron and aluminum, but the risk associated with individual metals could not be determined. Semchuk and colleagues (52) did not find an association between occupational exposure to aluminum and Parkinson's disease in an Alberta-based case-control study using self-reported work history. Evidence regarding the association between occupational aluminum exposure and ALS or motor neuron disease is sparse (53, 54).

While evidence from other aluminum-exposed workers has been used to infer potential neurological risks of MP (9, 10, 12, 55), exposure to aluminum through MP exposure differs in some ways from other occupational and non-occupational aluminum exposure (56, 57). Most non-occupational exposure to aluminum is dietary, with particular focus on exposure through antacids (38, 58) and drinking water (59, 60). On the other hand, occupational exposure is through inhalation of dusts and fumes, generally over the course of the full work shift (46).

In contrast with other sources of aluminum exposure, exposure to MP was characterized by very high, purposeful short-term exposure (3, 5). MP particle sizes were intentionally minimized based on a supposition that this would better protect against silicosis (4, 61), but this may have further increased the potential for neurotoxicity. There is limited evidence regarding the risk of neurological disease due to MP exposure among miners. To date there have only been two published epidemiological studies; one in Ontario by Rifat and colleagues (2) and one in Australia by Peters and colleagues (62). Other reports of this association include a conference abstract from a case-control study by McDonald et al. (63), and Rifat's PhD thesis (64) which formed the basis of the published Ontario study and subsequent unpublished follow-up report (65). More recently there have been toxicological studies on the chemical composition of the powder (66) and the aluminum concentration found in the lungs of MP-exposed miners (67). There has also been one qualitative study on the perceived impacts of MP exposure on miners in Ontario. While that study cannot provide any evidence of causation, it describes the individual and organizational impacts that MP has had on miners who were exposed to MP in Ontario mines (68).

Rifat and colleagues (2) used data from annual medical exam records to derive a sample of 6,604 underground miners for inclusion in a morbidity prevalence study in 1988/89. Among these miners, 2,414 (37%) has MP exposure. This database used to identify miners was the Mining Master File (MMF), a silicosis registry and system developed to certify that miners were healthy enough for underground mining in the province, used in the present study. The researchers found no difference in self- and proxy-reported neurological disease between the MP-exposed and unexposed workers, but found that exposed workers performed more poorly on cognitive function tests, which was suggestive of the development of neurological disorders associated with MP exposure (2). A follow-up study was completed in 1995, involving miner and informant interviews, neuropsychologic, neurological and physical examinations (65). The follow-up found no evidence of a dose-response relationship

for MP exposed miners with cognitive impairment but had challenges with tracing of subjects and power to detect elevations.

Peters and colleagues (2013) studied MP exposed Australian gold miners using a design somewhat similar to the current study (62). MP was utilized in Western Australian gold mines from the early 1950s until the late 1960s, ending about 10 years sooner than in Ontario mines. The cohort was comprised of 1,894 underground miners, with 647 (34%) exposed to MP according to annual chest X-ray records. The cohort was followed for neurological disease in the Western Australian Registrar General's Mortality Database for 1960 to 2009 and comparisons were made to the Western Australian population. Of the 1,577 miners who had died, 16 had Alzheimer's disease as the underlying cause. A suggested elevation in deaths from Alzheimer's disease (Standardized Mortality Rate (SMR) 1.38, 95% Confidence Interval (CI) 0.69-2.75) among the MP-exposed group was observed. Due to the nature of death certification, neurological diseases are unlikely to be listed as the cause of death (69, 70), so it is noteworthy that an elevation in a neurological disease as a cause of death, specifically Alzheimer's disease, was observed in this cohort (71). The study also observed that there was no protective effect of MP against silicosis. In the United Kingdom, McDonald et al. (63) examined dementia and Alzheimer's disease mortality among MP-exposed Cornish tin miners. Only a conference abstract reports this study and it describes few details and provides no risk estimates or sample size.

The relationship between MP exposure and neurological disease remains controversial, and several reviews have been undertaken with little consensus. A 2017 rapid systematic review was published by WorkSafeBC Evidence-Based Practice Group (9), a systematic review was reported by Intrinsik to the Workplace Safety and Insurance Board (WSIB) in 2017 (10), and a critical review of the Intrinsik report was commissioned by the Occupational Health Clinics for Ontario Workers in 2019 (71). This study of Ontario underground mining industry workers aims to contribute to a better understanding of the potential relationship between MP exposure and neurological disease outcomes. This study uses a cohort of miners derived from the Mining Master File (MMF), which contains individual level information including detailed job histories for approximately 90,000 miners who were employed in Ontario mines. This database also contains record of miners' exposure to MP. This large occupational cohort provides the opportunity to investigate the relationship between MP exposure to neurological disease development with far greater power than previous studies. Through linkage to existing administrative health databases, this study examined the association between MP exposure and neurological diseases including Alzheimer's disease, parkinsonism, Parkinson's disease and motor neuron disease.

For this research project the Occupational Cancer Research Centre (OCRC) has completed the following activities:

1. **Assessed the completeness of the electronic version of MMF** to ensure that the file contains all available data on miners from existing paper records, and assess whether the WSIB holds a complete set of paper records;
2. **Enhanced the MMF** with additional data on McIntyre Powder from available historical records located at the Occupational Cancer Research Centre (OCRC), WSIB, and Ontario Provincial Archives;
3. **Conducted MMF linkage** to hospital discharge, ambulatory care, and outpatient databases held at the Institute for Clinical and Evaluative Studies (ICES) to identify chronic neurological diseases;
4. **Completed cohort analysis** to compare the risk of neurological disease in miners who have been exposed to MP to the general population of Ontario and, in a separate analysis, to other miners in the cohort with no record of exposure to MP.

Activities 1 and 2 were completed previously and are described in detail in the Interim Report submitted to the WSIB (September 14, 2018). Activities 3 and 4 are described in the present report.

Methods

The derivation of the study cohort, linkage methods and data sources, and analytical approach are described in detail below. As a brief overview, the cohort of miners for this study was derived from the Mining Master File (MMF), which contains individual level information for approximately 90,000 miners who were employed in Ontario mines. The study cohort was linked to existing administrative databases to identify workers alive and in province, and workers eligible for disease follow-up were linked to hospital discharge, physician billing, and ambulatory care records to identify cases of neurological diseases of interest. The risk of neurological disease among MP-exposed workers was compared to miners who had never been exposed, as well as the general population of Ontario.

Mining Master File (MMF)

The MMF is an electronic database containing information on Ontario underground miners who underwent pre-employment and annual medical exams between 1928 and 1988. Pre-employment and annual chest x-ray examinations were required for underground miners by the Government of Ontario Ministry of Health beginning in 1928 (1). Annual exams were conducted by physicians at provincially run chest clinics. These clinics were held to certify that a miner was healthy enough to work underground with dust exposure and were focused on detecting signs of silicosis and other non-cancer respiratory illnesses. Employment information since last examination, the mine of employment, ore mined, and job classes, was also recorded on paper cards. Workers employed underground for fewer than 50 hours per month were exempt.

Starting in 1951, underground miners with radiological signs of silicosis or tuberculosis were included in a registry, and data were coded onto punch cards from the existing hard copy annual examination cards. In 1955 all those with 60 months of cumulative mining experience were recorded, irrespective of chest x-ray status. Beginning in the late 1960s, the MMF was created by transferring the data to computer format (1). The MMF was updated annually from 1951 to 1987. It has been utilized and modified for use in occupational epidemiology studies starting in 1974 with the Ontario uranium miner cohort, the 1976 Ham Commission report (72), studies of lung (73, 74) and stomach cancer (75), and the Occupational Disease Panel's Ontario hard rock mining report in 1994 (76). The electronic database of over 93,000 miners has not been updated since January 1988, but was converted to a SAS data file for the present study. After excluding duplicates and those refused certification, the MMF database contains work history information for approximately 90,000 Ontario miners.

The MMF was created long ago and has never, to our knowledge, been assessed for its completeness and accuracy compared to the paper records that were used to create it. Prior to initiating the present study, concerns were raised that the MMF hard copy cards located at the WSIB might contain more mining industry workers than the MMF electronic data file, or vice versa. This prompted a data cross-checking exercise in order to confirm if the electronic and paper files contained information on the same individuals. An assessment of completeness of the information contained within the electronic files was completed, with a particular focus on MP exposure information. This section describes briefly the OCRC's assessment of the MMF records, which preceded the present study, and was reported in detail in the Interim Report to the WSIB (September 14, 2018).

A random sample of 500 miners from the electronic file was generated using SAS® software, Version 9.4 (77) and these records were matched with the corresponding exam cards housed at the WSIB. An additional random

sample of 500 hard copy MMF exam cards was pulled from WSIB cabinets. Hard copy exam cards were sampled proportional to mining region size (# of miners certified by mining region). Cards were drawn systematically from the front middle and back of each region drawer section until the determined number of cards per region was reached, ensuring no recurring cards from the previous electronic file random sample list. These were also cross-referenced with the MMF electronic data file in order to ascertain if any of these were missing and whether all relevant information was accurately entered into the electronic file.

The sample of 1,000 mining industry workers represents only 2% of the workers in the MMF, but this exercise provided an assessment of the completeness of the file by identifying the proportion of workers missed or the proportion of records with missing data. Only 1 of the 500 randomly selected electronic database record was not found among the hard copy exam cards, and 3 of the 500 randomly selected exam cards were not found in the electronic database. Through comparison of hard copy and electronic records, discrepancies generally appeared to result from simplifying data entry and limitations of the database technology when the data were first transferred to the new electronic tape format. With a 99.6% overlap of records found in both electronic database and hard copy exam cards we determined missing data entry would not affect study conclusions.

Although the full MMF contains data on approximately 90,000 miners, inclusion and exclusion criteria were applied to establish the study cohort. Because health records were only available starting January 1, 1992, only workers who were alive and living in Ontario as of that point could be included. People whose records indicated that they were over 100 years old as of January 1, 1992 or who were younger than 15 or older than 65 years at beginning of follow-up were excluded to ensure that only people with accurate dates of birth and employment were included in the cohort. Individuals last observed prior to 1964 in previous follow-up were excluded. People with insufficient information for data linkage (complete name and birthdate and sex) were excluded. People with no work history to allow classification of exposure were excluded. Lastly, confirmed duplicate records were excluded after ensuring that no work history information is lost. These exclusion criteria were applied both before and after linkage to the RPDB, since the latter linkage provided additional information (See Figure 2).

McIntyre Powder exposure assessment

In the MMF electronic database transferred to the OCRC, MP exposure was recorded for each miner's annual medical examination record indicating YES/NO for exposure to MP. This information was separate from the work history, and information about mine of employment or job category in the electronic database. It is important to note that hard copy examination cards did not include a question about MP exposure until it was added in July 1951 (Appendix A, Figure A-1) where exposure was specified as Al. or Alum. on the record card. To fill this gap in information, MP exposures were backfilled in the database to 1943 for 39 gold and 9 uranium mines that were known to use MP by the maintainers of the MMF, the Workers' Compensation Board (WCB, now WSIB). Further, at some point an algorithm was added to the database that carried forward an affirmative or negative response once it was logged into subsequent exam records until manually changed or stopped. The database therefore has affirmative responses to MP exposure into the 1980's.

The validity of MP exposure information was evaluated and augmented using a variety of data sources to create a more comprehensive list of mines where MP was administered, including periods of use. These sources included primarily the McIntyre Research Foundation records held by the Provincial Archives of Ontario, historic Mines Accident Prevention Association (MAPAO) dust survey records from the Sudbury Office of the Ministry of Labour, now held at the OCRC, and cross-checked with the list reported by the McIntyre Powder Project (78). This resulted in the 51 mine sites (Appendix B, Table B-1), augmenting the original list of 48 sites listed in the

1985 MMF codebook. These activities are described in detail in the Interim Report to the WSIB (September 14, 2018²).

Workers were categorized as exposed or unexposed for each year of work history and were subsequently classified as 'ever exposed' or 'never exposed', using two exposure assessment approaches.

1. **First exposure assessment:** Data in the MMF database that captured MP exposure as reported by the worker at their annual medical examination. The MMF database indicated MP exposure among 10,405 men, but data cleaning reduced the number exposed to 9,548 (25.9%) in the study cohort. Data cleaning excluded self-reports for years and/or mines where MP was not administered according to available records, precluding the possibility of exposure.
2. **Second exposure assessment:** Considering that there may be limitations to self-reported data, a second exposure assessment approach was applied to assess MP exposure for individuals based on their year, mine of work, and broad job classification. All workers in underground mining and crushing occupations at mines that used MP were classified as exposed for the years when the mine was licensed by MRF. Based on this approach, 13,828 men (37.4%) were classified as MP-exposed.

Follow-up for neurological disease

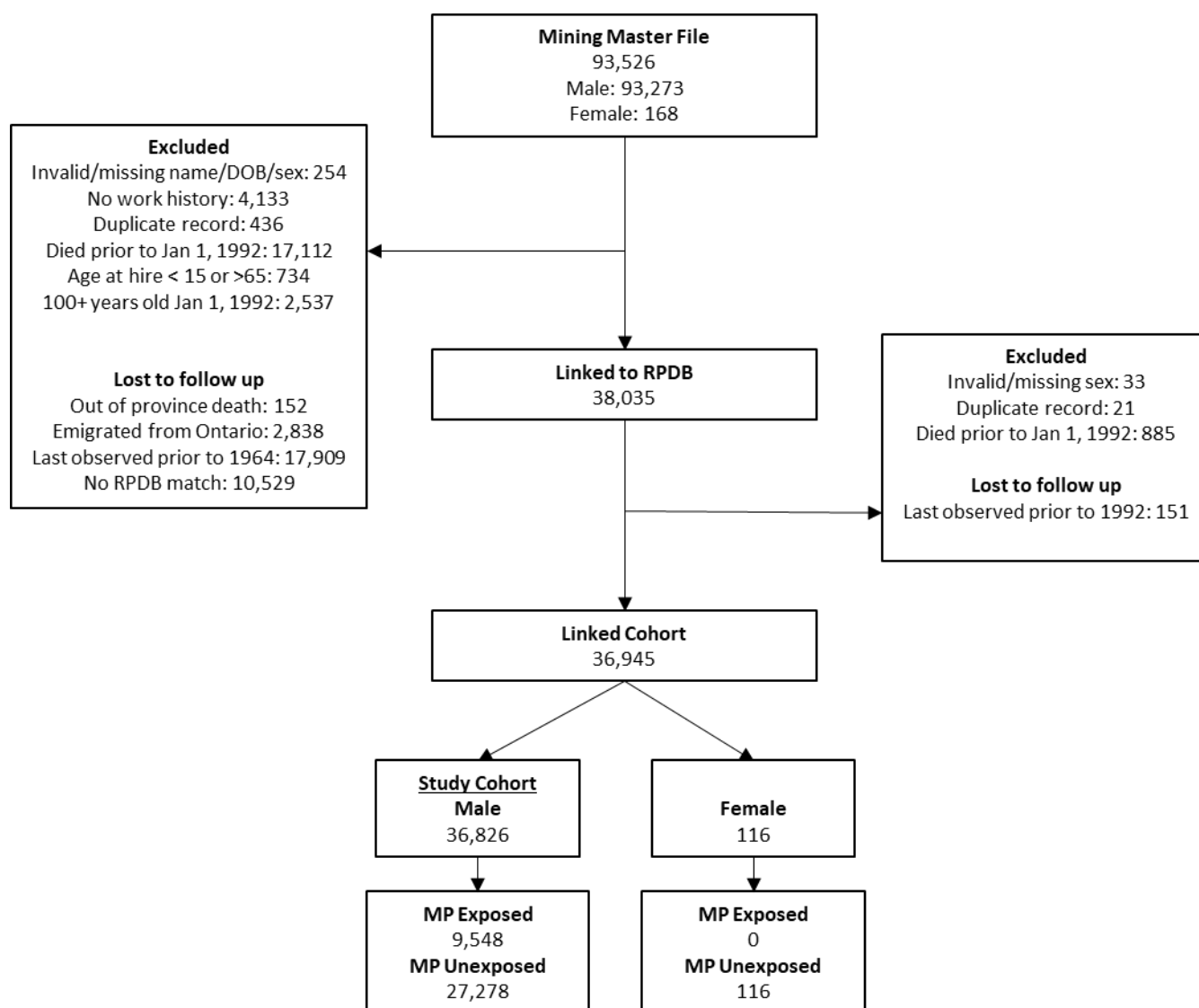
The MMF was processed for duplicates and missing information and the exclusion criteria were applied prior to transfer to the Institute for Clinical and Evaluative Sciences (ICES) for record linkage. The de-duplication process involved an internal linkage of the MMF nominal file to link multiple records belonging to the same miner using Automatch®, Version 4.2 (79) probabilistic record linkage software. This application was used to group multiple records for a single miner prior to the probabilistic linkage to the RPDB to reduce the number of records included in the data linkage process.

Miners identified in the MMF were followed up for selected neurological diseases through linkage of records to administrative health databases. These administrative health databases, described further below, capture diagnoses only from 1992 and onwards. At ICES, records from the MMF were linked to Ontario's Registered Persons Database (RPDB) (data from January 1, 1991 to June 31, 2019), using given names, surname, sex, date of birth. This was a probabilistic linkage in order to ascertain OHIP health card numbers (HCN). Next, deterministic linkage by HCN was used to identify cases of neurological disease among the Ontario Health Insurance Plan (OHIP) Claims Database (1992-2018), the Canadian Institute for Health Informatics (CIHI) Discharge Abstract Database (DAD) (1992-2018), and the National Ambulatory Care Reporting System (NACRS) (2000-2018). These databases are described in detail in the *Health Analyst's Toolkit* (80), and are summarized briefly below.

Vital status and emigration from Ontario among miners in the MMF were ascertained through a linkage with the Ontario Registered Persons Database (RPDB) (1991-2019). The Registered Persons Database (RPDB) contains information for Ontario Health Insurance Plan (OHIP) registrants including current and former Ontario residents (80). Each registered person is assigned a unique lifetime 10-digit health card number (HCN). RPDB data elements retrieved for the MMF linkage include the health card number, date of birth, sex, and date of death and last known residence location, where available.

The flow diagram in Figure 2 details the selection of the study cohort and reasons for record exclusion.

² Demers PA, Berriault CJ, Zeng X, Arrandale, VH. Investigation of Neurological Outcomes and McIntyre Powder Exposure in the Mining Master File Cohort: Progress Update. Toronto, Canada: Cancer Care Ontario, Sep 14, 2018. pp 15.

FIGURE 2 FLOW DIAGRAM FOR SELECTION OF THE STUDY COHORT

Note: Some records met multiple exclusion criteria

Neurological disease diagnoses

Workers diagnosed with neurological diseases were identified from three administrative health data sources.

The Hospital Discharge Abstract Database (DAD) (1992-2018) records contain information on discharges from inpatient hospitalizations and day procedures, which are submitted to the Canadian Institute for Health Information (CIHI) on a monthly basis by mandated institutions. Data submissions are continually monitored to identify gaps or underreporting in submissions. CIHI completes data quality assurance processes including identifying potential duplicate abstracts, validity checks, and cleaning. Mandatory data elements include sex, birthdate, admission date, most responsible diagnosis, and principal intervention. Diagnoses are coded using the International Classification of Diseases (ICD-10-CA and ICD-9).

The National Ambulatory Care Records System (NACRS) (2000-2018) records contain data for ambulatory care visits including emergency department visits, day procedures, medical day and night care and ambulatory clinics including dialysis, cardiac catheterization, and oncology. These records are then transferred to CIHI to undergo validity checks and data cleaning. Diagnoses are coded using ICD-10-CA and ICD-9.

The Ontario Health Insurance Plan (OHIP) Claims Database (1992-2018) contains records submitted by health care providers for billing and accounting purposes. This database contains health service data submitted by providers, primarily physicians, from independent health facilities, primary care, academic health science centres and hospitals. This database is used for identifying cases and contains diagnostic codes, procedure codes, and physician specialty information. Diagnostic codes used in this database are similar but not identical to ICD-9.

Case definitions

Diagnoses of neurological diseases were identified for workers in the study cohort using the case definitions in Table 1. The selected case definitions were informed by prior validation studies in Ontario by Jaakkimainen (81) and Butt (82) and colleagues. In these studies, a combination of codes in hospital discharge and physician billing records showed good sensitivity: they successfully detected over 70% of true cases of Alzheimer's disease and dementia (81) and parkinsonism (82), compared with using hospitalization codes alone (sensitivity 20-30%). Those studies also found similar positive predictive values (PPV) of over 70% both with and without the addition of OHIP codes. In the present study, based on the findings of these validation studies, a combination of hospitalization and outpatient codes were used with physician billing data to maximize the accuracy of case identification based on the PPV, and for Alzheimer's disease and parkinsonism, increased sensitivity with use of additional OHIP codes. Although the Parkinson's disease definition used in the present study was not included in a validation study, it can be inferred from the study of parkinsonism definitions (82) that the PPV may be around 70% as well. For motor neuron disease and ALS, physician billing codes were not included because they do not adequately separate ALS from other conditions. Both motor neuron disease and ALS are classified under 'other diseases of central nervous system (349)' in OHIP billing codes. Since they are a rare condition, using the broad 349 code can capture other diseases (false positives) that have equal or greater numbers than motor neuron disease, which can result in a lower PPV and specificity. Additional case definitions were explored to reduce potential misclassification of identified cases and non-cases, but they did not have meaningful impact on conclusions and are not included in this report.

TABLE 1 NEUROLOGICAL DISEASE CASE DEFINITIONS AND DATA SOURCES

Neurological Diseases (1992-2018)	ICD10 codes (DAD/NACRS)	ICD9 codes (DAD/NACRS)	OHIP codes	Definitions	DAD	NACRS	OHIP
<i>Neurological Diseases*</i>	G00-G99	320-359	320-359	One hospitalization code or one ambulatory care visit in any diagnosis, or two physician billing codes in a year	1+	1+	2+
Alzheimer's Disease	G30	331.0	331	One hospitalization code or one ambulatory care visit in any diagnosis, or two physician billing codes in a year	1+	1+	2+
Parkinsonism	G20, G21.0-0.4, G21.8-9, G22, F02.3	332.0-332.1	332	One hospitalization code or one ambulatory care visit in any diagnosis, or two physician billing codes in a year	1+	1+	2+
Parkinson's disease	G20	332.0	-	One hospitalization code or one ambulatory care visit in any diagnosis	1+	1+	-
Motor Neuron Disease	G12.2	335.2	-	One hospitalization code or one ambulatory care visit in any diagnosis	1+	1+	-
<i>Amyotrophic Lateral Sclerosis (2012-2018)*</i>	G12.20	335.20	-	One hospitalization code or one ambulatory care visit in any diagnosis	1+	1+	-

*Broad categories of neurological disease to be compared to the general population by standardized incidence ratio (SIR); DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; OHIP: Ontario Health Insurance Plan Claims Database.

Statistical analysis

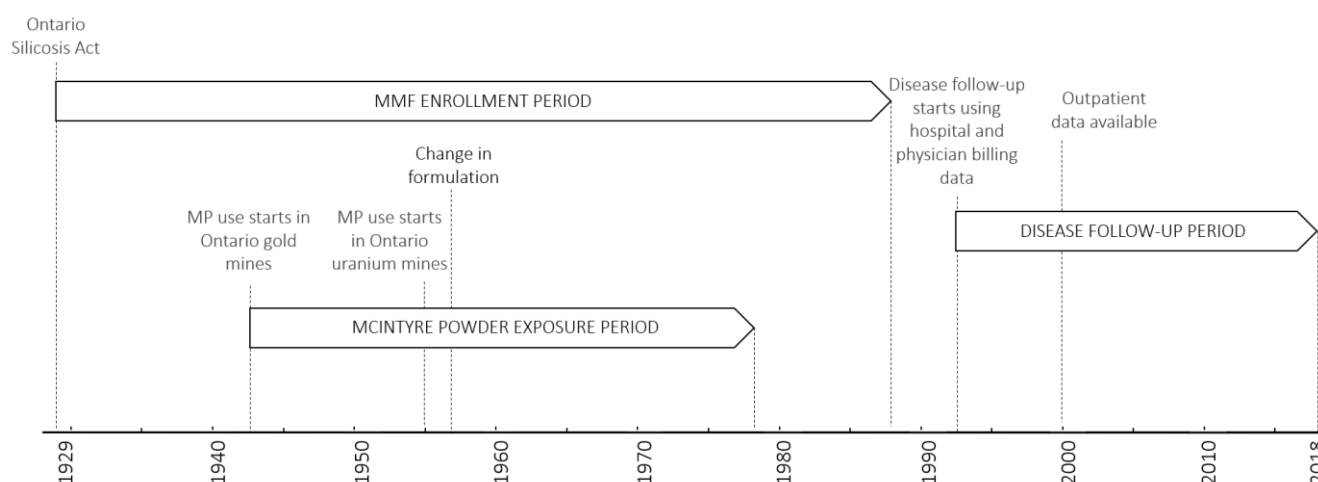
Follow-up for neurological disease diagnoses started on January 1, 1992. Follow-up ended on the earliest of date of diagnosis for each neurological disease, death date or last administrative date of contact with the Ontario health system or end of follow-up on December 31, 2018 (Figure 3). For the remaining workers, follow-up was ended at age 100 years old to reduce bias from loss to follow-up. Internal Poisson regression compared MP exposed and unexposed mining industry workers to estimate associations between MP exposure and incidence rates of neurological disease. External comparisons to the Ontario population used standardized incidence ratios (SIRs) based on age at diagnosis and year of diagnosis, calculated as the ratios of the observed to expected number of cases based on the Ontario population. Ontario reference population files for neurological disease incidence were provided by ICES. P-values and 95% confidence intervals for SIRs were calculated assuming neurological disease occurrence followed a Poisson distribution. All analyses were completed using SAS statistical software [SAS 9.4] (77). All models were adjusted for age and calendar period. All internal incidence rate ratio (RR) models were adjusted for birth year and age throughout the follow-up period to control for potential confounding by differences in age, birth cohort, and calendar year of follow-up between exposed and unexposed groups. The adjustment variables were specified in the model to maximize model fit. Case counts fewer than 6 are suppressed in the reported results due to confidentiality requirements.

All analyses were conducted independently using both the first assessment approach (self-reported MP) and the second exposure assessment approach (estimated MP). Cumulative duration of exposure was calculated as the sum of years exposed for each worker's entire observed work history.

In interpreting model results, RRs represent the incidence rate (number of cases diagnosed per worker per year of follow-up) in the exposed group divided by the rate in the unexposed reference group. RRs of one indicate the risk of disease is the same as the unexposed group and RRs greater than 1 indicate an excess risk of the disease in the exposed compared to the unexposed group.

Many models were constructed to estimate the health risks as a function of MP exposure, including time since last exposure and exposure time windows. Not all results are presented in this report as many had similar results. The models presented here were selected because they summarize the totality of the findings in the most straightforward manner. The complete results, including all model outputs, are available from the OCRC³.

FIGURE 3 TIMELINE OF MMF, USE OF MP, AND STUDY DISEASE FOLLOW-UP PERIOD



Results

Cohort description

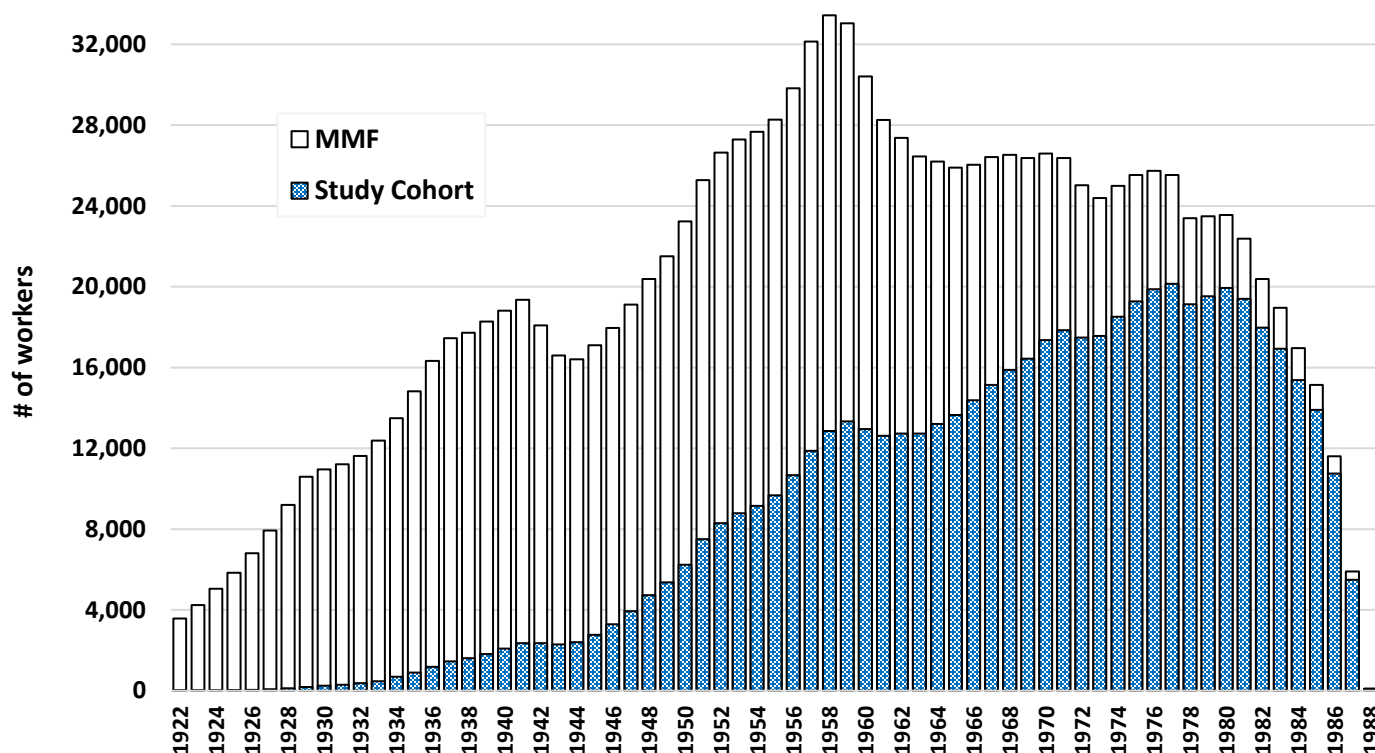
The total MMF included records for 93,273 men and 168 women (before removing duplicates, those refused certification, and those with insufficient data for linkage). Of these, 48,564 were considered eligible for inclusion in the study cohort based on data available within the MMF. Reasons for exclusion are detailed in Figure 2. The primary reasons for exclusion were confirmed death prior to the disease follow-up period (January 1, 1992), and last observed earlier than 1964 in prior follow-up. At ICES, 38,035 (78.3%) records were successfully matched to a RPDB record. Following this linkage, records for a further 1,090 individuals were excluded, primarily because of death prior to the study follow-up period. The final study cohort included 36,826 men. Records were successfully linked for 116 women, but none were exposed to MP and too few cases were observed to allow reporting, so women were subsequently removed from the study cohort.

The characteristics of workers in the full MMF and those successfully linked to the RPDB and administrative health data, including the numbers exposed to MP and the distribution of employment by ore are presented for

³ Supplemental results tables are available at <https://www.occupationalcancer.ca/2020/mcintyre-powder-study/>

males and females in Table 2. The number of workers employed by year, and the number of those workers that were included in the study cohort are depicted in Figure 4. As illustrated, likelihood of inclusion in the study cohort increased substantially with recency of employment. The earliest work history record in the MMF was for the year 1880 while the earliest linked work history record was from 1915.

FIGURE 4 WORKERS EMPLOYED ANNUALLY IN MMF AND STUDY COHORT, ONTARIO, 1922-1988



Compared to the broader mining workforce captured by the full MMF, men with linked records tended to be younger (Table 2). Mean age at cohort entry was 23.7 years (S.D. 6.0), and mean age at start of disease follow-up was 54.4 (S.D. 13.9). Duration of employment ranged from approximately one-half month to over 50 years, with an average of 13.1 years (S.D. 9.34). Among men in the study cohort, 34% were ever employed in a gold mine, 40% were ever employed in a uranium mine, and 51% were ever employed in a nickel or copper mine. Almost 50% of men in the study cohort had worked with more than one ore type.

TABLE 2 CHARACTERISTICS OF WORKERS IN THE MMF AND LINKED COHORT, MEN AND WOMEN

	Men		Women	
	MMF N=93,273	Linked Cohort N=36,826	MMF N=168	Linked Cohort N=116
MP-exposed, N (%)¹	25,199 (27.0)	9,548 (25.9)	0 (0)	0 (0)
Year of birth				
median	1925	1938	1952	1948
range	1853-1975	1894-1966	1920-1963	1920-1963
Duration of employment (years)				
mean (S.D.)	12.4 (9.5)	13.1 (9.3)	4.9 (2.9)	5.2 (2.6)
median	9.8	10.9	5.4	5.6
range	0.04-60.5	0.04-50.3	0.04-12.4	0.04-10.9
Age at first hire				
mean (S.D.)	25.8 (7.3)	23.7 (6.0)	27.0 (8.2)	29.1 (8.7)
median	24	22	26	29
range	15-75	15-65	16-49	16-49
Year of first hire				
median	1951	1963	1978	1979
range	1880-1987	1915-1987	1943-1985	1961-1985
Ore, N (%)²				
gold	43,494 (49.1)	12,598 (34.2)	6 (3.7)	<6 (-)
uranium	27,082 (30.6)	14,587 (39.6)	106 (65.0)	74 (63.8)
nickel or copper	39,084 (44.1)	18,962 (51.5)	18 (11.0)	11 (9.5)

¹ First exposure assessment approach (estimated MP exposure);

² Workers ever-employed in mining of ore; workers can appear in multiple groups.

McIntyre Powder exposure in the study cohort

Of the 36,826 men in the study cohort, approximately one-quarter (n=9,548, 25.9%) self-reported MP-exposure at least once during an annual medical exam (first exposure assessment method). This was similar to the 27% exposed among all male workers in the full MMF according to the first exposure assessment. According to the second MP-exposure assessment, 38% of the study cohort and full MMF were classified as exposed. Characteristics of males in the study cohort are described by MP exposure status in Table 3. MP-exposed workers were generally older than unexposed workers at the start of disease follow-up (59.6 years (S.D. 12.8) vs. 52.6 years (S.D. 14)). Patterns of employment by ore type reflect the use of MP in gold and uranium miners. Among exposed workers, almost 75% had at least one work history record associated with employment in a gold mine, while 50% were employed in a uranium mine. Only 20% of unexposed workers were ever employed in a gold mine, while 35% were ever employed in uranium. This is consistent with the MP exposure during the 1943-1979 exposure period within gold and uranium mines detailed below (McIntyre Powder exposure by ore). The average timespan between last MP exposure and disease follow-up, was 24.4 years (S.D. 9.2), with a range of 13 to 74 years.

As described previously, a second exposure assessment approach was applied to the MMF records, to account for potential limitations on the self-reported data. According to this approach, 13,829 men (37.6%) were classified as MP-exposed.

TABLE 3 DEMOGRAPHIC AND EMPLOYMENT CHARACTERISTICS OF MALES IN THE STUDY COHORT, BY MP EXPOSURE STATUS

	MP-Exposed ¹ N=9,548	MP-Unexposed N=27,278
Year of birth		
median	1932	1941
range	1894-1960	1896-1966
Duration of employment (years)		
mean (S.D.)	15.5 (10.1)	12.2 (8.9)
median	13.2	10.2
range	0.05-50.3	0.04-48.6
Age at first hire		
mean (S.D.)	23.1 (5.5)	23.9 (6.2)
median	22	22
range	15-58	15-65
Year of first hire		
median	1955	1966
range	1915-1979	1916-1987
Age at start of disease follow-up period (1992)		
mean (S.D.)	59.6 (12.8)	52.6 (14.0)
median	60	51
range	32-98	26-96
Ore, N (%)²		
gold	7,137 (74.8)	5,461 (20.0)
uranium	5,024 (52.6)	9,563 (35.1)
nickel or copper	3,331 (34.9)	15,631 (57.3)

¹ First exposure assessment approach (estimated MP exposure);

² Workers ever-employed in mining of ore; workers can appear in multiple groups.

S.D.: Standard Deviation

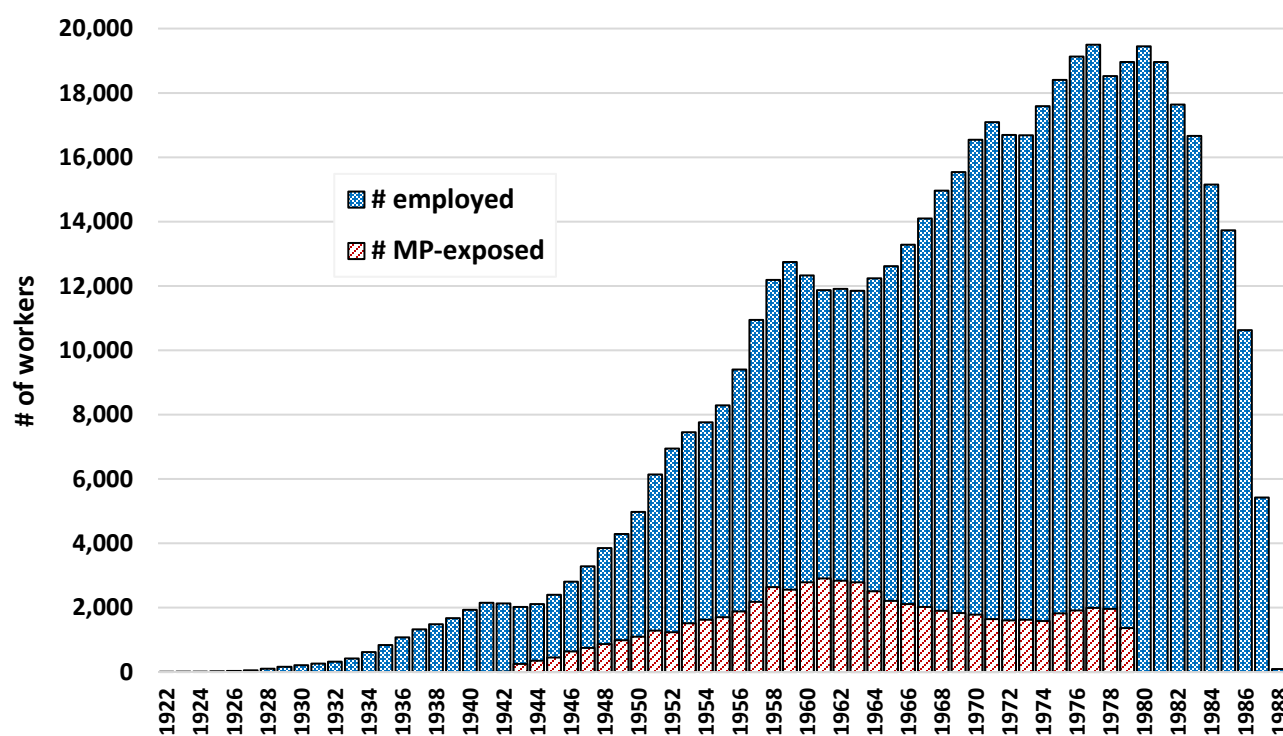
For all continuous variables, the p-value from the Mann-Whitney Wilcoxon test was p<0.0001.

McIntyre Powder exposure over time

MP exposure occurred between 1943 and 1979, which included exposure in a small number of mines prior to the broader use initiated in December 1944. Figure 5 presents the number of mining workers employed, and number exposed to MP by year. Among men that worked in underground mining during the 1943-1979 period during which MP was administered in Ontario, 28% of all underground miners were ever exposed to MP. The

proportion of miners exposed by year peaked in 1961, where 24.5% of Ontario's underground miners were exposed to MP in that year. By the 1970s, fewer than 10% of miners were exposed to MP on an annual basis, declining to 7% in 1979 before the practice was ceased.

FIGURE 5 MINING INDUSTRY WORKERS EMPLOYED AND REPORTING MP EXPOSURE ANNUALLY, FIRST ASSESSMENT APPROACH, STUDY COHORT, 1922-1988



McIntyre Powder exposure by ore

Figure 6 illustrates the number of workers employed by year in the gold and uranium mining sectors. Gold mining increased at the beginning of WWII to support wartime expenditures, but subsequently declined. The industry experienced another decline in the 1960s as rising production costs led to mine closures. The number of workers employed in uranium mines grew rapidly in the late-1950s during the nuclear arms race and boomed again in the 1980s to fuel nuclear power plants.

Figure 7 illustrates the number of those with MP exposure between 1943 and 1979 and the shift over time from being dominated by gold miners to increasingly split between gold and uranium miners. In the study cohort, 70% of gold miners and 32% of uranium miners were exposed at least once during the 1943-1979 period. In the early 1960s during the peak use of MP in Ontario gold mines, 60-62% of miners were exposed to MP in gold mines annually. In 1979, the last year of use, 38% of workers were exposed to MP in gold mines. Exposure in uranium mines started a decade later and occurred between 1955 and 1979. Exposure in uranium mining peaked in 1971, where 51% of workers were exposed, declining to about 13% in 1979. Exposures among the study cohort and the broader MMF were consistent. No exposure was reported among workers that were employed exclusively in mining of ores other than gold or uranium.

FIGURE 6 WORKERS EMPLOYED ANNUALLY IN GOLD AND URANIUM MINES, STUDY COHORT, 1922-1988

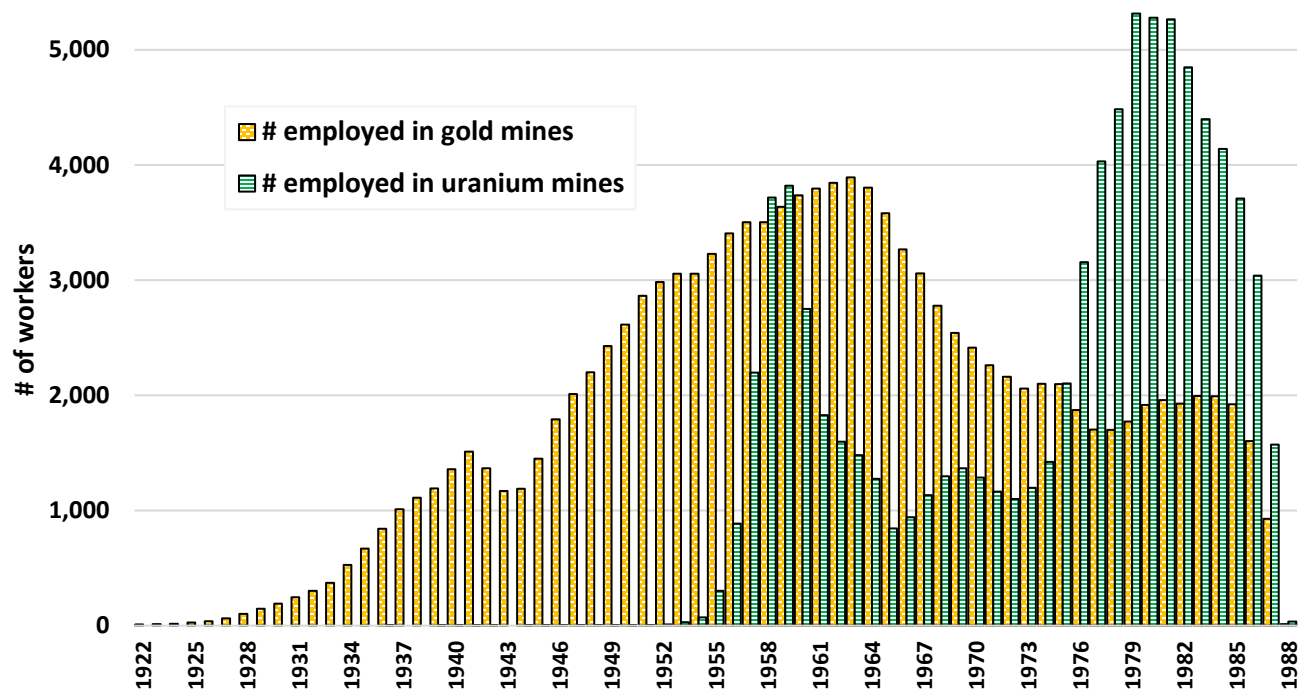
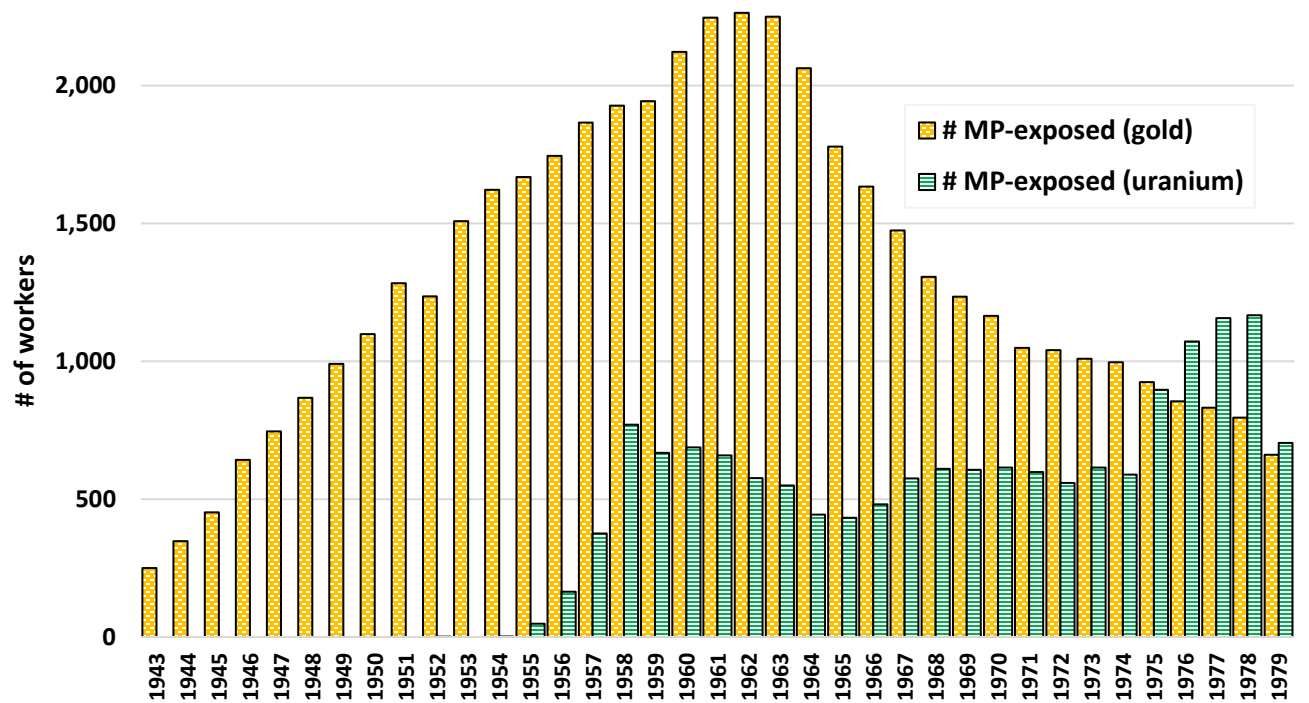


FIGURE 7 WORKERS EXPOSED TO MCINTYRE POWDER IN GOLD AND URANIUM SECTORS, FIRST ASSESSMENT APPROACH, 1943-1979



Associations between MP exposure and neurological disease

Table 4 presents the number of cases observed for the neurological diseases examined in this study among exposed and unexposed workers, and the risk of disease among mining workers ever exposed to MP compared to those never exposed. As described previously, MP exposure was assessed using two approaches. The first approach was based on the self-reported MP exposure captured during annual medical exams and recorded in the MMF. The second assessment approach categorized workers as exposed or unexposed based on their date, mine of employment and job classification. Associations between MP exposure and neurological disease were estimated using both the first and second exposure assessments and are presented in Table 4. Only 18 ALS cases were observed in the study cohort, and fewer than 6 cases were observed among MP-exposed miners, so results for this group were not reportable.

This study observed a positive association between any exposure to MP and the rate of Parkinson's disease in the study cohort. Workers who were ever exposed to MP experienced an incidence rate (number of cases per worker per year) of Parkinson's disease that was 34% higher than workers who were never exposed to MP. A 19% higher rate of parkinsonism was observed among MP-exposed workers. We did not observe any association between exposure to MP and the rate of Alzheimer's or motor neuron disease. The results using the second exposure assessment approach were very similar.

The case definition for parkinsonism includes cases coded at the 3-digit ICD-9 level that are used in the OHIP claims database, which do not differentiate between parkinsonism and Parkinson's disease. After excluded cases identified as Parkinson's disease based on the hospitalization and ambulatory care records, there were 113 cases of parkinsonism not specific to Parkinson's disease among workers with MP exposure, and 274 cases among unexposed workers. No association was observed for MP and other parkinsonism (RR 0.98, 95% CI 0.79-1.22). This finding was consistent using the second exposure assessment with 142 MP-exposed cases and 245 unexposed cases (RR 1.00, 95% CI 0.82-1.23). An additional analysis was conducted by restricting to only hospitalization and ambulatory care data, where Parkinson's disease and other parkinsonism cases can be differentiated. This approach identified 17 cases of other parkinsonism, and no association was observed for MP (RR 0.75, 95% CI 0.24-2.34).

TABLE 4 RISK OF NEUROLOGICAL DISEASE ASSOCIATED WITH MCINTYRE POWDER EXPOSURE, MALES, 1992-2018

Disease	First exposure assessment			Second exposure assessment approach		
	Exposed N=9,548	Unexposed N=27,278		Exposed N=13,828	Unexposed N=22,998	
Case definition	Cases	Cases	RR (95% CI)	Cases	Cases	RR (95% CI)
Alzheimer's disease						
1 DAD/NACRS or 2 OHIP billing in 1 year	334	728	0.96 (0.85-1.10)	399	663	1.01 (0.90-1.15)
Parkinsonism						
1 DAD/NACRS or 2 OHIP billing in 1 year	364	667	1.19 (1.05-1.36)	426	605	1.18 (1.04-1.33)
Parkinson's disease						
1 DAD/NACRS	251	393	1.34 (1.14-1.57)	284	360	1.32 (1.13-1.54)
Motor neuron disease						
1 DAD/NACRS	20	61	0.82 (0.49-1.37)	26	55	0.80 (0.50-1.28)

First exposure assessment approach: self-reported MP exposure; Second exposure assessment approach: estimated MP exposure;

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Reference group: Mining industry workers never exposed to MP.

In the absence of any direct measurements of MP exposure dose, cumulative dose to MP was approximated as duration of MP exposure in years using both the primary exposure assessment approach (Table 5) and the second exposure assessment approach (Table 6). With the second exposure assessment approach, the highest risks of parkinsonism and Parkinson's disease were observed for workers with more than 10 years of MP exposure and increasing duration of MP exposure was associated with increasing risk of Parkinson's disease. This pattern was not evident using the first exposure assessment approach, although all levels of duration showed elevation of risk for parkinsonism and Parkinson's disease. There was no evidence of associations between any duration of MP exposure and the rate of Alzheimer's or motor neuron disease.

TABLE 5 RISK OF NEUROLOGICAL DISEASE BY DURATION OF MP EXPOSURE, FIRST EXPOSURE ASSESSMENT APPROACH

Duration of MP exposure	N	Alzheimer's disease		Parkinsonism		Parkinson's disease		Motor neuron disease	
		Cases	RR (95% CI)	Cases	RR (95% CI)*	Cases	RR (95% CI)*	Cases	RR (95% CI)
>0-1 years	2,296	53	0.77 (0.59-1.02)	73	1.17 (0.92-1.49)	50	1.36 (1.01-1.82)	9	1.62 (0.81-3.27)
>1-5 years	3,833	121	0.98 (0.81-1.19)	132	1.18 (0.98-1.42)	90	1.34 (1.07-1.69)	<6	0.31 (0.10-1.00)
>5-10 years	1,655	68	1.04 (0.81-1.34)	66	1.15 (0.89-1.48)	48	1.35 (1.00-1.83)	<6	0.68 (0.21-2.16)
>10 years	1,764	92	1.04 (0.83-1.29)	93	1.27 (1.02-1.58)	63	1.30 (0.99-1.71)	<6	1.05 (0.41-2.68)

First exposure assessment approach: self-reported MP exposure;

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Reference group: Mining industry workers never exposed to MP.

*p-value for trend p<0.05.

TABLE 6 RISK OF NEUROLOGICAL DISEASE BY DURATION OF MP EXPOSURE, SECOND EXPOSURE ASSESSMENT APPROACH

Duration of MP exposure	N	Alzheimer's disease		Parkinsonism		Parkinson's disease		Motor neuron disease	
		Cases	RR (95% CI)	Cases	RR (95% CI)*	Cases	RR (95% CI)*	Cases	RR (95% CI)
>0-1 years	4,507	85	1.10 (0.88-1.38)	88	1.12 (0.90-1.41)	52	1.23 (0.92-1.65)	10	1.16 (0.59-2.29)
>1-5 years	4,503	115	1.00 (0.82-1.22)	124	1.15 (0.95-1.40)	80	1.28 (1.01-1.63)	6	0.58 (0.25-1.35)
>5-10 years	2,433	83	0.93 (0.74-1.16)	88	1.09 (0.87-1.36)	65	1.32 (1.02-1.73)	<6	0.45 (0.14-1.44)
>10 years	2,384	116	1.04 (0.85-1.27)	126	1.32 (1.09-1.61)	87	1.42 (1.12-1.80)	7	1.05 (0.48-2.34)

First exposure assessment approach: self-reported MP exposure;

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Reference group: Mining industry workers never exposed to MP.

*p-value for trend p<0.05.

Of the 9,548 MP-exposed workers in the study cohort, over 90% had some or all of their exposure in 1956 or later. The rate of parkinsonism and Parkinson's disease did appear to be higher among workers who were exposed to the new formulation introduced in 1956. Results by period of exposure are shown in Table 7. The results using the second exposure assessment approach were very similar and are not presented.

TABLE 7 RISK OF NEUROLOGICAL DISEASE AMONG MP-EXPOSED WORKERS, FIRST EXPOSURE ASSESSMENT APPROACH BY PERIOD OF EXPOSURE

MP exposure	N	Alzheimer's disease		Parkinsonism		Parkinson's disease		Motor neuron disease	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Only <1956	853	49	0.91 (0.68-1.22)	45	1.08 (0.80-1.48)	34	1.18 (0.83-1.69)	0	-
Ever 1956+	8,695	285	0.97 (0.85-1.12)	319	1.21 (1.06-1.38)	217	1.36 (1.16-1.61)	20	0.90 (0.54-1.50)
Only 1956+	6,459	164	0.96 (0.81-1.14)	192	1.16 (0.99-1.37)	125	1.34 (1.09-1.64)	16	1.01 (0.58-1.76)

First exposure assessment approach: self-reported MP exposure;

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Reference group: Mining industry workers never exposed to MP.

Table 8 and Table 9 present the rates of disease among workers by type of ore mined, but does not take in to account MP exposure. This analysis was conducted to determine patterns in rates of disease by mine type independent of MP exposure. Workers may appear in multiple groups if their work histories include employment in mining different ores, such as gold, nickel, or uranium. Associations between duration of employment and Parkinson's disease and parkinsonism were seen primarily among workers who had worked in gold mining. Workers that were ever employed in gold mining had an almost 30% greater rate of Parkinson's disease and a 20% greater rate of parkinsonism compared to workers with no employment in gold mining. Rates of these diseases increased with duration of employment in gold mining (Table 9). A statistically significant increased risk of Alzheimer's disease was observed among workers with less than one year of employment in uranium mining. An increased risk was also suggested for workers with more than 10 years of uranium mining, although this association was based on relatively few cases. In interpreting these results, it is important to keep in mind that 48% of workers had employment in mining of multiple ores during their work histories, and thus appear in multiple ore groups.

TABLE 8 RISK OF NEUROLOGICAL DISEASE BY ORE TYPE MINED (NO ASSESSMENT OF MP EXPOSURE)

Ore type mined	N	Alzheimer's disease		Parkinsonism		Parkinson's disease		Motor neuron disease	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Gold	12,598	442	0.97 (0.85-1.09)	462	1.19 (1.05-1.35)	312	1.29 (1.10-1.51)	31	1.11 (0.70-1.76)
Nickel-copper	18,962	550	0.96 (0.85-1.08)	522	0.90 (0.80-1.02)	322	0.89 (0.76-1.04)	36	0.68 (0.44-1.06)
Uranium	14,587	308	1.14 (0.99-1.31)	293	0.98 (0.85-1.12)	181	1.08 (0.91-1.30)	25	0.84 (0.52-1.36)

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Reference group: Mining industry workers employed in all other ore mines; Workers may appear in multiple ore type groups.

TABLE 9 RISK OF NEUROLOGICAL DISEASE BY DURATION OF EMPLOYMENT BY ORE MINED (NO ASSESSMENT OF MP EXPOSURE)

Duration of employment	Alzheimer's Disease			Parkinsonism		Parkinson's Disease		Motor Neuron Disease	
	N	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Gold									
>0-1 years	2,626	77	1.11 (0.87-1.41)	71	1.11 (0.86-1.42)	43	1.15 (0.84-1.58)	7	1.28 (0.58-2.83)
>1-5 years	3,704	101	0.84 (0.68-1.04)	96	0.91 (0.74-1.13)	70	1.10 (0.85-1.42)	8	0.97 (0.46-2.05)
>5-10 years	3,106	122	1.02 (0.84-1.25)	123	1.24 (1.02-1.52)	84	1.34 (1.05-1.71)	8	1.15 (0.54-2.44)
>10 years	3,162	142	0.95 (0.79-1.15)	172	1.46 (1.23-1.75)	115	1.49 (1.19-1.85)	8	1.10 (0.51-2.37)
Nickel-copper									
>0-1 years	2,355	44	0.87 (0.64-1.18)	52	0.97 (0.73-1.30)	31	0.98 (0.68-1.42)	<6	0.56 (0.17-1.80)
>1-5 years	3,598	75	0.92 (0.72-1.18)	76	0.89 (0.70-1.14)	53	1.05 (0.79-1.41)	<6	0.47 (0.17-1.32)
>5-10 years	3,562	87	0.94 (0.75-1.18)	82	0.86 (0.68-1.08)	46	0.79 (0.58-1.08)	10	1.09 (0.55-2.16)
>10 years	9,447	344	0.98 (0.86-1.13)	312	0.90 (0.78-1.04)	192	0.87 (0.73-1.04)	19	0.64 (0.37-1.10)
Uranium									
>0-1 years	5,450	116	1.28 (1.05-1.57)	103	1.00 (0.81-1.24)	64	1.15 (0.88-1.5)	10	0.93 (0.47-1.85)
>1-5 years	4,700	103	1.02 (0.83-1.26)	108	0.99 (0.80-1.21)	67	1.07 (0.83-1.39)	9	0.89 (0.44-1.81)
>5-10 years	3,135	45	1.03 (0.76-1.39)	46	0.91 (0.67-1.22)	30	1.12 (0.77-1.63)	<6	0.71 (0.25-1.98)
>10 years	1,302	44	1.25 (0.92-1.69)	36	0.96 (0.69-1.34)	20	0.91 (0.58-1.43)	<6	0.61 (0.15-2.52)

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Reference group: Mining industry workers employed in all other ore mines; Workers may appear in multiple ore type groups.

In order to determine if any associations between duration of MP exposure and neurological disease were modified by ore type, an analysis was conducted separating the study cohort to miners employed exclusively in gold mines and those employed exclusively in uranium mines. These restricted analyses ensured that the exposure to MP occurred within the same ore mine type. Associations between MP exposure and disease among workers employed only in gold mines, and only in uranium mines are reported in Table 10. Results for motor neuron disease are not reported because all strata had fewer than 6 cases. In this analysis, associations were observed for Parkinson's disease and parkinsonism among workers employed only in gold mines, with the strongest associations observed among workers with 1-5 years of MP exposure. A positive association was observed with any MP exposure and parkinsonism among only uranium miners, but too few cases were observed by duration to make meaningful inference. Few miners were employed in the mining of only one ore type and estimates in this analysis are based on small numbers and subject to more random error than other results. Results were consistent with the second exposure assessment approach.

TABLE 10 RISK OF NEUROLOGICAL DISEASE BY DURATION OF MP EXPOSURE, FIRST ASSESSMENT APPROACH, BY ORE MINED

Duration of MP exposure	Alzheimer's disease			Parkinsonism		Parkinson's disease	
	N	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Gold mines							
Any MP	1,843	68	0.66 (0.44-0.99)	100	1.30 (0.84-2.02)	67	1.69 (0.95-3.00)
>0-1 years	273	6	0.37 (0.16-0.89)	14	1.22 (0.63-2.35)	11	1.88 (0.85-4.14)
>1-5 years	642	30	0.91 (0.55-1.50)	42	1.65 (1.01-2.72)	29	2.30 (1.21-4.38)
>5-10 years	383	17	0.84 (0.47-1.51)	13	0.84 (0.43-1.64)	9	1.17 (0.51-2.72)
>10 years	545	15	0.45 (0.25-0.83)	31	1.28 (0.76-2.16)	18	1.38 (0.69-2.76)
Uranium mines							
Any MP	1,107	22	0.98 (0.59-1.60)	24	1.27 (0.77-2.07)	12	1.05 (0.53-2.07)
>0-1 years	348	7	1.09 (0.50-2.40)	8	1.45 (0.69-3.07)	<6	1.24 (0.43-3.55)
>1-5 years	592	11	0.94 (0.49-1.81)	9	0.93 (0.46-1.91)	6	1.01 (0.42-2.47)
>5-10 years	104	<6	1.17 (0.36-3.73)	<6	2.31 (0.92-5.82)	<6	0.78 (0.11-5.75)
>10 years	63	<6	0.53 (0.07-3.85)	<6	1.20 (0.29-4.95)	<6	0.98 (0.13-7.22)

First exposure assessment approach: self-reported MP exposure;

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Workers in these groups were employed and exposed to MP only in gold or only in uranium mines;

Reference group: Mining industry workers with no MP exposure within the same ore type;

Fewer than 6 cases were observed per strata for motor neuron disease, and results are not presented.

TABLE 11 RISK OF PARKINSONISM AND PARKINSON'S DISEASE AMONG GOLD MINERS NEVER EXPOSED TO MP

Employment in gold mines	Parkinsonism			Parkinson's disease	
	N	Cases	RR (95% CI)	Cases	RR (95% CI)
Ever gold mine (no MP exposure)	5,461	146	1.05 (0.87-1.27)	91	1.07 (0.85-1.36)
Only gold mine (no MP exposure)	836	27	1.05 (0.71-1.57)	15	0.85 (0.50-1.44)

No exposure based on first exposure assessment approach: self-reported MP exposure;

RR: Incidence rate ratio; CI: Confidence interval;

All models are adjusted by age, age², and birth year;

Ever gold mine: workers ever employed in gold mining with no record of MP exposure in any mine; Only gold mine: workers employed only in gold mining with no record of MP exposure in any mine.

Reference group: Never gold miners with no MP exposure.

Among workers who were never exposed to MP, the risk of parkinsonism and Parkinson's disease was compared between gold and non-gold miners. No association was observed between gold mining and parkinsonism or Parkinson's disease among workers with no MP exposure (Table 11).

The rates of neurological disease among miners in the study cohort were compared to Ontario population rates and are presented in Table 12. Compared to the general population of Ontario, no excess risk was observed for parkinsonism or Parkinson's disease for miners in general, but those with MP exposure had 14% and 27% increased risks, respectively, with the first exposure assessment approach. Risk estimates were consistent using the second exposure assessment approach. Mining industry workers had 21% increased risk of Alzheimer's disease diagnosis, and 31% increased risk of motor neuron disease, but this risk was not associated with MP exposure. Similar increased risks were observed for miners with no MP exposure for Alzheimer's disease and motor neuron disease (Table 12).

TABLE 12 STUDY COHORT NEUROLOGICAL DISEASE INCIDENCE COMPARED TO THE ONTARIO POPULATION (1992-2018)

Sub-groups compared to Ontario population	Alzheimer's disease		Parkinsonism		Parkinson's disease		Motor Neuron disease	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
Study cohort overall	1062	1.21 (1.14-1.28)	1031	1.02 (0.96-1.08)	644	1.05 (0.97-1.14)	81	1.31 (1.04-1.63)
MP-exposed ¹	334	1.15 (1.03-1.28)	364	1.14 (1.03-1.26)	251	1.27 (1.12-1.44)	20	1.11 (0.68-1.72)
MP-unexposed ¹	728	1.23 (1.14-1.32)	667	0.95 (0.88-1.03)	393	0.95 (0.85-1.04)	61	1.39 (1.06-1.78)
MP-exposed ²	399	1.22 (1.10-1.34)	426	1.13 (1.02-1.24)	284	1.24 (1.10-1.39)	26	1.13 (0.74-1.66)
MP-unexposed ²	663	1.20 (1.11-1.30)	605	0.95 (0.88-1.03)	360	0.94 (0.85-1.04)	55	1.41 (1.07-1.84)
Gold miners	442	1.16 (1.06-1.27)	462	1.13 (1.03-1.24)	312	1.21 (1.08-1.36)	31	1.36 (0.93-1.94)
Uranium miners	308	1.37 (1.23-1.54)	293	0.98 (0.87-1.10)	181	1.08 (0.93-1.25)	25	1.20 (0.78-1.77)
Nickel-Copper miners	550	1.19 (1.09-1.30)	522	0.97 (0.89-1.06)	322	1.00 (0.89-1.11)	36	1.08 (0.76-1.50)

Obs: Observed number of disease cases; SIR: Standardized Incidence Ratio; CI: Confidence Interval;

¹ First exposure assessment: Self-report MP exposure;

² Second exposure assessment: Estimated MP exposure.

Discussion

This study examined the relationship between exposure to MP and the risk of several neurodegenerative diseases among former Ontario miners. An association was found between MP exposure and Parkinson's disease. There was approximately a 30% increased risk of Parkinson's disease that was almost identical when using either exposure assessment approach. A similar increased risk was also observed when comparisons were made with the general population of Ontario. This study also observed a 20% increased risk of parkinsonism among MP-exposed miners, but it was driven by the Parkinson's disease cases. The manufacturing process of MP was modified around 1956 (4), with particle size becoming smaller. This reformulation was aimed at better counteracting the effects of fine silica particles (61). We found that the risk of Parkinson's disease was highest among workers that had at least some exposure to the post-1956 formulation. Using the first exposure assessment approach, the risk of Parkinson's disease was similar regardless of duration of exposure to MP, but the risk of Parkinson's disease increased with duration based on the second exposure assessment approach. This may indicate that the second exposure assessment approach, which assumes exposure during all years at an MP licensed mine, may be better at capturing duration.

The risk of Parkinson's was highest among MP-exposed gold miners. This raised the concern that the increased risk may not be due to MP alone, but to some other neurologic hazard or a combination of MP and other hazards. With studies such as this, it is sometimes difficult to disentangle the effects of different factors that change over time. We tried to examine this question using several approaches. There was an overall increase of Parkinson's disease among gold miners, which increased with duration, but there was no significantly increased risk among gold miners who had not been exposed to MP. This suggests that our findings are not solely attributable to some other neurological hazard alone. In addition, some evidence of an increased risk among MP-exposed uranium miners was also observed, although these subgroup analyses did not achieve statistical significance.

In almost all analyses, the risk of Alzheimer's disease and motor neuron disease among McIntyre powder-exposed miners was similar to, or less than, miners that had never reported exposure. These results were consistent across analyses and did not vary in a meaningful way by exposure assessment approach. However, miners overall had an increased risk of both Alzheimer's and motor neuron disease compared to the general population. In these analyses the risk of Alzheimer's was similar for both MP-exposed and unexposed miners,

and was highest for uranium miners, though also increased for gold and nickel-copper miners. Miners who had not been exposed to MP had a higher risk of motor neuron than those who had. While gold miners had a higher risk of motor neuron disease than uranium or nickel, these other miners also appeared to have an increased risk. The explanation for these excess risks is not clear, but miners have other exposures that have suspected links to neurodegenerative diseases (12, 76, 83-85), such as traumatic brain injury (86, 87), diesel exhaust (88), arsenic (89-91), radon (92) and whole body vibration (93).

There are several limitations that should be borne in mind when considering the findings of this report. Exposure to MP occurred over many decades ending in 1979. Our information on the cohort members work history in mining covered the full period of MP use and ended in 1988. However, our disease follow-up period only began in 1992. We were able to link approximately 37,000 miners to provincial health records, including at least 9,500 miners who had been exposed to McIntyre Powder. Unfortunately, many of the miners in the MMF who were employed in the early decades had died, been lost to follow-up, or otherwise failed to link to Ontario's hospital and outpatient records. Thus, we did not have the ability to assess the health of the great majority of early miners from those early decades that died prior to follow-up or were not linked, including almost 2/3rd of miners historically exposed to MP. Similarly, we may have missed disease cases among the cohort diagnosed prior to 1992. The gap between the end of MP exposure and the beginning of our follow-up period created some challenges in interpretation.

This study did not have information about other potential non-mining related confounders associated with neurological disease development including genetic predisposition, environmental exposures, and lifestyle factors such as smoking, alcohol consumption or physical activity or exposure to substances such as pesticides (37, 93, 94). The internal study comparison comparing MP-exposed miners to unexposed miners likely controlled for some of these factors (95).

Historical reconstruction of exposure is always a challenging exercise. Limited information was available on exposure to McIntyre Powder. The MMF did include information on individual miners that was recorded at the time of their annual examinations and this was used to construct the first exposure assessment approach. Given that historical information indicated that inhalation of MP prior to entering the mines was not voluntary, we suspected that this information was incomplete and constructed a second approach based on job categories and historical records on the use of MP by specific mines. These two approaches likely represent the range of capturing individuals exposed and, with the exception of duration of exposure, produced very similar results. The major limitation was that it was not possible to estimate the level of exposure, which was known to vary between mines and time periods. This would result in nondifferential misclassification of exposure, which would most likely reduce the strength of associations in this study (95).

To identify cases of neurological disease this study relied on the coding of diagnostic information using either the 9th or 10th revisions of the International Classification of Disease in hospitals, ambulatory care facilities, and physician's offices. Administrative health records are a recognized as being very good for identifying neurological disease incidence with a high degree of accuracy (81, 82, 96). While this represents a substantial improvement over the use of death certificates in traditional cohort studies, it does have its challenges. In the hospital and ambulatory care databases 4 or 5 digits of the ICD codes were used, allowing for more precise identification of cases. However, physician billing records contain only a single code, using only 3 digits, which did not allow for the differentiation of Parkinson's disease from parkinsonism, Alzheimer's disease from other forms of dementia, or motor neuron diseases from central nervous system diseases. Also, while it was of interest to examine the effects of MP on the risk of ALS, these cases could not be identified in the data. However, it has been reported

that approximately 70% of motor neuron disease cases are ALS (97). If MP was strongly associated with ALS risk, we would have expected to observe an association for motor neuron disease.

This is the largest study of the neurologic effects of MP exposure ever conducted. With a total cohort size of approximately 37,000 miners, including at least 9,500 miners who had been exposed to MP. Thus, we had the power to examine the risk of the more common neurodegenerative diseases. However, we still did not have the power to look specifically at the risk of ALS. Although the length of follow-up was sufficient to meet the study objectives, it may be that some cases of neurological diseases among MP-exposed workers have not yet developed, especially among the uranium mine workers who were exposed to MP more recently. It is worth noting that the median age at diagnosis for Parkinson's disease cases in this study was 79 years; the mean age at end of follow-up was 79 years for MP-exposed gold miners and 73 years for MP-exposed uranium miners. Thus, the difference between the results for gold and uranium miners may partially be explained by differences in age.

Although this study observed an association between MP exposure and Parkinson's disease, future research should explore other potential causes for the increased risk of Alzheimer's and motor neuron disease observed in the overall cohort of miners compared with the general population. Examples of these alternate exposures found in mining could include other metals with neurotoxic effects such as arsenic (89-91), mercury (98), and manganese (99) as well as other underground hazards including diesel engine exhaust (88), and radon or gamma radiation (92), traumatic brain injury (86, 87) and whole body vibration (93). In addition, the onset of the neurodegenerative diseases examined in this study occur at an advanced age and additional follow-up of this cohort may be warranted.

Conclusions

This study found an increased risk of Parkinson's disease associated with exposure to McIntyre Powder among Ontario miners, in comparison to both unexposed miners and the general population of Ontario. The risk appeared to increase with duration of exposure and was stronger for people exposed after 1956, when the formulation was changed to decrease the particle sizes. The association was also stronger for gold miners than uranium miners. No association was found between McIntyre Powder exposure and the risk of Alzheimer's disease or motor neuron disease, although miners overall had an increased risk compared to the general population. These other associations deserve further research to identify whether they may be related to other suspected neurological hazards in mining.

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FIGURE A-1 MASTER EXAMINATION RECORD CARD, 1951

FIGURE A-2 MASTER EXAMINATION RECORD CARD, 1975

A1

Appendix B

TABLE B-1 LIST OF 51 CONFIRMED ONTARIO MCINTYRE RESEARCH FOUNDATION LICENSEES (MCINTYRE POWDER USERS)

MRF License #	Mine Code	McIntyre Powder Licensee (Mine site)	Use Period	Mine Type
1	109	McIntyre Porcupine Mines Ltd (McIntyre)	1943-1979	Gold
		Pamour Porcupine Mines Ltd (Schumacher Division)		
7	121	Lake Shore Mines Ltd (Lake Shore)	1944-1965	Gold
8	110	Pamour Porcupine Mines Ltd (Pamour)	1944-1979	Gold
9	107	Hallnor Mines Ltd (Hallnor)	1944-1971	Gold
10	101	Aunor Gold Mines Ltd (Aunor)	1945-1972	Gold
16	125	Toburn Gold Mines Ltd (Toburn)	1944-1953	Gold
17	120	Kirkland Lake Gold Mining Co. Ltd (Kirkland Lake Gold)	1944-1960	Gold
18	128	Kerr-Addison Gold Mines Ltd (Kerr-Addison)	1944-1979	Gold
19	122	Macassa Mines Ltd (Macassa)	1944-1978	Gold
		Willroy Mines Ltd (Macassa Division)		
20	13907	Omega Gold Mines Ltd (Omega)	1944-1947	Gold
21	157	Macleod-Cockshutt Gold Mines Ltd (Macleod-Cockshutt)	1944-1953	Gold
22	139	Bidgood Kirkland Gold Mines Ltd (Bidgood)	1944-1948	Gold
23	103	Buffalo Ankerite Gold Mines Ltd (Buffalo Ankerite)	1944-1953	Gold
25	123	Sylvanite Gold Mines Ltd (Sylvanite)	1944-1961	Gold
26	131	Upper Canada Mines Ltd (Upper Canada)	1944-1971	Gold
28	105	Delnite Mines Ltd (Delnite)	1944-1964	Gold
29	106	Dome Mines Ltd (Dome)	1944-1979	Gold
30	104	Coniaurum Mines Ltd (Coniaurum)	1945-1961	Gold
31	151	Central Patricia Gold Mines Ltd (Central Patricia)	1944-1951	Gold
33	124	The Teck-Hughes Gold Mines Ltd (Teck Hughes)	1944-1968	Gold
34	156	Little Long Lac Gold Mines Ltd (Little Long Lac)	1944-1954	Gold
35	160	Mckenzie Red Lake Gold Mines Ltd (Mckenzie Red Lake)	1944-1953	Gold
37	152	Cochenour-Willans Gold Mines Ltd (Cochenour-Willans)	1944-1968	Gold
38	154	Hardrock Gold Mines Ltd (Hard Rock)	1944-1951	Gold
39	108	Hollinger Consolidated Gold Mines Ltd (Hollinger)	1944-1968	Gold
41	155	Leitch Gold Mines Ltd (Leitch)	1944-1965	Gold
42	153	Hasaga Gold Mines Ltd (Hasaga)	1944-1952	Gold
43	111	Paymaster Consolidated Mines Ltd (Paymaster)	1943-1966	Gold
44	112	Preston East Dome Mines Ltd (Preston East Dome)	1944-1968	Gold
49	158	Madsen Red Lake Gold Mines Ltd (Madsen Red Lake)	1944-1976	Gold
		Bulora Corporation (Madsen Division)		
50	102	Broulan Porcupine Mines Ltd (Broulan Reef)	1952-1965	Gold
51	102	Bonetal Gold Mines Ltd (Bonetal)	1944-1952	Gold
53	126	Wright-Hargreaves Mines Ltd (Wright Hargreaves)	1944-1965	Gold
54	162	Pickle Crow Gold Mines Ltd (Pickle Crow)	1944-1966	Gold

MRF License #	Mine Code	McIntyre Powder Licensee (Mine site)	Use Period	Mine Type
57	127	Chesterville Mines Ltd (Chesterville)	1944-1952	Gold
86	113	Hollinger Consolidated Gold Mines Ltd (Ross)	1944-1979	Gold
		Pamour Porcupine Mines Ltd (Ross Division)		
na	129	Matachewan Consolidated Mines Ltd (Matachewan Consolidated)	1945-1957	Gold
na	132	Hollinger Consolidated Gold Mines Ltd (Young Davidson)	1944-1956	Gold
164	142	Renabie Mines Ltd (Renabie)	1948-1970	Gold
179	161	Dickenson Mines Ltd (New Dickenson)	1952-1976	Gold
181	150	Campbell Red Lake Mines Ltd (Campbell Red Lake)	1952-1979	Gold
137	8&4	Rio Algom Mines Ltd (Nordic)	1957-1979	Uranium
197	9&1	Rio Algom Mines Ltd (Quirke)	1956-1968	Uranium
197	9&0	Rio Algom Mines Ltd (New Quirke)	1968-1979	Uranium
200	8&3	Denison Mines Ltd (Denison)	1957-1979	Uranium
204	9&4	Rio Algom Mines Ltd (Panel)	1957-1961	Uranium
na	8&0	Pronto Uranium Mines Ltd (Pronto)	1955-1960	Uranium
na	8&6	Rio Algom Mines Ltd (Milliken)	1958-1964	Uranium
na	9&5	Rio Algom Mines Ltd (Lacnor)	1957-1960	Uranium
206	5&1	Rio Algom Mines Ltd (Pronto Division - Pater)	1961-1970	Copper
na	38905	McIntyre Porcupine Mines Ltd (Castle-Trethewey)	1954-1966	Silver

NOTES: Grey shading indicates a mine site with an ownership change during the MP use period under the same license; na = license number not available