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## SYSTEMATIC REVIEW OF OCCUPATIONAL ALUMINUM EXPOSURE AND ADVERSE HEALTH CONDITIONS

### PLAIN LANGUAGE SUMMARY

The Workplace Safety and Insurance Board of Ontario (WSIB) is interested in determining whether workplace exposure to aluminum dust resulted in negative health conditions among workers in the Ontario mining industry, and in particular, whether there is a higher chance of developing disorders of the nervous system in workers exposed to McIntyre Powder. McIntyre Powder is a finely ground aluminum dust that was used as a preventative measure for protection against silicosis, a lung disease caused by exposure of workers to silica. In response, Intrinsic Corp. (Intrinsic) has prepared a systematic review of peer reviewed epidemiologic studies that assessed workplace aluminum exposure and negative health conditions. Epidemiological studies analyze the patterns, causes, and effects of health and disease conditions in defined populations. The purpose of this systematic review is to evaluate whether there is evidence for a relationship between workplace exposure to McIntyre Powder, aluminum from other sources (e.g., welding), or other aluminum compounds, and: (i) nervous system outcomes (such as Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis); or, (ii) other health outcomes.

Aluminum is a light-weight silvery-white metal obtained from aluminum containing minerals, such as bauxite. It is the most abundant metal and the third most abundant element in the Earth's crust, naturally occurring in air, water and soil. There are several different aluminum compounds. However, with respect to the potential for aluminum exposure in the workplace and this current systematic review, elemental aluminum and aluminum oxide (*i.e.*, alumina) are considered most relevant.

Aluminum can enter the body by breathing in aluminum dust, ingesting food and water that contains aluminum, and through skin contact with aluminum containing materials. Aluminum that is ingested or breathed in is poorly absorbed by the gastrointestinal tract. Aluminum is essentially not absorbed by the skin. Aluminum can be measured in the blood, urine and feces and is regularly found in healthy individuals due to its presence in most places, as well as in many food and consumer items. Measuring urinary aluminum may be the most appropriate method of measuring stable and continuous exposure of workers to aluminum.

The study search and evaluation process in this systematic review of workplace aluminum exposure and negative health outcomes was guided by the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, 2009). The systematic nature of the literature review is intended to provide a reproducible method, as well as reduce the risk for bias in the findings. The literature review included a search of epidemiological studies that investigate the health effects (primarily nervous system disorders) associated with workplace exposure to aluminum. The mechanism of toxicity of aluminum to the nervous system is not well understood and is the subject of much controversy. This review specifically excluded acute (short-term) health conditions such as contact dermatitis or other allergic reactions. The search strategy used controlled terms and keywords including terms for "Occupational", "Aluminum", "McIntyre Powder", "Alzheimer's disease", "Parkinson's disease", "Amyotrophic Lateral Sclerosis" and additional neurological (nervous system-related) and other conditions.

The peer reviewed and grey literature searched identified 63 studies, published between 1985 and 2016, which were selected to be included in the review. The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of included studies. Forty-eight studies investigated aluminum exposed workers at a single point in time (*i.e.*, cross-sectional study type), eight

followed workers over a period of time (*i.e.*, longitudinal cohort study type), and seven were case-control studies. One study was removed from the review due to unsatisfactory quality. Most studies reviewed had a comparison, or control population. Overall, the selected literature mainly studied nervous system-related (31 studies) or respiratory (17 studies) endpoints, but a variety of other health outcomes were also included, such as cancer, cardiovascular disease, mortality and immunological response. Most studies on nervous system-related or respiratory outcomes included various cognitive tests or lung function tests, respectively. As the included studies covered a broad range of health outcomes, study designs, workplace settings, *etc.*, the methods applied in understanding the information was also diverse. This literature review used a combination of statistical techniques, tabulation of study characteristics, and narrative review methods. Meta-analysis techniques use statistical analysis methods to combine data from similar studies.

Although the focus of this literature review was to consider possible effects of aluminum, specifically McIntyre Powder (aluminum powder) inhaled by workers for the purpose of acting as a preventative measure for silicosis, only three studies assessed this specific type of aluminum exposure. Due to the low number of studies, statistical analysis could not be conducted. Of the McIntyre worker studies, two found no increased risk of Alzheimer's disease related to McIntyre Powder exposure (McDonald *et al.*, 1996 and Peters *et al.*, 2013). The third study, Rifat *et al.* (1990), showed a positive association between McIntyre Powder exposure and decreased performance on cognitive tests of nervous system performance; there were no increases in diagnosed nervous system disorders in the exposed workers.

Findings for aluminum exposed workers in well-studied industries (*e.g.*, aluminum production and welding) are relevant to the McIntyre Powder exposed workers in that all workers were exposed to aluminum particles *via* inhalation. In addition, the forms of aluminum in McIntyre Powder (*i.e.*, 15% elemental aluminum and 85% aluminum oxide) were the forms most often studied in the literature. Accumulated aluminum exposure may have been higher for workers exposed to McIntyre Powder than for workers employed in other industries.

Statistical analysis was conducted to measure the relationship between workplace exposure to aluminum and risk of Alzheimer's disease. Four studies in total were included in this analysis, which found no increased risk of Alzheimer's disease related to workplace aluminum exposure. Additional statistical analysis was also conducted cognitive test results from aluminum exposed and non-aluminum exposed workers. The results revealed four (of seven) statistically significant effects of decreased cognitive test performance in workers occupationally exposed to aluminum.

Critical analysis of additional cognitive test outcomes (not included in the statistical analyses) did not detect systematic patterns of significant findings. However, results were difficult to interpret as not all workplace settings were similar and different studies used different types of cognitive tests. Workers of a powder-producing plant and those exposed to aluminum fumes during welding, who had relatively high aluminum exposure (*i.e.*, urinary aluminum concentrations >100 µg/l) did not show any cognitive decline after four to five years of exposure to aluminum dust (according to Letzel *et al.* (2000) and Kiesswetter *et al.* (2007), respectively).

Most studies examining lung function were designed to include data from spirometry testing, which measures how well the lungs breathe in and out. Statistical analysis conducted on these studies found slightly reduced function in two lung function tests in aluminum workers compared to referents (*i.e.*, controls). However, the averaged data indicated all aluminum exposed groups as having normal lung function. Critical analysis of additional lung function studies (not included

in the statistical analyses) mainly showed no differences between aluminum exposed workers and non-exposed workers in terms of lung function. Consideration of these additional studies weakened the significant associations found in the statistical analysis. Overall results indicate that there may be no difference between aluminum exposed workers and non-exposed workers in terms of lung function.

This report also summarizes the literature on more rarely studied health effects that are related to workplace aluminum exposures. These effects include cardiovascular diseases and related biological markers, cancer and related biological markers, diabetes, immunological effects, mortality, bone growth defects, and reproductive effects. Overall, the findings related to these health effects were very limited, with no conclusive evidence of negative effects related to workplace aluminum exposure.

Since the studies included in this review measured exposure of workers to aluminum using different methods, the main limitation of this review lies in interpreting aluminum exposure in the studies. Fewer than half of studies sampled aluminum in workplace air. Some studies measured levels of aluminum in urine, blood, and serum of workers. However, it is not well understood whether high levels of aluminum in the body automatically imply long-term exposure (*i.e.*, high aluminum levels in the body may not necessarily mean that the individual has been exposed to aluminum for a long period of time). In addition, as aluminum-exposed workers could have been exposed to other hazardous or toxic compounds, understanding effects of aluminum exposure alone was difficult. In general, workers exposed to aluminum (*e.g.*, miners, welders, aluminum production or refinery workers) are also often exposed to a mixture of hazardous substances.

Overall, two conditions could be suspected as possibly associated with the inhalation of McIntyre Powder that are only minimally considered in this review as not many suitable studies are published on them: pneumoconiosis and certain cancers. Pneumoconiosis is a disease of the lungs caused due to dust inhalation. In the miners who inhaled McIntyre powder, it was not reported that there was an increased prevalence of pneumoconiosis. The Peters *et al.* (2013) study in Australia did not find such an increase. As to cancer, the International Agency for Research on Cancer (IARC) has categorized aluminum production as a human carcinogen. This is because workplace exposures during aluminum production cause cancer of the bladder, and, to a lesser extent, of the lung. However, as noted in the review, the substance that causes the cancer, resulting in the increased incidence of these cancers is not aluminum itself, but other agents used in the production of aluminum (*e.g.*, polycyclic aromatic hydrocarbons or PAHs) that are carcinogenic.

Overall, the systematic review and the statistical analysis conducted showed that the question of health risks from workplace aluminum exposure is complicated. The findings across the literature were inconsistent. Epidemiological studies have failed to establish consistent associations or clear exposure response relationships between workplace aluminum exposure and nervous system-related diseases, cognitive outcomes, lung function outcomes, and other negative outcomes. Using the Bradford Hill criteria, which provide guidelines to determine whether a cause-and-effect relationship exists, it could not be sufficiently determined whether a causal relationship exists between exposure to aluminum in the workplace and increased risks of negative long-term health effects. Although these findings cannot conclusively state whether or not aluminum exposure leads to the development of negative health conditions, the evidence considered in total has not supported a link.