Received: 22 December 2021 | Revised: 28 June 2022 | Accepted: 30 June 2022

DOI: 10.1002/ajim.23415

HISTORICAL PERSPECTIVE

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE WILEY

McIntyre Powder and its potential contributions to cardiovascular disease risk: A literature review through the McIntyre Powder historical lens

Andrew Zarnke BSc[1,2,3] | Christine Oliver MD[2,4] | Sandra Dorman PhD[1,3]

[1]Laurentian University, Sudbury, Ontario, Canada

[2]The Occupational Health Clinics for Ontario Workers, Sudbury, Ontario, Canada

[3]The Centre for Research in Occupational Safety and Health (CROSH), Laurentian University, Sudbury, Ontario, Canada

[4]Dalla Lana School of Public Health, Division of Occupational and Environmental Health, University of Toronto, Toronto, Ontario, Canada

Correspondence
Andrew Zarnke, BSc, Laurentian University, 935 Ramsey Lake Rd, Greater, Sudbury, ON P3E 2C6, Canada.
Email: Azarnke@laurentian.ca

Abstract

McIntyre Powder (MP) is a fine aluminum powder that was developed to prevent silicosis in gold and uranium mine workers in Ontario, Canada, and was administered to miners there from 1943 to 1979. Mine workers were exposed to high concentrations (35.6 mg/m^3) of MP for approximately 10 min before every work shift. Contemporary physical and chemical characterizations of this powder have revealed that 12% of the powder is in the ultrafine particle size-range (nanoparticles); and the remaining 88%, in the fine particulate size range (below 2.5 µm in diameter). The confluence of ultrafine particulate (UFP) composition and high airborne concentration of MP would be expected to overwhelm the defense mechanisms of the lung and increase the lung dust burden of the mine worker exposed to respirable dust in the mine. Published studies revealing associations between air pollution particulates and increased risk for cardiovascular disease (CVD) shown a dose–response relationship with ambient $PM_{2.5}$ and UFP and suggest that miners exposed to MP may also be at increased risk of CVD. The historical perspective of the use of MP in northern Ontario hard-rock mines and its potential implications for CVD in exposed mine workers are discussed.

KEYWORDS

atherosclerosis, nanoparticles, particle translocation, $PM_{2.5}$, respiratory inflammation, ultrafine dust exposure

1 | INTRODUCTION

Silicosis is an occupational lung disease caused by the inhalation of crystalline silica dust. This dust is created from the cutting or breaking of many types of rocks, such as granite, sandstone, gneiss, and slate and some metallic ores. Silicon is one of the most common elements in the earth's crust. As such, when rocks are broken, small silica dust particles are released, which can be inhaled and then embed deep into the small airways and alveolar sacs of the lung. Silicosis is the most common occupational lung disease worldwide and is associated with many types of work exposures, key among them being mining. In 2019, it was estimated that there were approximately 2.65 million new cases of silicosis and 12,900 silicosis deaths globally. It was also reported that 100% of these new cases and deaths were caused by occupational exposures to crystalline silica.[1]

Due to the prevalence of this disease, innovative ideas were (and continue to be) developed for prevention. The idea of using a fine aluminum (Al) powder for the prevention of silicosis was first

published in 1937 in a preliminary report.[2,3] In the full report, Denny and colleagues[3–5] proposed that Al reduced the solubility of the crystalline silica in the lung and formed a coating around the silica particles aiding their clearance from the lung by expectoration. These reports prompted the establishment of the Porcupine Silicosis Clinic in Timmins, Ontario, where the first human trials using Al dust for the prevention of silicosis were conducted.[6] In 1943, the use of inhaled Al powder for this purpose was introduced across the hard-rock mining industry. For this treatment, underground miners were required before each work shift to inhale a chemical dust called McIntyre Powder (MP). The inhalation process involved the use of a specially designed airtight locker room (typically, the mine dry room) where the dust was dispersed into the air for them to inhale.

It is documented that 27,500 miners were exposed to MP in Ontario between 1943 and 1979. The use of MP in the mining industry spread to other parts of Canada, with 13 licensees in British Columbia and 18 in Quebec, and a small number of licensees in Manitoba, Saskatchewan, and the Northwest Territories. The McIntyre Research Foundation patented and distributed MP to licensees not only in Canada but also in other countries world-wide, including the United States, Mexico, Chile, Belgian Congo, and Western Australia. In the United Kingdom, independent evaluation of the efficacy of the Al dust treatment was conducted. The results were inconclusive and the practice was not adopted.[7] Although the original industry for which MP was designed was mining, MP was also used in several nonmining industries, such as pottery manufacture, foundries, silica brick manufacture, and refractories.[7]

The main health concerns studied to date related to MP exposure have been neurological diseases including cognitive dysfunction, Parkinson's disease, Alzheimer's disease, and motor neuron disease. There have been three epidemiological studies of MP-exposed miner cohorts published to date: two in Ontario by Rifat et al.[8] and Zeng et al.[9] and one in Australia by Peters et al.[10] Peters et al.[10] observed excess cardiovascular disease (CVD) mortality in an MP-exposed gold miner cohort in Australia when observed deaths were compared with expected deaths in the general male population in Western Australia: overall cohort standardized mortality ratio 1.31, 95% confidence interval (CI) 1.20–1.43, $n = 508$. CVD mortality was elevated and similar in never-MP-exposed and ever-MP-exposed miners. Cox proportional hazard models were used to examine within-cohort differences regarding MP exposure and CVD mortality. Compared to never-MP-exposed miners, ever-exposed miners had a 19% increase in risk for CVD death that was of borderline statistical significance: hazard ratio (HR) 1.19, 95% CI 0.99–1.44, $n = 223$. When MP dust exposure was considered as a continuous variable, a significant duration–response relationship was observed: HR 1.02, 95% CI 1.00–1.04 per year of exposure. The authors concluded that MP dust inhalation "may possibly increase the risk of cardiovascular disease."

Published studies revealing associations between air pollution particulates ($PM_{2.5}$) and increased risk for CVD raise the question of increased CVD risk for miners exposed daily to $PM_{2.5}$ and ultrafine particulate (UFP). Historical and contemporary characterizations of MP have demonstrated that 12% of the powder falls in the ultrafine size range defined as an aerodynamic diameter less than or equal to 0.1 µm (100 nm).[11,12] The diameter of inhaled particles is a critical component in airway physiology because it is directly related to "where" in the lungs the particles can deposit. The confluence of small particle size and high airborne concentration of MP would be expected to overwhelm the defense mechanisms of the lung and increase the lung dust burden mine workers exposed to respirable dust in the mine.

The American Heart Association (AHA) published a scientific statement in 2004 that included a comprehensive review of the epidemiological, toxicological, and mechanistic studies related to particulate air pollution and its influence on the risk of CVD. The AHA concluded that particulate matter (PM) has a direct contribution to cardiovascular morbidity and mortality.[13] Since then, many studies examining the physiological and molecular mechanisms involved in this relationship have been conducted, with findings that support the observed associations. The rate of new scientific literature on this topic prompted a second AHA statement in 2010 and the publication of several books reviewing the topic. For example, Brook et al.[14] outlined key physical and molecular characteristics of airborne PM that influence the risk of CVD. Of these, particle size was identified as an important factor, with particulates smaller than 2.5 µm in diameter ($PM_{2.5}$) being significantly, positively correlated with increase in CVD morbidity and mortality.[14] These findings indicate the importance of the characterization of MP particle size distribution to understanding the health effects of exposure.

The purpose of this paper is to discuss the historical perspective of MP use to prevent silicosis in metal miners; describe the physical and chemical properties of MP under these exposure conditions; and consider the potential risk for CVD in MP-exposed workers in context of the current literature.

2 | EXPOSURE CONDITIONS AND CHEMICAL AND PHYSICAL PROPERTIES OF MP

2.1 | Exposure conditions

The exposure protocol, recommended by the McIntyre Research Foundation to prevent silicosis, was 1 g of MP per 1000 cubic feet of locker room volume for an exposure time of 10 min (1 g/1000 ft^3 = 1 g/28.32 m^3 = 35.6 mg/m^3).[15] Based on worker narratives in Ontario, underground miners were required to breathe MP before every work shift for a minimum of 10 min. However, workers from different mines reported substantial variation in exposure times ranging from 10 to 45 min. Some mines were reported to require two inhalation sessions: immediately before and immediately after their work shift underground.

2.2 | Chemical properties

Al is the most abundant metallic element on earth and due to its high chemical reactivity, it never occurs in its pure metallic form in nature.[16] Al is particularly noted for its reactivity with water and its pro-oxidant activity. These properties raise significant concerns about the potential of MP to effect changes in the reactive oxygen

status of the lung by increasing the number of reactive oxygen species (ROS) and thereby inducing additional cell damage and death.[17] Oxidative stress occurs when there is an accumulation of ROS, also called free oxygen radicals. All free radicals, but particularly oxygen radicals, are unstable and are therefore able to react negatively with all cell components, causing damage to any molecule that they come in contact with, including but not limited to membranes, proteins, and DNA.[18] These injuries induce an innate, inflammatory response; and repeat inhalations of MP would be expected to induce a chronic inflammatory state.[17,19]

2.3 | Physical properties

Air particulate is measured in two ways: (1) the total mass of particulate in a volume of air; and (2) the size of the individual particles that make up that mass. With respect to size, the International Organization for Standardization (ISO) defines fine particulate ($PM_{2.5}$) as dust primarily composed of particles below 2.5 μm (2500 nm) in diameter and ultrafine particulate as dust primarily composed of particles ≤0.1 μm (≤100 nm) in diameter.[20]

In the case of particulate inhalation, the total mass is not the most important factor in determining the potential for adverse health effects. The principal factor is particle size, for two reasons. First, hairs and turbinates in the nasal passages, and the turbulence of air currents there, tend to filter particles larger than 10 μm out of inhaled air. Those that make it past the nasal passages are then caught in the mucociliary escalator of the upper airways and cleared relatively quickly (hours).[21,22] Particles smaller than 10 μm are better able to penetrate deep into the lower airways where they are retained longer (>24 h) than the larger particles, in part because of immune-mediated mechanisms.[22] Fine and UF particles are able to penetrate to the level of the alveoli,[23,24] where they can pass through alveolo-capillary membrane and enter the systemic circulation.[25]

Second, in the lower airways the biological effects of PM are positively correlated with total surface area rather than mass. The more surface area available, the greater the opportunity for chemical reaction. Chemical reactions include the generation of free radicals; of relevance for this paper, metals are highly reactive.[17] The surface area of any given mass is greater for small particles than the equivalent mass of large particles; and as such, small particles are more toxic on a gram-per-gram basis than large ones. For both reasons, even a low mass concentration of inhaled particulates can be harmful.

As described in Zarnke et al.,[11] approximately 70% of the Al particles in MP are below 0.5 μm (500 nm) in diameter, and 30% of the particles, below 0.2 μm (200 nm) 8 min after dispersal in air.[5,15] The McIntyre Research Foundation also observed that a significant number of particles were below the 0.2 μm (200 nm) analytical grain size detection limit and could not be categorized (Figure 1).

The MP particle characteristics would therefore be categorized as $PM_{2.5,}$ with a substantial fraction of the powder categorized as UF. Under the American Conference of Governmental Industrial Hygienists (ACGIH) definitions, MP would be considered a respirable PM, meaning it can reach the deepest part of the lung (i.e., alveolar space) (Figure 2A).

3 | RESPIRATORY RESPONSES TO INHALED PARTICULATE

Cherrie et al.[26] present a discussion about health effects from "nuisance" dust exposures and their potential to cause lung overload. Cherrie et al.[26] use the link between chronic obstructive pulmonary disease (COPD) and occupational exposure to "nuisance" dust to illustrate why an occupational exposure limit that considers the process of lung overload in response to peak respirable dust exposures is required. Research over the past 20 years has shown that many dusts previously thought to be inert contribute to COPD development.[27] A diagnosis of COPD is based on the demonstration of obstruction on spirometry, with a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of <0.70. The term COPD

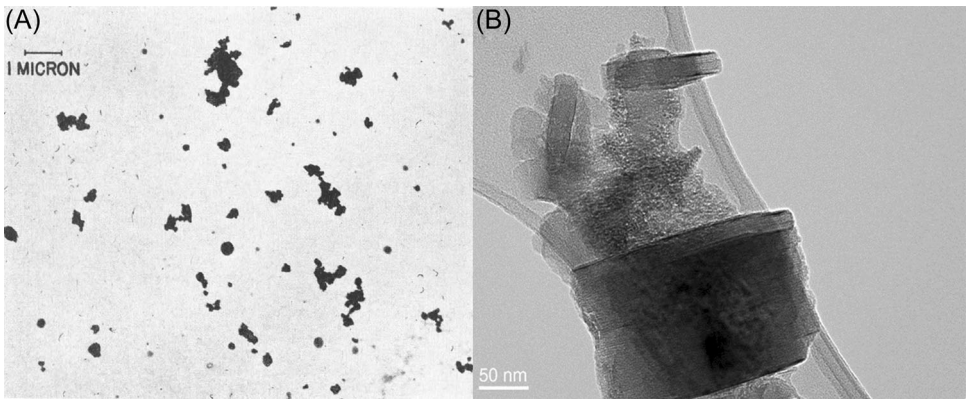

FIGURE 1 Microscopy images of fine and ultrafine McIntyre Powder (MP) particles. (A) 1944 electron micrograph of MP particles collected after dispersal in air. Example of particles ~200 nm or below which could not be sufficiently categorized.[15] (B) Transmission electron microscopy image of MP particles in the ultrafine size fraction.

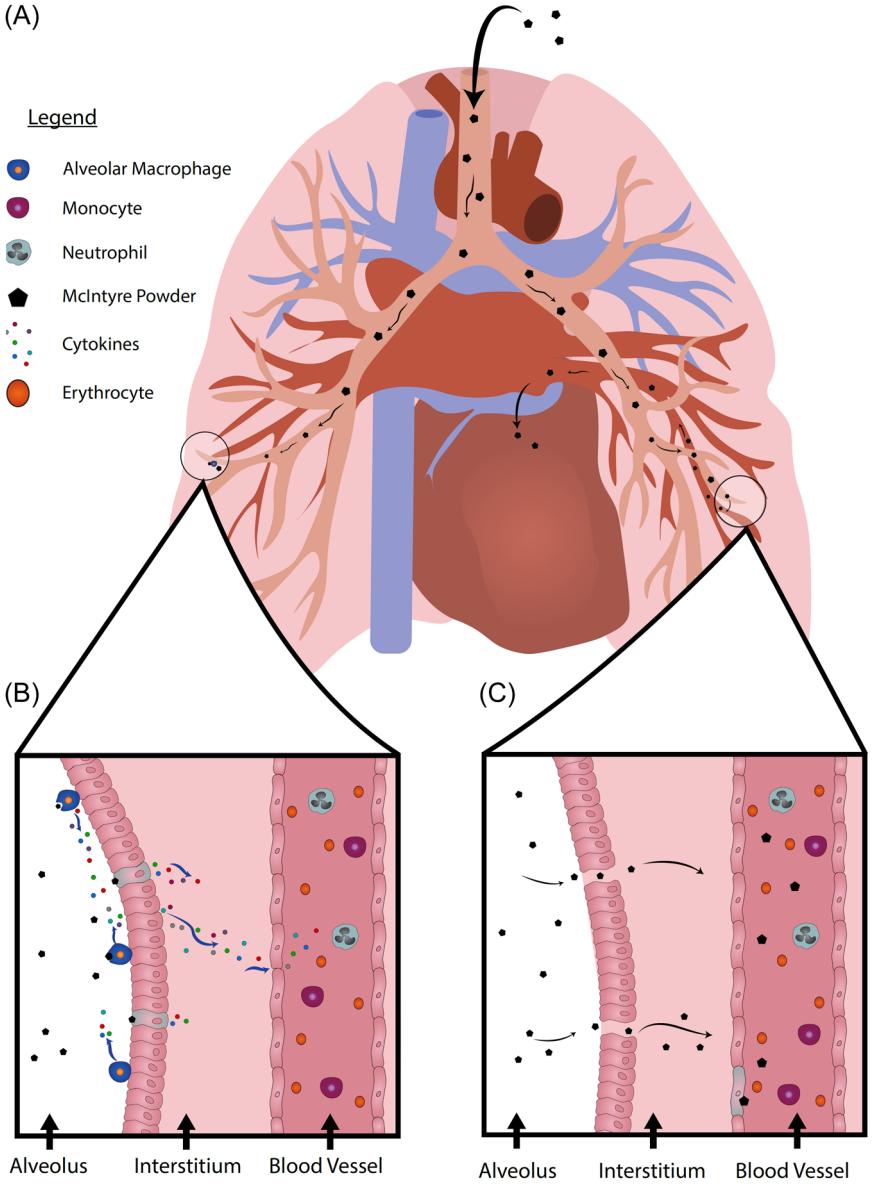

FIGURE 2 Lung response to inhalation of particulate matter including McIntyre Powder (MP). (A) Particle deposition: Once inhaled, MP makes its way through the respiratory tract to the terminal bronchioles and alveoli, with depth of penetration dependent on particle size. In the process, MP interacts with epithelial cells lining the airways and macrophages in the alveoli (AM), causing activation, and resulting in the release of pro-inflammatory mediators. (B) Activation of AM by contact with MP: A local inflammatory process is initiated by AM phagocytosis of MP particulates, with release of signaling markers, including chemokines and cytokines. These inflammatory mediators make their way through the alveolar epithelial barrier into the lung interstitium and from there into the circulatory or lymphatic system, resulting in the opportunity for systemic inflammatory effects. (C) Translocation of MP ultrafine particulates (UFPs): UFPs can penetrate the alveolar epithelial barrier directly and travel through the lung interstitium to the capillary where they enter the systemic circulation. Here, acute phase responses include increases in circulating levels of pro-inflammatory cytokines; increase in thrombogenic activity, with increase in fibrinogen levels and platelet activation and adhesion; and upregulation of endothelin expression.

includes the diseases emphysema and chronic bronchitis, and tends to be progressive and poorly reversible.[26]

Cherrie et al.[26] review toxicological studies relevant to the biological response of the lungs to respirable dust. Special focus is placed on particle dose, particle size, and the influence these parameters can have on the lung's ability to clear inhaled particles. Inhalation studies using laboratory animals have shown a critical dose at which clearance mechanisms involving AMs break down and dust accumulates in the lung in a linear fashion, with no effective clearance (lung overload). The literature shows that particle size can influence the particle dose required to achieve lung overload conditions, with smaller inhaled particles eliciting a stronger inflammatory response and accelerating lung overload, such that overload occurs at lower doses.[28]

In the upper respiratory tract, there are three major clearance mechanisms: mucous, cilia, and bronchial macrophages. In humans and in animal models, mucous and the cilia interact to create a

mucociliary escalator that moves PM up and out of the upper respiratory tract. In the lower respiratory tract (alveoli), the principal mechanism for clearing dust particulates is the alveolar macrophage (AM).[29] AMs are large, immunologically active cells that engulf and digest or otherwise attempt to remove foreign particles from the lungs. These particle-laden AMs may make their way to the mucociliary escalator to be transported out of the lungs.[29] Alternatively, AMs may undergo apoptosis following phagocytosis of PM, and be removed by AMs of a different phenotype (efferocytosis).[30] Contact with PM activates AMs and results in the release of pro-inflammatory mediators which have both local and systemic effects (Figure 2B). Similar reactions occur when PM contacts epithelial cells lining the airways of the lung.

With high dust exposure and overload of AMs, some particles penetrate the alveolar epithelial barrier directly to enter the lung interstitium, where they may then enter the circulatory or lymphatic system and be transported to other parts of the body (Figure 2C).[31] Particles that enter the bloodstream or lymphatic system in this manner are said to "translocate" out of the respiratory system. Human lungs (as opposed to animal models) have the ability to translocate fine/ultrafine dust particles throughout an inhalation–exposure period, even before lung overload is achieved.[32]

Since the size distribution of MP PM includes a 70% proportion of particles below 500 nm, 30% below 200 nm, and 12% below 100 nm, the dose required to elicit lung overload would be expected to be much lower than that of average mine dust containing larger particles. Moreover, the high dose rate of the MP would be expected to add to opportunity for lung overload. As Cherrie et al.[26] discuss, animal models show that during lung overload conditions, inhaled particulates accumulate with no effective clearance. In humans, this type of accumulation has been shown to be associated with increased translocation of inhaled particles from the alveoli to the lung interstitium and then to other organs via the circulatory system.[25] The fact that the MP exposures occurred directly before the workers' shift would be expected to increase the toxicity of the inhaled mine dust by increasing the lung burden of these dusts.

The time weighted average threshold limit value and typical exposure profiles under current Ontario exposure limits may not be relevant to MP-exposed miners for three reasons: (1) lung overload related to inhalation of MP under the circumstances described; (2) potential toxic effects of MP on the lungs separate and apart from its effect on clearance mechanisms; and (3) the potential for an interactive effect of MP and mine dusts on the lungs. Such interactive effects could enhance any existing risk for CVD and other related health effects (Figure 2A).[11]

4 | CVD AND PARTICULATE EXPOSURE

4.1 | Systemic inflammatory effects of particulate exposure and CVD

In addition to differences in biological effects of these discrepant dose rates of MP exposure, particle size distributions similar to those in MP have been shown to increase the toxicity of inhaled dusts regardless of their chemical composition.[33] Studies have also shown that small particles of Al oxide in the UFP range can cause more intense inflammatory responses in the lung when compared to respirable particles greater than 500 nm. In the last 20 years, there have been substantial advances in our understanding of PM-mediated biological mechanisms responsible for adverse cardiovascular effects. Seaton et al.[34] are widely credited with introducing the hypothesis that the systemic effects of particulate air pollution are mediated by the products of local pulmonary inflammatory reactions spilling over into the systemic circulation and inducing acute phase responses. More recently, a number of experiments have demonstrated rapid responses to air pollution causing a number of different systemic sequelae, including: increase in vascular leakage in the lungs[35]; increase in circulating levels of pro-inflammatory cytokines, including GM-CSF, IL-6, IL-4, and IL-1[36]; increases in fibrinogen[37] and thrombosis[38,39]; upregulation of endothelin expression[40]; and increased platelet activation and adhesion.[41,42] These responses suggest there are systemic signaling pathways created within hours of particulate inhalation.[14] The AHA's findings strongly support the integral role of ROS-dependent pathways at multiple stages of the PM-mediated biological response at the molecular level. These include instigation of pulmonary oxidative stress, systemic pro-inflammatory responses, vascular dysfunction, and atherosclerosis.[14,43]

Chronic biological effects have been associated with particulate air pollution. These include the promotion of atherosclerosis.[14,43] Three main pathways influencing extrapulmonary effects on the cardiovascular system in response to inhalation of PM have been identified.[14,43] The first pathway involves the release of pro-inflammatory mediators or vasoactive molecules from pulmonary-based immune cells.[44–47] The second pathway involves the perturbation of the autonomic nervous system balance by particle interactions with lung receptors or neurons.[14,48] The third pathway involves the translocation of UFP or particle constituents (organic compounds or metals) into the systemic circulation.[49,50]

Particle toxicity can arise from several mechanisms depending on whether the particles remain in the lung/lung tissue or are translocated from the lung or upper respiratory tract to other tissues in the body. Particles that remain in the lungs cause chronic inflammation via chemical reactions and oxidation, leading to tissue damage, necrosis, and scarring.[51] However, the induced inflammatory events in the airways also trigger systemic sequelae, including enhanced production of acute phase and coagulation proteins.[14,52,53] These systemic conditions can predispose an individual to a cardiovascular event through enhanced coagulability.

In addition, the injurious effects of airway inflammation can enhance translocation of particles as cells lining the airways slough away and cell barriers are lost.[14] Particles that escape the lungs and enter the circulation can subsequently cause endothelial cell injury (of the blood vessel walls) and prothrombotic effects (blood clot formation) through further chemical reactions and oxidative stress induction.[53] Points of injury to arterial walls create sites where

atherogenesis can occur.[43,53] Cardiovascular disease is caused by both chronic and acute events. In the long-term, the build-up of atherosclerotic plaque narrows the lumen of the arteries/arterioles and reduces blood flow to tissues, causing conditions such as angina pectoris and peripheral vascular diseases.[54] In addition, enhanced systemic inflammation increases coagulability and the risk of clot formation, which in turn increases risk for myocardial infarction and cardiac death.

4.2 | CVD epidemiological data related to the health effects of fine ($PM_{2.5}$) and UFP

Based on the AHA's comprehensive literature review, it is estimated that a 10 μg/m^3 increase in mean 24-h $PM_{2.5}$ concentration elevates the relative risk (RR) for daily CVD mortality by approximately 0.4%–1.0%.[55,56] Cohort studies estimate that the RR for CVD mortality is greater in areas with higher annual average PM concentrations over the long-term than for short-term PM excursions.[57] Pope and Dockery[55] cite studies of long-term exposure of sub-cohorts of the American Cancer Society (ACS) prospective cohort that show a range of increase in cardiovascular mortality with each 10 μg/m^3 increase in ambient $PM_{2.5}$: 14%–85%, adjusted RR 1.18 (95% CI: 1.14–1.23) to adjusted RR 1.49 (95% CI: 1.20–1.85).[57,58] A study by Bourdrel et al.[59] analyzed pooled epidemiological studies and reported that a 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ was associated with an increase of 11% in cardiovascular mortality.

In a report published by the World Health Organization (WHO) in 2002, it was estimated that 800,000 premature deaths per year are associated with $PM_{2.5}$ exposures, ranking it the 13th leading cause of mortality worldwide.[60] Using novel hazard ratio functions, Pozzer and colleagues calculated estimates of premature mortality due to air pollution that are double those previously reported. Their analysis revealed that between 40% and 80% of these premature deaths were due to cardiovascular events. The strongest associations were with $PM_{2.5}$ and ozone (O_3).[61]

In general, the epidemiological literature consistently shows acute increases in risk for ischemic cardiac events associated with elevated $PM_{2.5}$ concentrations. This effect has been shown to occur as rapidly as 1–2 h after exposure to elevated levels of $PM_{2.5}$ in case-cross-over analyses.[62–66]

Pope et al. (2006) examined the effect of short-term increases in ambient $PM_{2.5}$ on acute cardiovascular health outcomes in patients who had undergone coronary angiography.[56] Increasing numbers of and risk for ischemic cardiac events were observed in association with short-term increases in ambient $PM_{2.5}$ measured same day and lagged by 1–3 days. Exposure to average increases in ambient $PM_{2.5}$ of 10 μg/m^3 over the long-term was associated with significant increase in cardiovascular mortality from ischemic heart disease (IHD): RR ratio 1.18 (95% CI: 1.14–1.23).[57]

Dominici et al.[67] examined the effect of a 10 μg/m^3 same-day change in ambient $PM_{2.5}$ concentration on hospital admissions for CVDs in 204 urban counties in the United States. For IHD the increase in hospital admissions per 10 μg/m^3 increase in $PM_{2.5}$, with a 2-day lag, was 0.44 (95% percentage change [PI]: 0.02–0.86). An annual decline in hospital admissions for IHD of 1523 (95% PI: 69–2976) was observed for each 10 μg/m^3 decrease in $PM_{2.5}$ concentration.[67]

A 10-year prospective cohort study examining particulate air pollution exposure and CVD, called The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air), employed individual participant air pollutant monitoring to account for local variation in $PM_{2.5}$ levels. During the follow-up period, individual exposure estimates for PM, oxides of nitrogen (NOX), and black carbon were calculated for all participants in the study. The use of indoor and outdoor ambient air pollution sampling allowed for the inclusion of participant-specific residential infiltration efficiencies and time-location patterns, which had not been achievable in pervious studies.[68] The primary aim of the MESA Air study was to better understand the relationship between air pollution exposures and progression of atherosclerosis and cardiovascular disease. Coronary artery calcium (CAC) and carotid artery wall thickness (intima-media thickness) were assessed repeatedly by computed tomography over 10 years in 5835 participants to determine the extent and rate of development of atherosclerosis.[69] Associations between CAC progression and air pollutant exposures were assessed, adjusting for baseline age, sex, race/ethnicity, socioeconomic characteristics, cardiovascular risk factors, site, and computed tomography scanner technology. Participants' CAC measurements increased by 4.1 units/year (95% CI: 1.4–6.8) for each additional 5 μg/m^3 of $PM_{2.5}$ and 4.8 units/year (CI: 0.9–8.7) for each 40 ppb of NOX.[69] These findings suggest that increased concentrations of fine PM and traffic-related air pollution, in ranges commonly encountered, are associated with progression in CAC, which has been shown to be consistent with acceleration of atherosclerosis.[69]

5 | CONCLUSION

MP under the ISO definitions is classifiable as fine and ultrafine PM. The current scientific toxicological data support that exposure levels of 35.6 mg/m^3 for 10–45 min once or twice per day experienced by Ontario miners could impair the lungs' ability to effectively clear inhaled PM, thereby compounding any subsequent mine dust exposure and the resultant health effects. Because the MP particle size distribution is 100% below 2.5 μm and 12% below 100 nm, the dose required to elicit lung overload conditions would be lower than that of an average mine dust having larger particles. Moreover, the nature of the MP exposure, with high dose rate, short exposure time, and administration directly before underground shifts increase the probability that lung overload conditions would be met. Published studies revealing associations between air pollution particulates and increased risk for CVD show a dose–response relationship with ambient $PM_{2.5}$ and UFP. Importantly, epidemiological studies of the cardiovascular effects of exposure to ambient particulates in the form

of air pollution have not considered occupational exposure to particulates. The MESA studies measured *residential* exposure but not occupational exposure, which is a potentially significant and confounding source of risk.

In conclusion, characterizations of MP, the nature of the exposures, and published findings to date show increased risk of CVD associated with exposure to air pollution particulates and suggest that MP-exposed miners are at increased risk for CVD as a result of their exposure to MP. Targeted research is needed to determine the nature and extent of this increase in risk, if any, and whether monitoring for CVD by health care providers and employers is needed to prevent acute coronary events and reduce cardiovascular morbidity and mortality in exposed workers.

ACKNOWLEDGMENTS

The authors would like to acknowledge Mr. Tobias D. Mankis for the artwork. We would acknowledge all the miners who died from, or whose health was impacted by McIntyre Powder exposure and the families who suffered beside them. We would also acknowledge Janice Martell, Dave Wilken, and the Occupational Health Clinics for Ontario Workers for their continued efforts to support these workers.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

Andrew Zarnke was responsible for conceptualizing, drafting and revising the manuscript. Christine Oliver was responsible for conceptualizing and revising the manuscript for critical intellectual content. Sandra Dorman was responsible for conceptualizing and revising the manuscript for critical intellectual content. All authors approved the final manuscript version submitted for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ORCID

Andrew Zarnke http://orcid.org/0000-0002-1137-1611
Christine Oliver https://orcid.org/0000-0002-1866-2163

REFERENCES

1. Institute for Health Metrics and Evaluation. *Silicosis—Level 4 cause*. Global Health Metrics Web site. Accessed September 7, 2021. http://www.healthdata.org/results/gbd_summaries/2019/silicosis-level-4-cause
2. Denny JJ, Robson WD, Irwin DA. The prevention of silicosis by metallic aluminum: I. A preliminary report. *Can Med Assoc J*. 1937;37(1):1-11.
3. Denny JJ, Robson WD, Irwin DA. The prevention of silicosis by metallic aluminum II. *Can Med Assoc J*. 1939;40(3):213-228.
4. Newkirk TE, Hannon JWG, Campbell AD. *The Physical and Chemical Characteristics and the Commercial Manufacture of a New Mcintyre Aluminium Powder*. McIntyre Research Foundation; 1956.
5. Hannon JWG. Inventor; McIntyre Research Foundation, assignee. Method of producing an atmosphere protective against silicosis. US patent 28240431958.
6. Robson WD. Progress in aluminum therapy. *Can Inst Min Metall*. 1945;XLVII:172-179.
7. Jorgenson M, Sandlos J. Dust versus dust: aluminum therapy and silicosis in the Canadian and Global Mining Industries. *Can Hist Rev*. 2021;102(1):1-26.
8. Rifat SL, Eastwood MR, McLachlan DR, Corey PN. Effect of exposure of miners to aluminium powder. *Lancet*. 1990;336(8724):1162-1165.
9. Zeng X, MacLeod J, Berriault C, et al. Aluminum dust exposure and risk of neurodegenerative diseases in a cohort of male miners in Ontario, Canada. *Scand J Work Environ Health*. 2021;47(7):531-539.
10. Peters S, Reid A, Fritschi L, de Klerk N, Musk AW. Long-term effects of aluminium dust inhalation. *Occup Environ Med*. 2013;70(12):864-868.
11. Zarnke A, Rasmussen PE, David MO, et al. Physical and chemical characterization of McIntyre Powder: an aluminum dust inhaled by miners to combat silicosis. *J Occup Environ Hyg*. 2019;16(11):745-756.
12. Verma DK, Reid M, Purdham JT, des Tombe K. Chemical and physical characterization of McIntyre Powder using inductively coupled plasma mass spectroscopy and electron microscopy. *Am J Prev Med and Public Health*. 2020;6(3):50-55.
13. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the expert panel on population and prevention science of the American Heart Association. *Circulation*. 2004;109(21):2655-2671.
14. Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121(21):2331-2378.
15. Jacob AW. The engineering aspects of aluminum prophylaxis. *Can Inst Min Metall*. 1944;XLVII:185-202.
16. Driscoll CT, Schecher WD. The chemistry of aluminum in the environment. *Environ Geochem Health*. 1990;12(1):28-49.
17. Exley C. The pro-oxidant activity of aluminum. *Free Radic Biol Med*. 2004;36(3):380-387.
18. Li R, Jia Z, Trush MA. Defining ROS in biology and medicine. *React Oxyg Species (Apex)*. 2016;1(1):9-21.
19. Puukila S, Thome C, Brooks AL, Woloschak G, Boreham DR. The role of radiation induced injury on lung cancer. *Cancers*. 2017;9:7.
20. ISO. ISO/TR 27628:2007 Workplace atmospheres—Ultrafine, nanoparticle and nano-structured aerosols—Inhalation exposure characterization and assessment. 2007.
21. Swift DL. Aerosol deposition and clearance in the human upper airways. *Ann Biomed Eng*. 1981;9(5):593-604.
22. Henning A, Schneider M, Nafee N, et al. Influence of particle size and material properties on mucociliary clearance from the airways. *J Aerosol Med Pulm Drug Delivery*. 2010;23(4):233-241.
23. Deng Q, Ou C, Chen J, Xiang Y. Particle deposition in tracheobronchial airways of an infant, child and adult. *Sci Total Environ*. 2018;612:339-346.
24. Asgharian B, Hofmann W, Miller F. Mucociliary clearance of insoluble particles from the tracheobronchial airways of the human lung. *J Aerosol Sci*. 2001;32(6):817-832.
25. Choi HS, Ashitate Y, Lee JH, et al. Rapid translocation of nanoparticles from the lung airspaces to the body. *Nature Biotechnol*. 2010;28(12):1300-1303.

26. Cherrie JW, Brosseau LM, Hay A, Donaldson K. Low-toxicity dusts: current exposure guidelines are not sufficiently protective. *Ann Occup Hyg*. 2013;57(6):685-691.
27. Sadhra S, Kurmi OP, Sadhra SS, Lam KBH, Ayres JG. Occupational COPD and job exposure matrices: a systematic review and meta-analysis. *Int J Chronic Obstruct Pulm Dis*. 2017;12:725-734.
28. Monteiller C, Tran L, MacNee W, et al. The pro-inflammatory effects of low-toxicity low-solubility particles, nanoparticles and fine particles, on epithelial cells in vitro: the role of surface area. *Occup Environ Med*. 2007;64(9):609-615.
29. Joshi N, Walter JM, Misharin AV. Alveolar macrophages. *Cell Immunol*. 2018;330:86-90.
30. Hiraiwa K, van Eeden SF. Contribution of lung macrophages to the inflammatory responses induced by exposure to air pollutants. *Mediators Inflamm*. 2013;2013:619523.
31. Gibbs AR. Occupational lung disease. In: Hasleton PS, ed. *Spencer's pathology of the lung*. 5th ed. McGraw Hill; 1996:461-506.
32. Nikula KJ, Avila KJ, Griffith WC, Mauderly JL. Sites of particle retention and lung tissue responses to chronically inhaled diesel exhaust and coal dust in rats and cynomolgus monkeys. *Environ Health Perspect*. 1997;105(suppl 5):1231-1234.
33. Maynard A, Kuempel E. Airborne nanostructured particles and occupational health. *J Nanopart Res*. 2005;7:587-614.
34. Seaton A, Godden D, MacNee W, Donaldson K. Particulate air pollution and acute health effects. *Lancet*. 1995;345(8943):176-178.
35. Wang T, Wang L, Moreno-Vinasco L, et al. Particulate matter air pollution disrupts endothelial cell barrier via calpain-mediated tight junction protein degradation. *Part Fibre Toxicol*. 2012;9(1):1-12.
36. van Eeden SF, Tan WC, Suwa T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM10). *Am J Respir Crit Care Med*. 2001;164(5):826-830.
37. Ghio AJ, Hall A, Bassett MA, Cascio WE, Devlin RB. Exposure to concentrated ambient air particles alters hematologic indices in humans. *Inhal Toxicol*. 2003;15(14):1465-1478.
38. Nemmar A, Hoylaerts MF, Hoet PH, et al. Ultrafine particles affect experimental thrombosis in an in vivo hamster model. *Am J Respir Crit Care Med*. 2002;166(7):998-1004.
39. Nemmar A, Nemery B, Hoylaerts M, Vermylen J. Air pollution and thrombosis: an experimental approach. *Pathophysiol Haemost Thromb*. 2002;32(5-6):349-350.
40. Calderón-Garcidueñas L, Vincent R, Mora-Tiscareño A, et al. Elevated plasma endothelin-1 and pulmonary arterial pressure in children exposed to air pollution. *Environ Health Perspect*. 2007;115(8):1248-1253.
41. Nemmar A, Hoet PH, Dinsdale D, Vermylen J, Hoylaerts MF, Nemery B. Diesel exhaust particles in lung acutely enhance experimental peripheral thrombosis. *Circulation*. 2003;107(8):1202-1208.
42. Khandoga A, Stampfl A, Takenaka S, et al. Ultrafine particles exert prothrombotic but not inflammatory effects on the hepatic microcirculation in healthy mice in vivo. *Circulation*. 2004;109(10):1320-1325.
43. Brook RD, Rajagopalan S. Particulate matter air pollution and atherosclerosis. *Curr Atheroscler Rep*. 2010;12(5):291-300.
44. Simkhovich BZ, Kleinman MT, Kloner RA. Air pollution and cardiovascular injury epidemiology, toxicology, and mechanisms. *J Am Coll Cardiol*. 2008;52(9):719-726.
45. Møller P, Jacobsen NR, Folkmann JK, et al. Role of oxidative damage in toxicity of particulates. *Free Radic Res*. 2010;44(1):1-46.
46. Moller P, Loft S. Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution. *Environ Health Perspect*. 2010;118(8):1126-1136.
47. Kreyling WG, Semmler-Behnke M, Moller W. Ultrafine particle-lung interactions: does size matter? *J Aerosol Med*. 2006;19(1):74-83.
48. Rhoden CR, Wellenius GA, Ghelfi E, Lawrence J, Gonzalez-Flecha B. PM-induced cardiac oxidative stress and dysfunction are mediated by autonomic stimulation. *Biochem Biophys Acta*. 2005;1725(3):305-313.
49. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science*. 2006;311(5761):622-627.
50. Maher BA, Ahmed IA, Karloukovski V, et al. Magnetite pollution nanoparticles in the human brain. *Proc Natl Acad Sci USA*. 2016;113(39):10797-10801.
51. Donaldson K, Li XY, MacNee W. Ultrafine (nanometer) particle mediated lung injury. *J Aerosol Sci*. 1998;29:553-560.
52. Nemmar A, Hoet PH, Vermylen J, Nemery B, Hoylaerts MF. Pharmacological stabilization of mast cells abrogates late thrombotic events induced by diesel exhaust particles in hamsters. *Circulation*. 2004;110(12):1670-1677.
53. Nemmar A, Hoylaerts MF, Hoet PH, Nemery B. Possible mechanisms of the cardiovascular effects of inhaled particles: systemic translocation and prothrombotic effects. *Toxicol Lett*. 2004;149(1-3):243-253.
54. Cayley WE Jr. Diagnosing the cause of chest pain. *Am Fam Physician*. 2005;72(10):2012-2021.
55. Pope CA, 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc*. 2006;56(6):709-742.
56. Pope CA, 3rd, Muhlestein JB, May HT, Renlund DG, Anderson JL, Horne BD. Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution. *Circulation*. 2006;114(23):2443-2448.
57. Pope CA 3rd, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109(1):71-77.
58. Jerrett M, Burnett RT, Ma R, et al. Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology*. 2005;16(6):727-736.
59. Bourdrel T, Bind MA, Bejot Y, Morel O, Argacha JF. Cardiovascular effects of air pollution. *Arch Cardiovasc Dis*. 2017;110(11):634-642.
60. *World Health Report 2002*. World Health Organization; 2002.
61. Lelieveld J, Pozzer A, Klingmüller K, et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J*. 2019;40:1590-1596.
62. Al Rashida VJM, Wang X, Myers OB, et al. Greater odds for angina in uranium miners than nonuranium miners in New Mexico. *J Occup Environ Med*. 2019;61(1):1-7.
63. Bakand S, Hayes A. Toxicological considerations, toxicity assessment, and risk management of inhaled nanoparticles. *Int J Mol Sci*. 2016;17(6):929.
64. Costello S, Brown DM, Noth EM, et al. Incident ischemic heart disease and recent occupational exposure to particulate matter in an aluminum cohort. *J Exposure Sci Environ Epidemiol*. 2014;24(1):82-88.
65. Costello S, Neophytou AM, Brown DM, et al. Incident ischemic heart disease after long-term occupational exposure to fine particulate matter: accounting for 2 forms of survivor bias. *Am J Epidemiol*. 2016;183(9):861-868.
66. Costello S, Attfield MD, Lubin JH, et al. Ischemic heart disease mortality and diesel exhaust and respirable dust exposure in the diesel exhaust in miners study. *Am J Epidemiol*. 2018;187(12):2623-2632.
67. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA*. 2006;295(10):1127-1134.
68. Cohen MA, Adar SD, Allen RW, et al. Approach to estimating participant pollutant exposures in the Multi-Ethnic Study of

Atherosclerosis and Air Pollution (MESA Air). *Environ Sci Technol*. 2009;43(13):4687-4693.

69. Kaufman JD, Adar SD, Barr RG, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet*. 2016;388(10045):696-704.

How to cite this article: Zarnke A, Oliver C, Dorman S. McIntyre Powder and its potential contributions to cardiovascular disease risk: a literature review through the McIntyre Powder historical lens. *Am J Ind Med*. 2022;65:813-821. doi:10.1002/ajim.23415