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McIntyre Powder: Biological significance of the manner of exposure and particle size

Last updated: March 26, 2019

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Introduction

The purpose of this report is to identify the characteristics of McIntyre Powder (MP) prophylaxis that may elicit different biological and toxicological responses when compared to ambient mine dust inhalation. The main differences between the two exposures that will be discussed are the levels of exposure, dose rate and the MP particle size distribution. MP is a finely ground aluminum powder that was used between 1943 and 1979 as a prophylaxis for silicosis. In Canada, it is documented that 27,500 miners were exposed to MP in Ontario alone. The notion of using a fine aluminum (Al) powder for the prevention of silicosis was first published in 1937 as a preliminary report which was followed by a full report in 1939 [1, 2]. Denny *et al.* (1939) proposed that Al reduces the solubility of crystalline silica in the lung, and forms a coating around silica particles to aid their clearance from the lung. Early in the 1940's these reports prompted the establishment of the Porcupine Silicosis Clinic in Timmins, Ontario where the first human trials using Al dust to treat silicosis were conducted [3].

In 1943 the use of Al powder to prevent silicosis was introduced. Before every work shift underground, miners were locked in a specially-designed airtight locker room (the mine dry) and the dust was dispersed into the air for them to inhale. Characterization of this finely ground powder has demonstrated that there is a portion of the MP that is ultrafine, meaning a size range below 0.1µm (100 nm) (Figure 3). In addition to the small particle size, the level of exposure to MP was high, exceeding the Ontario Occupational Health and Safety Act (OHSA) "excursion criteria" which are set at five times the time-weighted average (TWA) threshold limit value (TLV) and which must not be exceeded at any time (O. Reg. 833/90). Both the particle size and dose rate must be considered when evaluating health effects, as these parameters created a greater risk for MP prophylaxis than typical exposures to respirable dust encountered in mining.

McIntyre Powder Characterization

The MP was described as a "lamp black" powder composed of 15% metallic Al and 85% Al oxide (as labeled on the MP canisters). Approximately 70% of the Al particles are below 0.5 µm (500 nm) in diameter (Figure 1) and 30% of the particles are below 0.2 µm (200 nm) (Figure 2) eight minutes after dispersal in the air [4, 5]. It was also observed by the McIntyre Research Foundation that there were a large number of particles below the 0.2 µm (200 nm) analytical grain size detection limit that could not be categorized (Figure 3). The International Organization for Standardization (ISO) defines fine particulates as dust primarily composed of particles below 2.5 µm (2500 nm) in diameter and ultrafine particulates as dust primarily composed of particles ≤0.1 µm (≤100 nm) in diameter [6]. The MP particles would thus be categorized as fine particulate matter, with the potential for a substantial fraction of the powder to be categorized as ultrafine particulate matter. The MP exposure level recommended by the McIntyre Research Foundation to prevent silicosis was one gram of MP per 1000 cubic feet of locker room volume (1g/1000 ft^3 = 1 g/28.32 m^3 = 35.3 mg/m^3). The recommended duration of exposure was 10 minutes. When the exposure for silicosis prophylaxis is time-weighted for an eight-hour work day, it equates to 0.74 mg/m^3. This TWA value for MP exposures is currently being used by the Workplace Safety & Insurance Board (WSIB) in cumulative dust exposure calculations.

Dose Rate of McIntyre Powder in Comparison to TWA

We propose that the TWA of 0.74 mg/m^3 for MP being used by the WSIB does not sufficiently consider the biological and physiological responses elicited by ultrafine particulates and relatively high exposure excursions, and will underestimate the related health effects. The American Conference of Government Industrial Hygienists (ACGIH) and the Ontario Ministry of Labour (MOL) currently recommend a TLV for Al metal and insoluble compounds of 1.0 mg/m^3 TWA for the respirable fraction [7, 8]. The Ontario OHSA Regulation 833/90 currently includes excursion criteria for substances that do not have a short term (15 minutes) exposure limit (STEL). The excursion criteria state that if a substance does not have a STEL, which is currently the case for Al, the exposure shall not exceed the following excursion limits: three times the TWA TLV for any 30 minute period or five times the TWA TLV at any time (O. Reg. 833/90). It is also interesting to note that between 1979 and 1985 the ACGIH recommended a STEL for metal and Al oxide of 20 mg/m^3 [7]. The establishment of this STEL happens to coincide with the abandonment of the MP prophylaxis program in 1979.

When the TWA TLV for aluminum of 1.0 mg/m^3 is converted to a 10 minute exposure similar to that used for MP silicosis prophylaxis, it equates to 48 mg/m^3 (1.0 mg/m^3 X (480 min ÷ 10 min) = 48 mg/m^3). This exposure would represent an Al exposure which is 2.4 (48 mg/m^3 ÷ 20.0 mg/m^3 = 2.4) times higher than the 1979 – 1985 STEL set by the ACGIH and 9.6 (48 mg/m^3 ÷ (1.0 mg/m^3 x 5) = 9.6) times higher than the excursion criteria set by the Ontario OHSA. This demonstrates the importance of the current excursion criteria and why high dose rate short duration exposures should not be time weighted over an eight hour work day. Receiving an entire eight hours' worth of dust in 10 minutes in this way would elicit substantially different biological responses that can reduce the lungs' ability to clear fine particulates and compound the effects of any subsequent dust exposures [9-11]. The lungs' ability to effectively clear particulate matter and function in response to high, near-instant assaults of respirable dust (high dose rate repeated acute exposure) results in lung overload and is vastly different from the response to low-level dust exposures over eight hours (low dose rate chronic exposure) [12-14]. Considering the excursion limit for Al metal and insoluble compounds is 5.0 mg/m^3 (1.0 mg/m^3 x 5) and MP is composed of 100% respirable particles, the MP exposure concentration of 35.3 mg/m^3 would exceed this limit by a factor of seven.

McIntyre Powder Particle Size Influence on Health Effects

In addition to differences in biological effects of these discrepant dose rates of MP exposure (TWA vs. STEL), particle size distributions in dusts similar to MP have been shown to increase the toxicity of inhaled particulate matter regardless of their chemical composition [15]. The increased toxicity can arise from several mechanisms dependent 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 may cause chronic inflammation leading to tissue damage and disease [16]. Particles that escape the lungs and enter blood circulation may cause endothelial cell injury (of the blood vessel walls) and prothrombotic effects (blood clot formation)

[17]. Studies have also shown that smaller particles of Al oxide in the ultrafine range (<0.1µm) can cause more intense inflammatory responses in the lung when compared to respirable particles greater than 500 nm. The adverse health effects increase with both elevated short term exposure excursions and as the particle size becomes smaller. The particle size effect increases with particle dose and has been linked to many chronic inflammatory diseases including COPD, pulmonary fibrosis, cancer and cardiovascular disease [18-21].

A recent study by Maher *et al.* (2016) detected magnetite ultrafine particles (10-150 nm in diameter) in the frontal cortex of preserved human brain tissues. The subjects had a large age range (3 to 92 years old) and included both males and females living in Mexico City and Manchester, UK. The preserved brains of the diseased subjects were analyzed for particulate matter consistent with air pollution from combustion engines. Maher *et al.* used high-resolution transmission electron microscopy (HRTEM), energy loss spectroscopy (EELS), and energy dispersive X-ray (EDX) analysis to identify and characterize magnetite particles in the subjects' brains. Using these techniques, Maher *et al.* were able to identify magnetite particles with morphological characteristics consistent with magnetite formed by combustion and/or friction-derived heating (typical of exhaust particulates). This finding suggests that environmental ultrafine magnetite particles from combustion engine exhaust can be translocated to the brain via the nasopharyngeal route (nose and sinus cavity), the olfactory bulb, or the olfactory nerves [22, 23]. This may be a critical mechanism involved in the potential transport of ultrafine MP particles to the brain of exposed workers and is particularly important in light of the occurrence of neurodegenerative disorders in some of the miners exposed to MP [24].

Lung Overload and Related Health Effects

Cherrie *et al.* (2013) present a thorough review of the most recent scientific literature related to health effects linked to occupational exposures to inhalable and respirable dusts [18]. Cherrie et al use the link between COPD and occupational dust exposures as a clear example of why there needs to be an occupational exposure limit which considers the process of lung overload in response to peak exposures of respirable dust. There is a large collection of data and literature which supports the link between exposures to high levels of dusts by coal miners and the development of coal workers' pneumoconiosis (CWP), a form of parenchymal lung disease. CWP is characterized by dust accumulation in the terminal bronchiolar walls, with minimal fibrosis and occasional nodule formation. Research over the past 20 years has shown that many dusts previously thought inert contribute to COPD development. A diagnosis of COPD is based on the demonstration of obstruction on spirometry, with a ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of <0.70. The term COPD includes the diseases emphysema and chronic bronchitis, and tends to be progressive and poorly reversible [18].

Cherrie *et al.* (2013) include an in-depth review of current toxicological studies relevant to the biological response to respirable dust. Special focus is placed on particle dose, particle size, and the influence these parameters can have on the lungs' ability to clear inhaled particles. Inhalation studies using laboratory animals have shown a critical dose at which clearance mechanisms involving alveolar macrophages break down and dust accumulates in the lung in a linear fashion,

with no effective clearance (lung overload). In the upper respiratory tract there are three major clearance mechanisms: mucous, cilia (hair like structures), and bronchial macrophages. In humans and in animal models, mucous and the cilia interact to create a mucociliary escalator that moves particulate matter 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. Alveolar macrophages are large immune cells that engulf and destroy or attempt to destroy foreign particles; these particle-laden alveolar macrophages may make their way to the mucociliary escalator to be transported out of the lungs. Alternatively, with high dust exposure and overload of alveolar macrophages, some particles penetrate alveolar epithelial cells to enter the lung interstitium, where they may enter the vascular or lymphatic systems and be transported to other parts of the body [25].

In the past there has been a debate over the relevance of "rat lung overload" to the human response to high doses of inhaled dust. Now it is known that the discrepancy between the two models is that human lungs have the ability to translocate fine/ultrafine dust particles throughout an exposure, whereas rats do not begin the translocation process until lung overload is achieved [26]. Cherrie *et al.* also discuss a growing body of literature which demonstrates that particle size can influence the particle dose required to achieve lung overload conditions. There is evidence that smaller inhaled particles elicit a stronger inflammatory response in the lung which accelerates the overloading of the alveolar macrophage clearance system and leads to particle accumulation in the lung at lower doses [27].

Principal Points

- McIntyre Powder under the ISO definitions is classifiable as fine and potentially ultrafine particulate matter.

- The nature of the MP exposure, with small particle size and high dose rate, makes it more likely that lung overload conditions would be met.

- The MP exposures as experienced during MP prophylaxis for silicosis are distinctly different from an average mine dust exposure and created the potential for these two exposures to interact in an additive or synergistic manner to increase the risk for exposure-related disease.

- The fact that the MP exposures occurred directly before the workers' shift would enhance the toxicity of the mine dust inhaled during the work shift by increasing the lung burden of mine dust, if nothing else.

- We propose that the TWA of 0.74mg/m^3 for MP being used by the WSIB does not sufficiently consider the biological and physiological responses elicited by fine/ultrafine particulates and relatively high exposure excursions, and will underestimate the related health effects.

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TABLE 1.—PERCENTAGE OF PARTICLES IN VARIOUS SIZE GROUPS

SIZE IN MICRONS	8 MINUTES AFTER DISPERSAL	60 MINUTES AFTER DISPERSAL
0.5 or less	71.7	69.1
0.5 to 1.0	21.9	21.1
1.0 to 2.0	4.1	8.8
2.0 to 3.0	1.1	0.5
3.0 to 4.0	0.7	0.4
4.0 to 5.0	0.3	..
5.0 to 6.25	..	..
6.25 to 7.50	0.2	0.2
TOTAL	100.0	100.1

Figure 1 – Image of data taken from an engineering report which describes the application of McIntyre Powder for the prevention of silicosis*: 8 ten gram cans of McIntyre Powder were dispersed in a 80,000 square foot mine change house as recommended. Samples of the airborne particles were collected with a thermal precipitator and particle counts and particle size distributions were measured. It was observed that there was a sizable fraction below 0.5µm (500nm) which could not be characterized sufficiently with this method.

* Jacob, A. W. (1944). "The Engineering Aspects of Aluminum Prophylaxis." Canadian Institute of Mining and Metallurgy **XLVII**: 185-202.

Table 2.—Size distribution of HM–38 and D–R powders 8 minutes after dispersal

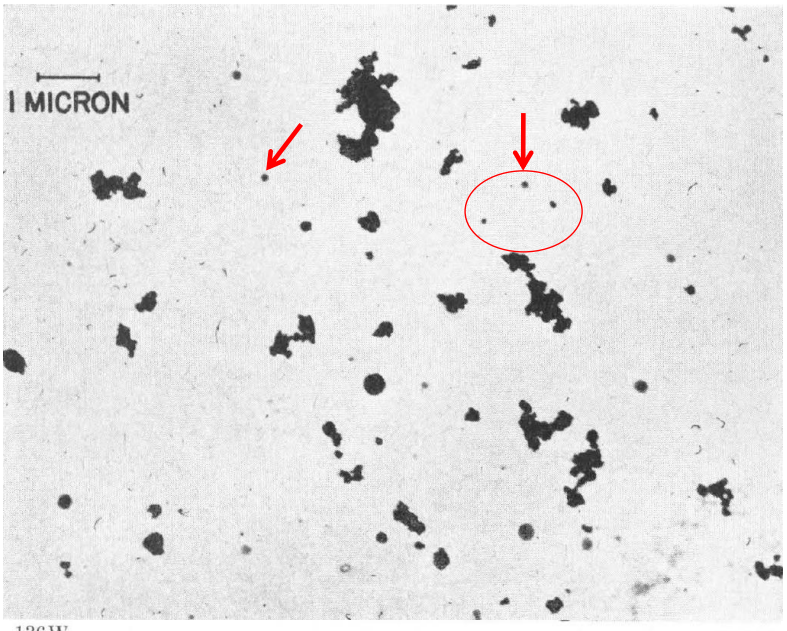
Size Group Mean Diameter (M.)	Percentage Occurrence		Percentage up to Max. Size of Group	
	HM–38[1]	D–R[2]	HM–38	D–R
Up to 0.2	24.60	2.69	24.60	2.69
0.2 to 0.4	30.85	5.83	55.45	8.52
0.4 to 0.8	32.58	20.18	88.03	28.70
0.8 to 1.2	8.64	19.73	96.67	48.43
1.2 to 1.6	1.72	17.04	98.39	65.47
1.6 to 2.0	0.79	16.14	99.18	81.61
Above 2.0	0.82	----------	----------	----------
2.0 to 2.5	----------	4.48	----------	86.09
2.5 to 3.0	----------	2.24	----------	88.33
3.0 to 4.0	----------	3.58	----------	91.91
4.0 to 5.0	----------	2.69	----------	94.60
Above 5.0	----------	5.40	----------	----------

[1] HM–38 represents the atmosphere produced by the specified aluminum powder in accordance with the present invention.

[2] D–R represents the optimum atmosphere produced under same conditions as HM–38 but using optimum powder available prior to the present invention.

Figure 2 – Image of data taken from a patent held by the McIntyre Research Foundation describing a method of producing an atmosphere that protects against silicosis: HM-38 was characterized as the most current version of Al powder using the invention described (large commercial ball-mill). D-R is Al powder characterized as the best powder produced prior to the previously described invention (small ball-mill which produced unfiltered powder).

*Hannon, J. W. G. (1958). Method of Producing an Atmosphere Protective Against Silicosis. U. S. P. Office, McIntyre Research Foundation.



136W ×10,000

Figure 9.—Aluminium dust sample No. 6. 100 c.c. Collected 66-82 minutes after blow.

Figure 3 – Electron micrograph of McIntyre Powder particles collected after dispersal in air. Arrows are pointing at examples of particles ~200nm or below which couldn't be sufficiently categorized. Jacob, A. W. (1944). "The Engineering Aspects of Aluminum Prophylaxis." Canadian Institute of Mining and Metallurgy **XLVII**: 185-202.