SCIENCE INTEGRITY KNOWLEDGE

SYSTEMATIC REVIEW OF OCCUPATIONAL ALUMINUM EXPOSURE AND ADVERSE HEALTH CONDITIONS

REVISED FINAL REPORT

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2018 REVISION TO FINAL REPORT

This report has been revised from the previous final version provided to WSIB on April 28, 2017, to correct an error arising from an incorrect exposure level provided in one of the report source documents. Specifically, the 1992 IDSP Report stipulated an airborne McIntyre Powder exposure level of 353 mg/m^3. Subsequent to the release of the 2017 report, WSIB was able to obtain McIntyre Research Foundation records from the Archives of Ontario (in particular Newkirk, 1972) that indicated the recommended dispersal was actually 1 gram of McIntyre Powder per 1000 cubic feet of air (equivalent to 1 mg/ft^3 or 35.6 mg/m^3), and that the 1992 IDSP Report was in error.

SYSTEMATIC REVIEW OF OCCUPATIONAL ALUMINUM EXPOSURE AND ADVERSE HEALTH CONDITIONS

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EXECUTIVE SUMMARY

The Workplace Safety and Insurance Board of Ontario (WSIB) is interested in determining whether historical occupational exposure to aluminum dust resulted in adverse health conditions among workers, and in particular, whether there is an increased risk of developing neurological disorders in workers exposed to McIntyre Powder. McIntyre Powder is a finely ground aluminum dust that was used as a prophylactic agent against silicosis. In response, Intrinsik Corp. (Intrinsik) has prepared this systematic review of the peer reviewed epidemiologic literature that evaluated occupational aluminum exposure and adverse health conditions. The systematic review is intended to specifically evaluate whether there is evidence for an association between occupational exposure to: (i) McIntyre Powder; (ii) aluminum oxides from other sources (*e.g.*, welding); or, (iii) other aluminum compounds, and neurological outcomes (such as Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis), and other health outcomes.

Aluminum is a silvery-white metal that is light-weight and obtained from aluminum containing minerals, such as bauxite. Aluminum 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 including aluminum oxide (Al_2O_3), aluminum chlorohydrate, aluminum hydroxide ($Al(OH_3)$), aluminum chloride ($AlCl_3$), aluminum lactate, aluminum phosphide (AlP), aluminum phosphate ($AlPO_4$), and aluminum nitrate ($Al(NO_3)_3$). With respect to the potential for aluminum exposure in the workplace and the current systematic review, elemental aluminum and aluminum oxide (*i.e.*, alumina) are considered most relevant.

Aluminum and its compounds can enter the body *via* inhalation of dust and particles in the air, ingestion of food and water, and through dermal contact. Aluminum is poorly absorbed *via* ingestion and inhalation pathways and is essentially not absorbed dermally. Aluminum can be measured in the blood, urine and feces and is routinely found in healthy individuals due to its ubiquitous nature and presence in many food and consumer items. While it is generally accepted that aluminum biomarker data do not demonstrate acute variations of exposure, urinary aluminum measures may be appropriate indicators in the case of stable and continuous exposure to aluminum.

The Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, 2009) governed the study search and evaluation process for the systematic review of occupational aluminum exposure and adverse health outcomes. The systematic nature of the literature review is intended to provide reproducible protocol and to reduce the potential for bias in the findings. The literature review included a search of epidemiological studies that investigate the health effects (primarily neurological disorders) associated with occupational exposure to aluminum. This review specifically excluded acute conditions such as contact dermatitis or other allergic reactions. The search strategy used controlled vocabulary terms and keywords including terms for "Occupational", "Aluminum", "McIntyre Powder", "Alzheimer's disease", "Parkinson's disease", "Amyotrophic Lateral Sclerosis" and additional neurological and other conditions.

The peer reviewed and grey literature searched identified 62 studies, published between 1985 and 2016, which were selected for inclusion in the review. The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of included studies. Forty-seven studies investigated aluminum exposed workers at a single point in time (cross-sectional study type), eight followed workers over a period of time (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, and varied on many characteristics. Overall, the selected literature primarily studied neurological (31 studies) or respiratory (17 studies) endpoints, but a variety of other health outcomes were also included, such as cancer,

cardiovascular disease, and mortality. Most studies on neurological or respiratory outcomes included various neurological tests or lung function tests, respectively. Because the included studies covered a broad range of health outcomes, study designs, occupational settings, *etc*., the methods applied in synthesizing the information was also diverse. This literature review used a combination of meta-analytic techniques, semi-quantitative tabulation of study characteristics, and narrative review methods.

A focus of the literature review was to consider possible effects of aluminum powder inhaled by workers for the purpose of acting as a prophylaxis for silicosis, referred to as McIntyre Powder. However, only three studies assessed this specific type of aluminum exposure. Therefore, there were insufficient studies to perform subgroup analyses for McIntyre Powder exposed workers. Of the McIntyre worker studies, two found no increased risk of Alzheimer's disease related to McIntyre Powder exposure (McDonald *et al.* 1996, 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; no differences in diagnosed neurological disorders were apparent in the exposed workers compared to non-exposed referent workers.

Findings for aluminum exposed workers in well-studied industries (*e.g.*, aluminum production and welding) are pertinent to the McIntyre Powder exposed workers, particularly because all occupational exposure to aluminum particles is via inhalation. In addition, the forms of aluminum in McIntyre Powder (*i.e.*, 15% elemental aluminum and 85% aluminum oxide) are the forms most often studied in the occupational health literature. Data on the amount of McIntyre Powder to which workers were regularly exposed is scarce, making it difficult to compare cumulative aluminum exposures for McIntyre Powder exposed workers to workers in other industries.

According to McIntyre Research Foundation records, the recommended dispersal amount of McIntyre Powder for group prophylaxis was one gram of powder per 1000 cubic feet of air, or the equivalent of 35.6 milligrams per cubic meter (mg/m^3), for 10 minutes per day (Newkirk, 1972).[1] While short-term exposure limits for occupational aluminum exposure have not been established, the reported McIntyre Powder exposure level averaged over an 8-hour workday equates to a 0.74 mg/m^3 time-weighted average; this is below the range of occupational exposure limits for aluminum (from 1 to 15 mg/m^3 8-hour TWA).

Because the purpose of many studies selected in the literature review was not to assess the risk of specific (*i.e.*, diagnosable) health outcomes but rather to more broadly examine the potential effects on neurobehavioral or respiratory performance, the results of the systematic review are ordered into ICD-diagnosable conditions versus other studied health outcomes (*i.e.*, non ICD-diagnosable conditions).

Diagnosable health outcomes considered in this systematic review included the following neurological diseases: Alzheimer's disease, Parkinson's disease, or ALS. Meta-analysis was conducted to systematically quantify the relationship between occupational exposure to aluminum and risk of Alzheimer's disease. Three case-control studies and one retrospective matched cohort study met the criteria for inclusion. Results of the meta-analysis indicated that occupational aluminum exposure was not associated with Alzheimer's disease (odds ratio, 1.28;

[1] This information was revised from the Final Report dated April 28th, 2017, which referenced McIntyre Powder exposure levels (353 mg/m^3 of air) contained within the 1992 IDSP Report. McIntyre Research Foundation records subsequently obtained from the Archives of Ontario indicate that the recommended dispersal was actually 1 gram of McIntyre Powder per 1000 cubic feet of air (equivalent to 1 mg/ft^3 or 35.6 mg/m^3).

95% confidence interval, 0.78 to 2.10). The literature review identified one study examining aluminum as a potential risk factor for ALS, and one study examining aluminum as a potential risk factor for Parkinson's disease; neither reported an association between aluminum and the neurological disease.

In addition to neurological disease, this systematic review also summarizes the epidemiological literature on more rarely studied diagnosable conditions, and there potential association with occupational aluminum exposure, including cardiovascular outcomes, cancer, diabetes, mortality, osteodystrophy, and reproductive effects. Weak associations, based on few cases, were reported between aluminum exposure and non-malignant respiratory disease mortality, cerebrovascular disease mortality, and cardiovascular mortality (Friesen *et al.*, 2009, Peters *et al.*, 2013). Of four studies investigating potential biomarkers of cancer, two found some evidence of association or correlation between aluminum exposure and DNA damage although the biologic significance of those findings is unknown (Botta *et al.*, 2006; Hou *et al.*, 2011). Overall, the findings related to other health outcomes provided suggestive but no conclusive evidence of adverse effects related to occupational aluminum exposure.

Results for the non ICD-diagnosable conditions, including neuropsychological and lung function test outcomes, make up a large part of this systematic review. Meta-analysis was applied to pool the effect sizes from cross-sectional studies comparing seven neuropsychological test results from aluminum exposed to non-aluminum exposed workers. The meta-analysis neuropsychological test results revealed four (of seven) statistically significant effects of decreased test performance in workers occupationally exposed to aluminum: i) Santa Ana Dexterity dominant hand; ii) simple reaction time; iii) digit symbol; and, iv) mini mental status examination (MMSE) score. While meta-regressions performed with the available exposure data showed no dose-response trends for these effects, these findings are uncertain given the limited number of studies that included exposure data and the inconsistent methods used to investigate dose across the different studies. Meta-analysis effect sizes for Santa Ana Dexterity non-dominant hand, digit span forward, and digit span backward were not statistically significant.

Critical analysis of additional neuropsychological test outcomes (not included in the meta-analyses) did not detect systematic patterns of significant findings by neuropsychological testing domain or aluminum exposure levels. However, results were difficult to interpret given the non-uniform nature of occupational settings, neuropsychological tests used, cognitive domains, different exposure parameters considered, as well as other factors. Longitudinal evidence from workers with relatively high aluminum exposure metrics (*i.e.*, urinary Al>100 µg/l) did not reveal any cognitive decline after four to five years of exposure to aluminum dust in workers of a powder-producing plant or exposure to aluminum fumes in welders (according to Letzel *et al.* (2000) and Kiesswetter *et al.* (2007), respectively).

Most studies examining lung function were cross-sectional study designs that included cross-sectional data from spirometry testing. Meta-analysis was conducted to pool the effect sizes from cross-sectional studies comparing three lung function test results from aluminum exposed to non-aluminum exposed workers: i) percent predicted forced vital capacity (ppFVC); ii) percent predicted forced expiratory volume in one second (ppFEV1); and, iii) percent predicated mean forced expiratory flow during mid-half of the FVC (ppFEF25-75). Meta-analyses detected a slight impairment in two lung function outcomes (ppFEV1 and ppFEF25-75) in aluminum workers compared to referents. However, mean data on the clinically relevant measure of ratio FEV_1/FVC characterized all aluminum exposed groups as having normal lung function. A number of studies examining respiratory effects did not have adequate data for inclusion in the meta-analysis and were instead assessed qualitatively. Findings from these additional studies mainly showed a lack of significant differences between aluminum exposed workers and non-

exposed workers in terms of lung function and did not support the potential effects on ppFEV$_1$ and ppFEF25-75 found in the meta-analysis.

The main limitation of this review lies in interpreting aluminum exposure across the body of literature. Namely, the collection of aluminum exposure data varied considerably depending on the individual study. Fewer than half of studies sampled aluminum in workplace air. Biomarker measures of aluminum body burden included aluminum in urine, aluminum in blood, and aluminum in serum. However, the importance of aluminum biomonitoring data in workers is questionable with different findings on how well biomarker measures correlate to chronic exposure. In addition, interpreting aluminum exposure data was limited due to potential confounding from other hazardous exposures. Occupational workers exposed to aluminum (*e.g.*, miners, welders, aluminum production or refinery workers) are also often exposed to a mixture of hazardous substances.

There are two conditions that are only minimally considered in this review because of the absence of suitable published studies: pneumoconiosis and certain cancers. The Peters *et al.* (2013) study in Australia did not find an excess of pneumoconiosis. As to cancer, the International Agency for Research on Cancer has categorized aluminum production as a human carcinogen. This is because occupational exposures during aluminum production cause cancer of bladder, and, to a lesser extent, of the lung. However, as noted in the review, the carcinogen that results in the increased incidence of these cancers is not aluminum itself, rather other agents (*e.g.*, PAHs) that are carcinogenic.

Overall, the systematic review and meta-analysis showed that the question of health risks from occupational aluminum exposure is complex. The findings across the literature were inconsistent. Epidemiological studies have failed to establish consistent associations or clear exposure response relationships between workplace aluminum and neurological diseases, neuropsychological outcomes, and lung function outcomes, and other adverse outcomes. Consideration of the evidence for neurological diseases, neuropsychological outcomes, and lung function outcomes in context of the Bradford Hill criteria for causality (temporality, strength, dose-response relationships, replicability, and biologic plausibility) found most of the criteria were not satisfied and judged the certainty of evidence for an association with occupational aluminum to be very low. Due to the small number of studies, the evidence for other diagnosable conditions (*e.g.*, cancer, diabetes, mortality) was insufficient to complete an assessment of causality. Although findings cannot conclusively state whether or not aluminum is a causative agent in development of adverse health conditions, the evidence considered in total has not supported a link.

SYSTEMATIC REVIEW OF OCCUPATIONAL ALUMINUM EXPOSURE AND ADVERSE HEALTH CONDITIONS

1.0 BACKGROUND AND SCOPE

1.1 Project Description

Intrinsik Corp. (Intrinsik) has prepared this systematic review of the peer reviewed epidemiologic literature that evaluated occupational aluminum exposure and adverse health conditions for the Workplace Safety and Insurance Board of Ontario (WSIB).

The WSIB is interested in determining whether historical occupational exposure to aluminum dust resulted in adverse health conditions among workers in the Ontario mining industry. The WSIB is requesting a systematic review to examine whether workers with occupational exposure to aluminum have an increased risk of developing adverse health conditions. The WSIB is particularly interested in whether there is an increased risk of developing neurological disorders in workers exposed to McIntyre Powder.

McIntyre Powder is a finely ground aluminum dust that was used as a prophylactic agent against silicosis. In the mining industry, a prophylaxis program using McIntyre Powder was implemented between 1943 and 1979 on hardrock miners in northern Ontario. This program ceased when a Ministry of Labour Scientific Task Force concluded that there was insufficient evidence of the benefits of inhaling aluminum dust and recommended that studies be conducted to identify potential health effects resulting from exposure to McIntyre Powder. As a result of this recommendation, the Northern Ontario Miner's Health Study was initiated in 1987 to identify any long-term health effects of exposure. The results of this study showed no increased incidence of neurological disorders in exposed miners; however, a higher proportion of exposed miners showed cognitive impairment compared with unexposed miners. Another study conducted by the Industrial Disease Standards Panel (IDSP) looked at linkages between aluminum blood levels and adverse health effects in the aircraft manufacturing industry, resulting in two reports. These reports concluded that evidence was "inadequate to allow the Panel to conclude that occupational aluminum exposure causes neurological health effects".

The systematic review is intended to specifically evaluate whether there is evidence for an association between:

1. occupational exposure to McIntyre Powder and
    a. Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS) and other neurological conditions
    b. other health conditions including, but not limited to, the peripheral nervous system, the respiratory system, the cardiovascular system and cancer outcomes
2. occupational exposure to aluminum oxides from other sources (*e.g.*, welding) and
    a. neurological outcomes as listed above
    b. other health conditions as listed above
3. occupational exposure to other aluminum compounds and
    a. neurological outcomes as listed above
    b. other health conditions as listed above

This information may be considered by the WSIB in reviewing the issue of entitlement for occupational disease claims among workers with occupational aluminum exposure.

1.2 Objectives of the Systematic Review

The information provided by this systematic review will be used to help inform WSIB's understanding of the association between aluminum exposure and various health effects. As such, the objectives of the systematic review are to:

- Describe the toxicokinetics and toxicodynamics of aluminum in humans, by aluminum compound;
- Examine the epidemiologic evidence for risk of developing adverse health conditions in McIntyre Powder-exposed workers;
- Examine the epidemiologic evidence for risk of developing adverse health conditions in other aluminum-exposed workers (*i.e.*, aluminum oxides from other sources, other aluminum compounds);
- Identify any subgroups of workers with occupational aluminum exposure who have an increased risk of developing adverse health conditions;
- Identify exposure-response relationships, such as increasing risk of developing adverse health outcome with increasing duration, frequency and/or intensity of exposure, or identify a minimum threshold of exposure below which no adverse health conditions were reported;
- Determine whether a causal relationship can be established for any health conditions based on the available scientific evidence; and,
- Assess whether the findings of aluminum-exposed workers in other industries/occupations (*e.g.*, workers in aluminum smelters, aircraft manufacturing or aluminum welding) are generalizable to McIntyre Powder-exposed workers.

1.3 Health Outcomes Included in the Systematic Review

In the Request for Proposals (RFP), the WSIB requested a systematic review "to examine whether workers with occupational exposure to aluminum have an increased risk of developing adverse health conditions." Therefore, the systematic review considered any chronic health outcome potentially associated with occupational exposure to aluminum. Per discussions with the WSIB, acute health effects (*e.g.*, acute dermatitis) were excluded. The International Statistical Classification of Disease and Related Health Problems (ICD 10th Revision) identifies the following health endpoints relevant to this systematic literature review (Table 1-1).

Table 1-1 ICD 9th and 10th Revision Codes for Specific Diseases and Health Problems

Disease/Health Problem	ICD-9	ICD-10
Disease of the nervous system	320-389	G00-G99
Parkinson disease	332	G20
Alzheimer disease	331	G30
Motor neuron disease (Lateral sclerosis: amyotrophic)	335.2	G12.2
Other disorders of the peripheral nervous system	350-359	G64
Organic, including symptomatic, mental disorders	290-319 (mental disorders)	F00-F09
Dementia in Alzheimer disease	290 (dementia)	F00
Dementia in Parkinson disease		F02.3
Symptoms and signs involving cognition, perception, emotional state and behavior	V40 (mental and behavioral problems)	R40-R46
Other and unspecified symptoms and signs involving cognitive functions and awareness		R41.8

Table 1-1 ICD 9th and 10th Revision Codes for Specific Diseases and Health Problems		
Disease/Health Problem	**ICD-9**	**ICD-10**
Diseases of the respiratory system Chronic lower respiratory diseases Pneumoconiosis Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors	460-519 490-496 500-508 506	J00-J99 J40-J47 J60-J65 J68
Diseases of the circulatory system	390-459	I00-I99
Neoplasms	140-239	C00-D48

Further, the RFP described "The WSIB is particularly interested in whether or not there is an increased risk of developing neurological disorders in workers exposed to McIntyre Powder". Because of the particular interest in neurological disorders (*e.g.*, Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis (ALS)), the epidemiology (*e.g.*, occurrence, known risk factors, *etc*.) of those particular disorders are summarized briefly in the sections below.

1.3.1 Alzheimer's Disease

The Agency for Toxic Substances and Disease Registry (ATSDR) (2009) defines Alzheimer's disease (AD) as "a neurodegenerative disorder, which is manifested clinically as a progressive deterioration of memory and cognition". Alzheimer's disease is the most common cause of dementia among older adults, with memory problems being one of the first and most common signs (NIH, 2016). Currently, 1 in 9 people >65 years has Alzheimer's disease (Alzheimer's Association, 2016). The risk of death from Alzheimer's disease increases significantly with age (CDC, 2014) (Figure 1).

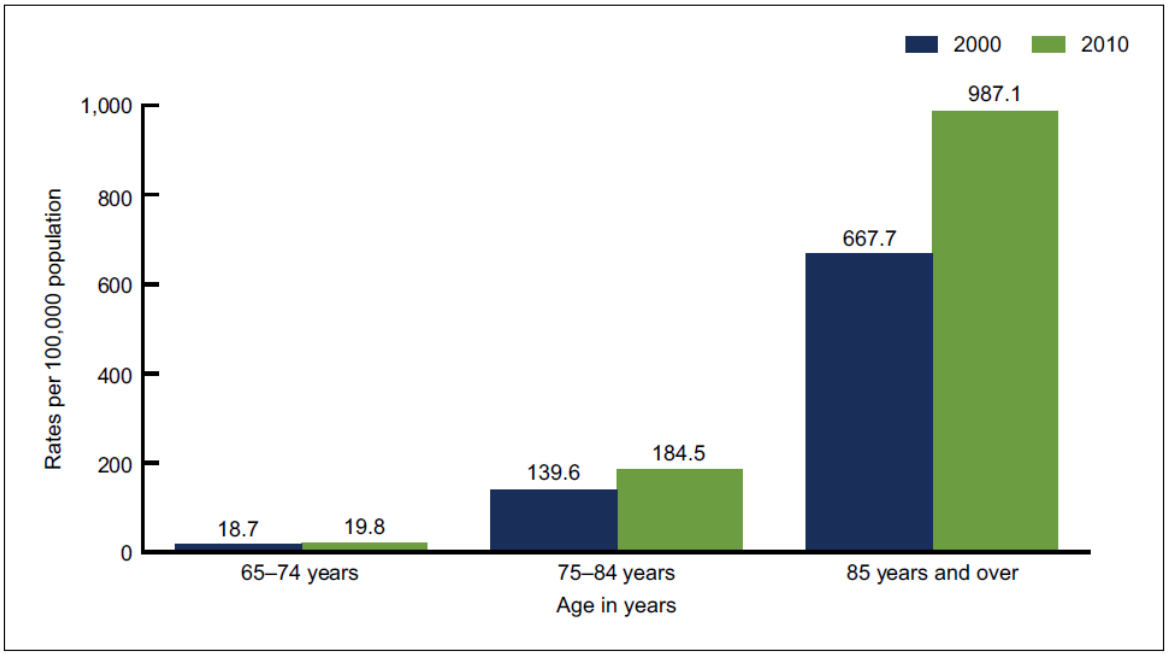

Figure 1-1 Age-adjusted death rates for Alzheimer`s disease: United States, 2000 and 2010 (Tejada-Vera, 2010)

Although the cause of Alzheimer's disease is not fully understood, genetic, environmental and lifestyle factors are thought to play a role (NIH, 2016). Once diagnosed, the symptoms of

Alzheimer's disease can be managed with medications that regulate neurotransmitters and may help to maintain thinking, memory and communication skills. However, there are no medications that impact the underlying disease process meaning that symptoms will progress and the disease cannot be cured at this time (NIH, 2016).

1.3.2 Parkinson's Disease

Parkinson's disease is a type of motor system disorder that is the result of a loss of dopamine-producing brain cells (NINDS, 2015). Parkinson's is a chronic and progressive disease of the nervous system that can cause tremors, muscle stiffness, slowed movements or changes in speech. More advanced stages can also include cognitive impairment, mood and behavioural disorders, and dementia. After Alzheimer's, Parkinson's disease is the second most common neurodegenerative disorder, with 100,000 people currently living with the disease in Canada, 1,000,000 in the US, and more than 10 million worldwide (PDF, 2016; UCB, 2016). As many as 6,000 new cases of Parkinson's disease are diagnosed each year in Canada (UCB, 2016). The majority of people diagnosed with Parkinson's are greater than 60 years old; however, approximately 5-10% of cases are younger than 50.

The risk factors associated with development of Parkinson's disease are thought to be a combination of genetic and environmental influences (NINDHS, 2015). It is estimated that as many as 15-20% of cases have a family history of the disease (NINDHS, 2015). Men are one-and-a-half-times more likely to develop Parkinson's disease than women. Certain factors have also been found to have a protective effect, including individuals with high levels of vitamin D having a lower likelihood of developing the disease when compared to people with very low levels of vitamin D in their blood stream (NINDHS, 2015).

There is currently no cure to stop or reverse the progression of Parkinson's disease; however, treatment options are available to manage symptoms including Deep Brain Stimulation (DBS) for the treatment of Parkinson's tremors. DBS is widely used to help control symptoms, and in some cases, has been found to improve motor function and quality of life even more than the most effective medications (NINDHS, 2015).

1.3.3 Amyotrophic Lateral Sclerosis (ALS)

ATSDR (2008) defines Amyotrophic Lateral Sclerosis, or ALS, as "a progressive disease of the central nervous system that is characterized by an accumulation of neurofibrillary tangles". Also known as *Lou Gehrig's disease*, ALS is a type of motor neuron disease that attacks the nerve cells responsible for voluntary muscle movement (NINDS, 2013). Worldwide, ALS is one of the most common neuromuscular diseases, affecting people of all races and ethnic backgrounds. It is more common among males and those age 60-69 years old. In the US, there are currently 12,000 diagnosed cases of ALS (NINDS, 2013).

The occurrence of ALS is not well understood, appearing to occur at random with no apparent risk factors for 90-95% of cases. The other 5-10% of cases are inherited (NINDS, 2013). There is currently no cure for ALS; however, medications are available to control symptoms and prolong survival by reducing damage to motor neurons. Despite medication to slow the damage, there is nothing currently available to repair damage that has already occurred (NINDS, 2013).

2.0 ALUMINUM TOXICOLOGY

2.1 Aluminum Compounds

Aluminum is a light-weight silvery-white metal that is obtained from aluminum containing minerals, such as bauxite (ATSDR, 2008). Once aluminum is recovered from mineral ores, it forms metals, compounds, complexes or chelates. There are several different aluminum compounds including aluminum oxide (Al_2O_3), aluminum chlorhydrate, aluminum hydroxide ($Al(OH_3)$), aluminum chloride ($AlCl_3$), aluminum lactate, aluminum phosphide (AlP), aluminum phosphate ($AlPO_4$), and aluminum nitrate ($Al(NO_3)_3$). With respect to the potential for aluminum exposure in the workplace and the current systematic review, elemental aluminum and aluminum oxide (*i.e.*, alumina) are considered most relevant.

2.2 Toxicokinetics and Toxicodynamics of Aluminum in Humans

Aluminum and its compounds can enter the body *via* inhalation of dust and particles in the air, ingestion of food and water, and through dermal contact. The fate and transport of aluminum is determined by environmental factors such as pH, salinity and the presence of the other elements with which it forms complexes. Aluminum is poorly absorbed *via* ingestion and inhalation pathways and is essentially not absorbed dermally (ATSDR, 2008).

The two types of aluminum that are most relevant to this systematic review are elemental aluminum (Al) and aluminum oxide (Al_2O_3). Where information is available, the absorption, distribution, metabolism and elimination/excretion are discussed in terms of these specific types of aluminum; however, in most cases no distinction was made.

2.2.1 Absorption

The percentage of aluminum that is absorbed following inhalation has not been reported in toxicokinetic studies; however, a fractional absorption of 1.5-2% was estimated based on airborne aluminum levels and urinary excretion (Yokel and MacNamara, 2001). Additionally, it has been suggested that absorption of aluminum from the lungs into the bloodstream is higher in individuals exposed to aluminum fumes compared to aluminum dust, which is consistent with the understanding of particle size and relative absorption (ATSDR, 2008). Several animal studies found that aluminum remained in the lungs after inhalation exposure to aluminum oxide; however, no significant increase was found in other tissues or serum, indicating retention rather than absorption occurring in the lungs (Steinhagen *et al.*, 1978; Stone *et al.*, 1979).

Aluminum present in food and drinking water is poorly absorbed in the gastrointestinal tract (ATSDR, 2008). Several human studies estimated aluminum absorption efficiencies of 0.07-0.39% following administration *via* drinking water. Other studies considering fractional bioavailability in urine and bone found that absorption rates were 0.04-0.06%, when liver and brain levels were considered, rates were estimated at 0.1% (Jouhanneau *et al.*, 1993; 1997). In the diet, aluminum bioavailability is highly dependent on its form and the presence of other food constituents with which it can form complexes, such as citric acid. Based on available evidence, it is likely that the oral absorption of aluminum can vary 10-fold depending on chemical form alone (ATSDR, 2008).

For dermal absorption, limited data is available; however, aluminum chlorohydrate salt present in antiperspirant was tested on two subjects with an absorption rate of 0.012% (Flarend *et al.*, (2001).

2.2.2 Distribution

Aluminum can be found naturally occurring in all bodily tissues with healthy individuals having a body burden of approximately 30-50 mg, and typical serum levels of 1-3 µg/L (ATSDR, 2008). Out of the total body burden of aluminum, about half can be found in bones and one quarter in the lungs (Ganrot, 1986). A normal level of aluminum in the lungs of adults is 20 mg/kg wet weight and increases with age due to accumulation of inhaled insoluble aluminum compounds (ATSDR, 2008). Limited information is available regarding the distribution of aluminum following inhalation exposure; however, one study found elevated levels of aluminum in the lungs, lymph nodes, liver and spleen of a deceased stone mason, presumed to have inhaled aluminum. When aluminum compounds are inhaled, they are deposited based on particle size. Large particles are exhaled or trapped in the upper respiratory system, while smaller particles may reach the alveoli and be transferred to blood (ATSDR, 2008). Once in the bloodstream, aluminum is thought to be present almost exclusively in the plasma where it binds to transferrin (>90% aluminum thought to bind this way). Any cellular uptake of aluminum into the body's organs and tissues is thought to be a slow process, due largely to the binding of transferrin (Ganrot, 1986).

2.2.3 Metabolism

In living organisms, aluminum is thought to exist in four different forms: (i) as free ions; (ii) as low-molecular-weight complexes; (iii) as physically-bound macromolar complexes, and (iv) as covalently bonded macromolar complexes (ATSDR, 2008). The free ion Al^{+3} easily binds to many different structures and substances, therefore, its metabolic fate is largely determined by the affinity and metabolism of these binding complexes. In general, the low-molecular-weight complexes are metabolically more active than the larger macromolar complexes. Aluminum can also form bonds with highly stable macromolecules that are essentially irreversible, inhibiting metabolism (ATSDR, 2008).

2.2.4 Elimination and Excretion

Following inhalation and oral exposures, the primary route of excretion for absorbed aluminum is through urine. Due to the natural presence of aluminum and its intake through common food items, all people will have some level of aluminum in their urine. In a survey of blood and urine levels of various metals, blood aluminum concentrations were typically less than 10 micrograms per deciliter (µg/dL) (ATSDR, 2004). It has been reported that the mean values of urinary aluminum concentrations in non-exposed persons fall within the range of 4 to 11 µg/l (Sinczuk *et al.*, 2003).

Evidence suggests that urinary excretion exists in two-phases, with the excretion half-life for the first phase from 7.5 to 9 days following exposure, and the second phase ranging from 6.8 to 24 weeks (Sjogren *et al.*, 1985; 1988; 1990). In a study on the aluminum uptake and excretion in new aluminum smelter potroom workers previously unexposed to aluminum, Rollin *et al.* (2001) showed a linear increase in the urinary excretion of aluminum from a mean baseline concentration of 24 µg/l to 49 µg/l over 36 months. The authors conclude that this suggests a slow rate of urinary elimination of aluminum.

2.2.5 Biomarkers of Exposure and Effect

Biomarkers of effect have been defined as "any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease" (NAS/NRC 1989).

Aluminum can be measured in the blood, urine and feces and is routinely found in healthy individuals due to its ubiquitous nature and presence in many food items; however, guidelines for aluminum exposure and specific health outcomes are not available. The 1992 report released by the Industrial Disease Standards Panel (IDSP) stated that "neither blood nor urine aluminum levels are good indicators for predicting occupational health risks, nor for estimating body burden of aluminum". Although there has been no update to this report since 1992, the ATSDR (2004) stated that since aluminum is poorly absorbed, it is not possible to equate exposure levels with urine or serum levels. While a 24-hour urine sample is best for determining whether aluminum is present in the body, it cannot be extrapolated to determine exposure levels. Additionally, there are no known simple, non-invasive tests which can be used as biomarkers of effects caused by aluminum (ATSDR, 2008). The IDSP also discussed the importance of distinguishing between the amount of aluminum exposure and the amount of aluminum that bypasses elimination and instead is absorbed by the body and accumulates in the tissues (IDSP, 1992).

> *"Unfortunately, exposure levels cannot be related to serum or urine levels very accurately, primarily because aluminum is very poorly absorbed by any route and its oral absorption in particular can be quite affected by other concurrent intakes. There is an indication that high exposure levels are reflected in urine levels, but this cannot be well quantified as much of the aluminum may be rapidly excreted. Aluminum can also be measured in the feces, but this cannot be used to estimate absorption"* (ATSDR, 2008).

Nonetheless, many epidemiological studies on occupational exposure to aluminum use biomonitoring measurements as an indicator of exposure. While it is generally accepted that aluminum biomarker data do not demonstrate acute variations of aluminum exposure, there is limited information regarding the long-term stability of aluminum biomonitoring data in workers. Given the slow biological processes of aluminum uptake and elimination as described in Section 2.2.4, aluminum-biomonitoring measures may be appropriate indicators in the case of stable and continuous exposure to aluminum. Kiesswetter *et al.* (2009), in a longitudinal study of aluminum welders and referents, performed repeated biomonitoring measurements. Over four years, three repeated measurements included total dust in air, and pre- and post-shift aluminum-plasma concentrations and creatinine adjusted aluminum-urine concentrations. There were no remarkable differences between pre- and post-shift measures of aluminum body burden, suggesting that aluminum-plasma and aluminum-urine data are not suitable as markers of acute shift-dependent changes in aluminum exposure. However, while aluminum-plasma demonstrated poor overall relation to dust exposure and high variability across measurement periods, post-shift creatinine adjusted aluminum-urine demonstrated a significant correlation with external dust exposure. Further, aluminum/g creatinine differentiated clearly between exposed and non-exposed workers across all examinations, while aluminum-plasma did not.

2.2.6 Mechanisms of Toxicity and Biological Plausibility

The exact biological mechanism of aluminum toxicity is unknown but it has been found to compete with cations (such as magnesium) in biological systems, affect secondary messenger systems and calcium availability, and bind to components of the cell nucleus (ATSDR, 2008). In cases where aluminum toxicity has occurred, the target organs seem to be the lung, bone and the central nervous system. No specific molecular mechanism has been identified for human toxicity to aluminum (ATSDR, 2008).

2.2.6.1 Neurotoxicity

Numerous studies have been performed to identify aluminum neurotoxicity; however, no single unifying mechanism has been identified, instead it is likely that multiple mechanisms are involved (ATSDR, 2008). Although studies have been conducted looking at neurological development and neurobehavioural changes in rats and mice, as well as neurodegenerative pathological changes in other species, the main sites of action are difficult to determine because of the variability of exposure methods and species used. Although evidence is insufficient to fully explain mechanisms of aluminum toxicity, some general processes have been identified. For example, studies done on certain species (*e.g.*, cats, rabbits, ferrets and nonhuman primates) have identified changes in cytoskeletal proteins within brain neurons for certain exposures (*e.g.*, intracerebral and intracisternal administration). These changes are similar to those identified in other neurodegenerative disorders, suggesting that abnormal neurological function could be related to cytoskeletal changes (ATSDR, 2008). In rodents, observed changes in neurobehavioural effects (*e.g.*, locomotor toxicity, learning and memory) have not shown changes in cytoskeletal pathology, but do suggest that aluminum could affect the following (ATSDR, 2008):

i. Permeability of the blood-brain barrier;
ii. Cholinergic activity;
iii. Signal transduction pathways;
iv. Lipid peroxidation;
v. Neuronal glutamate nitric oxide-cyclic GMP pathway; and,
vi. Metabolism of essential trace elements (*e.g.*, iron).

ATSDR (2008) states that extrapolating such effects from animal studies to humans cannot be conclusively determined because of the limitations of the human database. Information on the toxicity of aluminum is not sufficient, because much of the work has been conducted on individuals with renal deficiencies.

When it comes to aluminum toxicity, the highest at-risk population is in individuals with kidney failure. Early studies found that uremic patients who underwent dialysis (100%) and who did not undergo dialysis (82%) had increased body burden of aluminum (Alfrey, 1980). The reduction in renal function hindered the body's ability to excrete aluminum and a decrease of gastrointestinal absorption of phosphate and increase in aluminum ingestion *via* dialysis resulted in elevated body burden of aluminum. This increased body burden in uremic patients has been associated with dialysis encephalopathy (dialysis dementia), bone toxicity and hematopoietic toxicity (ATSDR, 2008). It was this early work that first established a possible connection between aluminum exposure and neurological effects. However, this population is considered high-risk due to renal failure and the results and outcomes from such studies cannot be extrapolated to healthy individuals.

Consequently, one of the most studied effects of aluminum exposure to date is dialysis encephalopathy, whose symptoms include speech disorders, neuropsychiatric abnormalities and multifocal myoclonus (Health Canada, 1998). Other, more subtle symptoms include "disturbances to tetrahydrobiopterin metabolism and abnormalities in a number of psycho-motor functions (*e.g.*, visual spatial recognition memory)", which have been found to occur at slightly elevated serum aluminum levels (59 µg/L). Additionally, elevated levels of aluminum in many tissues, including the cerebral cortex, was found in patients with dialysis dementia. A correlation between the levels of aluminum in the water used to prepare dialysis fluid and the incidence of dementia has been suggested; however, the mechanism of neurotoxicity has not been established (Health Canada, 1998).

Studies have observed subtle neurological effects in workers exposed to aluminum dust and fumes, but these studies only provide suggestive evidence of a relationship between chronic exposure and neurological effects. Aluminum toxicity in animals is better understood; however, whether chronic low doses of aluminum would manifest in humans in the same way remains to be determined (ATSDR, 2008).

2.2.6.2 Lung Toxicity

Over the past 50 years, the medical literature has revealed a few serious but mostly clinically mild cases of pneumoconiosis due to aluminum or aluminum oxide dust, largely associated with the production or use of aluminum powders (Riihimaki and Aitio, 2012). However, aluminum pneumoconiosis occurrence has drastically diminished as a result of improved working conditions (*i.e.*, decrease in aluminum dust exposures) over time. Several endpoints for inhalation of aluminum have been suggested including changes to the vital capacity of the lungs, alveolar inflammation, asthma and airway hyperreactivity (Riihimaki and Aitio, 2012). Studies have reported adverse respiratory effects in aluminum workers; however, the respiratory problems documented in potroom aluminum workers are generally associated with toxic chemicals other than aluminum in the workplace (Krewski *et al.*, 2007). Epidemiologic studies have established an increased risk of developing lung cancer for aluminum production workers, but this has attributed to exposure to Polycyclic Aromatic Hydrocarbons (PAHs), rather than to aluminum itself (Krewski *et al.*, 2007).

Mechanisms of inhalation absorption and toxicity are not well understood, although it is suggested that larger aluminum-containing particles deposited in the respiratory tract are cleared to the GI tract by ciliary action. For smaller aluminum particles, it is thought that aluminum penetrates the lungs and is dissolved into the bloodstream. The ATSDR (2008) has discussed the fact that because aluminum readily forms different complexes, it is difficult to identify a specific mechanism of toxicity resulting from inhalation of aluminum dust and fumes:

> *"Additional inhalation studies are needed to evaluate the mechanisms of lung toxicity to determine whether the effects are due to dust overload or aluminum; inhalation studies examining a wide-range of potential end points, including the nervous system, would be useful for identifying the most sensitive effect of inhaled aluminum"* (ATSDR, 2008).

2.2.6.3 Bone Toxicity

Osteomalacia, a softening of the bones, has been associated with exposure to aluminum in healthy individuals as well as in individuals with renal failure (ATSDR, 2008). This outcome has been attributed to ingestion on aluminum-containing antacids to treat symptoms of GI disorders such as ulcers, colic or gastritis. The mechanism of toxicity is the antacid binding to dietary phosphorous and inhibits GI absorption of phosphorous. Osteomalacia and rickets can be attributed to decreased body burden of phosphorous (ATSDR, 2008).

2.2.6.4 Carcinogenicity

Aluminum has not been classified as carcinogenic by the International Agency for Research on Cancer (IARC) (Krewski *et al.*, 2007); however, "aluminum production" has been classified as carcinogenic to humans (Group 1):

> *"There was sufficient evidence from epidemiological studies of a carcinogenic effect of occupational exposure in aluminium production, based on a relatively large number of studies that showed a consistent excess of cancer of the bladder and a somewhat less consistent excess of lung cancer"* (IARC, 2010).

In terms of aluminum smelter workers, the IARC monograph states:

> *"Overall, the cohort studies strongly support an association between work in aluminium smelters and bladder-cancer risk. Confounding or chance is not likely to explain the findings. There is an increased risk for cancer of the bladder from occupational exposure in aluminium smelters. An increased risk for lung cancer has been found in several but not all epidemiological studies in the aluminium-production industry. Some studies also show a dose–response trend in terms of B[a]P–years. Confounding from smoking or chance is not likely to explain the findings. Based on these observations, there is evidence that risk for cancer of the lung is causally associated with work in aluminium smelters. The exposure circumstances, especially levels of PAH in aluminium smelters, vary between industrial departments and also depend on the process used. However, data are not sufficient to disentangle the cancer risks associated with these different exposure situations"* (IARC, 2010).

While the report makes the point that it is not possible to separate individual chemical exposures involved in aluminum production in order to determine component-specific cancer risks, PAHs were the primary exposure of concern among the studies reviewed by IARC:

> *Workers in aluminium production are primarily exposed to polycyclic aromatic hydrocarbons (PAHs). Occupational exposures in this industry and the related carbon electrode-manufacturing industry have been monitored most intensively with respect to PAHs. Other potential exposures in these occupational settings include: sulfur dioxide and fluorides; aluminium fluoride; fibrous sodium aluminium tetrafluoride particles; fluorspar; alumina; carbon monoxide; carbon dioxide; various trace metals, such as vanadium, chromium and nickel; asbestos; extreme heat; and high static magnetic fields"* (IARC, 2010).

2.3 Mortality

Several deaths due to inhalation of finely powdered metallic aluminum used in paints, explosives and fireworks have been reported; however, the dust levels were extremely high (615-685 mg Al/m^3) with respirable dust concentrations of 51 mg Al/m^3. These events were from several decades ago and improvements in production technology have greatly reduced this type of exposure (Mitchell *et al.*, 1961). Additionally, of the experiments performed on animals, none has shown death from inhalation exposure to aluminum or its compounds following acute and chronic exposures (ATSDR, 2008).

With respect to ingestion of aluminum, no reports of aluminum-related death have occurred after oral exposure in humans. One aluminum compound that can be life-threatening if ingested is aluminum phosphide, but the toxicity is from the phosphine gas that is produced in the body following ingestion (ATSDR, 2008).

2.4 Aluminum Exposure in Non-Occupational Settings

Aluminum is the most abundant metal and the third most abundant element in the Earth's crust, naturally occurring in air, water and soil (Nayak, 2001). In nature, aluminum is widely distributed and found in combination with other elements such as oxygen, silicon and fluorine. Such compounds are typically found in soil, minerals (*e.g.*, rubies, sapphires, turquoise), rocks and clays. Aluminum in its pure elemental form is not found in nature due to its high reactivity (ATSDR, 2008).

Aluminum exposure is common due to its presence in the natural environment and its wide variety of uses and applications in everyday products such as beverage cans, cooking utensils, cosmetics, antiperspirants, sunscreens and food additives. The primary source of exposure to aluminum for most people is through food (ATSDR, 2008). Aluminum compounds may be added to processed foods such as flour, baking powder, food colouring and anticaking agents, whereas unprocessed foods (fresh fruits, vegetables, meats) typically only contain trace amounts. On average, an adult consumes 7-9 mg of aluminum per day through ingestion of food (ATSDR, 2008). Another source of exposure to aluminum is through the use of certain cosmetics, antiperspirants and pharmaceuticals:

- Antacids have 300-600 mg aluminum Hydroxide (approximately 104-208 mg Aluminum) per tablet, capsule, or 5 mL liquid dose;
- Buffered aspirin contains 10-20 mg of aluminum per tablet; and,
- Vaccines may contain small amounts of aluminum compounds (<0.85 mg/dose).

The majority of people inhale very little aluminum from breathing, with levels in ambient air ranging from 0.005 to 0.18 µg/m^3 depending on location, weather conditions, and density and nature of industrial activity in the vicinity (ATSDR, 2008). Aluminum levels in urban and industrial areas can be higher ranging from 0.4 to 8.0 µg/m^3. The majority of aluminum suspended in air is in the form of small dust or soil particles. Aluminum is also found in soil and water, although the concentration of aluminum in natural waters (*e.g.*, streams, ponds, lakes) is typically less than 0.1 mg/L. Drinking water can contain aluminum, especially if it is treated with aluminum salts. Typical levels of aluminum in drinking water are below 0.1 mg/L; however, some cities have reported as high as 0.4-1.0 mg/L. Levels of aluminum in soil are much higher, typically ranging from 7 to >100 mg/kg, and vary widely depending on the location (ATSDR, 2008).

2.5 Aluminum Exposure in Occupational Settings

Aluminum compounds have diverse industrial uses such as alums (aluminum sulfate) in water treatment and alumina in abrasives and furnace linings (ATSDR, 2008). Occupational exposure to aluminum not only occurs from refining of the metal, but also in industries that use aluminum products, such as aircraft, automotive and metals products) and in aluminum welding. Aluminum production involves three steps: (i) aluminum is extracted from bauxite ore, precipitated as aluminum hydroxide and converted to aluminum oxide; (ii) the oxide is dissolved in cryolite and electrolyzed to produce pure molten metal; and, (iii) the molten aluminum is poured into ingots in the foundry (ATSDR, 2008). Exposure to various aluminum compounds occurs throughout the process with aluminum hydroxide and oxide in the extraction and purification stages, aluminum fluoride in the potroom (as well as tar-pitch volatiles and PAHs) and to aluminum fumes in the foundry (ATSDR, 2008; IARC, 1984).

The majority of studies conducted on workers occupationally exposed to aluminum have involved inhalation of aluminum-containing dust. However, rarely are these workers exposed to dust that contains only aluminum and is devoid of any other substance. Therefore, exposures usually include a mixture of fine particles and other toxic chemicals in addition to the aluminum content. For example, an epidemiological study looking at an increase in bladder cancer among aluminum reduction workers found that volatile PAHs in coal tar pitch were actually the causative agents (Theriault *et al.*, 1984). Synergistic effects among various agents including metal dusts, fine particles, toxic chemicals (including PAHs) and cigarette smoke are all plausible causes of cancers appearing in workers for many industrial processes involving aluminum.

Miners have also been occupationally exposed to aluminum through inhalation of McIntyre powder, used as a prophylactic agent against silicosis (Rondeau, 2002). The powder was thought to provide a protective coating on the lungs that would help to prevent silicosis in miners and other workers potentially exposure to silica dust. It was comprised of 15% elemental aluminum and 85% aluminum oxide (Rifat, 1990). In order to administer the McIntyre powder, it would be pumped into an enclosed space *via* a pressurized pipe, where workers would inhale the dust for 10 minutes prior to their shifts (IDSP, 1992, Rifat, 1990). This practice was widespread, used in Canada, the US, Mexico, Chile, the Belgian Congo and Western Australia (RCI, 2015). In Canada, McIntyre powder was provided to gold and uranium miners from about 1944 to 1979 (Rifat, 1990, Beach *et al.*, 2001).

2.5.1 Occupational Exposure Limits

Several agencies have set limits for occupational exposure to various forms of aluminum, including the Occupational Safety and Health administration (OSHA), the American Conference of Governmental Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). Values for aluminum oxide, aluminum powder (elemental) and aluminum welding fumes are reported in Table 2-1.

Table 2-1 Occupational Exposure Limits for Aluminum

Aluminum	OSHA PEL (mg/m^3)	ACGIH TLV (mg/m^3)	NIOSH REL (mg/m^3)	UK 8-hr OELV (mg/m^3)	Australia TWA (mg/m^3)
Aluminum Oxide (respirable fraction)	5	1	Not established	4	Not established
Aluminum Oxide (total dust)	15	1	Not established	10	10
Aluminum (as Al), Metal (total dust)	15	Not established	10	10	10
Aluminum (as Al), Welding Fumes	Not established	Withdrawn in 2004	5	Not established	5

Notes: OSHA PEL (Permissible Exposure Limit) – time weighted average; ACGIH TLV (Threshold Limit Value) – time weighted average; NIOSH REL (Recommended Exposure Limit); UK 8-hr OELV – Long-term Occupational Exposure Limit Value; Australia TWA – Time Weighted Average.

The occupational exposure limits are based on different types of health endpoints. For example, the OSHA Permissible Exposure Limit (PEL) for aluminum metal (total dust) is based on physical irritation, the NIOSH Recommended Exposure Limit (REL) for aluminum metal (total dust) is based on changes in the lung that may lead to pulmonary fibrosis, and the NIOSH REL for exposure to aluminum welding fumes is based not just on lung changes that may potentiate to pulmonary fibrosis, but also chronic respiratory diseases such as pneumoconiosis and bronchitis.

Other potential health effects and hazards include respiratory effects, particularly impaired lung function and fibrosis in workers exposed to aluminum dust or fumes (ATSDR, 2008). Increased respiratory symptoms were reported in aluminum cast-house workers, who reported consistent and repeated breathing trouble, repeated wheezing, asthma attacks, and doctor-diagnosed asthma (van Rooy *et al.* 2011). These results were noted in comparison to a general population sample as well as an internal reference group that were used as controls (van Rooy *et al.*, 2011). In addition, long-term occupational exposure to aluminum dust and fumes may cause signs of cholestasis (Bogdanovic and Bulat 2008).

2.6 Overview of Existing Literature Reviews and Meta-Analyses

Several literature reviews and meta-analyses have been completed on aluminum exposure. A summary of these reviews that focus on chronic occupational and non-occupational exposure to aluminum and adverse health conditions is provided. Much of the focus is on the potential association between aluminum and dementia and associated disorders. The major findings and overall conclusions of some of these studies are discussed below and then contextualized in relation to occupational exposures to McIntyre powder.

A meta-analysis was conducted to combine estimates of neurobehavioural effect size in aluminum workers (Meyer-Baron *et al.*, 2007). The final sample considered in the analysis included nine studies looking at 449 exposed and 315 comparison subjects. Urinary aluminum concentrations ranged from 13 to 133 µg/l (mean) and a total of six neuropsychological tests were considered, producing ten performance variables. A statistically significant decline in performance on the digit symbol neurobehavioural test was found; however, no other significant effects were identified. The authors used an explorative approach to investigate the confounders of age, education and alcohol consumption and found that adjustment for confounding resulted in smaller effect sizes. Therefore, the authors acknowledge that the potential for confounding effects could not be ruled out. They conclude that "additional studies are necessary to verify and to differentiate the effect of aluminum on cognitive performance" (Meyer-Baron *et al.*, 2007).

A more recent meta-analysis, looking specifically at occupational exposure to aluminum and Alzheimer's disease, was conducted by Virk and Eslick (2015). The analysis was intended to systematically quantify the association between occupational aluminum exposure and risk of Alzheimer's disease and included controlled occupational studies published up until 2015. Three case-control studies, including 1,056 participants, met the inclusion criteria: Graves *et al.* (1998), Gun *et al.* (1997), and Salib *et al.* (1996). The results of the analysis found that occupational aluminum exposure was not associated with Alzheimer's disease (Odds Ratio 1.00; 95% confidence interval 0.59-1.68). The authors concluded that their findings do not support a causative role of aluminum in the pathogenesis of Alzheimer's disease. However, they state that "in the absence of prospective studies with more precise ascertainment of exposure, a role for aluminum cannot be definitively excluded" (Virk and Eslick, 2015).

A considerable number of studies have related elevated aluminum levels in drinking water to an increased risk of cognitive impairment and Alzheimer-type dementia. In a comprehensive literature survey, nine out of 13 published epidemiological studies of aluminum in drinking water and Alzheimer's disease have shown statistically significant positive relations, although the relative risks were generally not high (Flaten, 2001). Most of the studies were ecological in design in that they studied the relationship between rates of Alzheimer's disease in a geographical region and the concentration of aluminum in drinking water. Further, a major problem in their interpretation is that drinking water, even at high aluminum concentrations, only contributes a fraction of the total dietary intake of aluminum.

In a recent review, a meta-analysis of chronic exposure to aluminum and risk of Alzheimer's disease was completed (Wang *et al.*, 2016). The analysis included exposure to aluminum by any route, including occupational exposures and non-occupational exposures (*e.g.*, drinking water). A total of eight epidemiological studies (with 10,567 individuals) were included in the meta-analysis; four occupational and four drinking water studies. The overall results showed that individuals chronically exposed to aluminum were 71% more likely to develop Alzheimer's disease (OR: 1.71, 95% confidence interval 1.35-2.18). In this meta-analysis, chronic exposure was defined as concentration of aluminum in drinking water greater than 100 µg/L, a significant

daily consumption of aluminum, or occupational exposure to aluminum. In subgroup analyses, the effect estimate from studies examining aluminum exposure from drinking water (1.95, 95%CI: 1.47-2.59) was approximately 50% higher than the effect estimate for studies examining occupational aluminum exposure (1.25, 95%CI: 0.80-1.94). These findings raise questions given that people occupationally exposed to aluminum would experience aluminum levels that are orders of magnitude higher than communities exposed *via* public drinking water and therefore, if a relationship between aluminum and Alzheimer's disease does exist, one would expect it to be stronger in the studies of working populations. The findings may reflect different bioavailability of aluminum from different sources. For example, although aluminum is poorly absorbed in the gastrointestinal tract, its absorption may be increased in the presence of organic substances, which may be present in drinking water supplies. On the other hand, it is important to note that the amount of aluminum consumed in drinking water on average is only approximately 4% of the total aluminum dietary intake. The authors describe that limitations of their meta-analysis included the lack of consideration of other sources of aluminum exposure (including pharmaceuticals, processed foods, vaccinations, sun protection lotions, deodorants, and other sources) and no consideration of a dose-response relationship (Wang *et al.*, 2016). The strengths of the findings include the lack of significant heterogeneity among studies and the lack of apparent publication bias.

Another review that considered non-occupational exposures to aluminum was conducted by Willhite *et al.* (2014) and included consideration of pharmaceutical and consumer exposures, in addition to occupational exposures. The review was based on retrieval from databases containing peer-reviewed literature, resulting in 469 articles included in the review. The review describes in great detail, routes of exposure, health effects, toxicity, as well as standards and guidelines for aluminum. Overall, the authors concluded:

> *"The results of the present review demonstrate that health risks posed by exposure to inorganic Al depend on its physical and chemical forms and that the response varies with route of administration, magnitude, duration and frequency of exposure. These results support previous conclusions that there is little evidence that exposure to metallic Al, the Al oxides or its salts increases risk for AD, genetic damage or cancer"* (Willhite *et al.*, 2014).

Collectively, the systematic reviews and meta-analyses of the epidemiologic literature on aluminum exposure and health effects vary in quality, approach and findings. With respect to these reviews and how they relate to potential occupational exposure to aluminum, and McIntyre powder in particular, it is apparent that dose-response relationships have yet to be deciphered with respect to aluminum. There is general consensus that absorption of aluminum into bodily tissues is poor, rather it is largely excreted through urine and feces. Additionally, with the ubiquitous nature of aluminum, potential occupational exposures are complicated by the fact that aluminum is present in drinking water, foods and consumer products that are widely used (*i.e.*, antiperspirants, pharmaceuticals, *etc.*). Although there have been some epidemiological studies that support an association between aluminum and neurological disorders, the preponderance of evidence is against a significant role for environmental aluminum as a cause for neurological outcomes.

3.0 METHODS

3.1 Literature Search Strategy

The Cochrane Handbook for Systematic Reviews of Interventions governed the development of the study search and evaluation process for the systematic review of occupational aluminum exposure and adverse health conditions. The Cochrane Handbook is the standard for conducting reviews in healthcare and pharmaceutical industries. Cochrane reviews adhere to the principle that "science is cumulative" and by considering all available evidence, decisions can be made that reflect the best science available. The applicability of the Cochrane methodology is widespread across disciplines. As defined in the Cochrane handbook, a focused review begins with framing a question that specifies the population, interventions, outcomes, comparisons, and studies of interest; a formula referred to as the acronym PICOS (Population, Interventions, Comparisons, Outcomes, and Study Type). To guide the literature review, the study question will be defined as a search of epidemiological studies that investigate the health effects (primarily neurological disorders) associated with occupational exposure to aluminum. Additional inclusion and exclusion criteria for identifying studies will be specified to meet the project goals. For example, as described in the RFP, the review should specifically include studies of workers exposed to McIntyre Powder.

The search strategy (see Appendix A) used controlled vocabulary terms and keywords including terms for "Occupational", "Aluminum", "McIntyre Powder", "Alzheimer's disease", "Parkinson's disease", "Amyotrophic Lateral Sclerosis" and additional neurological and other conditions. An information specialist searched the following bibliographic databases: Ovid Medline (1946 to present; In- Process & Other Non-Indexed Citations), and Embase (1974 to 2013 June 07); PubMed (for non-Medline records only); Wiley's Cochrane Library (current Issue); and the Canadian Center for Occupational Health and Safety Databases (including, OSHLINE®, NIOSHTIC®, NIOSHTIC-2, HSELINE, CISILO, and Canadiana). A search for grey literature (literature that is not commercially published) was also conducted, incorporating different search strategies (1) grey literature databases, (2) targeted websites, and (3) a broad Internet search using the Google search engine. Grey literature databases identified by the US National Institutes of Health and Georgetown University were included in this strategy. Targeted websites of relevant health agencies such as the US Centers for Disease Control and Prevention (CDC), the US Environmental Protection Agency (EPA), other relevant resources identified by the BC Environmental and Occupational Health Research Network and websites of relevant professional associations (such as the Alzheimer's Association, the ALS Association, *etc.*) were also included. Finally, searches were supplemented by reviewing the bibliographies and abstracts of key papers.

3.2 Study Selection

Intrinsik followed the process described in the following sections to select the relevant literature. A flow diagram detailing the entire literature selection process is provided in Figure 3-1 below.

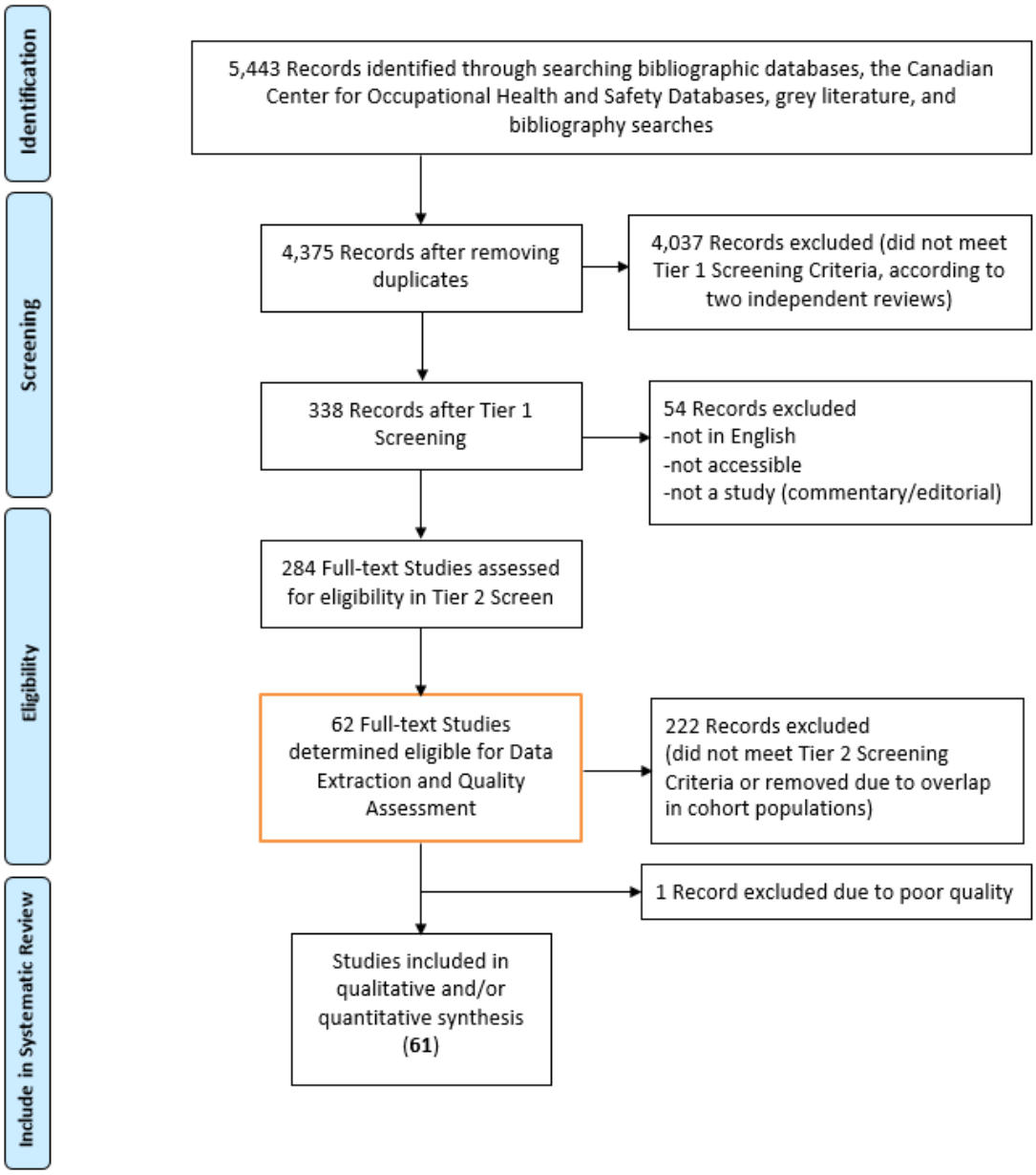

Figure 3-1 PRISMA Flow Diagram (based on Moher *et al.*, 2009)

3.2.1 Tier 1 Screening

The literature search strategy described in Section 3.1 resulted in **4,375** articles that were the subject of a Tier 1 abstract screening using the following inclusion and exclusion criteria:

Inclusion Criteria	Exclusion Criteria
- The study is published in English. - The study involved chronic occupational exposure to aluminum (McIntyre Powder, aluminum oxides from other sources like welding, and other aluminum compounds) and the risk of developing adverse health condition(s) that is/are identifiable by the International Classification of Diseases (9th and 10th Revision).	- The study is not published in English. - The study does not involve chronic occupational exposure to aluminum. - The study is not an epidemiologic study (not in humans). - The study examines the risk of developing occupational dermatitis or contact dermatitis. - The study does not examine the risk of developing an adverse health condition that is identifiable by the International Classification of Diseases (9^{th} and 10^{th} Revision).

Only English language articles were included to avoid the delays associated with translation of international articles. We do not believe this language restriction significantly decreased the effectiveness of the review because a large proportion of the indexed scientific literature is published in English.

The Tier 1 abstract screening involved two team members who simultaneously examined the abstracts. Results from these readers were compiled. A study was carried forward if either reviewer marked the study for inclusion; resulting in the selection of **338** records. During the retrieval of full-text versions of the selected abstracts, an additional 54 records were excluded for one the following reasons: full-text studies were inaccessible, not available in English, or were commentaries or editorials rather than actual studies. Therefore, **284** studies were eligible retained for Tier 2 review.

3.2.2 Tier 2 Screening

Full-text Tier 2 reviews were completed using the Tier 2 Screening Form (see Appendix B) and results were recorded in a Microsoft Access database. To ensure consistent adherence to the selection criteria, the screening of all papers was independently conducted by two reviewers. Results from the screeners were compiled and compared. Where there was disagreement, the reviewers met to discuss their reasoning for how the paper was screened and to reach consensus for study selection.

3.3 Quality Appraisal Approach

The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of included studies. The NOS is a scale for assessing the quality of published non-randomized studies (*i.e.*, observational studies) in meta-analyses. The NOS contains items, categorized into three dimensions including selection, comparability, and -depending on the study type- outcome (cross-sectional/cohort studies) or exposure (case-control studies). For each item a series of response options is provided (refer to the detailed NOS scoring sheets provided in Appendix C-1 to C-3). A star system is used to allow a semi-quantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item and resulting in a total range between zero to six or nine stars, depending on the type of study (Table 3-1).

The study quality was considered good, satisfactory, or unsatisfactory according to the number of stars. Studies with an unsatisfactory NOS rating were considered for exclusion.

Table 3-1 Newcastle-Ottawa Scale Ratings

Categories	Cross-Sectional (max. 6 stars)	Cohort (max. 9 stars)	Case Control (max. 9 stars)
Selection	★★★	★★★★	★★★★
Comparability	★★	★★	★★
Outcome/Exposure	★	★★★	★★★
Rank	**Rating Scale**		
Good	4-6	7-9	7-9
Satisfactory	2-3	4-6	4-6
Unsatisfactory	0-1	0-3	0-3

To ensure consistency of review, the NOS for each study was completed by two reviewers. Results from the screeners were compared; where there was disagreement, a third reviewer helped reach consensus for the final quality rating.

3.4 Data Extraction Approach

An electronic data collection form was created in Microsoft Access to accommodate information from the various studies (see Appendix D). Key information (such as study author, publication year, study country/location, follow-up duration, type of study, worker industry/occupation, sample size, mean age, length of employment, health condition, diagnostic criteria for health condition, and potential confounders such as smoking status of study population) contained in the scientific articles were entered into a Microsoft Access database. The data were extracted from each article by one reviewer and was verified by another. This process ensured quality control of the information extracted from the selected studies.

3.5 Meta-Analysis

For studies that were similar in terms of study design, study population, exposures, and/or outcomes, meta-analysis was performed to synthesize the data. For studies that were more diverse and it was not possible to pool the results with quantitative methods, semi-quantitative and narrative analysis methods were used to synthesize the information.

RevMan, the software used for preparing Cochrane Reviews, was used to conduct meta-analyses of effect size measures and their corresponding variances. Additional meta-statistics were performed using Stata statistical software. Heterogeneity was firstly assessed with statistical tests (Q test and I-squared [I^2] statistic) to determine whether a fixed effects model (for homogeneous data) or random effects model (for heterogeneous data) was appropriate for analyzing the data. The overall effect size for each outcome assessed with meta-analytic methods was calculated as a weighted mean of the individual results using the random effects model to account for potential variability between the studies. Each overall effect size was tested for statistical significance using a significance level of $p<0.05$.

Other meta-analysis statistical methods used to analyze and display the data included forest plots, sensitivity analysis, and meta-regression. Forest plots are used to display the individual and overall effects. Sensitivity analyses was performed by systematically removing studies with a significant effect on the pooled effect size to determine if the results change.

Regardless of whether analysis included meta-analysis or qualitative analysis methods, subgroup analysis assessed the potential for an increased risk of a significant effect according to variables such as age, level of education, smoking rates, years of exposure to aluminum, and the level of aluminum in biomonitoring samples (urine, blood, *etc.*). For meta-analyzed outcomes, differences by these factors were investigated using meta-regression. The regression model for each risk factor was:

$$\text{Outcome}_j = \text{constant} + \text{risk factor (exposure} - \text{control)}_j + \text{residual}_j + \text{random error term, for studies } j$$

Since meta-analysis relies on summary data, a p-value of less than 0.10 is considered statistically significant in meta-regression. The level of exposure as measured in ambient air, detected by urine or blood, or assumed by duration of employment was an important factor for assessing the outcomes. Level of exposure was closely inspected by meta-regression in order to draw conclusions about the potential for a dose response relationship.

4.0 RESULTS

4.1 Study Characteristics

The peer-reviewed search and subsequent Tier 1 and Tier 2 screenings identified **62** articles for the systematic review and potential meta-analysis of quantitative data. Of the studies, two were conducted in occupational populations exposed to aluminum powder as a prophylaxis (*i.e.*, McIntyre Powder): Rifat *et al.* (1990) and Peters *et al.* (2013). The literature search identified one abstract specific to McIntyre Powder exposure that was not available as a full-text report (McDonald *et al.* 1996). The abstract was also retained for discussion.

Table 4-1 describes the study design characteristics, population, and health outcome measured, organized by category of health outcome, of the selected literature. Countries of study included Australia, Austria, Canada, China, Denmark, Egypt, England, Finland, France, Germany, Italy, New Zealand, Norway, Poland, Sudan, Sweden, Turkey, the US, and Yugoslavia. Publication dates range from 1985 to 2016. Forty-seven studied aluminum exposed workers at a single point in time (cross-sectional study type), eight followed workers over a period of time (longitudinal cohort study type), and seven were case-control studies. Most studies had a comparison, or control, population. Overall, the studies vary on many characteristics, including, for instance, types of occupational setting (*e.g.*, aluminum production workers vs. welders), average length of exposure (*e.g.*, 5 to 31 years), biomarkers used to determine exposure level (*e.g.*, blood *versus* urine) and methods of assessing outcomes (*e.g.*, diagnosis of disease *versus* tests indicative of cognitive performance).

Overall, the selected literature primarily studied neurological (31 studies) or respiratory endpoints (17 studies), but a variety of other health outcomes were also included: i) cancer or biomarkers of cancer (6 studies); ii) markers of cardiovascular disease (2 studies); iii) morbidity/mortality due to various diseases (2 studies); iv) bone disease (1 study); and, v) reproductive outcomes (1 study). As seen in Table 4-1 under the heading “Diseases/Outcomes Measured”, most of the studies on neurological outcomes investigated the performance of workers occupationally exposed to aluminum by means of administering various neurological tests. Additionally, most of the studies on respiratory outcomes investigated the performance of workers occupationally exposed to aluminum by means of administering lung function tests or spirometry.

Section 4.2 presents the quality assessment of all articles retained through the literature screening steps. The McIntyre Powder studies are presented in Section 4.3 followed by the individual health outcomes analyses in Section 4.4 through 4.5. Section 4.4 includes the analyses of ICD-diagnosable conditions and Section 4.5 includes the analyses of other health outcomes (*i.e.*, non ICD-diagnosable conditions) that were studied.

Table 4-1 Summary of Evaluated Studies

Study ID	Year	Country	Study Type	Occupational Setting	Exposure Measurements	Diseases/Outcomes Measured	No. of Exposed[1]	No. of Referents	Years of Exposure
Bone Disease									
Schmid1995	1995	Germany	Cross-Sectional	Aluminum Powder Plant	Urine, plasma, workplace air	Osteodystrophy (bone mineral content, bone density)	32	29	12.6
Cancer/Markers of Cancer									
Aronson1996	1996	Canada	Case-control	Various	Based on job history	Prostate cancer	449	2083	N/A
Parent2000	2000	Canada	Case-control	Various	Based on job history	Oesophageal cancer	99	533	N/A
Ahmed2013	2013	Sudan	Cross-Sectional	Aluminum Industry	None	Cytological atypical changes in sputum specimens	50	157	>1
Botta2006	2006	France	Cross-Sectional	Welding	Blood and urine	DNA damage in lymphocytes	30	22	>3
Cantone2011	2011	Italy	Cross-Sectional	Steel Workers	Workplace air	Histone modifications	63	none	>1
Hou2011	2011	Italy	Cross-Sectional	Steel Workers	Blood, workplace air	Changes in DNA methylation	63	none	>1
Cantone2014	2014	Italy	Cross-Sectional	Steel Workers	Workplace air	Extracellular histone modifications	63	none	>1
Markers of Cardiovascular Disease									
Cavallari2008	2008	USA	Cross-Sectional	Boilermaker construction workers	Workplace air	Heart rate variability	26	none	NR
Liu2016	2016	China	Cross-Sectional	Coke oven	Urine	Diabetes, hyperglycemia, and normoglycemia	1493	none	>1
Morbidity/Mortality due to Various Disease									
Friesen2009[2]	2009	Australia	Cohort	Mining/Refining	Based on job history	Cerebrovascular disease, non-malignant respiratory disease, all circulatory disease, all cardiovascular disease	5770	NR	14.1
Fritschi2008[2]	2008	Australia	Cohort	Mining/Refining	Based on job history	Mortality and various cancer sites, circulatory and respiratory disease. Morbidity and various cancer sites.	6485	General Australian population	10 year latency analysis
Neurological Disease or other Neurological Outcomes									
Akila1999	1999	Finland	Cross-Sectional	Welding	Urine	Neurological tests	51	28	NR
Bast-Pettersen1994	1994	Norway	Cross-Sectional	Aluminum Production	Urine and serum	Neurological tests	22	16	19
Bast-Pettersen2000	2000	Norway	Cross-Sectional	Welding	Urine	Neurological tests	20	20	8.1
Camerino1993	1993	Italy	Cross-Sectional	Welding	Workplace air	Neurological tests	18	400	<1
Deschamps2009	2009	France	Cross-Sectional	Aluminum Salvage/ Recycling	Blood and urine, airborne particulate sampling	Neurological tests, Symptoms	30	60	6.5
Dick1997	1997	USA	Cross-Sectional	Aluminum Production	Historical workplace measurements	Tremor	63	37	NR
Giorgianni2014	2014	Italy	Cross-Sectional	Welding	Blood, workplace air	Neurological tests	86	90	15.8
Graves1998	1998	USA	Case-control	Various	Based on job history	Alzheimer's Disease	89	89	N/A
Gun1997	1997	Australia	Case-control	Various	Based on job history	Alzheimer's Disease	170	170	N/A
Guo1999	1999	China	Cross-Sectional	Aluminum Production	Urine, breathing zone of subjects	Neurological tests	104	64	16.6
Halatek2005a	2005	Poland	Cross-Sectional	Aluminum Production	Blood, urine, breathing zone	Neurological/neurophysiological biomarkers	66	42	14.8
Halatek2008	2008	Poland	Cross-Sectional	Aluminum Smelting	Blood and urine, workplace air	Symptoms, biomarkers, EEG and visual evoke potentials (VEP)	50	42	14.8
Hanninen1994	1994	Finland	Cross-Sectional	Welding	Urine and serum	Neurological tests	17	None	15
Iregren2001	2001	Sweden	Cross-Sectional	Various	Blood and urine	Neurological tests	157	39	5
Kiesswetter2007	2007	Germany	Cohort	Welding (train body and truck trailer construction)	Plasma, Urine, Personal Air	Neurological tests	44	37	14.8
Kiesswetter2009	2009	Germany	Cohort	Welding (car-production workers)	Plasma, Urine, Personal Air	Neurological tests	98	50	8.8
Kilburn1998	1998	USA	Cross-Sectional	Aluminum Recycling	None	Neurological tests	41	32	NR
Letzel2000	2000	Germany	Cohort	Aluminum Powder Plant	Urine, plasma, glucose, and serum	Neurological tests	32	30	12.6
Lu2014	2014	China	Cross-Sectional	Aluminum Smelting	Serum	Cognitive functions and rate of mild cognitive impairment (MCI)	66	70	30.2
McGuire1997	1997	USA	Case-control	Various	Based on job history	Amyotrophic lateral sclerosis (ALS)	174	348	N/A
Peters2013	2013	Australia	Cohort	Gold Mining (with Al dust as prophylaxis)	Based on job history	Alzheimer's disease (and Cardiovascular, Cerebrovascular, Pneumoconiosis)	647	1247	follow-up 48 years after exposure
Polizzi2002	2002	Italy	Cross-Sectional	Aluminum Salvage/ Recycling	Serum and historical workplace air	Neurological tests	64	32	30.7
Rifat1990	1990	Canada	Cross-Sectional	Mining	Historical exposure to McIntyre powder	Neurological tests	261	346	0.5 – 36
Riihimaki2000	2000	Finland	Cross-Sectional	Welding	Urine and serum	Neurological tests	65	25	12.3

Table 4-1 Summary of Evaluated Studies

Study ID	Year	Country	Study Type	Occupational Setting	Exposure Measurements	Diseases/Outcomes Measured	No. of Exposed[1]	No. of Referents	Years of Exposure
Salib1996	1996	England	Case-control	Various	Based on job history	Alzheimer's, Other Dementias	362	340	N/A
Semchuk1993	1993	Canada	Case-control	Various	Based on job history	Parkinson's disease (PD)	130	260	N/A
Sim1997	1997	USA	Cross-Sectional	Aluminum Production	Workplace air	Neurological tests	63	37	10
Sinczuk-Walczak2003	2003	Poland	Cross-Sectional	Aluminum Production	Urine and workplace air	Symptoms, EEG changes	67	57	14.6
Sjogren1990	1990	Sweden	Cross-Sectional	Welding	Questionnaire	Symptoms	65	217	46% exp. for 10-19 years
Yang1998	1998	China	Cross-Sectional	Aluminum Smelting	Blood and urine, ambient air sampling	Neurological tests	33	40	9.9
Yang2015	2015	China	Cross-Sectional	Aluminum Production	Serum	DNA methylation, MMSE test scores, mild cognitive impairment (MCI) prevalence	366	None	21.2
Zawilla2014	2014	Egypt	Cross-Sectional	Aluminum Production	Blood, workplace air	Neurological tests	54	51	>5
Reproductive Outcomes									
Hovatta1998	1998	Finland	Cross-Sectional	Refinery and Polyolefin factory	Spermatozoa	Fertility (sperm motility)	27	45	NR
Respiratory Disease or other Respiratory Outcomes									
Abbate2003	2003	Italy	Cross-Sectional	Shipyard Workers	Blood, personal air samples	Lung function tests	50	50	11.8
Dennekamp2015	2015	Australia	Cohort	Mining/Refining	Based on job history	Lung function tests, respiratory symptoms	187	267	7 years of follow-up
Elserougy2015	2015	Egypt	Cross-Sectional	Aluminum Production	Urine	Lung function tests	56	52	10.1
Fishwick2004	2004	New Zealand	Cross-Sectional	Welding	Based on job history	Lung function tests	49	26	18.5
Friis1989	1989	Denmark	Cross-Sectional	Cryolite Production	Questionnaire	Lung function tests, respiratory symptoms	101	0	8.2
Fritschi2001	2001	Australia	Cross-Sectional	Alumina Refining	Workplace air	Lung function tests, respiratory symptoms	2404	4845	NR
Halatek2006	2006	Poland	Cross-Sectional	Various	Blood and urine, workplace air	Lung function tests, lung biomarkers (Serum CC16)	66	42	15- 29
Haluza2014	2014	Austria	Cohort	Welding	None	Lung function tests	1982	none	NR
Hansell2014	2014	New Zealand	Cross-Sectional	Various	None	Respiratory symptoms; doctor diagnosis of COPD/chronic bronchitis/emphysema	40	977	NR
Kilburn1992	1992	USA	Cross-Sectional	Aluminum Production	None	Lung function tests, Clinical features (asthma, *etc.*), irregular opacities in the chest	670	659	5
Kraus2006	2006	Germany	Cross-Sectional	Aluminum Powder workers	Plasma and urine	Lung function tests, High-resolution computed tomography	62	none	Average of up to 15
Larsson1989	1989	Sweden	Cross-Sectional	Aluminum Production	Workplace air (total dust)	Lung function tests, Respiratory symptoms, and bronchial provocation tests	38	20	13.6
Musk2000	2000	Australia	Cross-Sectional	Aluminum Powder workers	Workplace air	Lung function tests, respiratory symptoms	2388	0	10
San1998	1998	Turkey	Cross-Sectional	Aluminum Production	Serum	Lung function tests	55	30	9.7
Sjogren1985a	1985	Sweden	Cross-Sectional	Welding	None	Chronic bronchitis, lung function tests	64	64	5
Townsend1985	1985	USA	Cross-Sectional	Mining/ Refining	Total dust	Lung function tests	1142	291	NR
Townsend1988	1988	USA	Cross-Sectional	Mining/ Refining	Total dust	Radiographic abnormalities	788	none	NR

NR not reported

[1] For Case-control studies, this column reports the number of cases

[2] Overlap in cohort but different mortality and morbidity outcome measurements presented

4.2 Quality Assessment

Quality assessment ratings for cross-sectional, case control, and cohort studies according to the NOS are shown in Tables 4-2, 4-3, and 4-4, respectively. Of the cross-sectional studies, 11 (22%) received a "satisfactory" rating and 37 (76%) received a "good" rating. Only one study, Kilburn (1998), met the criteria for "unsatisfactory" and was removed from consideration in the systematic review. In brief, Kilburn (1998) received zero stars for selection due to the nonrandom selection of exposed individuals who were motivated by health concerns and zero stars for comparability because the reference group, who were friends or relatives of the exposed persons, were not comparable to the exposed group in terms of age and other factors.

Of the case control studies, one was 'satisfactory' and the remaining six studies received a "good" rating. Of the cohort studies, two were "satisfactory" and the remaining six studies received a "good" rating.

The results of the quality assessment will be used in subsequent sections of this report to inform the findings of the meta-analysis and systematic review of the literature.

Table 4-2 Quality Assessment Results, Cross-Sectional Studies

Study ID	Selection	Comparability	Outcome	NOS Rating
Abbate2003	★	★	★	3
Ahmed2013	★	★★	★	4
Akila1999	★★★	★★	★	6
Bast-Pettersen1994	★★★		★	4
Bast-Pettersen2000	★★	★★	★	5
Botta2006	★★	★★	★	5
Camerino1993	★	★★	★	4
Cantone2011	★★	★★	★	5
Cantone2014	★★	★★	★	5
Cavallari2008	★	★★	★	4
Deschamps2009	★★	★★	★	5
Dick1997	★★★	★	★	5
Elserougy2015	★	★★	★	4
Fishwick2004	★★★	★★	★	6
Friis1989	★	★	★	3
Fritschi2001	★★★	★★	★	6
Giorgianni2014	★★	★★	★	5
Guo1999	★★	★★	★	5
Halatek2005a	★★	★★	★	5
Halatek2006	★★	★★	★	5
Halatek2008	★★	★★	★	5
Haluza2014		★★	★	3
Hanninen1994	★	★	★	3
Hansell2014	★	★★	★	4
Hou2011	★	★★	★	4
Hovatta1998	★	★	★	3
Iregren2001	★★	★	★	4
Kilburn1992		★★	★	3
Kilburn1998			★	1
Kraus2006	★★	★★	★	5
Larsson1989	★★		★	3

Table 4-2 Quality Assessment Results, Cross-Sectional Studies				
Study ID	**Selection**	**Comparability**	**Outcome**	**NOS Rating**
Liu2016	★★★	★★	★	6
Lu2014	★★★	★★	★	6
Musk2000	★★	★★	★	5
Polizzi2002	★★	★★	★	5
Rifat1990	★★★	★★	★	6
Riihimaki2000	★★★	★★	★	6
San1998	★		★	2
Schmid1995	★★	★	★	4
Sim1997	★★★		★	4
Sinczuk-Walczak2003	★★	★	★	4
Sjogren1985a	★★★	★★	★	6
Sjogren1990	★★	★		3
Townsend1985	★★	★★	★	5
Townsend1988	★★	★★	★	5
Yang1998	★★		★	3
Yang2015	★★		★	3
Zawilla2014	★★★	★★	★	6

Table 4-3 Quality Assessment Results, Case Control Studies				
Study ID	**Selection**	**Comparability**	**Exposure**	**NOS Rating**
Aronson1996	★★★★	★★	★	7
Graves1998	★★★★	★★	★★	8
Gun1997	★★★	★★	★★	7
McGuire1997	★★★★	★★	★	7
Parent2000	★★★	★★	★★★	8
Salib1996	★★★★	★★	★★	8
Semchuk1993	★★★	★★	★	6

Table 4-4 Quality Assessment Results, Cohort Studies				
Study ID	**Selection**	**Comparability**	**Outcome**	**NOS Rating**
Dennekamp2015	★★★★	★★	★★	8
Friesen2009	★★★★	★★	★★★	9
Fritschi2008	★★	★	★★★	6
Haluza2014		★★	★★	4
Kiesswetter2007	★★★	★★	★★	7
Kiesswetter2009	★★★	★★	★★★	8
Letzel2000	★★★	★★	★★	7
Peters2013	★★★	★	★★★	7

4.3 McIntyre Powder Exposed Workers

A focus of the literature review was to consider possible effects of McIntyre Powder, the aluminum powder inhaled by workers for the purpose of acting as a prophylaxis for silicosis. However, there were only three studies that assessed this specific type of aluminum exposure. Due to the very small number of studies, subgroup analysis could not be performed to compare effects among McIntyre-exposed workers and workers exposed to other forms of aluminum. Instead, the following summaries detail the relevant literature on McIntyre Powder exposure and human health effects.

Rifat *et al.* (1990): In this cross-sectional study 261 underground miners exposed to McIntyre Powder as a prophylactic agent against silicotic lung disease in mines in Ontario, Canada, were compared to 346 non-exposed control miners. Aluminum exposure was ascertained using number of years exposed to McIntyre Powder, as per Ontario mining industry and McIntyre Research Foundation Records. Exposure duration for the subjects examined by Rifat *et al.* (1990) ranged from about 20 to 39 years. Subjects were interviewed and also given three cognitive state tests: i) Mini-Mental State Examination (MMSE) for general cognitive function; ii) a Ravens coloured progressive matrices test (CPM) for reasoning; and, iii) the Symbol Digit Modalities Test (SDMT) for spatial perceptual accuracy and information processing. Results indicated that exposed miners performed less well than unexposed miners on cognitive state examinations. In addition, the proportion with scores in the impaired range was greater in the exposed than the non-exposed group. Increasing duration of exposure also increased likelihood of scores in the impaired range. Differences between exposed and non-exposed miners were adjusted for factors that could have influenced the effects such as age, head injury, and education. There were no significant differences between exposed and non-exposed miners in diagnoses of neurological disorder.

Peters *et al.* (2013): This longitudinal study investigated the association between aluminum dust inhalation and cardiovascular, cerebrovascular and Alzheimer's disease mortality in a group of 647 male miners who ever worked in an underground gold mine in Kalgoorlie, Australia and were exposed to aluminum dust as a prophylaxis during the 1950s and 1960s. The reference group consisted of 1,247 male underground gold miners never exposed to aluminum dust. Workers were exposed to aluminum dust for an average of 10 years (range of 1 to 15 years). At the time of employment, the chest clinic physician recorded whether or not each miner was having aluminum therapy on the miners' health record. Using death certificates, Peters *et al.* (2013) compared mortality among the mining cohort to mortality among the general Australian population. Peters *et al.* (2013) found increased mortality related to Alzheimer's disease among miners ever exposed to aluminum dust, although it was based on very few cases (n=8 in the exposed group) and was not statistically significant (SMR=1.38; 95% CI 0.69 to 2.75). Peters *et al.* (2013) also performed a subgroup analysis separating those with one to nine years of aluminum powder exposure and those with greater than ten years of aluminum powder, compared to no aluminum exposure. The hazard ratios suggested the possibility of a duration-response relationship for Alzheimer's disease mortality (0-9 years: HR= 2.37, 95%CI: 0.63 to 8.88; ≥10 years: HR=3.59, 95% CI: 0.88 to 14.7) but neither were statistically significant. It is also important to note that these HRs were calculated based on very small numbers of Alzheimer's disease cases (four cases in each exposure group).

The Alzheimer's prevalence rate observed in this study, 1.2%, is considerably small and below the general population risk of Alzheimer's disease. However, Alzheimer's disease is not always recognized on death certificates likely leading to an underestimation of Alzheimer's disease among the mining cohort.

> *"The coding issue will have affected the numbers of Alzheimer's deaths among the exposed cohort members and the general population in the same proportion, since we have used the same method of case identification in both groups. Therefore, the observed association between aluminum dust exposure and the disease would probably not be affected. However, more accurate figures of the number of cases would have provided more statistical power for the current analyses on Alzheimer's disease."* (Peters *et al.,* 2013).

Other outcomes examined in Peters *et al.* (2013) included cerebrovascular mortality, cardiovascular mortality, and pneumoconiosis. Aluminum dust inhalation did not affect the risk of cerebrovascular mortality. There was some indication of an increased risk of cardiovascular

mortality among miners with a history of aluminum dust exposure over those who never inhaled aluminum (SMR=1.30, 95%CI: 1.00 to 1.70). Mortality rates for pneumoconiosis were significantly increased for all underground miners, whether they inhaled aluminum dust or not, and no difference in the association between duration of work underground and pneumoconiosis was observed between the groups with or without aluminum dust exposure.

McDonald *et al.*, (1996): This study was published only as an abstract and therefore could not be included in the quality assessment. The authors looked at the potential association between inhalation of McIntyre Powder and the development of Alzheimer's disease and dementia. Death certificates were obtained for two groups of Cornish tin miners, one group from a mine (Geevor) that historically used McIntyre Powder as a prophylactic against silicosis (1940s-1964) and another that did not (South Crofty). None of the miners exposed to McIntyre Powder at Geevor were certified as dying from dementia or Alzheimer's disease. In the unexposed group at South Crofy, two dementia deaths were recorded (a standardized mortality rate of 80.0, which is marginally less than would be expected based on death rates for England and Wales). The authors concluded that the study found no causal link between regular exposure to aluminum powder (McIntyre Powder) *via* inhalation and development of Alzheimer's disease. The total number of miners in each study group was not provided in the abstract. An attempt to reach the study author for more information was unsuccessful. As in Peters *et al.* (2013), the use of death certificate data likely led to an underestimation of Alzheimer's disease among both mining cohorts.

4.4 ICD-Diagnosable Conditions

4.4.1 Neurological Disease

4.4.1.1 Alzheimer's Disease

The literature retrieval steps identified a total of four epidemiological studies among occupational workers with an outcome of clinically diagnosed Alzheimer's disease. This includes one retrospective matched cohort study (Peters *et al.* 2013) and three case-control studies (Graves *et al.* 1998, Gun *et al.* 1997, and Salib *et al.* 1996) that reported either an odds ratio or hazard ratio with the associated 95% confidence interval. This data is sufficient to conduct meta-analysis to determine a pooled odds ratio from the individual odds ratios and hazard ratios. When available, adjusted odds ratios were abstracted from the studies, otherwise, unadjusted odds ratios were used.

The pooled odds ratio, presented in the forest plot provided in Figure 4-1, represents the risk of Alzheimer's disease in populations occupationally exposed to aluminum compared to similar persons not occupationally exposed to aluminum. The increased odds (OR=1.28 (95%CI: 0.78 to 2.10) of Alzheimer's disease in populations occupationally exposed to aluminum is not statistically significant. The low heterogeneity (I^2=11%, p=0.34) is consistent with the forest plot which shows the individual studies to have insignificant effects with wide overlapping confidence intervals. The pooled estimate based on the three case-control studies was OR=1.08 (95%CI: 0.67 to 1.76), with low heterogeneity I^2=0%, test of homogeneity p=0.56. The risk of Alzheimer's disease for the matched cohort study was OR=2.79 (95%CI: 0.88 to 8.82).

There were similarities in the studies with respect to the participants, such as mean age (from 75 to 80 years of age), the reported exposure duration (at least 10 years), and exposure defined by occupational histories. Participants in the Graves *et al.* (1998) study were assigned exposure based on industrial hygienist conducted interviews, and self-reported whether or not they ever inhaled aluminum dust. Participants in Gun *et al.* (1997) were also assessed by a

panel of occupational hygienists, and participants in the study by Salib and Hillier (1996) identified aluminum exposure by self-reporting with a structured questionnaire.

The proportion of the cases with occupational exposure to aluminum varied across the studies, with two studies having higher proportions (Graves *et al..* 1998, 19.1%; Salib and Hillier, 1996, 11.1%) and one study with only 1% of the cases having prior occupational exposure to aluminum (Gun *et al.,* 1997, 0.6%). Although none of the studies reported a significant effect, the two studies with reasonable number of cases with aluminum exposure are important to review farther. The study by Salib *et al.* (1996) shows a clear insignificant effect, OR= 0.98 (0.53, 1.75). The other study, Graves *et al.* (1998), the odds of Alzheimer's disease is 1.46 higher in those with a history of occupation exposure (OR= 1.46, 95%CI: 0.62, 3.42).

An important difference between these two studies was the recruitment method and the determination of aluminum exposure. Salib *et al.* (1996) selected clinically diagnosed probable or possible Alzheimer's disease cases using the established National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria. However, all of the patients were at a psychogeriatric unit in England where the study was conducted and were all patients of the first author of the study. Aluminum exposure was determined by the study participants through a detailed and structured questionnaire. For the study by Graves *et al.* (1998), subjects were identified from University of Washington Alzheimer's disease patient registry. Diagnosis was also based on the ADRDA-NINCDS criteria. Due to the small study size and lack of statistical power, the difference in the presence of exposure between cases and self-reported controls was only five individuals (17/89 *versus* 12/89 cases), not indicating a robust presence of an increased risk based on the study by Graves *et al.* (1998). This is consistent with the author's conclusion, "[a] non-significant association with Alzheimer's disease was found, and dose-response analyses were not significant for duration of exposure in years, intensity of exposure, and age at which half the cumulative lifetime exposure was achieved."

Peters *et al.* (2013) was a different study design where the cohort was not selected on the basis of cases with Alzheimer's disease and controls without Alzheimer's disease. Instead, the cohort included all underground gold miners in 1961-1962 and 1974-1975 from a Western Australian mining town. At the time of employment, the chest clinic physician recorded whether or not each miner was having aluminum therapy on the miners' health record. Using death certificates, Peters *et al.* (2013) compared mortality among the mining cohort to mortality among the general Australian population. In the cohort of 1,894 miners, there were 16 deaths with Alzheimer's disease either listed as the cause of death or with otherwise listed on the death certificate, representing a prevalence of 1.2%. This rate is considerably below the general population risk of Alzheimer's disease. For example, as estimated by the longitudinal Framingham study, the cumulative risk of developing Alzheimer's disease by age 75 is predicted to be 10.2% for men, and 18.5% for women (Seshadri *et al.*, 1997). However, as noted by the authors, Alzheimer's disease is not always recognized on death certificates which likely led to an underestimation of Alzheimer's disease amongst the mining cohort.

> *"The coding issue will have affected the numbers of Alzheimer's deaths among the exposed cohort members and the general population in the same proportion, since we have used the same method of case identification in both groups. Therefore, the observed association between aluminum dust exposure and the disease would probably not be affected. However, more accurate figures of the number of cases would have provided more statistical power for the current analyses on Alzheimer's disease"* (Peters *et al.* 2013).

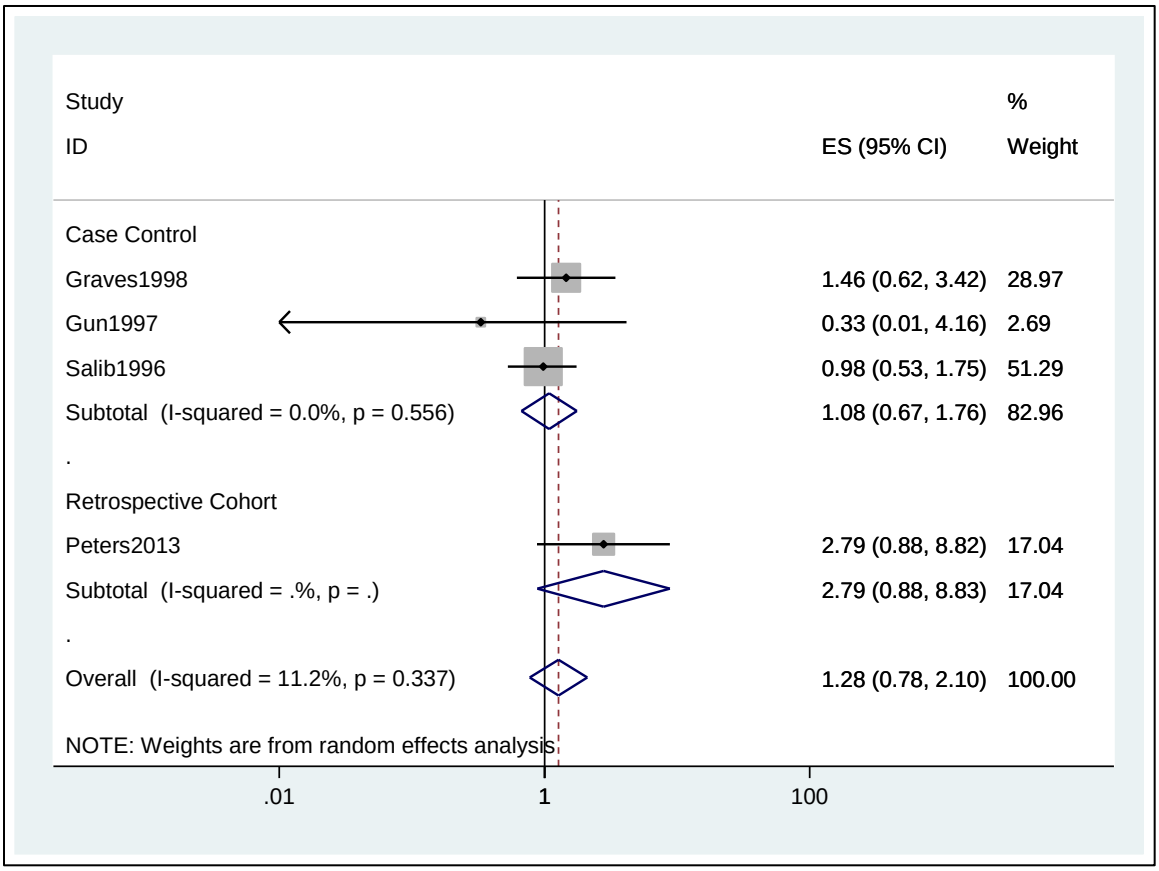

Figure 4-1 Forest Plot - Alzheimer's Disease

4.4.1.2 Other Neurological Disease

There were two case-control studies that examined neurological disease other than Alzheimer's disease. One study considered aluminum exposures and ALS by identifying cases with ALS (N=174) and comparing their exposure histories to matched referents (N=348). Exposure histories were ascertained by conducting interviews of possible occupational exposures to aluminum and other substances. Although an association was found between ALS and exposure to agricultural chemicals, no association was found for aluminum (McGuire *et al.*, 1997). The second study looked at cases of neurologist confirmed Parkinson Disease (PD) (N=130) compared to age-matched referents (N=260) and used interviews to estimate potential exposures to aluminum and obtain family and occupational history (Semchuk *et al.*, 1993). The study found that an increase in crude PD risk estimates associated with 4 of 5 variables (*i.e.*, family history, head trauma, occupational herbicide use, and family history of essential tremor), but no association between aluminum exposures and PD.

4.4.2 Other Diagnosable Conditions

Several of the studies retrieved from the literature looked at diagnosable conditions other than neurological diseases; however, there were too few studies on any individual condition to perform meta-analyses. A summary of the studies, including details on aluminum exposures and study quality is provided in Table 4-5. The outcomes have been grouped to facilitate analysis and dissemination of information. A discussion of study findings and general trends is also provided.

Table 4-5 Summary of results from studies of other outcomes

Study	Neuro	Cardio	Cancer	Other	Type of Exposure/ Occupation	Exposure Levels	Association found between outcome and Al?	Quality Assessment Rating
Ahmed *et al.*, 2013			X		50 Al industry workers (exposed to Al dust >8 h/d for > 1 yr)	Exposure expressed as duration of employment (years)	No association between Al dust exposure duration and lung cancer indicators	4/6: cases not randomly selected and referents drawn from different population
Aronson *et al.*, 1996			X		449 confirmed cases of prostate cancer (various substances, occupations and industries)	Qualitative - survey of occurrence, frequency and concentration (low, med, high)	No increased risk of prostate cancer for workers exposed to Al alloy dust	7/9: survey not blinded to case/control status
Botta *et al.*, 2006			X		Welders involved in manual metal arc welding, tungsten inert gas welding, and metal inert/active gas welding (>3 yrs)	Measured in blood and urine (rough estimates from Figure 1 and 2): mean = 70 µg/L in blood; mean = 25 µg/g in urine	Positive correlation between blood concentration of Al and DNA damage in lymphocytes; however no difference in blood Al between exposed and referents	5/6: subjects not randomly selected and from different facilities
Cantone *et al.*, 2011			X		63 steel production workers (employed at the plant >1 yr)	Mean and standard deviation Al concentration in air 8.50 ± 18.07 µg/m^3 (range: 0.40-84.07 µg/m^3)	Al not associated with histone modification (lung cancer biomarker)	5/6: subjects selected from different areas of the same plant; no identified referents
Cantone *et al.*, 2014		X			63 male workers, free of cancer and cardiopulmonary disease, working in a steel production plant for at least 1 year	Mean aluminum exposure in workplace air = 8.5 +/- 18.07 ug/m^3	None	5/6: non-random sampling, no reference group used
Cavallari *et al.*, 2008		X			26 male boilermaker construction workers exposed to metal-rich welding fumes	Al exposure measured as a component of $PM_{2.5}$. Median Al workplace air concentration = 4.58 ug/m^3	Statistically significant ($p<0.05$) decline in heart rate variability per 1 µg/m^3 increase in aluminum as component of $PM_{2.5}$.	4/6: risk of bias, as subject population were a selected group, no reference group used
Friesen *et al.*, 2009				X	5,770 male workers from four bauxite mines and three alumina refineries (58 excluded) employed for an average of 14.1 years	Used average company monitoring data Mean alumina exposure = 14.5 mg/m^3 per year	Cumulative alumina dust exposure may be associated with an excess risk of death from cerebrovascular disease but not for incident cancers	9/9: cohort representative of average target population
Fritschi *et al.*, 2008			X	X	5,828 male workers and 657 female workers in bauxite mine and alumina refinery followed up over 19 years	Total time spent working in production or maintenance jobs	Overall little evidence for increased cancer incidence or mortality in cohort	6/9: exposure levels not quantified, cohort representative of average target population
Hou *et al.*, 2011			X		63 steel production workers (employed at the plant >1 yr)	Mean and standard deviation Al concentration in air 8.50 ± 18.07 µg/m^3 (range: 0.40-84.07 µg/m^3)	Mean DNA methylation of four tumour suppressor genes (biomarker for cancer) showed one borderline significant association with Al (βstd = 0.14, 95% CI: 0.00-0.29) and three non-significant associations	4/6: subjects selected from different areas of the same plant; no identified referents

Table 4-5 Summary of results from studies of other outcomes

Study	Neuro	Cardio	Cancer	Other	Type of Exposure/ Occupation	Exposure Levels	Association found between outcome and Al?	Quality Assessment Rating
Hovatta *et al.*, 1998				X	27 employees of a refinery and polyolefin factory	Al concentration in semen of exposed population: 0.93 +/- 0.69 mg/kg in spermatozoa and 0.54 +/-0.61 mg/kg in seminal plasma	Al concentration in seminal plasma was higher in exposed group than control. A high concentration of Al in spermatozoa was correlated with decreased sperm motility	3/6: study population was a non-randomly selected group of workers, hence risk of selection bias possible, control population from a different source
Liu *et al.*, 2016				X	1493 coke oven workers (1282 males and 211 females) who worked more than 1 year in a coking plant	Al concentration measured in urine in different groups, including diabetes group, hyperglycemic group and normo-glycemic group (control)	Al was not significantly associated with any of the measured outcomes	6/6: representative sample population included for study, study controlled for age, BMI, gender and smoking
McGuire *et al.*, 1997	X				174 patients newly diagnosed with ALS and met eligibility criteria (several occupational circumstances, substances and industries)	Self-reported workplace exposures to 28 chemical agents (grouped: metals, solvents, agricultural chemicals)	No association between Al and ALS found	7/9: exposures were only determined *via* interview (not blind); no discussion of non-response rate
Parent *et al.*, 2000			X		99 new histologically confirmed oesophageal cancer cases (several occupational circumstances, substances and industries)	Qualitative survey of exposures to various substances (frequency and duration)	Odds ratios showed positive but non-significant associations between subjects ever exposed to alumina dust and oesophageal cancers	8/9: referents not well described and issues around confounding factors (*e.g.*, exposure to several agents)
Peters *et al.*, 2013	X	X			647 male miners who ever worked in an underground gold mine and were exposed to Al dust	Average worker exposure period = 10 years (range = 1-15 years); not quantified further	No protective effect against silicosis was observed from Al dust inhalation. Conversely, exposure to Al dust may possibly increase the risk of cardiovascular disease and dementia of the Alzheimer's type	7/9: non- random sampling, reference group from different source, indirect measurement of Al exposure, study controlled for age and smoking.
Schmid *et al.*, 1995				X	32 aluminum powder-production workers exposed for an average of 12.5 years	Al concentration measured in plasma, urine and bone mineral content in lumbar spine	Significantly increased average Al concentrations in production workers than control. No other significant differences between exposed and reference groups was found.	4/6: the study did not provide an adequate description of the sampling strategy
Semchuk *et al.*, 1993	X				130 patients with neurologist-confirmed idiopathic Parkinson Disease (various occupational histories and substance exposures)	Obtained exposure estimates *via* interview (occupational history and contact with various substances including aluminum)	Increased crude PD risk estimates associated with 4 of 5 variables (family history, head trauma, occupational herbicide use, and family history of essential tremor)	6/9: selection of cases not clearly described; exposures only self-reported; no discussion of non-response rate

Notes: 'neuro' = neurological outcomes; 'cardio' = cardiovascular outcomes; 'cancer' = cancer outcomes; 'other' = all other health outcomes

4.4.2.1 Cardiovascular Outcomes and Biomarkers

Three studies investigated cardiovascular outcomes of aluminum exposure. Cantone *et al.* (2014) studied workers from a steel production plant, Cavallari *et al.* (2008) selected boilermaker construction workers exposed to metal-rich welding fumes as participants, and Peters *et al.* (2013) studied miners exposed to aluminum dust as a prophylaxis. Both studies quantified aluminum exposure as a measure workplace air concentration. The median aluminum exposure from personal samples was 2.05 µg/m^3 and 4.58 µg/m^3 in the two studies, respectively. Cantone *et al.* (2014) did not find an association between aluminum exposure and extracellular histone modification or any cardiovascular-related outcomes. Cavallari *et al.* (2008) found a statistically significant inverse relationship between heart rate variability and increasing aluminum air concentration, however, the only consistent exposure-response relationship observed among the metal fumes studied was for manganese. Neither study compared the exposed population to a reference group.

As summarized previously in Section 4.3, Peters *et al.* (2013) found aluminum dust inhalation did not affect the risk of cerebrovascular mortality, while there was some indication of an increased risk of cardiovascular mortality among miners with a history of aluminum dust exposure over those who never inhaled aluminum (SMR=1.30, 95%CI: 1.00 to 1.70).

4.4.2.2 Cancer and Biomarkers of Cancer

There were seven studies that looked at cancer or biomarkers of cancer as their health endpoint (Ahmed *et al.*, 2013; Aronson *et al.*, 1996; Botta *et al.*, 2006; Cantone *et al.*, 2011; 2009; Fritschi *et al.*, 2008; Hou *et al.*, 2011 and, Parent *et al.*, 2000). There were two case-control studies looking at prostate cancer (Aronson *et al.*, 1996) and oesophageal cancer (Parent *et al.*, 2000), one retrospective cohort study of an Australian bauxite mining/Al refining cohort looking at all incident cancers (Fritschi *et al.*, 2008) with the remaining studies focusing on cancer indicators or biomarkers (DNA damage, histone modification, DNA methylation, *etc.*). The majority of the studies selected subjects or cases with occupational exposure to aluminum *via* inhalation of dusts or fumes. Exposure characterization was highly variable with some studies relying on qualitative descriptions of exposure or duration of employment (Ahmed *et al.*, 2013; Aronson *et al.*, 1996; Fritschi *et al.*, 2008; Parent *et al.*, 2000), while others collected samples of air (Cantone *et al.*, 2011; Hou *et al.*, 2011), or blood and urine (Botta *et al.*, 2006). Neither case-control study reported significant odds ratios related to aluminum exposure and prostate cancer (Aronson *et al.*, 1996) or oesophageal cancer (Parent *et al.*, 2000). Fritschi *et al.* (2008) reported the incidence of all cancers combined as similar to the Australian rate; the cohort had a borderline higher risk of melanoma (although no dose-responses were seen) and also an increased risk of mesothelioma which was associated with exposures outside the aluminum industry. Out of the four studies investigating potential biomarkers of cancer, two found limited evidence of association or correlation between aluminum exposure and DNA damage although the biologic significance of those findings is unknown (Botta *et al.*, 2006; Hou *et al.*, 2011).

4.4.2.3 Other Effects

Diabetes

One study (Liu *et al.*, 2016) investigated the association of urinary metal levels, including aluminum, with type 2 diabetes risk in coke oven workers exposed to aluminum for at least one year. Health outcomes studied included diabetes, hyperglycemia, and normoglycemia. Aluminum concentration in urine (in µg/L) among different groups was: Diabetes group: 60.36 (25th - 75th percentile: 32.42-90.22); Hyperglycemia group: 60.85 (33.14-94); Normoglycemia

group: 51.68 (30.95-90.67). The normoglycemic group was considered to be the reference group and compared to the diabetes and hyperglycemic groups. The study found that although urinary copper and zinc were positively associated with risk of diabetes and hyperglycemia, aluminum exposure was not significantly associated with any of the measured outcomes.

Mortality

Three studies included mortality as an endpoint of effects of aluminum exposure. The studies used workers from bauxite mines and alumina refineries (Fritschi *et al.*, 2008 and Friesen *et al.*, 2009) as subjects, or underground gold miners exposed to aluminum dust as a prophylaxis (Peters *et al.*, 2013). Two of the studies measured aluminum exposure only as total time spent in the respective participant professions, and one study obtained workplace aluminum concentrations in air. Fritschi *et al.* (2008) found that overall, there was no significant relationship between alumina exposure and mortality risk. However, Friesen *et al.* (2009) reported suggestive, but inconclusive evidence of associations between bauxite exposure and non-malignant respiratory disease mortality and between alumina exposure and cerebrovascular disease mortality. The associations were based on very few cases and therefore may be chance findings.

Osteodystrophy

One study used determination of bone mineral content by X-ray absorptiometry in the evaluation of osteodystrophy among workers exposed to aluminum powders (Schmid *et al.*, 1995). The study participants were aluminum-powder production workers exposed for an average time period of 12.5 years. They measured aluminum concentration in participants' blood, urine and the bone mineral content of the lumbar spine. The aluminum air concentrations averaged to a mean of 12.1 mg/m^3. The study also included 32 non-exposed workers from same factory as the reference group. The health outcomes studied include alkaline phosphatase levels (U/l), bone mineral content (g), and bone mineral density (g/cm^2). The study concluded that although there was significantly increased average aluminum concentration in production workers than control, no other significant differences between exposed and reference groups were found.

Reproductive effects

One study (Hovatta *et al.*, 1998) investigated the concentrations of aluminum and other metals (lead and cadmium) in seminal plasma and spermatozoa, as well as semen quality in employees of a refinery and polyolefin factory in Finland. Forty-five consecutive sperm donor candidates from a sperm bank were selected as the reference group. Exposure was ascertained *via* collection of semen samples for measurement of aluminum in spermatozoa and seminal plasma of study participants and referents. While there was an overall significant correlation between aluminum concentration in spermatozoa and sperm motility when the factory workers and control population were analyzed together, aluminum concentrations in semen were higher in the reference group than the factory workers.

4.5 Other Studied Health Outcomes

As summarized in Section 4.1, the literature selection steps identified a large number of studies where aluminum exposed workers were administered various neuropsychological or lung function tests. The purpose of such studies was not to assess the risk of specific (*i.e.*, diagnosable) health outcomes but rather to more broadly examine the potential effects on neurobehavioral or respiratory performance. Results for neuropsychological and lung function test outcomes are provided in Sections 4.5.1 and 4.5.2, respectively.

4.5.1 Neuropsychological Outcomes

The studies investigating the neurobehavioral performance of workers occupationally exposed to aluminum are primarily cross-sectional in design (*i.e.*, data collected at a single point in time). In total, there are 21 studies with cross-sectional data from neuropsychological testing. A few longitudinal studies with neuropsychological test data (Kiesswetter *et al.* 2007, Kiesswetter *et al.* 2009, and Letzel *et al.* 2000) are also included in this count by treating them as cross-sectional and using data only from the first examination.

Neuropsychological tests were not consistently applied across studies. To determine the test outcomes that are available for quantitative *versus* qualitative analysis, the neuropsychological tests were tabulated by study ID (see Table 4-6). Table 4-6 is organized according to the main cognitive domain assessed (*e.g.*, psychomotor function, attention, *etc.*) according to the classifications of Akila *et al.* (1999) and others. To perform quantitative meta-analysis on an outcome, means and standard deviations must be presented in the published study report. The Table shows an empty circle if a test was performed but the study authors did not present the results in a manner that can be combined with other study results, and a check mark if the data meets the criteria for meta-analysis (check marks are summed in the “Count” column). As described in the following section, the analysis depends on the frequency of each test.

Table 4-6 Summary of Neuropsychological Tests tabulated by Study ID

Neuropsychological Test	Count	Akila 1999	Bast-Pettersen 1994	Bast-Pettersen 2000	Camerino 1993	Deschamps 2009	Dick 1997	Giorgianni 2014	Guo 1999	Hanninen 1994	Iregren 2001	Kiesswetter 2007	Kiesswetter 2009	Letzel 2000	Lu2014	Polizzi 2002	Rifat 1990	Riihimaki 2000	Sim1997	Yang 1998	Yang 2015	Zawilla 2014
PSYCHO MOTOR FUNCTION																						
tapping speed (10 sec)	2	✓									✓											
tapping speed (20 sec)	2											✓	✓									
tapping endurance (60 sec)	1										✓											
Santa Ana dexterity	3	✓							✓											✓		
simple reaction time	7	✓		✓	o				✓	o	✓	✓	✓							✓		
steadiness	2											✓	✓									
line tracing	2											✓	✓									
aiming	2											✓	✓									
pursuit aiming	2				o				✓											✓		
static steadiness	2		✓	✓																		
pegboard	1										✓											
Luria-Nebraska motor scale	1										✓											
tracking	1										✓											
continuous performance test	1			✓																		
ATTENTION																						
digit span	8	✓			o	✓			✓	o	✓	✓	✓	o				✓		✓		
digit symbol	4	✓			o				✓					o				✓		✓		
symbol digit coding	1										✓											
interference call (stroop)	1	✓																				
Stroop test	1	✓						o														
dual task	2	✓																✓				
switching attention	1											✓	✓									
Bourson-Wiersma dot cancellation	1																	✓				
attention matrices	0							o														
sustained attention	0													o								
VERBAL																						
similarities recall	1	✓																				
synonyms[1]	3	✓									✓							✓				
vocabulary	0													o								
VISUOSPATIAL AND CONSTRUCTION																						
embedded figures	1	✓																				
block design - easy/hard items	1	✓																				
block design	2											✓	✓	o								
MEMORY AND LEARNING																						
paired associate	1	✓																				
memory for design	2	✓																✓				
interference recall	1	✓																				
symbol-digit substitution (SDS) test	2											✓	✓									
visual recognition	0				o																	
serial digit learning	0				o																	
syndrome short	0													o								
Wechsler memory scale	0							o														

Table 4-6 Summary of Neuropsychological Tests tabulated by Study ID

Neuropsychological Test	Count	Akila 1999	Bast-Pettersen 1994	Bast-Pettersen 2000	Camerino 1993	Deschamps 2009	Dick 1997	Giorgianni 2014	Guo 1999	Hanninen 1994	Iregren 2001	Kiesswetter 2007	Kiesswetter 2009	Letzel 2000	Lu2014	Polizzi 2002	Rifat 1990	Riihimaki 2000	Sim1997	Yang 1998	Yang 2015	Zawilla 2014
symbol learning	0									○												
associative learning	0									○												
Benton visual retention	2								✓											✓		
SCREEN FOR COGNITIVE IMPAIRMENT																						
Standard progressive matrices test	2											✓	✓									
MMSE	4					✓									✓	✓	○				✓	
clock drawing test	2					✓										✓						
Addenbroke's cognitive examination	1																					✓
trail making	2											✓	✓	○								
trail making test A	1		✓																			
trail making test B	1		✓																			
Raven's coloured progressive matrices	0																○					
Symbol digit modalities test	0																○					
PHYSICAL DOMAIN																						
tremor	1						○				✓											
postural stability test	1																		✓			
auditory evoked event-related potential	1															✓						
Total number of unique tests	**52**	**15**	**3**	**3**	**6**	**3**	**1**	**3**	**6**	**5**	**10**	**11**	**11**	**7**	**1**	**2**	**3**	**6**	**1**	**6**	**1**	**1**

Legend: ✓: means and standard deviations for test are presented in report; ○: means and standard deviations are not available (results presented in some other way)

[1] Various synonym tests applied so measures were inconsistent

4.5.1.1 Meta-Analysis of Neuropsychological Tests

Tests with reported means and standard deviations from at least three studies had sufficient information to conduct a meta-analysis of effect size, or the mean difference (MD) between the values of an exposed and reference group. There are a total of five different neuropsychological tests that meet the criteria for a common outcome (Table 4-7). Some of the tests measure different variables (dominant *versus* non-dominant hand by the Santa Ana dexterity test) for a total of seven neuropsychological test variables. Three of the variables relate to psychomotor function and three to attention. The Mini–Mental State Examination (MMSE) is a screening questionnaire that is used extensively in clinical and research settings to measure cognitive impairment and is commonly used in medicine to screen for dementia.

Table 4-7 Neuropsychological Outcome Variables to Include in Meta-Analysis

Cognitive Domain	Outcomes	Study IDs	Count
Psychomotor Function	Santa Ana Dexterity		
	Dominant hand	Guo1999, Akila1999, Yang1998	3
	Non-dominant hand	Guo1999, Akila1999, Yang1998	3
	Simple Reaction Time	Guo1999, Akila1999, Bast-Pettersen2000, Yang1998, Iregren2001, Kiesswetter2007, Kieswetter2009, Sim1997	8
Attention	Digit Span		
	Forward	Guo1999, Akila1999, Riihimaki2000, Yang1998, Deschamps2009, Iregren2001, Kiesswetter2007, Kieswetter2009	8
	Backward	Guo1999, Akila1999, Yang1998, Kiesswetter2007, Kieswetter2009	5
	Digit symbol	Guo1999, Akila1999, Riihimaki2000, Yang1998	4
Cognitive Impairment	MMSE	Lu2014, Deschamps2009, Polizzi2002	3

For each outcome and study listed in the table above, the abstracted data (*i.e.*, means, standard deviations, exposure data, and other relevant study characteristics) were imported into Review Manager (RevMan) Software for meta-analysis. For studies where the outcome data were reported for subgroups (*e.g.*, Akila *et al.* (1999) reported all results separately for a low exposure and high exposure group), each subgroup is included as a separate study to avoid excluding valuable information. In total, there were 21 studies or study subpopulations which reported a comparison of neurological outcomes suitable for meta-analysis (Table 4-8). This includes three study populations without reference group data. Overall, the studies included an average of 55 subjects in the exposed group and 27 subjects in the reference group. There were no meaningful differences between the exposed and reference groups for age (average of 42 to 43 years), education level (average of 9 years) or percentage of smokers (70 to 72%). There were important differences in aluminum levels in terms of blood aluminum (exposed 2.4-times higher than referents), urine aluminum (exposed 7.6-times higher than referents), urine aluminum adjusted for creatinine levels (exposed 4.4-times higher than referents) and serum aluminum (exposed 5.3-times higher than referents).

Table 4-8 Study Characteristics for Meta-Analysis of Neurological Outcomes

Study Characteristic	Exposed		Referents		Exposed minus Referents
	N	Mean (min, max)	N	Mean (min, max)	
Study size, N	21	55 (16,184)	18	27 (13,70)	28
Age, years	21	43 (30,67)	18	42 (30,68)	1[ND]
Education, years	12	9 (5,11)	9	9 (6,11)	0 [ND]
Smoking percentage	9	70 (52,76)	6	72 (43, 86)	-2[ND]
Al Air (mg/m^3)	8	4.6 (0.5, 14.7)			
Al blood (µg/l)	6	6.4 (1, 12.5)	6	2.7 (1, 5.9)	3.7 (2.4x)

Table 4-8 Study Characteristics for Meta-Analysis of Neurological Outcomes					
Study Characteristic	**Exposed**		**Referents**		**Exposed minus Referents**
	N	**Mean (min, max)**	**N**	**Mean (min, max)**	
Al urine (µg/l)	15	77.1 (4, 269.3)	14	10.1 (3, 15.1)	67.1 (7.6x)
Al urine adj. (µg/g creat.)	8	45.8 (4.2, 110.7)	8	10.4 (4.7, 17.7)	35.4 (4.4x)
Al serum (µg/l)	8	25.2 (1.7, 78.4)	5	4.8 (1.3, 10.0)	20.4 (5.3x)
Santa Ana Dexterity-Dominant Hand	6	36.9 (18.1, 47.3)	6	39.0 (19.9, 49.2)	-2.1
Santa Ana Dexterity-non-Dominant Hand	6	34.5 (17.0, 44.1)	6	35.1 (18.0, 43.4)	-0.6
Simple Reaction Time	13	277 (221, 368)	13	264 (223, 342)	+13
Digit Span Forward	12	7.9 (5.7, 11.6)	12	8.2 (5.4, 12.6)	-0.3
Digit Span Backward	8	5.0 (4.3, 6.4)	8	5.2 (4.4, 6.4)	-0.2
Digit Symbol	6	42.1 (33.8, 51.9)	6	46.7 (26.2, 52.1)	-4.6
Mini–Mental State Examination (MMSE)	6	27.3 (26.1, 28.3)	3	27.9 (26.9, 28.8)	-0.6

[ND] No meaningful difference in baseline characteristics between exposure and reference groups; x: times

The results for the seven outcomes with sufficient data for meta-analysis are described one at a time below.

Santa Ana Dexterity Dominant Hand (SADDH)

There were three individual studies and six comparisons total which provided sufficient comparative data for meta-analysis of SADDH data. The Santa Ana test is a test of manual dexterity which requires rapid eye-hand coordinated movements. The equipment consists of a base plate with 48 square holes and equal number of fitted pegs. Participants are asked to turn each peg 180° as fast as possible in 30 seconds and the unit of measure is the number of turned pegs.

The meta-analysis of SADDH resulted in an overall effect of -1.87 (95%CI: -2.74 to -0.99), p<0.01 with an absence of heterogeneity I^2=0%, p=0.93 (Figure 4-2). Within each study the mean values of the number of pegs rotated by exposed workers was highest in the Akila *et al.* (1999) study (47 pegs) because the study reported the sum of two tests, lower in the Guo *et al.* (1999) study (32 to 39 pegs), and lowest in the Yang *et al.* (1998) study (18 pegs). However, the difference in the number of pegs rotated between the exposed and reference groups was ranged between -0.9 and -3.1 pegs. The interpretation of the MD in the number of pegs is limited without well-established normative data or a clinically defined minimally important difference. However, a difference of -1.87 pegs *versus* the reference group average of 39.0 pegs is approximately a 5% decrease (1.87/39.0 = 5.1%).

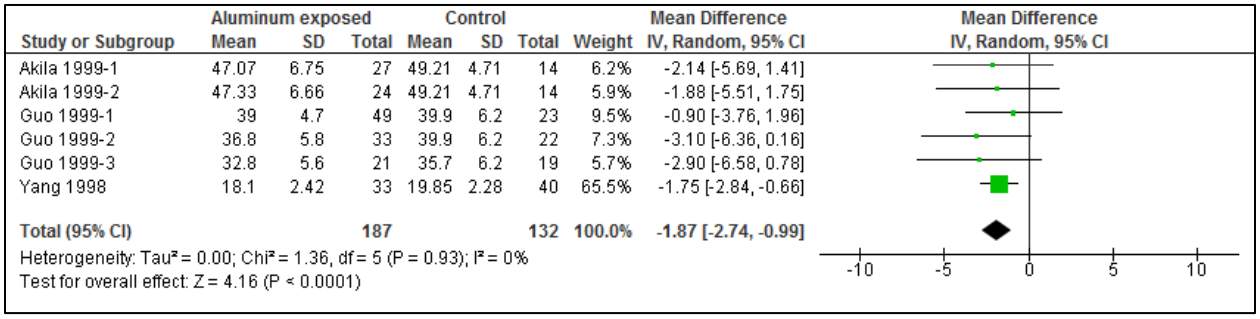

Figure 4-2 Forest Plot, Santa Ana dexterity dominant hand (count)

Meta-regression was used to investigate differences by study characteristics, or covariates, that may influence the size of the MD for SADDH. Because only a subset of SADDH studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in SADDH effect size for age, education,

smoking, or Al urine. There was insufficient data available to analyze the effect of aluminum in blood, aluminum in urine adjusted for creatinine, or aluminum in serum on the outcome (see Meta-regression output in Appendix E-1).

Santa Ana dexterity non-dominant hand (SADNDH)

There were three individual studies and six comparisons total which provided sufficient comparative data for meta-analysis of SADNDH. The overall MD SADNDH was -0.83 (95%CI: -1.73 to 0.06), p =0.07 with an absence of heterogeneity I^2=0%, p=0.69 (Figure 4-3). Therefore, the MD in the number of pegs is less than one peg. All individual studies had small differences between exposed and reference groups, ranging from -2.3 pegs (95%CI: -5.34 to 0.74) (Guo 1999-3), and +0.72 pegs (95%CI: 0.12 to 1.32). A difference of -0.83 pegs *versus* the reference group average of 35.2 pegs is approximately a 2% decrease (0.83/35.2 = 2.4%).

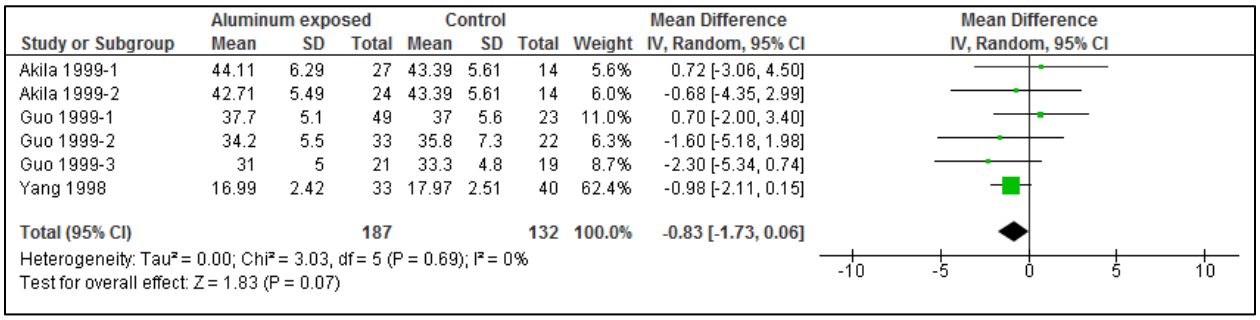

Figure 4-3 Forest Plot, Mean Santa Ana dexterity non-dominant hand (count)

Meta-regression was used to investigate differences by study characteristics that may influence the size of the MD for SADNDH. Because only a subset of SADNDH studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in SADNDH effect size for age, smoking, or aluminum in urine levels. The number of years of education significantly impacted the mean difference of SADNDH. A one year increase in years of education in the exposure group relative to the reference group increased the number of pegs rotated by subjects in the exposure group in the non-dominant hand by 1.55 (95%CI: -0.20 to 3.31) p =0.070. The effect of education is larger than the overall mean differences, indicating level of education is more significant than aluminum exposure for SADNDH. There was insufficient data available to analyze the effect of aluminum in blood, aluminum in urine adjusted for creatinine, or aluminum in serum on the outcome (see Meta-regression output in Appendix E-2).

Mean Simple Reaction Time (SRT) to a visual stimulus

Simple reaction time (SRT) measures how fast a person reacts to visual stimuli. There were eight studies, which included 13 comparisons, providing sufficient comparative data for the meta-analysis of simple reaction time. Unlike the other neurological outcomes where a larger value indicates better performance, an increased simple reaction time indicates poorer performance. The overall effect is a statistically significant increase in simple reaction time +10.97 milliseconds (95%CI: 4.50 to 17.44), p<0.01, with low heterogeneity, I^2=21% (p=0.23) (Figure 4-4).

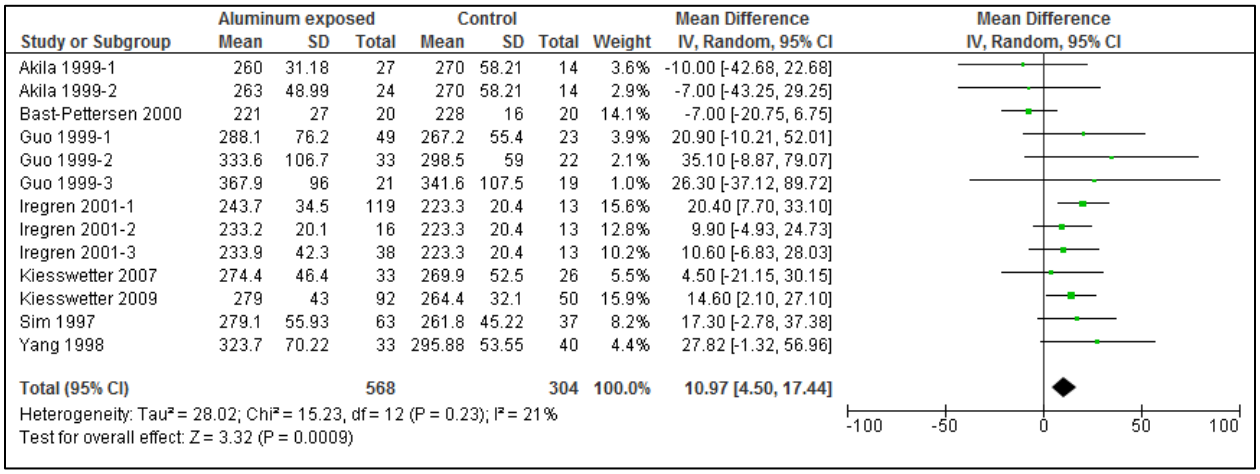

Figure 4-4 Forest Plot, Mean simple reaction time (msec)

Based on the forest plot, most of the studies have increases in SRT, with two studies reaching statistical significance for slower reaction time among aluminum exposed groups, Iregren 2001-1 and Kieswetter 2009. The Iregren *et al.* (2001) study was stratified by type of occupational exposure with smelters (Iregren 2001-1, N=119), flake powder production workers (Iregren 2001-2, N=16), and welders (Iregren 2001-3, N=38). Probably due to sample sizes, only the largest group had a statistical increase in simple reaction time, 20.40 msec (95%CI: 7.70, 33.10). The other study Kieswetter *et al.* (2009) included welders in Germany with an increase in simple reaction of +14.60 msec (95%CI: 2.10, 27.10). The study by Akila *et al.* (1999) reported data by low exposure (Akila 1999-1) and high exposure (Akila 1999-2) for welders in Finland, both of which reported faster reaction time for the aluminum exposed groups.

The overall increase in simple reaction time between the exposed relative to the reference group of +10.97 msec should be compared to the average reaction time among the reference group of 264 msec. This represents an increase of 4.0% (10.97/264) in reaction time in milliseconds, a relatively minor increase.

Meta-regression was used to investigate differences by study characteristics that may influence the size of the MD for SRT. Because only a subset of SRT studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. Both years of education and urine aluminum levels were found to significantly impact the mean difference of SRT. A one year increase in years of education in the exposure group relative to the reference group decreased simple reaction time in the exposure group by -31.9 msec (95%CI: -66.5 to 2.62) p =0.064. The effect of education is larger than the overall mean differences, indicating level of education is more significant than aluminum exposure for SRT. Counterintuitively, urine aluminum was a significant risk factor in the reduction in the mean difference of simple reaction time, with an increase of one unit of urine aluminum in the exposure group reducing the mean difference of simple reaction time by -0.09 msec (95%CI: -0.20, to 0.02), p =0.094. Urinary aluminum adjusted for creatinine content, generally recognized as a better measure of Al exposure, did not significantly change the SRT effect size. There was insufficient data available to analyze the effect of aluminum blood or aluminum serum on the outcome (see Meta-regression output in Appendix E-3).

Digit span forward

The Digit span test is a test of short term memory comprised of progressively longer sequences of random numbers read aloud. The subject has to repeat each sequence exactly as heard. The unit of measure is the count of recalled digits. There were eight studies, which included 14 comparisons, providing sufficient comparative data for the meta-analysis of digit span forward results. The overall effect is a reduction in counts of -0.11 (95%CI: -0.38 to 0.16), p =0.44, with low heterogeneity, I^2=39% (p=0.07), indicating a non-significant decrease among those exposed to aluminum (see Figure 4-5). The individual studies reported a MD ranging from -1.3 (Iregren 2001-3) to +0.85 (Riihimaki 2000-2). The overall effect represents a 1% decline (-0.11/ 8.2 count) relative to the reference group average.

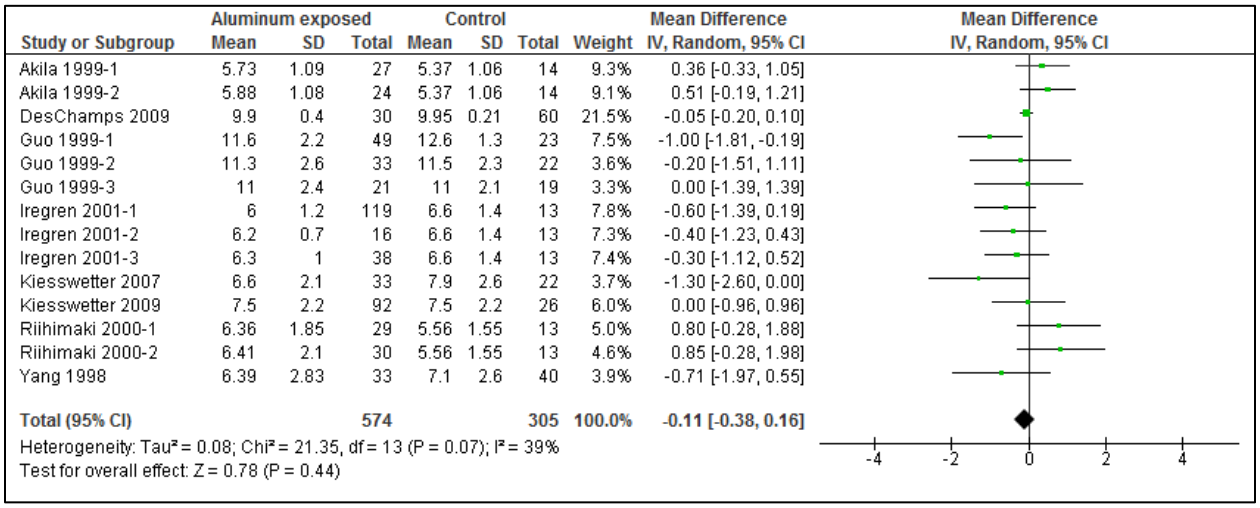

Figure 4-5 Forest Plot, Mean digit span forward (count)

Meta-regression was used to investigate differences by study characteristics, or covariates, that may influence the size of the MD for digit span forward. Because only a subset of digit span forward studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in digit span forward effect size for age, education, smoking, aluminum in blood, aluminum in urine, or aluminum in urine adjusted for creatinine. There was insufficient data available to analyze the effect of aluminum in serum on the outcome (see Meta-regression output in Appendix E-4).

Digit span backward

There were five studies, which included eight comparisons, providing sufficient comparative data for the meta-analysis of digit span backward results. The overall effect is a non-significant reduction in digits counted of -0.16 (95%CI: -0.43 to -0.10), p<0.01, with an absence of heterogeneity I^2 = 0% (p=0.83). The studies reported a mean difference in the number of digit span backward ranging from -0.70 (Kieswetter 2007) to +0.10 (Guo 1999-1). The overall effect represents a 3% decline (-0.16/5.2 count) relative to the reference group average.

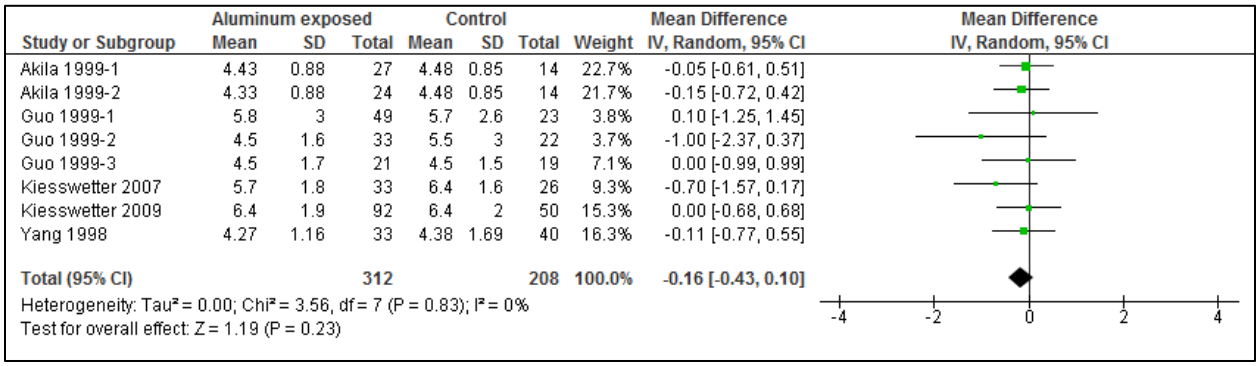

Figure 4-6 Forest Plot, Mean digit span backward (count)

Meta-regression was used to investigate differences by study characteristics, or covariates, that may influence the size of the MD for digit span backward. Because only a subset of digit span backward studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in digit span backward effect size for age, education, aluminum in urine, or aluminum in urine adjusted for creatinine. There was insufficient data available to analyze the effect of smoking, aluminum in blood, or aluminum in serum on the outcome (see Meta-regression output in Appendix E-5).

Digit Symbol

In this test, the subject is required to fill in the blank spaces with symbols associated with the numbers 1 to 9. The symbols to be substituted are always visible in a key printed above the blank. The score of this test is the number of blank spaces filled within the time limit of 90 seconds. There were four studies, which included 8 comparisons, providing sufficient data for the meta-analysis of digit symbol. The overall effect was a statistically significant reduction in the number of symbols -4.69 (95%CI: -6.87, -2.51), p<0.01, with low heterogeneity I^2=7% (p=0.38) (see Figure 4-7). All of the studies reported a mean decrease in the number of digit symbols. The study by Guo *et al.* (1999), which included workers involved in electrolysis, smelting or welding exposed to aluminum in China, provided data by age groups: 25-34 years (Guo 1999-1, N=49), 35-44 years (Guo 1999-2, N=33), 45-60 years (Guo 1999-3, N=21). Most of the test outcomes for Guo *et al.* (1999) (SADDH, SADNDH, SRT, and DSF) did not show any difference and it was only the outcome digit symbol and digit span backward where there was a similar variation by age groups. However, the difference between subgroups is not statistically meaningful.

Unlike other neurological outcomes, the mean difference in digit symbol count is a larger effect relative to the mean of the reference group level, a decrease of 10% (-4.69/46.7). The digit symbol count has been a topic of research to attempt to establish normative data. Two studies were designed to provide normative values, a large community survey (Joy *et al.*, 2004) and a recent meta-analysis of 138 studies (Hoyer *et al.*, 2004). The data suggest that both the values for digit symbol count for the reference group and exposed group in the meta-analysis are lower than the community sample mean of 74.25 ± 15.50 (Joy *et al.*, 2004, Table 4-9 below) and the mean value for younger adults of 69.3 (range 51.2–82.7) (Hoyer *et al.* 2004), and similar to the older adults mean of 48.2 (range 38.8–66.8) (Hoyer *et al.* 2004). Thus, while we see difference in the digit symbol count between our exposed and referent groups, it appears that both groups have lower than normal values.

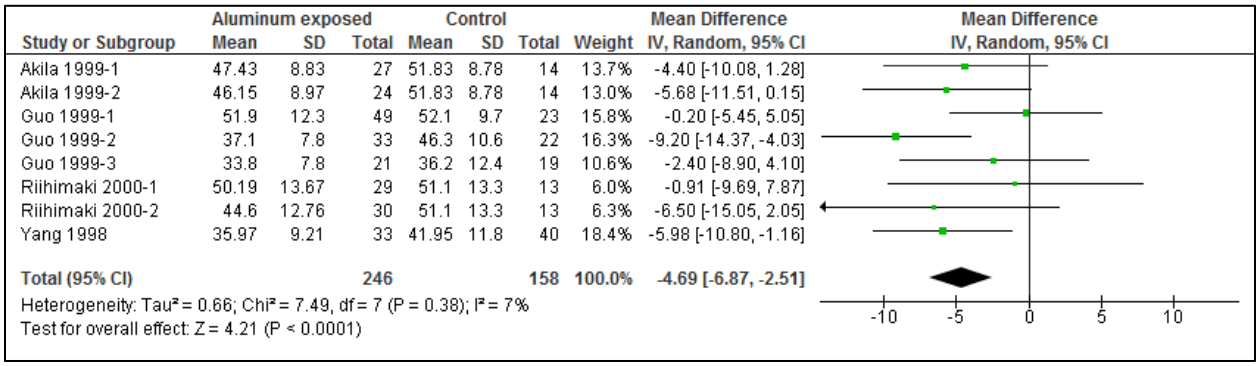

Figure 4-7 Forest plot Mean digit symbol (count)

Table 4-9 Normative data for Digit Symbol test (Joy *et al.*, 2004)

Test	Younger[a]		Older[b]	
	High school[c]	College[d]	High school[c]	College[d]
Digit Symbol	74.25 ± 15.50	80.26 ± 14.76	47.04 ± 17.06	56.53 ± 14.17
Symbol Copy	116.18 ± 18.66	122.70 ± 13.86	82.37 ± 26.71	94.05 ± 23.67
Pairing	13.52 ± 3.91	13.52 ± 4.02	8.68 ± 4.09	9.98 ± 4.20
Free Recall	7.45 ± 1.26	7.56 ± 1.31	6.24 ± 1.58	6.72 ± 1.40

[a] Ages 16–49
[b] Ages 50–89
[c] ≤12 years of education
[d] >12 years of education

Meta-regression was used to investigate differences by study characteristics, or covariates, that may influence the size of the MD for digit symbol. Because only a subset of digit symbol studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in digit symbol effect size for age, education, smoking, or aluminum in urine. There was insufficient data available to analyze the effect of aluminum in blood, aluminum in urine adjusted for creatinine or aluminum in serum on the outcome (see Meta-regression output in Appendix E-6).

We further investigated the effect of covariates for the digit symbol outcome because the meta-analysis suggested that the mean difference may be meaningful. Based on the meta-regression of each risk factor, the mean difference in digit symbol count was still significantly different between exposure and reference groups, being represented by the constant (_cons) in the regression output, even after adjusting for differences in age (p=0.010), education (p=0.090), and urine aluminum (p=0.006). However, after adjusting by level of smoking the mean difference of digit symbol count was no longer significant (p=0.214) (see Meta-regression output in Appendix E-6). The data in the studies was not adjusted for by smoking, so this factor may explain the difference in results.

Mini–Mental State Examination (MMSE) score

There were three studies available for the meta-analysis of MMSE scores. The overall effect is a statistically significant decrease in MMSE -1.17 (95%CI: -2.03 to -0.31), p<0.01, with high heterogeneity I^2=75% (p=0.02) (Figure 4-8). The high heterogeneity was driven by the variation in the mean effect across studies with two studies reporting statistically significant effects (Lu 2014 and Polizzi 2002) and one study reporting a non-statistically significant effect (Deschamps 2009). The overall effect can be compared to published information about the clinical meaning of MMSE scores. Burback *et al.* (1999) estimated a minimally clinically important difference

(MCID) for the MMSE to be 3.7 for Alzheimer's disease. In addition, normative data for MMSE considers 24 to 30 to be normal function. The three studies' results for both exposed and control subjects are within the range of normal values.

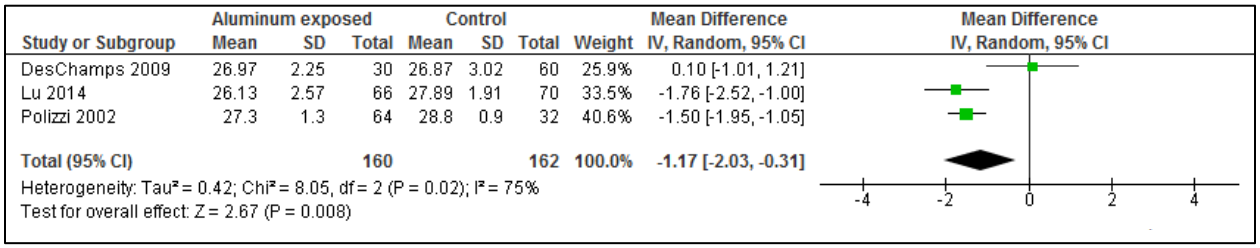

Figure 4-8 Forest plot Mean Mini–Mental State Examination (MMSE) score

Meta-regression was used to investigate differences by study characteristics that may influence the size of the MD for MMSE. There were no significant changes in MMSE scores by age. There was insufficient data available to analyze the effect of education, smoking, aluminum in blood, aluminum in urine, or aluminum in serum on the outcome (see Meta-regression output in Appendix E-7).

4.5.1.2 Additional Analysis of Neuropsychological Tests

As discussed in Section 4.3.2, many individual neuropsychological tests were not applied frequently enough across studies to be pooled via meta-analysis. The studies that did not fit into the meta-analysis are equally as important to take into account when considering the weight of the evidence. In order to consider the results from all neuropsychological testing performed, the number of significant differences between aluminum-exposed and control populations out of the total number of tests performed in each study were tabulated in Table 4-10. The table presented each study's results according to occupational setting, study characteristics including number of participants, exposure metrics, and neuropsychological testing domain (*i.e.*, psychomotor function, attention, verbal, visuospatial and construction, memory and learning, cognitive impairment, and physical domain). Again, these neuropsychological studies are almost all cross-sectional with exception of Letzel *et al.* (2000), Kiesswetter *et al.* (2007), and Kiesswetter *et al.*, (2009), comparing the performances of aluminum-exposed workers to unexposed reference groups. Table 4-10 shows that mainly aluminum production workers and welders were examined in the studies.

Table 4-10 Significant Tests (between Exposed and Unexposed Group) According to Testing Domain and Measures of Exposure

Study ID	*n* exposed (referents)	Exposure Metrics (mean)						Testing Domain (number of significant tests/total number of tests)						
		Yrs.	Al-A	Al-U	Al-U_c	Al-B	Al-S	Psychomotor function	Attention	Verbal	Visuospatial & Construction	Memory & Learning	Cognitive Impairment	Physical Domain
Aluminum Production														
Bast-Pettersen1994 (1)	14 (16)	19.2		12.6			3.6	1/2					0/2	
Bast-Pettersen1994 (2)	8 (16)	19.6		9.9			4.1	0/2					0/2	
Guo1999	104 (64)	16.6	5.3	29.9	41.79			1/9	2/3			0/1		
Iregren2001 (1)	16 (39)	8		83.0	59.0	9.0		1/18	0/3	0/1				
Letzel2000	32 (30)	12.6		110	87.6	8.7			0/3	0/1	0/1	0/1	0/1	
Sim1997	63 (37)	>10	0.5					0/17		0/1				0/6
Yang1998	33 (40)	9.9	1.9				1.7	2/7	1/4			1/1		
Zawilla2014	54 (51)	21.7	10.3				20.3						1/1	
Welding														
Akila1999	51 (28)			60.7/270				0/6	5/21	1/5	2/3	1/9		
Bast-Pettersen2000	20 (20)	8.1	1.2	50.2				$4/6_1$						
Giorgianni2014	86 (90)	15.8	19.5				24.2		1/2			1/1		
Iregren2001 (2)	38 (39)	15		22.0	24.0	3.0		0/18	0/3	0/1				
Kiesswetter2007	44 (37)	14.8	7.3	186	111	13		0/5	0/2		1/1	0/1	0/2	
Kiesswetter2009	98 (50)	8.8	0.8	77.4	43	9.3		0/5	0/2		0/1	0/1	0/2	
Riihimaki2000	59 (25)	12.3		54/237			13.5		4/6	1/1		1/1		
Aluminum Salvage/Recycling														
Deschamps2009	30 (60)	6.5	2.2	11.0		3.8			0/1				0/2	
Polizzi2002	64 (32)	30.7	14.7				14						5/5	1/1
Smelting														
Lu2014	66 (70)	30.2					25.2						1/1	
Iregren2001 (3)	119 (39)	15		4.0	4.2	1.0		4/18	0/3	0/1				
Mining														
Rifat1990	261 (346)												1/1	

Al-A: aluminum in air (mg/m^3), Al-U: aluminum in urine (µg/l), Al-Uc: aluminum/gram creatinine in urine (µg/g creat.), Al-B: aluminum in blood (µg/l), Al-S: aluminum in serum (µg/l)
Bast-Pettersen1994- two Al exposure groups compared to single reference group (1) potroom workers, (2) foundry workers
Iregren2001 - three Al exposure groups compared to since reference group (1) flake powder production, (2) welders, (3) smelters
[1] Exposed performed better than referents on 4 measures of the static steadiness test

The collection of exposure metric data differs considerably between studies. Most studies report the average duration of exposure to aluminum, showing a range from 8.0 to 30.7 years. Fewer than half of studies sampled aluminum in workplace air. Studies with aluminum air data show lower concentrations to be in the range of 0.5 to 5.3 mg/m^3 (Bast-Petterson *et al.*, 2000, Deschamps *et al.*, 2009, Guo *et al.*, 1999, Sim *et al.*, 1997, and Yang *et al.*, 1998) and higher concentrations to be in the range of 10.3 to 19.5 mg/m^3 (Giorgianni *et al.,* 2014, Polizzi *et al.*, 2002, and Zawilla *et al.*, 2014). Biomarker measures of aluminum body burden include aluminum in urine (µg/l), aluminum/gram creatinine in urine (µg/g creat.), aluminum in blood (µg/l), and aluminum in serum (µg/l). However, even consistent biomarker measures (*e.g.,* aluminum in urine) may represent either single samples or means of several samples, and samples with varying distances to the last exposure. The reported group means of the internal aluminum loads of exposed workers varied between 4.0 and 270 µg Al/l urine, 4.2 and 111 µg/g creatinine in urine, 1.0 and 13 µg Al/l blood, and 1.7 to 25.4 µg Al/l serum. There are four studies that stand out as having workers with the highest measures of aluminum in biomarkers (*e.g.*, >100 µg Al/l urine): the "high" exposure group from Akila *et al.* (1999) comprised of 24 workers in aluminum welding jobs from various companies, the "high" exposure group from Riihimaki *et al.* (2000) comprised of 30 workers in aluminum welding jobs from various companies, Letzel *et al.* (2000) study of 32 aluminum dust-exposed workers from an aluminum powder-producing plant, and the Kiesswetter *et al.* (2007) study of 44 aluminum welders in the train and truck construction industry. The high exposure studies of Akila *et al.* (1999) and Riihimaki *et al.* (2000), Finnish studies with the same authors, seem to be based on overlapping study samples. Both published designs compare steel welders with selected aluminum welders of low and high exposure, classified based on urinary aluminum concentrations.

The majority of neuropsychological tests were performed in the domain of psychomotor function. Within this domain, there were overall very few number of significant differences between exposed and control populations (<10% across all studies) and no discernable pattern of significant test results related to exposure metrics. In one study, aluminum welders performed better than the referents in tests of psychomotor function (Bast-Pettersen *et al.*, 2000). Although, as a group, they performed better than the referents, there was a statistically significant relation between longer reaction times and aluminum in air. The study population showing the number of positive findings in the psychomotor function domain, from Iregren *et al.* (2001), included a group of 119 aluminum smelter workers with exposure metrics indicating lower levels of aluminum exposure compared to other studies. The authors concluded that these findings of significance were probably due to factors other than aluminum.

In the attention domain, there was a moderately low number of significant findings across all studies. Most of the significant findings in the attention domain were reported by Akila *et al.* (1999) and Riihimaki *et al.* (2000), the overlapping study cohorts. In these publications, significant findings were for digit symbol, dual task, counting backwards, and Bourson-Wiersma dot cancellation. Giorgianni *et al.* (2014) studied 86 aluminum welders in a shipyard with high airborne exposure to aluminum (19.5 mg/m^3) and reported that the time needed to carry out the Stroop test (of concentration) was significantly longer for exposed welders compared to the clerical referents (matched for age, sex and schooling). Many of the significant findings for attention domain, were for the tests of digit span and digit forward, and were discussed in the meta-analysis results (Section 4.3.2.1).

Relatively few tests were performed and with few significant findings in the verbal, memory and learning, visuospatial and construction, and physical domain. On the other hand, four out of ten (40%) of the studies with comparisons in the cognitive impairment domain found significant relationships between aluminum exposure and cognitive impairment (Zawilla *et al.*, 2014, Polizzi *et al.,* 2002, Lu *et al.*, 2014, and Rifat *et al.*, 1990) . Zawilla *et al.* (2014) investigated the

cognitive status of workers exposed to aluminum dust in an aluminum factory in Southern Cairo with Addenbrooke's Cognitive Examination (ACE-R). Scores were significantly lower in the exposed group compared to an unexposed group of workers (82.7/100 *versus* 93.7/100). According to the authors, the significance of the low score is unknown because there are no published cut-off scores for the ACE-R which would provide a threshold to distinguish between those with and without cognitive impairment. Regardless, the authors believe the study demonstrates cognitive impairment due to occupational exposure to aluminum, mainly in aluminum smelters, with a mean exposure level of 10.3 µg/m^3 aluminum.

As summarized previously in the meta-analysis, Section 4.3.2.1, cognitive impairment results from Polizzi *et al.* (2002) and Lu *et al.* (2014) were based on significantly lower MMSE scores among the exposed populations; however, the differences were not clinically important. Lastly, Rifat *et al.* (1990) was a cross-sectional study 261 underground miners exposed to McIntyre Powder in mines in Ontario, Canada, compared to 346 non-exposed control miners. Subjects were given three cognitive state tests: MMSE; a Ravens coloured progressive matrices test (CPM) for reasoning; and the Symbol Digit Modalities Test (SDMT). Results of all three tests were summed and comparisons indicated that exposed miners performed less well than unexposed miners on cognitive state examinations. Exposure duration also correlated with lower test results, however, the clinical implications of these findings are unclear.

Although the biomarker data for unexposed subjects is not shown in Table 4-10, significantly higher internal exposure to aluminum was found in exposed compared to reference groups for a number of the studies (Letzel *et al.*, 2000, Kiesswetter *et al.*, 2007, Kiesswetter *et al.* 2009, Guo *et al.*, 1999). Other studies assumed that urinary aluminum was related to exposure without providing any information about the representativity or validity of the used biomonitoring data (Akila *et al.*, 1999, Riihimaki *et al.,* 2000).

The findings summarized in this section show some significant relationships between exposure data and neuropsychological test results. Systematic patterns of significant findings by testing domain and exposure measures were not identified. However, results are difficult to interpret given the non-uniform nature of occupational settings, neuropsychological tests used, cognitive domains, different exposure parameters considered, as well as other factors. Overall, there does not appear to be a trend that the number of changes increases with exposure.

It is important to note that the tabulation of significant effects ignores the frequency of numerous insignificant results. Additionally, the cross-sectional studies used univariate statistics, studying each single dependent variable separately without adjusting for multiple testing. This overestimates the significance of effects compared to insignificant effects. For example, if the test-wise error rate ‘alpha’ for a wrong rejection of hypothesis H_0 is fixed to 5%, with 10 univariate tests the examination-wise error rate inflates to 40%.

4.5.1.3 Other Evidence Related to Neuropsychological Outcomes

A subset of the studies looking at neuropsychological outcomes did not report results as means and standard deviations or the results of statistical significance for performance tests. Therefore, they could not be included in the meta-analysis or the tabulated results in Section 4.5.1.1. However, these studies are equally as important to take into account when considering the weight of the evidence and are summarized below.

Camerino *et al.* (1993): This study aimed to establish the prevalence of neurobehavioural scores of occupationally exposed subjects below the 10th percentile rank of normalized curves obtained on a referent population. The exposed population included workers exposed to various

compounds including 18 welders exposed to aluminum for less than 1 year. The referent population was made up of 400 drivers from private and public firms. The Milan Automated Neurobehavioural System (MANS) was administered to exposed and referent subjects. The MANS includes six tests: Profile of Mood State (POMS), simple visual reaction time, digit span, serial digit learning, digit symbol, visual recognition and aiming pursuit II. The exposures for aluminum exposed workers ranged from 1.6-3.5 mg/m^3 collected from personal samplers (4 hr). The authors found that the prevalence of results below the 10th percentile rank was lowest for aluminum exposed workers compared to workers exposed to other hazardous compounds (and also lower than the reference group for most of the neurobehavioural measures).

Dick *et al.* (1997): In this cross-sectional study, 63 current and former aluminum potroom workers and 37 comparison workers were tested for evidence of neurological dysfunction, specifically focusing on arm/hand and leg tremors. The estimated mean respirable aluminum concentrations were calculated from measurements collected in 1988. Estimated mean respirable aluminum in the exposure group (potroom) was 0.50 mg/m^3. For the comparison group, the estimated respirable aluminum exposure was 0.08 mg/m^3 for casthouse workers and 0.15 mg/m^3 for carbon plant workers. Both hand/arm and leg tremors were measured with no statistically significant differences due to exposure to aluminum between potroom workers and comparison workers.

Hanninen *et al.* (1994): This cross-sectional study investigated internal aluminum load and central nervous system function in 17 male aluminum workers in a shipyard in Finland. The mean aluminum concentration measured in study subjects' serum and urine was 0.21 (range 0.03-0.64) and 2.8 (range 0.9-6.1) µmol/L, respectively. Neuropsychological tests for reaction time, psychomotor speed, visual and spatial ability, memory, and verbal ability; symptom and mood questionnaires; quantitative electroencephalography (QEEG); and P300 evoked responses were used to examine central nervous system functions in the subjects. The results indicated that although the subjects performed normally on neuropsychological tests, a negative association existed between all four memory tests and serum aluminum. Additionally, the study also found a positive association between the variability of visual reaction times and measured aluminum concentration in the serum. The QEEG results indicated that slower delta and theta activity and less alpha activity in the frontal region correlated with higher levels of serum aluminum in welder.

Sinczuk-Walczak *et al.* (2003): The study covered a selected group of 67 male workers, with a mean age of 38.7 years, employment duration of 2 to 34 years, employed in an aluminum foundry with exposure to aluminum oxide in concentrations ranging from 0.13 to 1.95 mg/m^3. The workers were matched to a reference group of 57 workers from the same foundry without aluminum exposure. Both groups were assessed with electroencephalography (EEG) and results were classified as normal, borderline, or abnormal. There were statistically significant differences between the study group and reference group with more common abnormal/borderline EEG recordings in the exposed group. Comparisons in EEG results according to aluminum exposure duration, exposure to Al_2O_3 in workplace air, or urine aluminum concentrations did not reveal any dose response patterns. The authors conclude that occupational exposure to aluminum is responsible for subclinical effects on the nervous system; however, the clinical implications of abnormal EEG results are not provided.

Sjogren *et al.* (1990): This study on neuropsychiatric symptoms was conducted with 65 workers exposed to aluminum fumes for at least 10 years and 217 referent railroad track welders from different locations in Sweden. Welders who had at least thirteen years of full time exposure to aluminum had significantly more neuropsychiatric symptoms than welders not exposed to aluminum; there were no significant differences for welders with fewer than thirteen

years of exposure. The authors conclude that long-term exposure to aluminum may pose a risk to the central nervous system. However, the questionnaire used in the study (Q16) had not been validated for early detection of neuropsychiatric effects.

As mentioned previously, the vast majority of neuropsychological studies are cross-sectional studies; this type of study is limited in its ability to give rise to inferences about causality. Longitudinal studies are always preferred over cross-sectional studies because longitudinal studies collect data from the same sample on more than one occasion over a period of time so that changes over time can be evaluated. This study design can also explain performance differences between groups and potential exposure effects, reducing potential misinterpretation. Given the advantages of the longitudinal study design, the relevant studies are summarized in detail below.

Letzel *et al.* (2000): This longitudinal study compared nervous system effects between 32 aluminum dust-exposed workers to 30 non-exposed referents, all of whom worked in a German aluminum powder-producing plant. The subjects were matched for age, gender, professional training and education level. Study participants were subjected to biologic monitoring of urine, plasma, glucose, and serum gamma-GT, evaluation of P300 potentials, and a battery of neuropsychological tests. Five years later, all available subjects from both groups were reassessed using the same methods. The results indicated significantly higher median aluminum urine and plasma concentrations in the exposed group *versus* the reference group. Following the result of the first investigation, improvement in occupational hygiene at the workplace led to a significant reduction in renal aluminum excretion. The psychometric tests and evaluation of P300 potentials indicated no significant exposure-related differences between the two study groups. The five-year longitudinal comparison between the first and second evaluations revealed improved test performance. Additionally, no dose-effect relationship was found between the length of exposure or internal aluminum concentrations in plasma or urine with any of the primary neurologic variables. However, there was a high rate of loss to follow-up with 21 of 32 exposed workers and 15 of 30 non-exposed referents participating in the follow-up examination.

Kiesswetter *et al* (2007): This longitudinal study investigated aluminum exposure and neurobehavioral health of 20 (initially 44) male aluminum welders in the train and truck construction industry ages 41 to 45 (group mean) over a four year period. Exposure, biomarker data, neuropsychological test outcome data (on verbal intelligence, logic thinking, psychomotor behaviour, memory, and attention) were collected three times over the four years. The mean total dust load during welding, near to the routinely worn ventilated helmets, was in the range of 5–8 mg/m^3. Welders were characterized by high body burden of aluminum (pre-shift: 88–140 µg Al/g creatinine in urine; 13–16 µg Al/l Plasma in the exposed group). Explorative regression and covariance analyses revealed neither a correlation between biomonitoring and performance variables nor a significant difference between aluminum exposed and referents in the performance courses during the four year period.

Kieswetter *et al.* (2009): This was the second of two parallel longitudinal studies investigating aluminum exposure and neurobehavioral health of aluminum welders over a four year period. The repeated measurement design comprised four years with three measurements in two-year intervals with 92 male aluminum welders in the automobile industry compared to 50 non-exposed workers of the same industry and of similar age. While the first published study was in the train and truck construction industry and followed welders from mean age 41 to 45, the present study in the automobile industry followed the development from 35 to 39. Although no conspicuous neurobehavioral developments were detected in the first study, which exhibited the higher exposure, this study examined the potential for exposure effects to appear in earlier life

and exposure stages. The mean environmental dust load during welding, 0.5–0.8 mg/m^3, and the mean internal load of the welders (pre-shift: 23–43 µg Al/g creatinine in urine; 5–9 µg Al/L plasma) were significantly lower than in the parallel study. The biomonitoring and neurobehavioral results, consistent with the results of the first published study, showed no adverse neurobehavioral effects of aluminum welding in repeated measures models.

A limitation of these longitudinal studies is the occurrence of some loss of participants over time, which could bias results.

4.5.2 Lung Function Outcomes

The studies investigating the respiratory performance of workers occupationally exposed to aluminum are primarily cross-sectional in design (*i.e.*, data collected at a single point in time). In total, there are 15 studies with cross-sectional data from spirometry testing of lung function. Included in this count are two studies with longitudinal data which are treated as cross-sectional using data only from the first examination.

As with neuropsychological tests, lung function tests were not consistently applied across studies. To determine the test outcomes that are available for quantitative *versus* qualitative analysis, the lung function tests were tabulated by study ID (see Table 4-11). To perform quantitative meta-analyses on an outcome, means and standard deviations must be presented in the published study report. The table shows an empty circle if a test was performed but the study authors did not present the results in a manner that can be combined with other study results, and shows a check mark if the data meets the criteria for meta-analysis (check marks are summed in the “Count” column). As described in the following section, the analysis depends on the frequency of each test.

Table 4-11 Lung Function Tests in the Retrieved Literature

Lung Function Test	Count	Abbate 2003	Dennekamp 2015	Elserougy 2015	Fishwick 2004	Friis 1989	Fritschi 2001	Halatek 2006	Haluza 2014	Kilburn 1992	Kraus 2006	Larsson 1989	Musk 2000	San 1998	Sjogren 1985a	Townsend 1985
FVC	2	·	✓	·			✓	·	○	·		·	○	·	○	
FEV_1	2	·	✓	·	○		✓	·	○	·		·	○	·	○	○
FEV_1/FVC	2	·	✓	·			·	·		·		·	○	✓		
% pred FVC	6	✓	✓	✓		○	·	✓		✓		·	○	✓		
% pred FEV_1	7	✓	✓	✓		○	·	✓		✓		✓	○	✓		
% pred FEV_1/FVC	2	·	✓	✓			·	·		·		·		·		
% pred VC	2	✓	·	·			·	·		·	○	✓		·		
% pred FEV_1/VC	1	✓	·	·			·	·		·	○	·		·		
% pred FEF50	1	·	·	·			·	✓		·		·		·		
% pred FEF25–75%	3	✓	·	·			·	·		✓		·		✓		
% pred PEFR	2	·	·	✓			·	·		·		·		✓		
% pred MVV	1	·	·	·			·	·		·		·		✓		
% pred TLC	2	·	·	·			·	·		✓	○	·		✓		
% pred RV	2	·	·	·			·	·		·		✓		✓		
RV/TLC	1	·	·	·			·	·		·		·		✓		
% pred DLCO	1	·	·	·			·	·		·		·		✓		
% pred MTT	1	·	·	·			·	·		·		✓		·		
% pred MEF50	1	·	·	·			·	·	○	·		✓		·		
No. of unique tests	**18**	**5**	**6**	**4**	**1**	**2**	**2**	**3**	**3**	**4**	**3**	**5**	**5**	**10**	**2**	**1**

Check mark: means and standard deviations for test are presented in report;
empty circle: means and standard deviations are not available (results presented in some other way)
FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; VC: vital capacity; FEF50: forced expiratory flow in 50% VC;
FEF25-75: mean forced expiratory flow during mid-half of the FVC; PEFR: peak expiratory flow rate; MVV: maximum voluntary ventilation; TLC: total lung capacity; RV: residual volume;
DLCO:carbon monoxide difusing capacity; MTT: mean transit time; MEF50: the maximal expiratory flow at 50% of the expired FVC; % pred: percent predicted

4.5.2.1 Meta-Analysis of Lung Function Tests

Tests with reported means and standard deviations from at least three studies had sufficient information to conduct a meta-analysis of effect size, or the mean difference (MD) between the values of an exposed and reference group. There are a total of three different lung function tests that meet this criteria: percent predicted FVC, percent predicted FEV_1, and percent predicted FEF25-75 (Table 4-12). Insufficient information from the studies was available for meta-analysis of the ratio FEV_1/FVC, instead we provide a non-quantitative analysis of this outcome based on available data.

Table 4-12 Lung Function Outcome Variables to Include in Meta-Analysis

Outcomes	Study IDs	Count
Percent predicted Forced Vital Capacity (%pred FVC)	Abbate2003, Dennekamp2015, Elseroughy2015, Halatek2006, Kilburn1992, San1998	6
Percent predicted Forced Expiratory volume in 1 second (%pred FEV_1)	Abbate2003, Dennekamp2015, Elseroughy2015, Halatek2006, Kilburn1992, Larsson1989, San1998	7
Percent predicated mean forced expiratory flow during mid-half of the FVC (%pred FEF25-75)	Abbate2003, Kilburn1992, San1998	3

For each outcome and study listed in the table above, the abstracted data (means, standard deviations, exposure data, and other relevant study characteristics) were imported into RevMan Software for meta-analysis. For studies where the outcome data were reported for subgroups (*e.g.*, Halatek *et al.* 2006 reported all results separately by three occupational groups including smelters, locksmiths, and sawyers/auxiliary workers), each subgroup is included as a separate study to avoid excluding valuable information. In total, there were nine studies or study subpopulations which reported a comparison of lung function outcomes suitable for meta-analysis (Table 4-13). Overall, the study patient samples were moderately aged with a mean age of 41 years, with a minimum years of exposure of 10 but up to 28 years, the mean age years of exposure was 15 years. The important confounder of smoking was relatively similar across the exposed and reference groups, 59% and 63%.

The body burden of aluminum was higher in the exposed than the reference group according to blood aluminum (5.5-times higher), urine aluminum (3.3-times higher), and serum aluminum (1.5-times higher). Only one study reported the concentration of aluminum in workplace air. The respiratory characteristics of the exposed and reference groups indicated a generally healthy population, where 80% is the threshold for respiratory decline for $ppFEV_1$ and ppFVC. Specifically, lung function in just the aluminum exposed groups, mean ppFVC of 96%, mean ppFEV1 of 90% and mean ppFEF25-75 of 70% describe workers in good respiratory health. However, the selection bias of employment in physically demanding jobs may explain the normal percent predicted values, a phenomenon known as the 'healthy worker effect'.

Table 4-13 Study Characteristics in Meta-analysis for Respiratory Outcomes

Study Characteristic	Exposed		Control		Exposed Minus Control
	N	mean (min, max)	N	mean (min, max)	
Study size, N	9	125 (5,670)	9	124 (14,659)	1 [ND]
Age	8	41 (32,53)	8	41 (32,53)	0 [ND]
Years exposure	7	15 (10,28)	-	-	
Smoking	7	59 (37,78)	7	63 (40,81)	4 [ND]
Air Aluminum (mg/m^3)	3	0.4 (0.3, 0.6)	-	-	
Blood Aluminum (µg/l)	1	33 (33,33)	1	6 (6,6)	27 (5.5x)
Urine Aluminum (µg/l)	4	40 (20,44)	4	12 (10,16)	28 (3.3x)
Serum Aluminum (µg/l)	4	28 (12,73)	4	19 (15,31)	9 (1.5x)
predicted FVC	8	96 (80,113)	8	98 (84,110)	-2

Table 4-13 Study Characteristics in Meta-analysis for Respiratory Outcomes					
Study Characteristic	**Exposed**		**Control**		**Exposed Minus Control**
	N	**mean (min, max)**	**N**	**mean (min, max)**	
predicted FEV_1	9	90 (79,99)	9	97 (90,110)	-7
predicted FEF25-75	3	74 (61, 88)	3	99 (85,107)	-25

ND no meaningful difference in baseline characteristics between exposed and reference groups; x: times

Percent predicted FVC

As mentioned above, 80% is typically considered the threshold for respiratory decline for ppFVC and the mean lung function in both the aluminum exposed groups (mean ppFVC of 96%) and control group (mean ppFVC of 98%) indicate generally good respiratory health. The overall MD of percent predicted FVC in the meta-analysis shows a decrease of -2.87% among those occupationally exposed to aluminum compared to the referents that is not statistically significant (95%CI: -10.65, 4.90). From the forest plot and the high I^2 = 97% (p<0.001), there is high heterogeneity driven by two outliers – Abbate *et al.* (2003) had a difference in ppFVC=-16.09 (95%CI: -18.47, -13.71) and San *et al.* (1998) had a difference in ppFVC= -16.00 (95%CI: -21.49, -10.51) – both of which are statistically significant.

The study by Abbate *et al.* (2003) was conducted in Italy with aluminum sheet cutters and aluminum welders with a sample of 50 exposed workers and 50 referents. Abbate *et al.* (2003) performed environmental monitoring of the airborne breathable amount of aluminum from five different work areas; results ranged from 6.2 to 20.2 mg/m^3, with all five areas exceeding the threshold limit value time weighted average (TLV-TWA) of 5 mg/m^3. Blood aluminum levels were about five times higher in the exposed workers compared to the referents (32.6±8.7 ng/ml vs. 6.4±1.0 ng/ml). The quality assessment (Section 4.2) found Abbate *et al.* (2003) to have a satisfactory rating of 3/6 stars because the authors provided no description of how subjects were recruited into the study and no information about the reference population except that they were age-matched to controls (*e.g.*, whether or not they were also industrial workers).

The study by San *et al.* (1998) was conducted in Turkey on aluminum factory workers with a sample of 55 exposed workers and 30 referents. San *et al.* (1998) does not provide any data regarding the levels of airborne aluminum to which workers were exposed, however, exposure assessment via biomonitoring of serum aluminum levels showed the aluminum workers had serum aluminum levels over twice as high as the referents (72.7±9.9 ng/ml vs. 31.1±3.9 ng/ml). The quality assessment (Section 4.2) found San *et al.* (1998) to have a low satisfactory rating of 2/6 stars because the authors provided no description of how workers were recruited into the study, the referents came from a separate population (not workers), and the authors did not report on any study population characteristics that may have differed between the exposed and reference groups (*e.g.*, age, smoking). Neither of these two studies recognizes or discusses the presence of respiratory hazards, other than aluminum, to which workers may be also exposed.

Excluding the outlier studies by Abbate *et al.* (2003) and San *et al.* (1998) results in an increase of 1.65% predicted FVC (95%CI: -2.66 to 5.96), with still high heterogeneity (I^2=81.5% p <0.001) driven by the study by Kilburn and Warshaw (1992). Further removing all three outlier studies produces a small non-significant decrease of MD = -0.26% (95%CI: -2.16 to 1.64), with an absence of heterogeneity I^2=0.0%, p= 0.45.

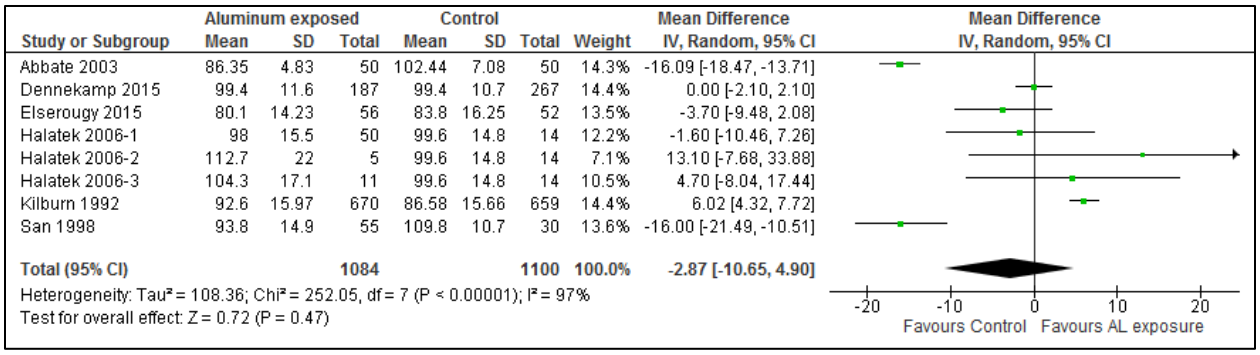

Figure 4-9 Forest plot Mean difference (MD) of percentage predicted forced vital capacity (FVC)

Meta-regression was used to investigate differences by study characteristics, or covariates, which may influence the size of the MD for ppFVC (see meta-regression output in Appendix F-1). Because only a subset of ppFVC studies included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in ppFVC effect size for age, smoking, aluminum in air, or aluminum in urine. Years of exposure had a significant impact on MD ppFVC but the direction of effect was counterintuitive. For example, an increase in years of exposure by one year increased MD ppFVC positively by 1.5% (p=0.09), which may be due to one outlier. In addition, differences in serum aluminum also produces a significant effect on MD ppFVC. For every unit difference in serum aluminum, the MD ppFVC decreased -0.041% (95%CI: -0.9, 0.1), p=0.076. However, the difference in serum level of aluminum is driven by one study (San 1998) which has a much higher concentration of serum aluminum (exposed group serum =72.1 µg/l, reference group serum =31.1 µg/l, *versus* other studies with serum aluminum <20 µg/l. For the other three studies, there was no significant effect on MD ppFVC.

Percent predicted FEV_1 (ppFEV1)

The overall mean difference of ppFEV1 was -7.53% (95%CI: -13.36, -1.70), which indicated a small but statistically significant decrease in lung function among those occupationally exposed to aluminum compared to the referents. Similar to ppFVC, the heterogeneity was high I^2=94% (p<0.01) and the heterogeneity was driven by the studies by Abbate 2003 and San 1998. Removing the two negative outliers produced a small but statistically significant MD ppFEV1 = -2.7% (95%CI: -5.1 to -0.2), with low heterogeneity I^2=45.1%, p=0.09.

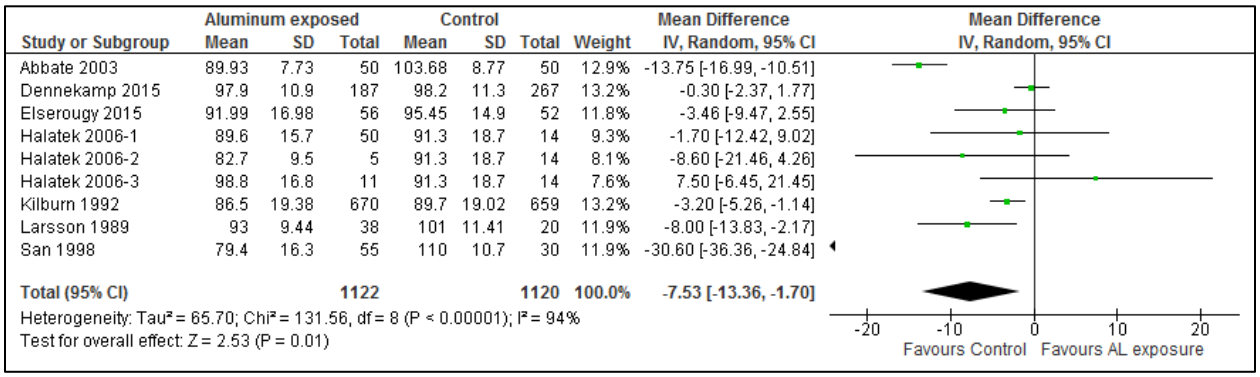

Figure 4-10 Forest Plot - Percent Predicted Forced Expired Volume in one second (ppFEV1)

Meta-regression was used to investigate differences by study characteristics, or covariates, which may influence the size of the MD for ppFEV1 (see meta-regression output in Appendix F-2). Because only a subset of ppFEV1 included data for each study characteristic, meta-regressions were limited to only include subsets of studies. There were no significant changes in ppFEV1 effect size for age, years of exposure, smoking, aluminum in air, or aluminum in urine. Only the difference in serum levels of aluminum was a significant predictor of differences in MD ppFEV1. For every unit rise in serum aluminum, the MD of ppFEV1 is -0.7% (95%CI: -1.1 to -0.2), p=0.026. Again, the difference in serum level of aluminum is driven by one study (San 1998) which has a much higher concentration of serum aluminum (exposed group serum =72.1 µg/l, reference group serum =31.1 µg/l, *versus* other studies with serum aluminum <20 µg/l. For the other three studies, there was no significant effect on MD ppFEV1.

Percent Predicted Forced Expiratory Flow mid of the FVC (ppFEF25-75)

The percent predicted FEF25-75 (the average forced expiratory flow during the mid-portion of the FVC) may be an early indicator of small airway obstructive disease (*i.e.,* asthma). Many clinicians will interpret a ppFEF25-75 of less than 50% as indication that early obstructive disease is present, even if the ppFEV1/FVC is greater than 80%. Interpretation of the ppFEF25-75 should be done cautiously, as it has high variability (Baptist and Sanders, 2005).

The overall mean difference of ppFEF25-75 was -24.56% (95%CI: -43.23 to -5.88) with high heterogeneity with I^2=95.1%, p<0.01 (see Figure 4-11). The study with the largest MD ppFEF25-75 was San *et al.* (1998) with a difference of FEF25-75 of -46.1% (95%CI: -55.91, -36.29). The large difference was driven by the very high levels in the referents, mean FEF25-75= 107.4 (sd=23.2). While some of the studies had referents which worked in other areas of the aluminum industry such as office workers, in the study by San *et al.* (1998), the referents were 30 men living and working far from aluminum factory. Removing the outlier and low-quality study by San *et al.* (1998), results in a smaller magnitude mean difference of -12.96% ppFEF25-75 (95%CI: -17.13 to -8.79), with low heterogeneity I^2=16%, p=0.28.

The overall effect for ppFEF25-75 was provided by only three studies (Abbate *et al.*, 2003; Kilburn and Warshaw, 1992; and San *et al.*, 1998) and each provided a value that appears to be much larger decrement in respiratory function than ppFEV1 or ppFVC. However, the scale ppFEF25-75 is more variable than the other measures. Further, as a value of less than 50% ppFEF25-75 is indicative of early pulmonary function decline, the exposed populations appear to represent generally healthy subjects.

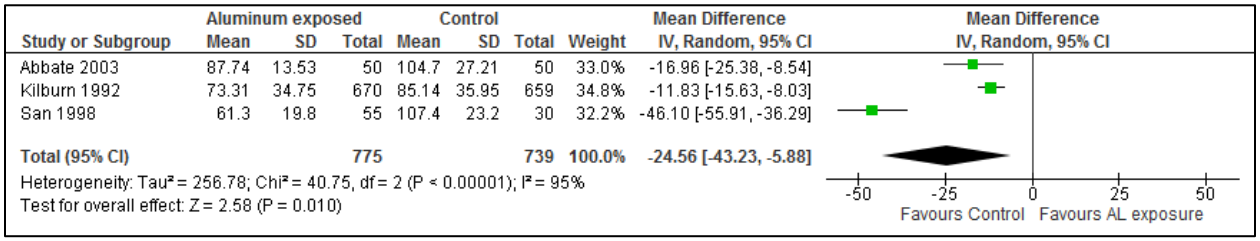

Figure 4-11 Forest Plot- Percent Predicted Forced Expiratory Flow mid of the FVC (ppFEF25-75)

Due to the small number of studies reporting an outcome of ppFEF25-75, there was insufficient data to explore the effects of aluminum levels and other factors with meta-regression.

4.5.2.2 Additional Analysis of FEV_1/FVC Ratio

While both values of FVC and FEV_1 are routinely measured as part of a pulmonary function test, the diagnostic criterion for Chronic Obstructive Pulmonary Disease (COPD) is the FEV_1/FVC ratio and FEV_1, as described in Table 4-14.

Table 4-14 Diagnostic criterion for COPD, using the GOLD standard criteria

COPD Stage	Description
Stage I: Mild COPD	Mild airflow limitation (FEV_1/FVC < 70%; FEV_1 > 80% predicted) and sometimes, but not always, chronic cough and sputum production. At this stage, the individual may not be aware that his or her lung function is abnormal.
Stage II: Moderate COPD	Worsening airflow limitation (FEV_1/FVC < 70%; 50% < FEV_1 < 80% predicted), with shortness of breath typically developing during exertion. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.

Source: http://advantage.ok.gov/CHCC/Publications/Spirometric%20Classifications%20of%20COPD.pdf

Data were not sufficient to include FEV_1/FVC ratio in the meta-analytic results of lung function due to the lack of standard deviation measures for the ratios. However, the FEV_1/FVC ratios were calculated for comparison to the diagnostic criterion for COPD (see Table 4-15). Only one study's exposure group has a FEV_1 less than 80%, with a value of 79%. However, the ratio FEV_1/FVC is typically between 70% and 80% in normal adults and a value less than 70% indicates airflow limitation and the possibility of COPD. In Table 4-15, where the mean FEV_1/FVC ratio estimated by study, we see that the lowest values were reported Halatek 2006-2 with a mean FEV_1 of 83%, and low FEV_1/FVC of 73%, both of which were in the lower range of normal. These values were the subgroup of locksmith workers in an aluminum foundry in Poland, who were exposed to Al_2O_3, but the subgroup was only from a very small sample of only five workers.

Table 4-15 FEV_1/FVC Ratio Estimated by Study

Study	Identifier	FEV_1 exposed	FVC exposed	FEV_1/FVC exposed	FEV_1 control	FVC control	FEV_1/FVC control	FEV_1/FVC MD
1	Abbate 2003	90	86	105%	104	102	102%	3%
2	Dennekamp 2015	98	99	99%	98	99	99%	0%
3	Elserougy 2015	92	80	115%	95	84	113%	2%
4	Halatek 2006_1	90	98	92%	91	100	91%	1%
5	Halatek 2006_2	83	113	73%	91	100	91%	-18%
6	Halatek 2006_3	99	104	95%	91	100	91%	4%
7	Kilburn 1992	87	93	94%	90	87	103%	-10%
8	Larsson 1989	93	.		101	.		
9	San 1998	79	94	84%	110	110	100%	-16%

4.5.2.3 Other Evidence Related to Lung Function Tests

A subset of the studies looking at lung function outcomes did not report results as means and standard deviations for performance tests. Therefore, they could not be included in the meta-analysis and are instead discussed through a narrative analysis. The studies that did not fit into the meta-analysis are equally as important to take into account when considering the weight of the evidence. The results are summarized in Table 4-16, organized by type of occupational setting, and discussed in this section.

There was one study on mining workers exposed to bauxite dust carried out at three bauxite mines in Western Australia (Beach *et al.*, 2001). Bauxite ore is the primary source of aluminum. All employees were invited to participate and 86% consented, resulting in 572 exposed and 79

unexposed male subjects. Cumulative exposure to bauxite dust was estimated based on work history. Median cumulative dust exposure was 5.9 mg/m^3 years. Lung function tests, including FVC and FEV_1, were performed for each participant. After adjusting for age, height, smoking, there were no significant differences in lung function (FEV_1, FVC, FEV_1/FVC ratio) between exposed and unexposed workers. When cumulative bauxite exposure and lung function were investigated, no clear exposure-response relationship was found.

A majority of these additional studies examined occupational workers in aluminum refining or production settings. One hundred and one male cryolite production workers in Denmark were included in a cross-sectional study that investigated the relationship between work-related cryolite exposure and lung function (Friis *et al.*, 1989). Cryolite is a raw mineral in the production of aluminum. Degree of exposure to cryolite dust was ascertained by means of a questionnaire; however, exposure to aluminum, specifically, was not quantified in this study. Lung function tests (forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1)) were performed using spirometry. Results indicated that no significant correlation existed between length of exposure to cryolite dust and FEV_1 or FVC results. No reference group was used. By means of questionnaire, study participants described a group of symptoms that appeared 15 to 30 minutes post heavy cryolite dust exposure, including nausea, followed by epigastric pain with relief after spontaneous or provoked vomiting.

Two cross-sectional studies were carried out in refineries in Western Australia performing the refining of alumina from bauxite: one study of 2,404 employees of three alumina refineries and an alumina shipping port (Fritschi *et al.*, 2001) and one study in a similar cohort of 2,388 male employees of three alumina refineries (Musk *et al.*, 2000). Fritschi *et al.* (2001) estimated cumulative exposure to alumina and bauxite dust based on work history. Median cumulative bauxite exposure was 1.1 mg/m^3 years and median cumulative alumina exposure was 1.6 mg/m^3 years. Workers were categorized according to quartile of cumulative exposure to bauxite and alumina. Lung function (FEV_1, FVC) measurements for workers with the highest cumulative alumina and/or bauxite exposure did not differ from lung function of those with lower exposures. Musk *et al.* (2000) examined the prevalence of work-related respiratory symptoms and lung function among different types of workers within the three refineries. Air concentration of alumina was highest in Refinery 1 (mean = 2.18 mg/m^3 in calcination or shipping group workers, and mean = 1.56 mg/m^3 in maintenance group workers). The study concluded that although significant differences existed in work related symptoms and lung function between different process groups and the three refineries, these differences were mainly inconsistent and clinically not relevant. Neither Australian study used an unexposed reference group for comparison.

Townsend *et al.* (1985) conducted a cross-sectional study of 1,142 male employees of a bauxite refinery and alumina production company in the US, examining the relationship of lung function (FEV_1) to smoking and dust exposure from the mining and refining of bauxite to alumina. The authors estimated cumulative exposure to total dust, rather than respirable dust or aluminum, because air sampling prior to 1975 included only total dust measurement, based on work history. Non-smokers with cumulative total dust exposure >100 mg/m^3 year and over 20 years of exposure had significantly lower FEV_1 than predicted values and an increase in the prevalence of FEV_1<80%. In the same refinery, Townsend *et al.* (1988) conducted a cross-sectional study of 788 male employees examining the relationship of radiographic abnormalities to smoking and dust exposure. Nonsmokers who had accumulated higher dust exposures showed a moderate increase in the prevalence of small, irregular opacities on chest radiographs with increasing duration. The authors suggest that lung function decreases as profusion of small opacities increases. However, workers included in this older study experienced dustier conditions with much higher exposures than other study populations.

Kraus *et al.* (2006) investigated whether high-resolution computed tomography (HRCT) findings could be detected in 62 male aluminum powder workers from eight departments of two aluminum producing plants in Germany. HRCT findings are known to be consistent with early stages of aluminosis. Biomarkers of aluminum exposure were measured in plasma and urine. The results found that 15 workers displayed HRTC findings consistent with early stages of aluminosis. Higher internal exposure to aluminum was observed in affected workers (33.5 µg/L plasma vs.15.4 µg/L plasma) and (340.5 µg/g creatinine *versus* 135.1 µg/g creatinine). Higher duration of exposure (>120 days) was associated with aluminosis. As the purpose of the study was to determine the utility of the diagnostic tool, authors concluded that use of HRCT allows for the detection of early stages of aluminosis and that biological monitoring of aluminum may be used to identify high-risk workers.

As seen in Table 4-16, three studies provide information for workers occupationally exposed to aluminum fumes from welding. Fishwick *et al.* (2004) investigated the cross-sectional relationship between workplace exposures of specific welding metal fumes (including aluminum) and acute falls in forced expiratory volume in one second (FEV_1) among 75 workers in New Zealand. Mean personal exposure to aluminum ranged from 0.001 to 0.1955 mg/m^3 in four work sites. Individual exposure of study subjects was ascertained by work history in welding jobs. A 15-minute work-related exposure to "high" aluminum was significantly associated with an acute fall in FEV_1 of at least 5% compared to "low" exposure to aluminum. However, the authors do not define "low" *versus* "high" exposure and further, do not indicate what the chronic respiratory effects, if any, of the short-term acute change in lung function may be.

The other two studies in welding populations reported no association between aluminum exposure and impaired lung function. Sjogren and Ulfvarson (1985) conducted a cross-sectional study of 64 aluminum welders and 64 referents (nonwelding industrial workers), all working in the railroad industry in Sweden. Median exposure time for welders was 15 years. Lung function tests, including FVC and FEV_1, were performed for each participant. There were no differences in pulmonary function between the exposed and reference group; nor did the duration of exposure period affect pulmonary function among aluminum welders. Haluza *et al.* (2014) investigated annual changes in lung function over nine years in 1,982 welders in Austria including 245 participants with aluminum exposure. Lung function tests (FVC, FEV_1 and midexpiratory flow at 50% of vital capacity (MEF50)) were performed using spirometry. After accounting for smoking, the duration of exposure to aluminum was not associated with annual changes in lung function.

Lastly, Hansell *et al.* (2014) was a large population-based study investigated the relationship between various occupations and occupational exposures and COPD in a New Zealand population. COPD diagnoses and chronic bronchitis symptoms were based on self-report. Occupational exposures were also based on self-report. The number of individuals in the study with aluminum dust exposure was very limited (N=40). There was no evidence of increased COPD or respiratory effects in those occupationally exposed to aluminum dust compared to those with no exposure.

Table 4-16 Significant Respiratory Effects According to Occupational Setting						
Identifier (Country)	**Form of Aluminum Exposure**	**No. Exp/ No. Control**	**Average Years of Exposure**	**Aluminum in Air**	**Sig. Effect on lung function?**	**Findings**
Mining/Refining						
Townsend1985 (USA)	Bauxite and/or alumina dust	1142/291	NR	cumulative dust exposures <100 mg/m^3 compared to those with >100 mg/m^3	Yes	Non-smokers with cumulative total dust exposure >100 mg/m^3 and >20 years of exposure had significantly lower FEV_1 than predicted values
Friis1989 (Denmark)	Cryolite (Na_3AlF_6) dust	101/NA	8.2	No measures	No	No significant correlation between years of work-related exposure and lung function (FEV_1, FVC)
Musk2000 (Australia)	Bauxite and/or alumina dust	2388/NA	10	mean 4-hr time weighted samples ranging from 0.98 to 2.18 mg/m^3	No	Significant differences in FEV_1, FVC, and FEV/FVC ratio by refinery and/or job function were not consistent; no relationship to exposure.
Fritschi2001 (Australia)	Bauxite and/or alumina dust	2404/4845	NR	cum. alumina exposure (mg/m^3 yr) according to quartile: <0.36, 0.36-1.57, 1.57-7.78, >7.78	No	No significant differences in lung function (FEV_1, FVC) according to exposure to alumina
Beach2001 (Australia)	Bauxite and/or alumina dust	572/79	NR	median cumulative dust exposure 5.9 mg/m^3 year	No	No significant differences in lung function (FEV_1, FVC, FEV_1/FVC ratio) between exposed and unexposed workers after adjusting for age, height, smoking
Welding						
Fishwick2004 (New Zealand)	Aluminum fumes	49/26	18.5	mean exposure ranges from 0.001 to 0.1955 mg/m^3 in four factories	Yes	A fall in FEV_1 of at least 5% after 15 minutes of work was significantly associated with high *versus* low aluminum exposure
Sjogren1985a (Sweden)	Aluminum fumes	64/64	5	No measures	No	No differences in FVC or FEV_1 between aluminum welders and the referents
Haluza2014 (Austria)	Aluminum fumes	1982/NA	9	No measures	No	After accounting for smoking, duration of exposure to aluminum not associated with measures of lung function
Various Occupations						
Hansell2014 (New Zealand)	Aluminum dust	40/977	NR	No measures	No	No increase in COPD diagnoses or chronic bronchitis symptoms in aluminum exposed workers.

NR= Not reported

5.0 SUMMARY OF FINDINGS

5.1 Toxicology

Aluminum has varying absorption in the human body, depending on its chemical form and route of exposure. Consistent with the differences in particle size and relative absorption, it has been suggested that absorption of inhaled aluminum from the lungs to the bloodstream is higher in individuals exposed to aluminum fumes compared to those exposed to aluminum dust (ATSDR, 2008). In living organisms, aluminum potentially exists in four different forms: (i) as free ions; (ii) as low-molecular-weight complexes; (iii) as physically-bound macromolar complexes, and (iv) as covalently bonded macromolar complexes. Compared to other forms, the free ionic form of aluminum binds more easily to different complexes. Although the metabolic activity of aluminum-complexes of lower molecular weight is higher, aluminum can also form stable macromolecules that may not metabolize, thereby inhibiting metabolism (ATSDR, 2008). Excretion of aluminum has been suggested to be *via* urine, albeit at a slow rate (Rollin *et al.,* 2001).

Aluminum can be measured in the blood, urine and feces and is regularly found in healthy individuals due to its ubiquitous nature and presence in many food items. However, guidelines for aluminum exposure and specific health outcomes are generally unavailable. As a result, over the years, many epidemiological studies on occupational exposure to aluminum have been conducted using biomonitoring measurements as an indicator of exposure. One such longitudinal study by Kiesswetter and others (2009), found a significant correlation between aluminum concentration in the urine and external aluminum dust exposure.

Toxicological studies of aluminum have primarily focused on potential effects to the nervous system, lungs, bones, and cancer-related outcomes. Numerous studies have been conducted in order to identify the mechanism of aluminum neurotoxicity. Results indicate that rather than a unifying mechanism, aluminum exposure may lead to neurotoxicity *via* multiple mechanisms (ATSDR, 2008). Studies in rodents, in order to identify neurological development and neurobehavioural changes due to aluminum exposure, have shown both neurodegenerative disorders and neurobehavioural effects (*e.g.*, locomotor toxicity, learning and memory) (ATSDR, 2008). In addition, the rodent studies suggest possible impact of aluminum exposure on other neurophysiological processes, such as permeability of the blood-brain-barrier, cholinergic activity and the signal transduction pathways. However, as many of these studies were conducted on animals, extrapolation of effects to humans may not be entirely conclusive (ATSDR, 2008).

Lung toxicity due to exposure to aluminum or aluminum oxide dust has mostly been described to result in clinically mild cases of pneumoconiosis (Riihimaki and Aitio, 2012). Similar to its mechanism of neurotoxicity, the mechanism of lung toxicity due to inhalation of aluminum is poorly understood (ATSDR, 2008). Conversely, the mechanism of bone toxicity in humans *via* exposure to aluminum-containing antacids to treat GI disorders has been described as the binding of antacid to dietary phosphorous, thereby inhibiting GI absorption of phosphorous. This may lead to osteomalacia and rickets (ATSDR, 2008). Last, although not classified as a carcinogen itself (Krewski *et al.*, 2007), “aluminum production”, due to increased exposure of workers to PAHs, is considered carcinogenic to human (Group 1) (IARC, 2010).

5.2 Literature Review

The Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, 2009) governed the study search and evaluation process for the systematic review of occupational aluminum exposure and adverse health outcomes. The systematic nature of the

literature review is intended to provide a reproducible protocol and to reduce the potential for bias in the findings.

A total of 62 studies were selected for inclusion in the review. Because the studies covered a broad range of health outcomes, study designs, occupational settings, *etc*., the methods applied in synthesizing the information were also diverse. This literature review used a combination of meta-analytic techniques, semi-quantitative tabulation of study characteristics, and narrative review methods. The findings, according to broad health outcome categories, are summarized below.

5.2.1 McIntyre Powder Exposed Workers

A focus of the literature review was to consider possible effects of McIntyre Powder, however, there were only three studies that assessed this specific type of aluminum exposure.

The first study, Rifat *et al.* (1990), was a cross-sectional study of 261 underground miners exposed to McIntyre Powder in Ontario mines and 346 non-exposed control miners; workers had experienced long-term exposure to McInyre Powder over 20 to 39 years. Exposed miners performed less well than unexposed miners on cognitive state examinations. The proportion of workers with scores in the cognitively impaired range was greater in the exposed than the non-exposed group and increasing duration of exposure also increased likelihood of scores in the impaired range. There were no significant differences between exposed and non-exposed miners in diagnoses of neurological disorder.

Peters *et al.* (2013) investigated cardiovascular, cerebrovascular and Alzheimer's disease mortality in 647 male Australian gold miners to aluminum dust as a prophylaxis during the 1950s and 1960s, compared to 1,247 gold miners never exposed to aluminum dust. Workers had been exposed to aluminum dust for an average of 10 years (range of 1 to 15 years). Using death certificate data, Peters *et al.* (2013) reported an increase in mortality related to Alzheimer's disease among miners exposed to aluminum dust that was not statistically significant (SMR=1.38; 95% CI 0.69 to 2.75) and was based on very few cases of Alzheimer's disease (n=8 in the exposed group). Aluminum dust inhalation did not affect the risk of cerebrovascular mortality. There was some indication of an increased risk of cardiovascular mortality among miners with a history of aluminum dust exposure.

McDonald *et al.*, (1996), published only as an abstract, compared Alzheimer's disease and dementia mortality in two groups of Cornish tin miners, one from a mine that historically used McIntyre Powder as a prophylactic against silicosis (1940s-1964) and another that did not. Similar to Peters *et al.* (2013), McDonald *et al.* (1996) used death certificate data to compare mortality rates between the two groups. None of the miners exposed to McIntyre Powder were certified as dying from dementia or Alzheimer's disease. In the unexposed group, two dementia deaths were recorded. The authors concluded that the study found no causal link between regular exposure to McIntyre Powder *via* inhalation and development of Alzheimer's disease.

5.2.2 ICD-Diagnosable Conditions

This review investigated whether occupational exposure to aluminum may be related to an increased risk for neurological diseases including: Alzheimer's disease, Parkinson's disease, or ALS. Meta-analysis was conducted to systematically quantify the relationship between occupational exposure to aluminum and risk of Alzheimer's disease. Three retrospective case control studies and one retrospective matched cohort study met the criteria for inclusion.

Occupational aluminum exposure was associated with a 1.28 increase in odds of Alzheimer's disease but this increase was not statistically significant (OR=1.28, 95%CI: 0.78 to 2.10).

The literature review identified one study examining aluminum as a potential risk factor for ALS, and one study examining aluminum as a potential risk factor for Parkinson's disease. These studies were similar in design where cases diagnosed with disease were selected and then interviewed (or interviewed by a proxy) about their past occupational exposure histories. Both studies reported no association between aluminum and the neurological disease; however, the power of the studies to identify significant results was limited by the small number of cases and referents reporting exposure to aluminum.

This report also summarized the literature on more rarely studied health outcomes in the context of occupational aluminum exposures. Those outcomes included cardiovascular outcomes and biomarkers, cancer and biomarkers of cancer, diabetes, mortality, osteodystrophy, and reproductive effects. Weak associations, evaluated based on few cases, were reported between aluminum exposure and non-malignant respiratory disease mortality, cerebrovascular disease mortality, and cardiovascular disease mortality (Friesen *et al.,* 2009, Peters *et al.,* 2013). Out of the four studies investigating potential biomarkers of cancer, two found limited evidence of association or correlation between aluminum exposure and DNA damage, although the biologic significance of those findings is unknown (Botta *et al.*, 2006; Hou *et al.*, 2011). Overall, the findings related to other health outcomes provided suggestive but no conclusive evidence of adverse effects related to occupational aluminum exposure.

5.2.3 Other Studied Health Outcomes

5.2.3.1 Neuropsychological Outcomes

Meta-analysis was also used to pool the effect sizes from cross-sectional studies comparing seven neuropsychological test results from aluminum exposed to non-aluminum exposed workers. The meta-analysis neuropsychological test results revealed four (of seven) statistically significant effects of decreased test performance in workers occupationally exposed to aluminum: Santa Ana Dexterity dominant hand: -1.87 (95%CI: -2.74 to -0.99), $p<0.01$; simple reaction time: 10.97 (95%CI: 4.50 to 17.44), $p<0.01$; digit symbol: -4.69 (95%CI: -6.87, -2.51), $p<0.01$; MMSE score: 1.17 (95%CI: -2.03 to -0.31), $p<0.01$. Based on an analysis of magnitude of effect and comparisons to normative values, when available, the positive results from the meta-analyses were small differences between exposed and reference groups. The largest magnitude of effect relative to the reference group was found for digit symbol count, a difference of -10% (-4.69/46.7). Meta-regressions performed with the available exposure data showed no dose-response trends for these effects. Meta-analysis effect sizes for Santa Ana Dexterity non-dominant hand, digit span forward, and digit span backward were not statistically significant.

For individual neuropsychological tests that were not applied frequently enough across studies to be pooled *via* meta-analysis, the number of significant differences between aluminum exposed and control populations out of the total number of tests performed in each study were tabulated. Systematic patterns of significant results by testing domain and exposure measures were examined. Results are challenging to interpret given the non-uniform nature of occupational settings, neuropsychological tests used, different exposure parameters considered, as well as other factors. However, no systematic patterns of effect according to exposure were identified.

While most neuropsychological test studies were cross-sectional in design, three studies were conducted using longitudinal approaches. This included two parallel longitudinal studies investigating aluminum welders over a four year period with repeated comparisons made to

reference groups (Kiesswetter *et al.*, 2007, Kiesswetter *et al.*, 2009). Kiesswetter *et al.* (2007) followed 20 welders in the train and truck construction industry from mean age 41 to 45 and Kiesswetter *et al.* (2009) followed 92 welders in the automobile industry from mean age 35 to 39. The mean dust load during welding was in the range of 5–8 mg/m^3 in Kiesswetter *et al.* (2007) and an order of magnitude lower, 0.5–0.8 mg/m^3 in Kiesswetter *et al.* (2009). Accordingly, welders in Kiesswetter *et al.* (2007) were characterized by higher body burden of aluminum (pre-shift: 88–140 µg Al/g creatinine in urine; 13–16 µg Al/l Plasma) compared to welders Kiesswetter *et al.* (2009) (pre-shift: 23–43 µg Al/g creatinine in urine; 5–9 µg Al/L plasma). Explorative regression and covariance analyses revealed neither a correlation between biomonitoring and neuropsychological test performance nor a significant difference between aluminum exposed and referents during the four year period. These results were consistent across the two studies, despite differences in exposure circumstances and age of workers.

In workers exposed to aluminum powder, the five-year longitudinal comparison between the first and second evaluations revealed improved test performance (Letzel *et al.*, 2000). This may be explained in part by improvement in occupational hygiene at the workplace which led to a significant reduction in aluminum excretion over the same time period. Nonetheless, no dose-effect relationship was found between the length of exposure or internal aluminum concentrations with any of the neuropsychological outcome variables.

5.2.3.2 Lung Function Outcomes

This review investigated potential respiratory effects following occupational exposure to aluminum, largely assessed using spirometry measurements of lung function.

Meta-analysis was conducted to pool the effect sizes from cross-sectional studies comparing three lung function test results from aluminum exposed to non-aluminum exposed workers: i) percent predicted forced vital capacity (ppFVC); ii) percent predicted forced expiratory volume in 1 second (ppFEV1); and, iii) percent predicated mean forced expiratory flow during mid-half of the FVC (ppFEF25-75). These measures of pulmonary function (ppFVC, ppFEV1, and ppFEF25-75), are typically used to diagnose lung disease such as COPD and asthma. Overall, the aluminum exposed populations in these studies had generally healthy measures of lung function (*i.e.*, there was no evidence of COPD, asthma, or other respiratory impairment). The overall MD of ppFVC indicates a small non-significant decrease among those occupationally exposed to aluminum compared to the referents, MD ppFVC = -2.87% (95%CI: -10.65, 4.90). The overall mean difference of ppFEV1 was -7.53% (95%CI: -13.36, -1.70), which indicated a small statistically significant decrease in lung function among those occupationally exposed to aluminum compared to the referents. The overall effect for ppFEF25-75 was provided by only three studies (Abbate *et al.*, 2003, Kilburn *et al.*, 1992, and San *et al.*, 1998). San *et al.* (1998) was identified as a low quality outlier study and removed from the analysis. After removing the outlier, the mean difference, based on only two studies, was a significant decrease, ppFEF25-75 = -12.96% (95%CI: -17.13 to -8.79). Because the mean population measures of ppFVC, ppFEV1, and ppFEF25-75 for aluminum exposed populations in these studies describe workers that are in generally good respiratory health, the meaning of the small differences between the exposed and referents in unclear and should be considered in the context of the additional findings described below.

A number of studies examining respiratory effects were not included in the meta-analysis either because they did not provide data in the adequate format (means and standard deviations) or different measures of lung function were used. One large Australian study investigated mining workers exposed to bauxite dust. Bauxite ore is the primary source of aluminum. The authors concluded that there were there were no significant differences in lung function (FEV_1, FVC,

FEV_1/FVC ratio) between exposed and unexposed workers after adjusting for age, height, and smoking.

The study findings for occupational workers in aluminum refining or production settings were more varied. One Danish study of cryolite production workers and two Australian studies of bauxite refinery workers concluded that workers' lung function with the highest cumulative exposures did not differ significantly from lung function of those with lower exposures (Friis *et al.*, 1989; Fritschi *et al.*, 2001; Musk *et al.*, 2000). Conversely, an earlier series of studies conducted in a bauxite refinery in the US concluded that higher cumulative dust exposure was associated with both lower FEV_1 and higher prevalence of irregular opacities on chest radiographs (Townsend *et al.*, 1985; Townsend *et al.*, 1988). Workers in this older study experienced much higher cumulative exposures than other studies that reported cumulative exposure.

Two studies in welding populations reported no association between aluminum exposure and impaired lung function (Sjogren and Ulfvarson, 1985; Haluza *et al.*, 2014) while another study of workers exposed to welding reported an acute fall in FEV_1 of at least 5% in workers exposed to "high" compared to "low" levels of aluminum (Fishwick *et al.*, 2004). The chronic respiratory effects of the short-term acute change in lung function are unknown.

The additional study findings showed mainly a lack of significant differences between aluminum exposed workers and non-exposed workers in terms of lung function. In the context of the meta-analytic results, the additional study findings do not support the potential effects on $ppFEV_1$ and ppFEF25-75 found in the meta-analysis. Considering all the evidence, the literature leans towards no significant difference between aluminum exposed workers and non-exposed workers in terms of lung function.

6.0 DISCUSSION

6.1 Causation and Hill's Criteria

As discussed in Section 1.2, one primary objective of this report was to determine whether a causal association can be established between increased risks of adverse chronic health effects due to occupational exposure to aluminum. A determination of causality considered the "Bradford Hill criteria", commonly used guidelines for assessing causal relationships in epidemiologic studies. These criteria include:

1. Temporality: What is the evidence that the exposure precedes the outcome? Temporality is the only absolutely necessary criterion that must be satisfied to establish causality.
2. Strength: How strong is the association? The stronger the association, the more likely it is that the association is causal.
3. Dose-response relationship: Is there a relationship between the magnitude of the exposure and the amount of disease observed?
4. Replicability: Have other studies demonstrated the same findings or relationship between the exposure and outcome? Systematic reviews are particularly important to determining if findings are consistent across different populations and circumstances.
5. Biologic Plausibility: Is this relationship consistent with current biological knowledge?
6. Alternative Explanations: Have alternative explanations for the observed results been explored?
7. Cessation of Exposure: Does the outcome diminish if the exposure is removed?
8. Specificity: Does the exposure have specific effects or generalized effects?
9. Coherence: How compatible are the findings with existing theory or knowledge?

As definitive proof for causality rarely exists in epidemiology, it is not required that all of these criteria be met. Often epidemiologists focus on the first five criteria for assessing causal relationships. In addition, while the likelihood of a causal association is increased if the third criterion (a dose-response relationship) can be demonstrated, this relationship is often difficult to demonstrate with epidemiological research. It is also important to recognize that for many environmental exposures the dose-response relationship may be non-linear (*i.e.*, a relationship that cannot be expressed simply as the change in response being proportional to the amount of change of dose, may be represented by a U shaped curve, J shaped curve, or some other shape).

A final determination of causality used an approach similar to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for reporting on the quality of evidence for outcomes in systematic reviews. The Grade approach expresses the quality of evidence using four levels of certainty ratings ("high", "moderate", "low", or "very low") (Schunemann *et al.* 2013). Below, the assessment of causality is presented according to health outcome.

6.1.1 ICD-Diagnosable Conditions

Neurological Disease (Alzheimer's disease, Parkinson's disease, ALS)

Of the studies that examined neurological disease endpoints, five were case-control studies and one was a retrospective cohort study. In a case-control or retrospective cohort study, details about aluminum exposure are gathered after a diagnosis of neurological disease has already

occurred and, therefore, information gathered from subjects about past exposures is subject to recall bias.

The meta-analysis of Alzheimer's disease outcomes found a positive association between aluminum exposure and disease; however, the strength of the association is weak and it was not statistically significant. Neither the study looking at Parkinson's disease nor the study looking at ALS reported an association between aluminum exposures and disease.

Only one of the studies examining neurological disease endpoints also included an analysis of a potential exposure-response relationship. Specifically, Peters *et al.* (2013) performed a subgroup analysis separating those with one to nine years of aluminum powder exposure and those with greater than ten years of aluminum powder, compared to no aluminum exposure. The hazard ratios suggested the possibility of a duration-response relationship (0-9 years: HR= 2.37, 95%CI: 0.63 to 8.88; ≥10 years: HR=3.59, 95% CI: 0.88 to 14.7) but neither were statistically significant. It is also important to note that these HRs were calculated based on very small numbers of Alzheimer's disease cases (four cases in each exposure group).

The findings across the literature on occupational exposure to aluminum and neurological disease were inconsistent. This inconsistency is demonstrated by the forest plot (Figure 4-1) in which studies reported effects fall on either side of the middle line (null effect), meaning that some studies show adverse effects among workers while others are contradictory, with no evident pattern of favoring one direction or the other.

As summarized in Section 2.2.6, the mechanism of aluminum neurotoxicity and other target organ toxicities have not been fully identified. Information on the toxicity of aluminum with respect to dialysis encephalopathy is not sufficient, because much of the work has been conducted on individuals with renal deficiencies. However, animal studies on certain species (*e.g.*, cats, rabbits, ferrets and nonhuman primates) have identified changes in cytoskeletal proteins within brain neurons similar to those identified in other neurodegenerative disorders, suggesting that abnormal neurological function could be related to cytoskeletal changes (ATSDR, 2008).

Based on the assessment of criteria for causality, our overall certainty in the evidence for aluminum exposure and neurological disease is "very low".

Other Diagnosable Conditions

Due to the small number of studies, the evidence for other diagnosable conditions (*e.g.*, cancer, diabetes, mortality) was insufficient to complete an assessment of causality.

6.1.2 Other Studied Health Outcomes

Neuropsychological Outcomes

A causal relationship requires the exposure to precede the outcome. The majority of neuropsychological studies available in the literature and reviewed herein were cross-sectional in design. Cross-sectional studies are limited by the fact that they are carried out at one time point and give no indication of whether exposure occurred before, after or during the onset of the health outcome. On the other hand, longitudinal studies are ideal for assessing causality because exposed subjects are assessed at baseline and then followed up over time. Longitudinal evidence from workers with relatively high aluminum exposure metrics (*i.e.*, urinary Al>100 µg/l) did not reveal any cognitive decline after four to five years of exposure to aluminum

dust in workers of a powder-producing plant or exposure to aluminum fumes in welders (according to Letzel *et al.* (2000) and Kiesswetter *et al.* (2007), respectively).

The strength of positive associations reported in the literature, with regard to aluminum-induced neurological effects, were typically small in magnitude. This is evident in the meta-analysis results showing the effect size, for individual outcomes, relative to the baseline measure. For outcomes with statistically significant associations, the effect sizes ranged from a 4% (simple reaction time) to 10% decrease (digit symbol test) in aluminum exposed workers compared to referents.

There was not clear evidence that higher exposures resulted in higher effects, although data on exposures was limited and primarily involved using biomarkers (*e.g.*, urine, plasma, serum) as a surrogate for exposure. Meta-regressions performed with the available data on exposure variables concluded that none of the statistically significant effects suggested an exposure-response. In addition, tabulated information on magnitude of exposure and neuropsychological outcomes failed to reveal any systematic patterns of significant findings by measured exposure levels including years of exposure, aluminum in air and aluminum in biomarkers.

The findings across the literature on occupational exposure to aluminum and effects were inconsistent. This inconsistency is demonstrated by the forest plots (in Section 4.3.2.1 and 4.3.3.1) in which studies reported effects fall on either side of the middle line (null effect), meaning that some studies show adverse effects among workers while others are contradictory, with no evident pattern of favoring one direction or the other.

Based on the assessment of criteria for causality, our overall certainty in the evidence for aluminum exposure and neuropsychological outcomes is “very low”.

Lung Function Outcomes

As with neuropsychological outcomes, the majority of lung function studies available in the literature and reviewed herein were cross-sectional in design. Due to the absence of longitudinal evidence for lung function, the temporality criteria is undetermined.

The strength of positive associations reported in the literature, with regard to aluminum-induced lung function effects, were small in magnitude. This is evident in the meta-analysis results for ppFVC (-0.3%) and ppFEV1 (-3%) after removal of outlier studies. The meta-analysis effect estimate was stronger for ppFEF25-75 but after removing an outlier study only two studies remained.

Meta-regressions performed with the available data on exposure variables concluded that none of the statistically significant effects suggested an exposure-response. However, data on exposures was limited and primarily involved using biomarkers (*e.g.*, urine, plasma, serum) as a surrogate for exposure. A few additional studies not included in the meta-analysis examined lung function outcomes related to cumulative exposures to bauxite dust. When cumulative bauxite exposure and lung function were investigated by Beach *et al.* (2001) and Fritschi *et al.* (2001), no exposure-response relationships were found. While Townsend *et al.* (1985) did find an association between long term cumulative total dust exposure among workers at a bauxite mine and alumina refinery in Arkansas U.S.A., this older study did not specifically assess bauxite/alumina exposure (only measurements for total dust were available).

The findings across the literature on occupational exposure to aluminum and lung function effects were inconsistent. This inconsistency is demonstrated by the forest plots (in Section

4.5.2.1) in which studies reported effects fall on either side of the middle line and in Table 4-16 which shows a few lung function studies to report significant findings of lung function effects while the majority of studies reported no significant findings.

While it is known that pneumoconiosis can occur due to inhalation of aluminum or aluminum oxide dust, the mechanisms of aluminum-related lung toxicity are not well understood. Specifically, it is not known whether effects are due to dust overload or aluminum itself. However, the potential for biologic plausibility cannot be ruled out.

Based on the assessment of criteria for causality, our overall certainty in the evidence for aluminum exposure and lung function outcomes is “low”.

6.2 Limitations

The results of this systematic review and meta-analysis should be regarded in the context of several methodological and analytical limitations.

Bias, or a systematic under-estimation or over-estimation of an effect, was considered. Healthy worker effect is a phenomenon sometimes observed in studies of occupational diseases where workers usually exhibit lower mortality or morbidity than the general population because the severely ill and chronically disabled are ordinarily excluded from employment. To avoid bias due to healthy worker effect, the use of the general population as a comparison group in occupational epidemiology should be avoided if possible. Because most of the studies included in this review used a reference group of other workers (not occupationally exposed to aluminum), healthy worker effect in this systematic review should be minimal.

Another type of bias that may be present in the individual studies is confounding due to multiple hazardous exposures. Aluminum exposure was primarily studied in the sectors of welding and aluminum refining/production. In general, workers in these and other industries are not exposed to pure aluminum without exposure to other potentially hazardous materials. For example, most aluminum welders are also exposed to the neurotoxic metals manganese and lead which might confound study results (Keisswetter *et al.*, 2007). Iregren *et al.* (2001) controlled for different types of welding exposures but most studies did not. In addition to alumina, workers in aluminum production are exposed to polycyclic aromatic hydrocarbons, sulfur dioxide and fluorides; aluminum fluoride; carbon monoxide; carbon dioxide; various trace metals; asbestos; extreme heat; and high static magnetic fields (IARC, 2010). Confounding due to other hazardous exposures could also impact findings related to referent workers, given that other workers (*e.g.*, miners or welders not exposed to aluminum) are also exposed to many hazards. Therefore, confounding due to other hazardous exposures may have resulted in an under- or over-estimation of effect attributed to aluminum exposure.

As evidenced by the literature, occupational settings with aluminum exposure is dominated by males. Most studies dealt with the low prevalence of females in the study cohort by excluding them from analyses since they represented such a small proportion of the study population. Women may have different susceptibility to aluminum exposure than men. Therefore, it is unknown whether the results of the systematic review are generalizable to women.

A limitation of the meta-analyses is that there were not enough studies reporting outcomes for portions of the analysis. First, there were less than the 10 studies recommended to evaluate the presence of publication bias with Funnel plots and Egger’s regression test. Publication bias refers to an absence of neutral or “negative” effect studies available in the literature because of a bias to publish results that appear significant. If publication bias is present, correction of this bias

would most likely shift results to the null. Second, there were fewer than the recommended 10 studies for each outcome for conducting meta-regression, therefore the meta-regression results should be interpreted with caution.

6.3 Concluding Comments

The Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, 2009) governed the study search and evaluation process for the systematic review of occupational aluminum exposure and adverse health outcomes. The literature review included a search of epidemiological studies that investigate the health effects (primarily neurological disorders) associated with occupational exposure to aluminum. The search strategy used controlled vocabulary terms and keywords including terms for "Occupational", "Aluminum", "McIntyre Powder", "Alzheimer's disease", "Parkinson's disease", "Amyotrophic Lateral Sclerosis" and additional neurological and other conditions.

A total of 62 epidemiological studies were selected for inclusion in the review, covering a broad range of health outcomes, study designs, occupational settings, forms of aluminum to which workers were exposed, and other factors. The focus of most of the research was on the potential role of aluminum as a risk factor for Alzheimer's disease and dementia. The reports mainly investigated this role through performing a variety of neuropsychological tests or examining other indicators of pre-clinical impacts (*e.g.*, EEG findings).

A focus of this review was on McIntyre-exposed workers; however, there were insufficient studies to perform subgroup analyses for McIntyre-exposed workers. Of the three 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; no differences in diagnosed neurological disorders were apparent in the exposed workers compared to non-exposed referent workers.

Findings for aluminum exposed workers in well-studied industries (*e.g.*, aluminum production and welding) are pertinent to the McIntyre Powder exposed workers, particularly because all occupational exposure to aluminum particles is via inhalation. In addition, the forms of aluminum in McIntyre Powder (*i.e.*, 15% elemental aluminum and 85% aluminum oxide) are the forms most often studied in the occupational health literature. Data on the amount of McIntyre Powder to which workers were regularly exposed is scarce, making it difficult to compare cumulative aluminum exposures for McIntyre Powder exposed workers to workers in other industries.

According to McIntyre Research Foundation records, McIntyre Powder exposures were reportedly 35.6 mg/m^3 for 10 minutes per day (Newkirk, 1972).[2] While short-term exposure limits for occupational aluminum exposure have not been established, the reported McIntyre Powder exposure level averaged over an 8-hour workday equates to a 0.74 mg/m^3 time-weighted average; this is below the range of occupational exposure limits for aluminum (from 1 to 15 mg/m^3 8-hour TWA, see Section 2.5.1).

[2] This information was revised from the Final Report dated April 28th, 2017, which referenced McIntyre Powder exposure levels (353 mg/m^3 of air) contained within the 1992 IDSP Report. McIntyre Research Foundation records subsequently obtained from the Archives of Ontario indicate that the recommended dispersal was actually 1 gram of McIntyre Powder per 1000 cubic feet of air (equivalent to 1 mg/ft^3 or 35.6 mg/m^3).

Because the purpose of many studies selected in the literature review was not to assess the risk of specific (*i.e.*, diagnosable) health outcomes but rather to more broadly examine the potential effects on neurobehavioral or respiratory performance, the results of the systematic review are ordered into ICD-diagnosable conditions versus other studied health outcomes (*i.e.*, non ICD-diagnosable conditions).

Diagnosable health outcomes considered in this systematic review included the following neurological diseases: Alzheimer's disease, Parkinson's disease, or ALS. Meta-analysis was conducted to systematically quantify the relationship between occupational exposure to aluminum and risk of Alzheimer's disease. Three case-control studies and one retrospective matched cohort study met the criteria for inclusion. Results of the meta-analysis indicated that occupational aluminum exposure was not associated with Alzheimer's disease (odds ratio, 1.28; 95% confidence interval, 0.78 to 2.10). The literature review identified one study examining aluminum as a potential risk factor for ALS, and one study examining aluminum as a potential risk factor for Parkinson's disease; neither reported an association between aluminum and the neurological disease.

In addition to neurological disease, this systematic review also summarizes the epidemiological literature on more rarely studied diagnosable conditions, and there potential association with occupational aluminum exposure, including cardiovascular outcomes, cancer, diabetes, mortality, osteodystrophy, and reproductive effects. Weak associations, based on few cases, were reported between aluminum exposure and non-malignant respiratory disease mortality, cerebrovascular disease mortality, and cardiovascular mortality (Friesen *et al.*, 2009, Peters *et al.*, 2013). Of four studies investigating potential biomarkers of cancer, two found some evidence of association or correlation between aluminum exposure and DNA damage although the biologic significance of those findings is unknown (Botta *et al.*, 2006; Hou *et al.*, 2011). Overall, the findings related to other health outcomes provided suggestive but no conclusive evidence of adverse effects related to occupational aluminum exposure.

Results for the non ICD-diagnosable conditions, including neuropsychological and lung function test outcomes, make up a large part of this systematic review. Meta-analysis was applied to pool the effect sizes from cross-sectional studies comparing seven neuropsychological test results from aluminum exposed to non-aluminum exposed workers. The meta-analysis neuropsychological test results revealed four (of seven) statistically significant effects of decreased test performance in workers occupationally exposed to aluminum: i) Santa Ana Dexterity dominant hand; ii) simple reaction time; iii) digit symbol; and, iv) mini mental status examination (MMSE) score. While meta-regressions performed with the available exposure data showed no dose-response trends for these effects, these findings are uncertain given the limited number of studies that included exposure data and the inconsistent methods used to investigate dose across the different studies. Meta-analysis effect sizes for Santa Ana Dexterity non-dominant hand, digit span forward, and digit span backward were not statistically significant.

Critical analysis of additional neuropsychological test outcomes (not included in the meta-analyses) did not detect systematic patterns of significant findings by neuropsychological testing domain or aluminum exposure levels. However, results were difficult to interpret given the non-uniform nature of occupational settings, neuropsychological tests used, cognitive domains, different exposure parameters considered, as well as other factors. Longitudinal evidence from workers with relatively high aluminum exposure metrics (*i.e.*, urinary Al>100 µg/l) did not reveal any cognitive decline after four to five years of exposure to aluminum dust in workers of a powder-producing plant or exposure to aluminum fumes in welders (according to Letzel *et al.* (2000) and Kiesswetter *et al.* (2007), respectively). Additional good quality, longitudinal assessments would be of benefit in clarifying the neurological effects from aluminum.

Meta-analysis was conducted to pool the effect sizes from cross-sectional studies comparing three lung function test results from aluminum exposed to non-aluminum exposed workers: i) percent predicted forced vital capacity (ppFVC); ii) percent predicted forced expiratory volume in one second (ppFEV1); and, iii) percent predicated mean forced expiratory flow during mid-half of the FVC (ppFEF25-75). Meta-analyses detected a slight impairment in two lung function outcomes (ppFEV1 and ppFEF25-75) in aluminum workers compared to referents. However, mean data on the clinically relevant measure of ratio FEV_1/FVC characterized all aluminum exposed groups as having normal lung function. A number of studies examining respiratory effects did not have adequate data for inclusion in the meta-analysis and were instead assessed qualitatively. Findings from these additional studies mainly showed a lack of significant differences between aluminum exposed workers and non-exposed workers in terms of lung function and did not support the potential effects on $ppFEV_1$ and ppFEF25-75 found in the meta-analysis.

The main limitation of this review lies in interpreting aluminum exposure across the body of literature. Namely, the collection of aluminum exposure data varied considerably depending on the individual study. Fewer than half of studies sampled aluminum in workplace air. Biomarker measures of aluminum body burden included aluminum in urine, aluminum in blood, and aluminum in serum. However, the importance of aluminum biomonitoring data in workers is questionable with different findings on how well biomarker measures correlate to chronic exposure. In addition, interpreting aluminum exposure data was limited due to potential confounding from other hazardous exposures. Occupational workers exposed to aluminum (*e.g.*, miners, welders, aluminum production or refinery workers) are also often exposed to a mixture of hazardous substances.

There are two conditions that are only minimally considered in this review because of the absence of suitable published studies: pneumoconiosis and certain cancers. The Peters *et al.* (2013) study in Australia did not find an excess of pneumoconiosis. As to cancer, the International Agency for Research on Cancer (IARC) has categorized aluminum production as a human carcinogen. This is because occupational exposures during aluminum production cause cancer of bladder, and, to a lesser extent, of the lung. However, as noted in the review, the carcinogen that results in the increased incidence of these cancers is not aluminum itself, rather other agents (*e.g.*, PAHs) that are carcinogenic.

Overall, the systematic review and meta-analysis showed that the question of health risks from occupational aluminum exposure is complex. The findings across the literature were inconsistent. Epidemiological studies have failed to establish consistent associations or clear exposure response relationships between workplace aluminum and neurological diseases, neuropsychological outcomes, lung function outcomes, and other adverse outcomes. Consideration of the evidence for neurological diseases, neuropsychological outcomes, and lung function outcomes in context of the Bradford Hill criteria for causality (temporality, strength, dose-response relationships, replicability, and biologic plausibility) found most of the criteria were not satisfied and judged the certainty of evidence for an association with occupational aluminum to be very low. Due to the small number of studies, the evidence for other diagnosable conditions (*e.g.*, cancer, diabetes, mortality) was insufficient to complete an assessment of causality. Although findings cannot conclusively state whether or not aluminum is a causative agent in development of adverse health conditions, the evidence considered in total has not supported a link.

7.0 REFERENCES

Abbate, C; Giorgianni, C; Brecciaroli, R; Tringali, M A & D'Arrigo, G. 2003. Spirometric function in non-smoking workers exposed to aluminum. American Journal of Industrial Medicine 44(4):400-404.

Akila, R; Stollery, B T & Riihimaki, V. 1999. Decrements in cognitive performance in metal inert gas welders exposed to aluminum. Occupational and environmental medicine 56(9):632-639.

Alzheimer's Association. 2016. 2016 Alzheimer's disease facts and figures. Available at: http://www.alz.org/documents_custom/2016-facts-and-figures.pdf.

Aronson, K. J.; Siemiatycki, J.; Dewar, R.; Gerin, M. 1996. Occupational Risk Factors for Prostate Cancer: Results from a Case-Control Study in Montreal, Quebec, Canada. American Journal of Epidemiology, Vol. 143, No. 4, pages 363373.

ASC. 2016. Dementia numbers in Canada. Alzheimer's Society of Canada. Available at: http://www.alzheimer.ca/en/About-dementia/What-is-dementia/Dementia-numbers.

ATSDR. 2004. Health Consultation, blood and urine tests. U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry. Available at: https://www.atsdr.cdc.gov/HAC/pha/BloodUrineTestResults051104-FL/BloodUrineTestResultsHC051104.pdf.

ATSDR. 2008. Toxicological Profile for Aluminum. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Baptist A & Sanders G. 2005. Pulmonary Function Tests (PFTs). The University of Michigan – Division of Allergy and Immunology. March 5, 2005. Available at: http://www.med.umich.edu/intmed/allergy/edu/syllabus/TOPICS/PFTs/pft.htm.

Bast-Pettersen, R; Drablos, P A; Goffeng, L O; Thomassen, Y & Torres, C G. 1994. Neuropsychological deficit among elderly workers in aluminum production. American Journal of Industrial Medicine 25(5):649-662.

Bast-Pettersen, R; Skaug, V; Ellingsen, D & Thomassen, Y. 2000. Neurobehavioral performance in aluminum welders. American journal of industrial medicine 37(2):184-192.

Beach, J R; de Klerk, N H; Fritschi, L; Sim, M R; Musk, A W; Benke, G; Abramson, M J & McNeil, J J. 2001. Respiratory symptoms and lung function in bauxite miners. International archives of occupational and environmental health 74(7):489-494.

Bogdanovic, M. and Bulat, P. (2008). Biliary Function in Workers Occupationally Exposed to Aluminum Dust and Fumes. Archives of Industrial Hygiene and Toxicology 59(2): 135-9.

Burback D, Molnar FJ, St John P *et al.* 1999. Key methodological features of randomized controlled trials of Alzheimer's disease therapy. Minimal clinically important difference, sample size and trial duration. Dement Geriatr Cogn Disord10:534–40.

Camerino, D; Cassitto, M G & Gilioli, R. 1993. Prevalence of abnormal neurobehavioral scores in populations exposed to different industrial chemicals. Environmental Research 61(2):251-257.CDC. 2014. FastStats: Alzheimer`s disease. Available from: https://www.cdc.gov/nchs/fastats/alzheimers.htm.

Dennekamp, Martine; de Klerk, Nicholas Hubert; Reid, Alison; Abramson, Michael John; Cui, Jisheng; Del Monaco, Anthony; Fritschi, Lin; Benke, Geza Paul; Sim, Malcolm Ross & Musk, Arthur William. 2015. Longitudinal analysis of respiratory outcomes among bauxite exposed workers in Western Australia. American journal of industrial medicine 58(8):897-904.

Deschamps, Frederic J; Lesage, Francois Xavier; Chobriat, Jeremy; Py, Nadine & Novella, Jean Luc. 2009. Exposure risk assessment in an aluminium salvage plant. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 51(11):1267-1274.

Dick, R B; Krieg, E F Jr; Sim, M A; Bernard, B P & Taylor, B T. 1997. Evaluation of tremor in aluminum production workers. Neurotoxicology and teratology 19(6):447-453.

Doll SR. 1993. Review: Alzheimer's disease and environmental aluminium. *Age and aging* 1993;22:38-153.

Fishwick, David; Bradshaw, Lisa; Slater, Tania; Curran, Andrew & Pearce, Neil. 2004. Respiratory symptoms and lung function change in welders: are they associated with workplace exposures? The New Zealand medical journal 117(1193):U872.

Flarend R, Bin T, Elmore D, *et al.* 2001. A preliminary study of the dermal absorption of aluminum from antiperspirants using aluminum-26. Food Chem Toxicol 39(2):163-168.

Flaten TP. 2001. Aluminum as a risk factor in Alzheimer's disease, with emphasis on drinking water. Brain Res Bull 55:187–196.

Flaten TP, Alfrey AC, Birchall JD, Savory J, Yokel RA. 1996. Status and future concerns of clinical and environmental aluminium toxicology. *Journal of toxicology and environmental health* 48:527-541.

Friesen, M C; Fritschi, L; Del Monaco, A; Benke, G; Dennekamp, M; de Klerk, N; Hoving, J L; MacFarlane, E & Sim, M R. 2009. Relationships between alumina and bauxite dust exposure and cancer, respiratory and circulatory disease. Occupational and environmental medicine 66(9):615-618.

Friis, H.; Clausen, J.; Gyntelberg, F. 1989. Cross-Sectional Study of Health Effects of Cryolite Production. Journal of the Society of Occupational Medicine, Vol. 39, No. 4, pages 133-135.

Fritschi, L; De Klerk, N; Sim, M; Benke, G & Musk, A. 2001. Respiratory morbidity and exposure to bauxite, alumina and caustic mist in alumina refineries. Journal of Occupational Health 43(5):231-237.

Fritschi, Lin; Hoving, Jan Lucas; Sim, Malcolm R; Del Monaco, Anthony; MacFarlane, Ewan; McKenzie, Dean; Benke, Geza & de Klerk, Nicholas. 2008. All cause mortality and incidence of cancer in workers in bauxite mines and alumina refineries. International journal of cancer 123(4):882-887.

Ganrot PO. 1986. Metabolism and possible health effects of aluminum. Environ Health Perspect 65:363-441.

Gibbs GW, Horowitz I. 1979. Lung cancer mortality in aluminum reduction plant workers. J Occup Med 21:347-353. Cited In: ATSDR, 2008.

Giorgianni, Concetto Mario; D'Arrigo, Graziella; Brecciaroli, Renato; Abbate, Adriana; Spatari, Giovanna; Tringali, Maria Antonietta; Gangemi, Silvia & De Luca, Annamaria. 2014. Neurocognitive effects in welders exposed to aluminium. Toxicology and industrial health 30(4):347-356.

Graves AB, Rosner D, Echeverria D, Mortiner JA, Larson EB. 1998. Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease. *Journal of Occupational and Environmental Medicine* 55:627-633.

Graves AB, White E, Koepsell TD, *et al.* 1990. The association between aluminum-containing products and Alzheimer's disease. J Clin Epidemiol 43:35-44

Gun RT, Korten AF, Henderson AS *et al.* 1997. Occupational risk factors for Alzheimer disease: a case control study. *Alzheimer's disease and associated disorders* 11:21-27.

Guo, G., Ma, H., Wang, X. and Liang, Y. 1999. Age-dependent differences of neurobehavioural function among workers exposed to aluminium. J. Environ. Med 1():81-85.

Halatek, T; Sinczuk-Walczak, H & Rydzynski, K. 2005. Prognostic significance of low serum levels of Clara cell phospholipid-binding protein in occupational aluminium neurotoxicity. Journal of Inorganic Biochemistry 99():1904-1911.

Halatek, Tadeusz; Trzcinka-Ochocka, Malgorzata; Matczak, Wanda & Gruchala, Jacek. 2006. Serum Clara cell protein as an indicator of pulmonary impairment in occupational exposure at aluminum foundry. International journal of occupational medicine and environmental health 19(4):211-223.

Halatek, T; Sinczuk-Walczak, H & Rydzynski, K. 2008. Early neurotoxic effects of inhalation exposure to aluminum and/or manganese assessed by serum levels of phospholipid-binding Clara cells protein. Journal of Environmental Science and Health - Part A Toxic/Hazardous Substances and Environmental Engineering 43(2):118-124.

Haluza, D; Moshammer, H & Hochgatterer, K. 2014. Dust is in the air. Part II: Effects of occupational exposure to welding fumes on lung function in a 9-year study. Lung 192(1):111-117.

Hanninen, H; Matikainen, E; Kovala, T; Valkonen, S & Riihimaki, V. 1994. Internal load of aluminum and the central nervous system function of aluminum welders. Scandinavian journal of work, environment {\&} health 20(4):279-285.

He, S C; Qiao, N & Sheng, W. 2003. Neurobehavioral, autonomic nervous function and lymphocyte subsets among aluminum electrolytic workers. International Journal of Immunopathology and Pharmacology 16(2):139-144.

Health Canada. 1998. Aluminum. Available at: http://healthycanadians.gc.ca/publications/healthy-living-vie-saine/water-aluminum-eau/alt/water-aluminum-eau-eng.pdf.

Hovsovski, E; Vidakovic, A & Hovsovski, M. 1998. Dermal and bronchial responsiveness of aluminium smelter workers. Journal of Occupational Health 40(1):44-49.

Hovatta, O; Venalainen, E R; Kuusimaki, L; Heikkila, J; Hirvi, T & Reima, I. 1998. Aluminium, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men. Human reproduction (Oxford, England) 13(1):115-119.

Hoyer WJ, Stawski RS, Wasylyshyn C, Verhaeghen P. 2004. Adult age and digit symbol substitution performance: a meta-analysis. Psychol Aging 19:211–214.

IARC. 1984. Polynuclear aromatic compounds. Part 3: Industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. Vol. 34. Lyon, France: World Health Organization, International Agency for Research on Cancer, 37-64.

IARC. 2010. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum. 2010;92:1–853.

IDSP. 1992. Interim report to the worker's compensation board on aluminum. Industrial Disease Standards Panel. IDSP Report of Findings No. 9.

Iregren, A; Sjogren, B; Gustafsson, K; Hagman, M; Nylen, L; Frech, W; Andersson, M; Ljunggren, K G & Wennberg, A. 2001. Effects on the nervous system in different groups of workers exposed to aluminium. Occupational and environmental medicine 58(7):453-460.

Jouhanneau P, Lacour B, Raisbeck G, *et al.* 1993. Gastrointestinal absorption of aluminum in rats using Al and accelerator mass spectrometry. Clin Nephrol 40(4):244-248.

Jouhanneau P, Raisbeck GM, Yiou F, *et al.* 1997. Gastrointestinal absorption, tissue retention, and urinary excretion of dietary aluminum in rats determined by using 26Al. Clin Chem 43(6 Part 1):10231028.

Joy, S, Kaplan, E and Fein, D. 2004. Speed and memory in the WAIS-III Digit Symbol–Coding subtest across the adult lifespan. Archives of Clinical Neuropsychology, 19: 759–767.

Kiesswetter, E; Schaper, M; Buchta, M; Schaller, K H; Rossbach, B; Scherhag, H; Zschiesche, W & Letzel, S. 2007. Longitudinal study on potential neurotoxic effects of aluminium: I. Assessment of exposure and neurobehavioural performance of Al welders in the train and truck construction industry over 4 years. International archives of occupational and environmental health 81(1):41-67.

Kiesswetter, Ernst; Schaper, M; Buchta, M; Schaller, K H; Rossbach, B; Kraus, T & Letzel, S. 2009. Longitudinal study on potential neurotoxic effects of aluminium: II. Assessment of exposure and neurobehavioral performance of Al welders in the automobile industry over 4 years. International archives of occupational and environmental health 82(10):1191-1210.

Kilburn, K H & Warshaw, R H. 1992. Irregular opacities in the lung, occupational asthma, and airways dysfunction in aluminum workers. American Journal of Industrial Medicine 21(6):845-853.

Kilburn, K H. 1998. Neurobehavioral impairment and symptoms associated with aluminum remelting. Archives of environmental health 53(5):329-335.

Kilburn KH. 1999. Does exposure to fine aluminium dust affect the brain? *The Lancet* 354:1575-1577.

Krewski, D., Yokel, R.A., Nieboer, E., Borchelt, D., Cohen, J., Harry, J., Kacew, S., Lindsay, J., Mahfouz, A.M. and Rondeau, V. 2007. Human health risk assessment for aluminum, aluminum oxide, and aluminum hydroxide. J Toxicol Environ Health Crit Rev 10 (1):1-269.

Larsson, K; Eklund, A; Arns, R; Lowgren, H; Nystrom, J; Sundstrom, G & Tornling, G. 1989. Lung function and bronchial reactivity in aluminum potroom workers. Scandinavian Journal of Work, Environment and Health 15(4):296-301.

Letzel, S; Lang, C J G; Schaller, K H; Angerer, J; Fuchs, S; Neund{\{o}}rfer. 2000. Longitudinal study of neurotoxicity with occupational exposure to aluminum dust. Neurology ():997-1000.

Liu, B; Feng, W; Wang, J; Li, Y; Han, X; Hu, H; Guo, H; Zhang, X & He, M. 2016. Association of urinary metals levels with type 2 diabetes risk in coke oven workers. Environmental Pollution 210():42743.

Lu, Xiaoting; Liang, Ruifeng; Jia, Zhijian; Wang, Hao; Pan, Baolong; Zhang, Qinli & Niu, Qiao. 2014. Cognitive disorders and tau-protein expression among retired aluminum smelting workers. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 56(2):155-160.

McDonald, B., Haszard, R., Spenee, A. and Obbourne, K. 1996. A mortality study of Alzheimer's disease and aluminin exposure through inhalation of McImyre powder in Cornish Tin Miners. Fifth International Conference on Alzheimer’s Disease:S122-S123.

McGuire V, Longstreth WT Jr, Nelson LM, Koepsell TD, Checkoway H, Morgan MS, van Belle G. 1997. McGuire V1, Longstreth WT Jr, Nelson LM, Koepsell TD, Checkoway H, Morgan MS, van Belle G. Am J Epidemiol. 145(12):1076-88.

Mclachlan DRC. 1995. Aluminium and the risk for Alzheimer's disease. *Environmetrics* 6:233-275.

Meyer-Baron, M., Schaper, M., Knapp, G., and van Thriel, C. 2007. Occupational aluminum exposure evidence in support of its neurobehavioral impact. Neurotoxicologu 28:1068-1078.

Milham S Jr. 1979. Mortality in aluminum reduction plant workers. J Occup Med 21(7):475-480. Cited In: ATSDR, 2008.

Mitchell J, Manning GB, Molyneux M, *et al.* 1961. Pulmonary fibrosis in workers exposed to finely powdered aluminum. Br J Ind Med 18:10-20.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Mur JM, Moulin JJ, Meyer-Bisch C, *et al.* 1987. Mortality of aluminum reduction plant workers in France. Int J Epidemiol 16:257-264. Cited In: ATSDR, 2008.

Musk, A W; De Klerk, N H; Beach, J R; Fritschi, L; Sim, M R; Benke, G; Abramson, M & McNeil, J J. 2000. Respiratory symptoms and lung function in alumina refinery employees. Occupational and Environmental Medicine 57(4):279-283.

Mussi I, Calzaferri G, Buratti M, *et al.* 1984. Behaviour of plasma and urinary aluminum levels in occupationally exposed subjects. Int Arch Occup Environ Health 54(2):155-161.

Nayak P. 2002. Aluminum: Impacts and disease. Environ Res 89(2):101-115.

NewKirk, T.E. 1972. Standard Practices and Procedures for Application and Assessment of Aluminum Prophylaxis to Prevent the Development of Silicosis. McIntyre Research Foundation. April 1972.

NIH. 2016. Alzheimer's Disease Fact Sheet. National Institute on Aging, National Institute of Health. Available at: https://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet.

NINDS. 2013. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. National Institute of Neurological Disorders and Stroke, National Institutes of Health. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet.

NINDS. 2015. Parkinson's Disease: Challenges, Progress, and Promise. National Institute of Neurological Disorders and Stroke, National Institutes of Health. Available from: https://www.ninds.nih.gov/Disorders/All-Disorders/NINDS-Parkinsons-Disease-Information-Page/Parkinsons-Disease-Challenges.

Parent, M.-E.; Siemiatycki, J & Fritschi, L. 2000. Workplace exposures and oesophageal cancer. Occupational and Environmental Medicine 57(5):325-334.

PDF. 2016. Statistics on Parkinson's. Parkinson's Disease Foundation Inc. Available at: http://www.pdf.org/en/parkinson_statistics.

Peters, Susan; Reid, Alison; Fritschi, Lin; de Klerk, Nicholas & Musk, A W Bill. 2013. Long-term effects of aluminium dust inhalation. Occupational and environmental medicine 70(12):864-868.

Pigott GH, Gaskell BA, Ishmael J. 1981. Effects of long term inhalation of alumina fibres in rats. Br J Exp Pathol 62(3):323-331. Cited In: ATSDR, 2008.

Polizzi, Salvatore; Pira, Enrico; Ferrara, Mauro; Bugiani, Massimiliano; Papaleo, Andrea; Albera, Roberto & Palmi, Silvana. 2002. Neurotoxic effects of aluminium among foundry workers and Alzheimer's disease. Neurotoxicology 23(6):761-774.

RCI. 2015. McIntyre Powder: inhaling aluminum powder to prevent lung disease. Radio Canada International. Available at: http://www.rcinet.ca/en/2015/11/30/mcintyre-powder-decades-of-inhaling-aluminium-powder-to-prevent-lung-disease/.

Rifat, S L; Eastwood, M R; McLachlan, D R & Corey, P N. 1990. Effect of exposure of miners to aluminium powder. Lancet (London, England) 336(8724):1162-1165.

Riihimaki, V. and Aitio, A. 2012. Occupational exposure to aluminum and its biomonitoring in perspective. Critical Reviews in Toxicology, 42(10):827-853.

Riihimaki, V; Hanninen, H; Akila, R; Kovala, T; Kuosma, E; Paakkulainen, H; Valkonen, S & Engstrom, B. 2000. Body burden of aluminum in relation to central nervous system function among metal inert-gas welders. Scandinavian journal of work, environment & health 26(2):118-130.

Rockette HE, Arena VC. 1983. Mortality studies of aluminum reduction plant workers: Potroom and carbon department. J Occup Med 25:549-557. Cited In: ATSDR, 2008.

Rollin HB, Theodorov P, Noguier CM, Levin J. 2001. Aluminium uptake and excretion in potroom workers of a new primary aluminium smelter during the construction stage. J Environ Monit 3:560–564.

Salib, E & Hillier, V. 1996. A case-control study of Alzheimer's disease and aluminium occupation. The British journal of psychiatry: the journal of mental science 168(2):244-249.

San, L N; Uysal, H; Gokbel, H; Bediz, C S & Sayal, A. 1998. Pulmonary function of workers in the aluminum industry. American journal of industrial medicine 33(3):305-307.

Santibanez, M., Bolumar, F. and Garcıa, A.M. 2007. Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies. Occup Environ Med 64:723–732.

Schmid, K; Angerer, J; Letzel, S; Sturm, G & Lehnert, G. 1995. Use of bone mineral content determination by X-ray absorptiometry in the evaluation of osteodystrophy among workers exposed to aluminium powders. Science of the Total Environment 163():147-151.

Schünemann, H., Brożek, J., Oxman, G., 2013. Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE Approach.

Semchuk, K M; Love, E J & Lee, R G. 1993. Parkinson's disease: A test of the multifactorial etiologic hypothesis. Neurology 43(6):1173-1180.

Seshadri S, Wolf P, Beiser A, *et al.* 1997. Lifetime risk of dementia and Alzheimer's disease. Neurology 49:1498–504.

Sim, M; Dick, R; Russo, J; Bernard, B; Grubb, P; Krieg, E Jr; Mueller, C & McCammon, C. 1997. Are aluminium potroom workers at increased risk of neurological disorders?. Occupational and environmental medicine 54(4):229-235.

Sinczuk-Walczak, Halina; Szymczak, Maria; Razniewska, Grazyna; Matczak, Wanda & Szymczak, Wieslaw. 2003. Effects of occupational exposure to aluminum on nervous system: clinical and electroencephalographic findings. International journal of occupational medicine and environmental health 16(4):301-310.

Sjögren B, Elinder C-G, Lidums V, *et al.* 1988. Uptake and urinary excretion of aluminum among welders. Int Arch Occup Environ Health 60(2):77-79.

Sjögren B, Gustavsson P, Hogstedt C. 1990. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. Br J Ind Med 47(10):704-707.

Sjögren, B; Iregren, A; Frech, W; Hagman, M; Johansson, L; Tesarz, M & Wennberg, A. 1996. Effects on the nervous system among welders exposed to aluminium and manganese. Occupational and environmental medicine 53(1):32-40.

Sjögren B, Lidums V, Hakansson M, *et al.* 1985. Exposure and urinary excretion of aluminum during welding. Scand J Work Environ Health 11(1):39-43.

Sjögren, B & Ulfvarson, U. 1985. Respiratory symptoms and pulmonary function among welders working with aluminum, stainless steel and railroad tracks. Scandinavian journal of work, environment & health 11(1):27-32.

StatCan. 2014. Parkinson's disease: Prevalence, diagnosis and impact. Statistics Canada. Available at: http://www.statcan.gc.ca/pub/82-003-x/2014011/article/14112-eng.pdf.

Steinhagen WH, Cavender FL, Cockrell BY. 1978. Six month inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. J Environ Pathol Toxicol 1:267-277.

Stone CJ, McLaurin DA, Steinhagen WH, *et al.* 1979. Tissue deposition patterns after chronic inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. Toxicol Appl Pharmacol 49:71-76.

Tejada-Vera, B. 2010. Mortality from Alzheimer`s Disease in the United States: Data for 200 and 2010. Available from: https://www.cdc.gov/nchs/data/databriefs/db116.pdf.

Theriault G, Cordier S, Tremblay C, *et al.* 1984. Bladder cancer in the aluminum industry. Lancet 1(8383):947-950.

Townsend, M C; Enterline, P E; Sussman, N B; Bonney, T B & Rippey, L L. 1985. Pulmonary function in relation to total dust exposure at a bauxite refinery and alumina-based chemical products plant. The American review of respiratory disease 132(6):1174-1180.

Townsend, M C; Sussman, N B; Enterline, P E; Morgan, W K; Belk, H D & Dinman, B D. 1988. Radiographic abnormalities in relation to total dust exposure at a bauxite refinery and alumina-based chemical products plant. The American review of respiratory disease 138(1):90-95.

UCB. 2016. Parkinson's Disease. Available at: http://www.ucb-canada.ca/en/Patients/Conditions/Parkinson-s-Disease.

van Rooy, F.G., Houba, R., Stigter, H., Zaat, V.A., Zengeni, M.M., Rooyackers, J.M., Boers, H.E., Heederik, D.J. (2011). A cross-sectional study of exposures, lung function and respiratory symptoms among aluminium cast-house workers. Occup Environ Med. 68(12): 876-82.

Virk, S.A. and Eslick G.D. 2015. Occupational exposure to aluminum and Alzheimer's disease: a meta-analysis. Journal of Occupational and Environmental Medicine 57(8):893-896.

Wang, Z., Weia, X., Yanga, J., Suoa, J., Chena, J., Liub, X. and Zhaoa, X. 2016. Chronic exposure to aluminum and risk of Alzheimer's disease: A meta-analysis. Neuroscience Letters 610:200-206.

Willhite, C.C., Karyakina, N.A., Yokel, R.A., Yenugadhati, N., Wisniewski, T.M., Arnold, I.M.F., Momoli, F., and Krewski1, D. 2014. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts. Crit Rev Toxicol; 44(S4): 1–80.

Yang, H G; Lee, B L; Liang, Y X; Zheng, Y X & Ong, C N. 1998. The effects of exposure to aluminium on neurobehavioural function and dopaminergic metabolism. International Journal of Environmental Health Research 8(2):101-110.

Yang, X; Yuan, Y; Lu, X; Yang, J; Wang, L; Song, J; Nie, J; Zhang, Q & Niu, Q. 2015. The Relationship between Cognitive Impairment and Global DNA Methylation Decrease among Aluminum Potroom Workers. Journal of Occupational and Environmental Medicine 57(7):713-717.

Yokel RA, McNamara PJ. 2001. Aluminium toxicokinetics: An updated minireview. Pharmacol Toxicol 88(4):159-167.

Zawilla, N H; Taha, F M; Kishk, N A; Farahat, S A; Farghaly, M & Hussein, M. 2014. Occupational exposure to aluminum and its amyloidogenic link with cognitive functions. Journal of inorganic biochemistry 139():57-64.

SCIENCE INTEGRITY KNOWLEDGE

SYSTEMATIC REVIEW OF OCCUPATIONAL ALUMINUM EXPOSURE AND ADVERSE HEALTH CONDITIONS

APPENDICES

FINAL REPORT

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APPENDICES

APPENDIX A LITERATURE SEARCH STRATEGY

The broad search strategy is presented below:

```
((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR
("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR
("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
(("humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]) OR
("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]) OR
("disease"[MeSH Terms] OR "disease"[All Fields]))
```

In addition to the broad search strategy, additional searches were conducted to include search terms for the health conditions of concern:

Alzheimer's disease

```
((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR
("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR
("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
(("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR
"alzheimer disease"[All Fields] OR ("alzheimer's"[All Fields] AND "disease"[All Fields]) OR "alzheimer's
disease"[All Fields]))
```

Parkinson's disease

```
((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR
("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR
("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
(("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR
"parkinson disease"[All Fields] OR ("parkinson's"[All Fields] AND "disease"[All Fields]) OR "parkinson's
disease"[All Fields]))
```

Amyotrophic Lateral Sclerosis

(((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR ("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR ("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
(("amyotrophic lateral sclerosis"[MeSH Terms] OR ("amyotrophic"[All Fields] AND "lateral"[All Fields] AND "sclerosis"[All Fields]) OR "amyotrophic lateral sclerosis"[All Fields]))

Neurological Disorders

(((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR ("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR ("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
(("nervous system diseases"[MeSH Terms] OR ("nervous"[All Fields] AND "system"[All Fields] AND "diseases"[All Fields]) OR "nervous system diseases"[All Fields] OR ("neurological"[All Fields] AND "disorders"[All Fields]) OR "neurological disorders"[All Fields]))

Respiratory Disorders

(((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR ("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR ("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
((Respiratory[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "disorders"[All Fields]))

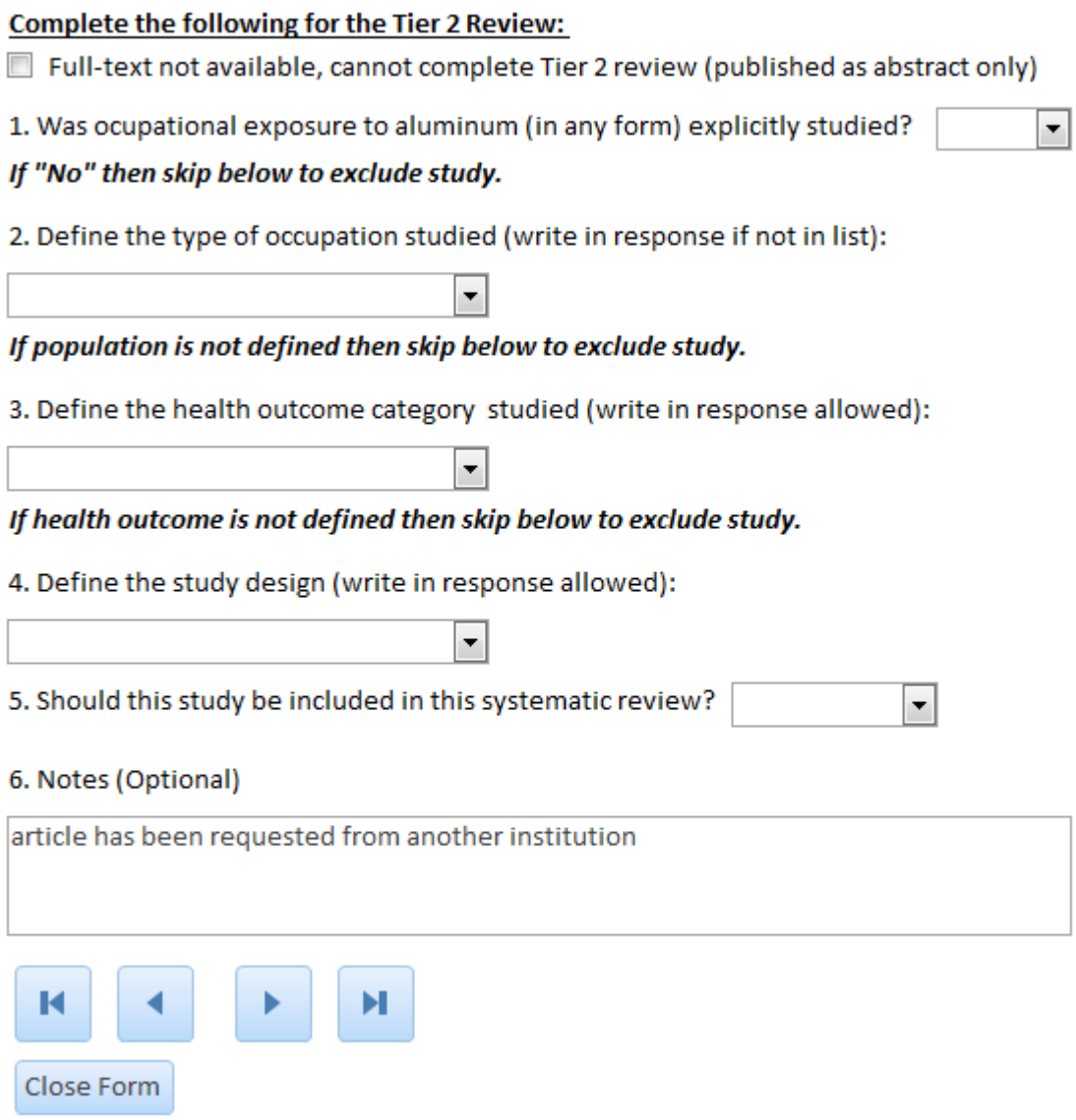
Cardiovascular Conditions

(((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR ("industry"[MeSH Terms] OR "industr$"[All Fields]))
AND
(("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR ("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields])))
AND
(("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields] OR ("cardiovascular"[All Fields] AND "disorders"[All Fields]) OR "cardiovascular disorders"[All Fields]))

Cancer

((("occupations"[MeSH Terms] OR "occupation$"[All Fields] OR McIntyre[All Fields] OR ("industry"[MeSH Terms] OR "industr$"[All Fields])) AND (("aluminum"[All Fields] OR "aluminum"[MeSH Terms] OR "aluminum"[All Fields]) OR ("aluminium"[All Fields] OR "aluminium"[MeSH Terms] OR "aluminium"[All Fields]))) AND (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]))

Appendix B Snapshot of Tier 2 Review Form from Access Database



Appendix C-1 Quality Assessment Form, Cross-Sectional Studies

Newcastle Ottawa Scale - Cross Sectional Studies

Study Identifier

Sum of Total Number of Stars (0-6) 0

Selection (Maximum 3 stars)

1. Representativeness of the exposed population:

a) Truly representative of the average in the target population. * (all subjects or random sampling)
b) Somewhat representative of the average in the target population. * (non-random sampling)
c) Selected group of users.
d) No description of the sampling strategy.

2. Representativeness of the non-exposed population:

a) Drawn from the same community as the exposed cohort. *
b) Drawn from a different source.
c) No description of non-exposed population.

3. Ascertainment of the exposure (aluminum):

a) Direct measurement (air samples, biomonitoring).*
b) Indirect measurement (structured interview or questionnaire) or use of exposure task matrix.*
c) Self-report, informal questionnaire, or no description of the measurement tool.

Notes about Selection

Comparability (Maximum 2 stars)

1. The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (select one). *
b) The study control for any additional factor. *
c) Study does not control for any confounders

Notes about Comparibility:

Outcome (Maximum 1 star)

1. Assessment of the outcome:

a) Independent blind assessment. *
b) Record linkage. *
c) Self report.
d) No description.

Notes about Outcome:

Appendix C-2 Quality Assessment Form, Cohort Studies

Newcastle Ottawa Scale - Cohort Studies

Study Identifier

Sum of Total Number of Stars (0-9): 0

Selection (Maximum 4 stars)

1. Representativeness of the exposed cohort:

a) Truly representative of the average in the target population. * (all subjects or random sampling) *
b) Somewhat representative of the average in the target population * (non-random sampling)
c) Selected group of volunteers
d) No description of the derivation of the cohort

2. Selection of the nonexposed cohort:

a) Drawn from the same community as the exposed cohort *
b) Drawn from a different source
c) No description of the derivation of the non exposed cohort

3. Ascertainment of the exposure:

a) Direct measurement (air samples, biomonitoring).*
b) Indirect measurement (structured interview/questionnaire or use of task exposure matrix). *
c) Written self report or informal questionnaire
d) No description

4.Demonstration that outcome of interest was not present at start of study/baseline health testing performed

a) Yes *
b) No

Notes about Selection

Comparability (Maximum 2 stars)

1. Comparability of cohorts on the basis of the design or analysis

a) Study controls for _____ (select the most important factor) *
b) Study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
c) Study does not control for any confounders

Notes about Comparibility:

Appendix C-2 Quality Assessment Form, Cohort Studies (continued)

Outcome (Maximum 3 stars)

1. Assessment of the outcome:

a) Independent blind assessment. *
b) Record linkage. *
c) Self report.
d) No description.

2. Was follow-up long enough for outcomes to occur:

a) Yes (select an adequate follow up period for outcome of interest) *
b) No/Unsure

3. Adequacy of follow up of cohorts

a) Complete follow up - all subjects accounted for *
b) Subjects lost to follow up unlikely to introduce bias - small number lost to follow up, or description provided of those lost (justification that lost to follow up did not significantly impact results) *
c) Follow up rate <80% (select an adequate %) OR no description of those lost
d) No statement

Notes about Outcome:

Appendix C-3 Quality Assessment Form, Case-Control Studies

Newcastle Ottawa Scale - Case Control Studies

Study Identifier

Sum of Total Number of Stars (0-9): 0

Selection (Maximum 4 stars)

1. Is the case definition adequate?

a) Yes, with independent validation *
b) Yes, eg record linkage or based on self reports
c) No description

2. Representativeness of the cases

a) Consecutive or obviously representative series of cases *
b) Potential for selection biases or not stated

3. Selection of Controls

a) Community controls *
b) Hospital controls
c) No description

4.Definition of Controls

a) No history of disease (endpoint) *
b) No description of source

Notes about Selection

Comparability (Maximum 2 stars)

1. Comparability of cases and controls on the basis of the design or analysis

a) Study controls for _____ (select the most important factor) *
b) Study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
c) Study does not control for any confounders

Notes about Comparibility:

Appendix C-3 Quality Assessment Form, Case-Control Studies (continued)

Exposure (Maximum 3 stars)

1. Ascertainment of the exposure:

a) Secure record (eg surgical records) *
b) Structured interview where blind to case/control status *
c) Interview not blinded to case/control status
d) Written self report or medical record only
e) No description

2. Same method of ascertainment for cases and controls:

a) Yes *
b) No

3. Non-Response rate

a) Same rate for both groups *
b) Non respondents described
c) Rate different and no designation

Notes about Exposure:

Appendix D Data Collection Form

Data Extraction Form

Identifier			
Title			
Authors			
FinalScreen			
Occupation(s)		Outcome Category	
Study Design			

Country			
N Exposed	0	Age Exposed: Average (Range)	
N Controls	0	Age Controls: Average (Range)	
Short Description of Exposed Population			
Short Description of Control Population			
Duration of follow-up if longitudinal study design (otherwise "N/A")			
If N/A, how many years were workers exposed to Aluminum? Average (Range)			

Ascertainment of aluminum exposure (i.e., measured in workplace, measured in blood/urine, etc).

Aluminum exposure in exposed group (i.e., concentrationin workplace, concentration in blood/urine). Provide mean, standard deviation, units and media for all measures. Example: 60.2 +/- 24.3 ug Al/l urine

Appendix D Data Collection Form (Continued)

Aluminum exposure in exposed group (i.e., concentrationin workplace, concentration in blood/urine). Provide mean, standard deviation, units and media for all measures. Example: 60.2 +/- 24.3 ug Al/l urine

Aluminum exposure in control group (as above)

List other potentially toxic chemical agents to which workers were exposed (e.g., lead, fluoride, mercury)

List all health outcomes studied:

Ascertainment/measurement of health outcomes (e.g., self-report, clinical diagnosis, motor test)

Means and SDs in Exposed Group (for each value specify the corresponding health outcome) ?

Means and SDs in Control Group (for each value specify the corresponding health outcome) ?

Type of Statistical Analysis (i.e., multiple regression, logistic regression, descriptive statistics):

Does the study report one of the following effect estimates: Odds Ratio, Relative Risk, Hazard Ratio? (Yes/No)

List all Confounders Adjusted for in Analyses:

Summarize Authors Conclusions

Other Important Notes

Appendix E-1 Meta-regression of factors for Mean Santa Ana dexterity dominant hand (count)

1. Age

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
    MD_saddh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |   .0154657    .088969     0.17   0.870    -.2315517    .2624832
       _cons |  -1.991444   .2278168    -8.74   0.001    -2.623964   -1.358923
------------------------------------------------------------------------------
```

2. Education

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
    MD_saddh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_edu |  -.3228789   .5230218    -0.62   0.570     -1.77502    1.129262
       _cons |  -2.089639   .2817353    -7.42   0.002    -2.871861   -1.307416
------------------------------------------------------------------------------
```

3. Smoking

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
    MD_saddh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |   .0211459   .0561911     0.38   0.743     -.220625    .2629167
       _cons |  -1.940313   .5245159    -3.70   0.066    -4.197123     .316497
------------------------------------------------------------------------------
```

4. AL Blood (insufficient data)

5. AL urine

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
    MD_saddh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |   .0005682   .0020502     0.28   0.795    -.0051241    .0062605
       _cons |  -2.048784   .3261971    -6.28   0.003    -2.954452   -1.143116
------------------------------------------------------------------------------
```

6. AL urine adjusted for creatinine (insufficient data)
AL serum (insufficient data)

Appendix E-2 Meta-regression of factors for Mean Santa Ana dexterity non-dominant hand (count)

1. Age

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   .9363
% residual variation due to heterogeneity               I-squared_res  =  64.53%
Proportion of between-study variance explained          Adj R-squared  = -66.13%
With Knapp-Hartung modification
------------------------------------------------------------------------------
   MD_sadndh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |  -.0327439   .2279916    -0.14   0.893    -.6657501    .6002623
       _cons |  -.4326796   .5324034    -0.81   0.462    -1.910869    1.045509
------------------------------------------------------------------------------
```

2. Education

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =  .06916
% residual variation due to heterogeneity               I-squared_res  =   1.70%
Proportion of between-study variance explained          Adj R-squared  =  87.73%
With Knapp-Hartung modification
------------------------------------------------------------------------------
   MD_sadndh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_edu |    1.55713   .6336664     2.46   0.070    -.2022103     3.31647
       _cons |    .346439   .3626285     0.96   0.393    -.6603791    1.353257
------------------------------------------------------------------------------
```

3. Smoking

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =   .6502
% residual variation due to heterogeneity               I-squared_res  =  13.48%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
   MD_sadndh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |  -.0038866   .0738901    -0.05   0.963    -.3218099    .3140367
       _cons |  -.9450201   .7101343    -1.33   0.315    -4.000481    2.110441
------------------------------------------------------------------------------
```

4. AL blood (insufficient data)

5. AL urine

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   .9137
% residual variation due to heterogeneity               I-squared_res  =  63.48%
Proportion of between-study variance explained          Adj R-squared  = -62.12%
With Knapp-Hartung modification
------------------------------------------------------------------------------
   MD_sadndh |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |  -.0004139   .0050733    -0.08   0.939    -.0144995    .0136717
       _cons |  -.3996058   .6840974    -0.58   0.590    -2.298965    1.499753
------------------------------------------------------------------------------
```

6. AL urine adjusted for creatinine (insufficient data)
7. Al serum (insufficient data)

Appendix E-3 Meta-regression of factors for Mean Simple reaction time (sec)

1. age

```
Meta-regression                                         Number of obs  =      13
REML estimate of between-study variance                 tau2           =   139.2
% residual variation due to heterogeneity               I-squared_res  =  74.59%
Proportion of between-study variance explained          Adj R-squared  = -13.40%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_srt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |   .2034425   1.382755     0.15   0.886    -2.839981    3.246866
       _cons |   7.872225   4.379041     1.80   0.100     -1.76598    17.51043
------------------------------------------------------------------------------
```

2. education

```
Meta-regression                                         Number of obs  =       7
REML estimate of between-study variance                 tau2           =   63.82
% residual variation due to heterogeneity               I-squared_res  =  39.38%
Proportion of between-study variance explained          Adj R-squared  =  63.33%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_srt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_edu |  -31.93424   13.44235    -2.38   0.064    -66.48889    2.620408
       _cons |  -9.885016   6.058089    -1.63   0.164    -25.45783    5.687799
------------------------------------------------------------------------------
```

3. smoking

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_srt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |   .1088499   .9956192     0.11   0.923    -4.174954    4.392654
       _cons |   26.84036   9.706654     2.77   0.110      -14.924    68.60472
------------------------------------------------------------------------------
```

4. AL blood (insufficient data)

5. AL urine

```
Meta-regression                                         Number of obs  =      11
REML estimate of between-study variance                 tau2           =   103.4
% residual variation due to heterogeneity               I-squared_res  =  73.44%
Proportion of between-study variance explained          Adj R-squared  =  21.01%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_srt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |  -.0921776   .0492464    -1.87   0.094    -.2035806    .0192254
       _cons |   15.68502   5.822489     2.69   0.025     2.513632     28.8564
------------------------------------------------------------------------------
```

6. AL urine adjusted for creatinine

```
Meta-regression                                         Number of obs  =       8
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_srt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
diff_urin_adj |  -.1598091   .1241392    -1.29   0.245    -.4635668    .1439486
        _cons |   19.79167   5.065823     3.91   0.008     7.396052     32.1873
------------------------------------------------------------------------------
```

7. AL serum (insufficient data)

Appendix E-4 Meta-regression of factors for Mean Digit span forward (count)

1. Age

```
Meta-regression                                         Number of obs  =      12
REML estimate of between-study variance                 tau2           =   .2167
% residual variation due to heterogeneity               I-squared_res  =  76.92%
Proportion of between-study variance explained          Adj R-squared  = -15.28%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |   -.002671   .0584345    -0.05   0.964    -.1328713    .1275292
       _cons |  -.1758371   .1767518    -0.99   0.343    -.5696647    .2179906
------------------------------------------------------------------------------
```

2. Education

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   .2479
% residual variation due to heterogeneity               I-squared_res  =  78.10%
Proportion of between-study variance explained          Adj R-squared  =  15.98%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_edu |   .9862978     .71782     1.37   0.241     -1.00669    2.979286
       _cons |   .3920099   .3984597     0.98   0.381    -.7142916    1.498311
------------------------------------------------------------------------------
```

3. smoking

```
Meta-regression                                         Number of obs  =       5
REML estimate of between-study variance                 tau2           =   .1329
% residual variation due to heterogeneity               I-squared_res  =  35.55%
Proportion of between-study variance explained          Adj R-squared  = -17.68%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |     .01213   .0386381     0.31   0.774    -.1108337    .1350937
       _cons |  -.2995091   .2824374    -1.06   0.367    -1.198351    .5993327
------------------------------------------------------------------------------
```

4. AL blood

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_blood |  -.0692473   .0445086    -1.56   0.195    -.1928231    .0543285
       _cons |    -.03592   .0831937    -0.43   0.688    -.2669029    .1950628
------------------------------------------------------------------------------
```

5. Al urine

```
Meta-regression                                         Number of obs  =      12
REML estimate of between-study variance                 tau2           =   .1458
% residual variation due to heterogeneity               I-squared_res  =  70.58%
Proportion of between-study variance explained          Adj R-squared  =  22.43%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |   .0024319   .0017385     1.40   0.192    -.0014418    .0063056
       _cons |  -.3085197   .1965109    -1.57   0.147    -.7463732    .1293338
------------------------------------------------------------------------------
```

6. AL urine adjusted for creatinine

```
Meta-regression                                         Number of obs  =       8
REML estimate of between-study variance                 tau2           =  .00588
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_dsf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
diff_urin_adj |  -.0044346    .006645    -0.67   0.529    -.0206944    .0118251
        _cons |  -.3302546    .267692    -1.23   0.263    -.9852734    .3247643
------------------------------------------------------------------------------
```

7. Al serum (insufficient data)

Appendix E-5 Meta-regression of factors for Mean Digit span backward (count)

1. age

```
Meta-regression                                         Number of obs  =       8
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsb |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |  -.0222992   .0165863    -1.34   0.227    -.0628845    .0182861
       _cons |  -.0745643   .0434223    -1.72   0.137    -.1808149    .0316863
------------------------------------------------------------------------------
```

2. education

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsb |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_edu |   .1647883   .1321493     1.25   0.280     -.202117    .5316936
       _cons |  -.0705452   .0448838    -1.57   0.191    -.1951625    .0540721
------------------------------------------------------------------------------
```

3. smoking (insufficient data)
4. AL blood (insufficient data)
5. AL urine

```
Meta-regression                                         Number of obs  =       8
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_dsb |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |  -.0004557   .0003645    -1.25   0.258    -.0013477    .0004363
       _cons |  -.0372092   .0647252    -0.57   0.586    -.1955861    .1211677
------------------------------------------------------------------------------
```

6. AL urine adjusted for creatinine

```
Meta-regression                                         Number of obs  =       5
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_dsb |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
diff_urin_adj |   -.007441     .00698    -1.07   0.365    -.0296545    .0147726
        _cons |   .0981573   .3921597     0.25   0.819     -1.14987    1.346184
------------------------------------------------------------------------------
```

7. AL serum (insufficient data)

Appendix E-6 Meta-regression of factors for Mean Digit symbol (count)

1. age

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   1.692
% residual variation due to heterogeneity               I-squared_res  =  41.84%
Proportion of between-study variance explained          Adj R-squared  = -195.61%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_ds |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |  -.1682953   .4322523    -0.39   0.717     -1.36842     1.03183
       _cons |  -4.807902   1.029005    -4.67   0.010    -7.664878   -1.950926
------------------------------------------------------------------------------
```

2. **education**

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   .5549
% residual variation due to heterogeneity               I-squared_res  =  44.74%
Proportion of between-study variance explained          Adj R-squared  =   3.04%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_ds |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_edu |   1.247565   2.201266     0.57   0.601     -4.86413     7.35926
       _cons |  -4.636374   .9669035    -4.80   0.009    -7.320928   -1.951819
------------------------------------------------------------------------------
```

3. **smoking**

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =   15.84
% residual variation due to heterogeneity               I-squared_res  =  67.32%
Proportion of between-study variance explained          Adj R-squared  = -80.28%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_ds |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |  -.1016334   .2847221    -0.36   0.755    -1.326694    1.123427
       _cons |  -5.065299   2.818724    -1.80   0.214    -17.19329    7.062691
------------------------------------------------------------------------------
```

4. AL blood (insufficient data)

5. **AL urine**

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =  39.79%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       MD_ds |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |  -.0056236   .0046441    -1.21   0.293    -.0185178    .0072706
       _cons |  -4.218385   .8040529    -5.25   0.006    -6.450794   -1.985976
------------------------------------------------------------------------------
```

6. **AL urine adjusted for creatinine(insufficient data)**
7. AL serum (insufficient data)

Appendix E-7 Meta-regression of factors for Mean Mini–Mental State Examination (MMSE) score

1. age

```
Meta-regression                                         Number of obs  =       3
REML estimate of between-study variance                 tau2           =   .5143
% residual variation due to heterogeneity               I-squared_res  =  78.80%
Proportion of between-study variance explained          Adj R-squared  =  23.03%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_mmse |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |  -.4760041   .3710661    -1.28   0.422    -5.190846    4.238838
       _cons |  -1.368771   .5009176    -2.73   0.223    -7.733533    4.995991
------------------------------------------------------------------------------
```

2. education (insufficient data)

3. smoking (insufficient data)

4. AL blood (insufficient data)

5. Al urine (insufficient data)

6. AL urine adjusted for creatinine (insufficient data)

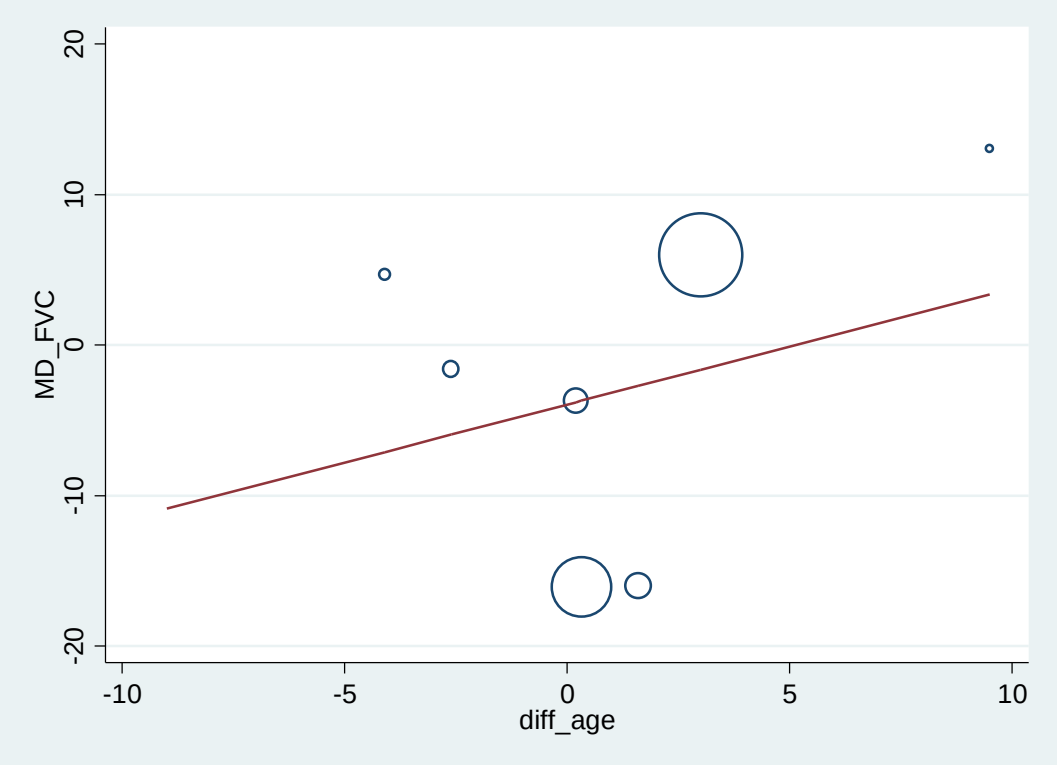
7. AL serum (insufficient data)

Appendix F-1 Meta-regression of factors for ppFVC

Comparison 1. Differences in age between exposed and control group

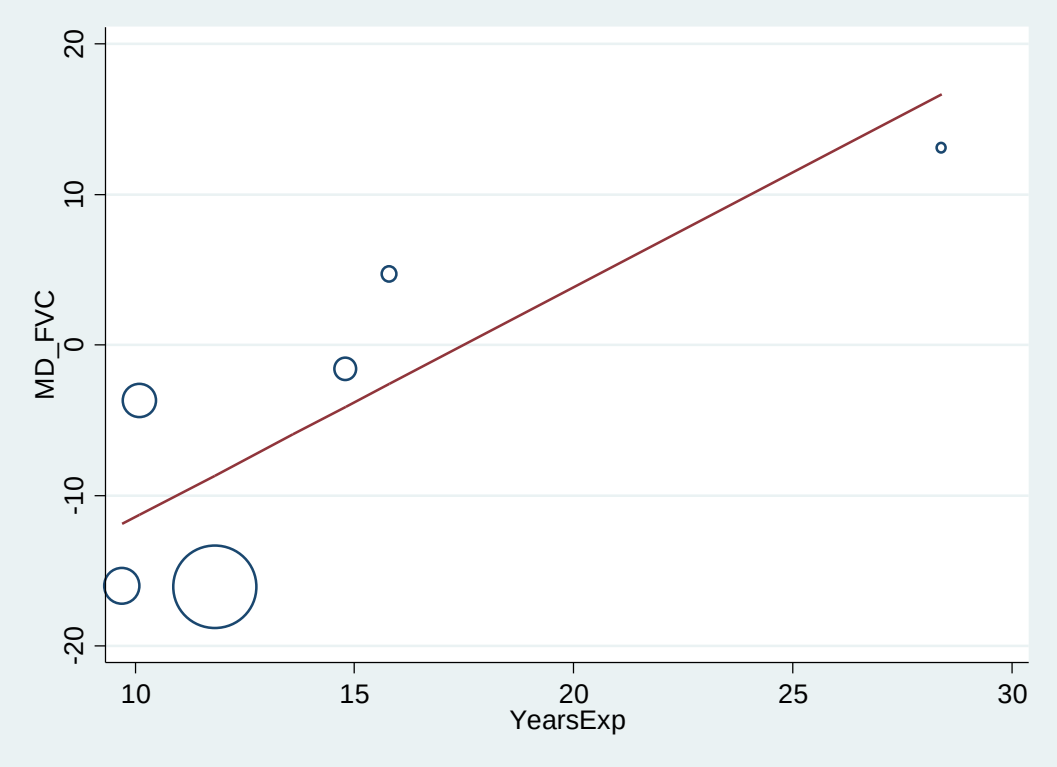
I.E., MD FVC j = constant + (age difference exposure minus control)j + residual j + random error term

```
Meta-regression                                         Number of obs  =       7
REML estimate of between-study variance                 tau2           =     107
% residual variation due to heterogeneity               I-squared_res  =  95.87%
Proportion of between-study variance explained          Adj R-squared  = -12.31%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_FVC |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |   .7704302   1.239448     0.62   0.561    -2.415671    3.956532
       _cons |  -3.956116   4.372913    -0.90   0.407    -15.19705    7.284816
------------------------------------------------------------------------------
```



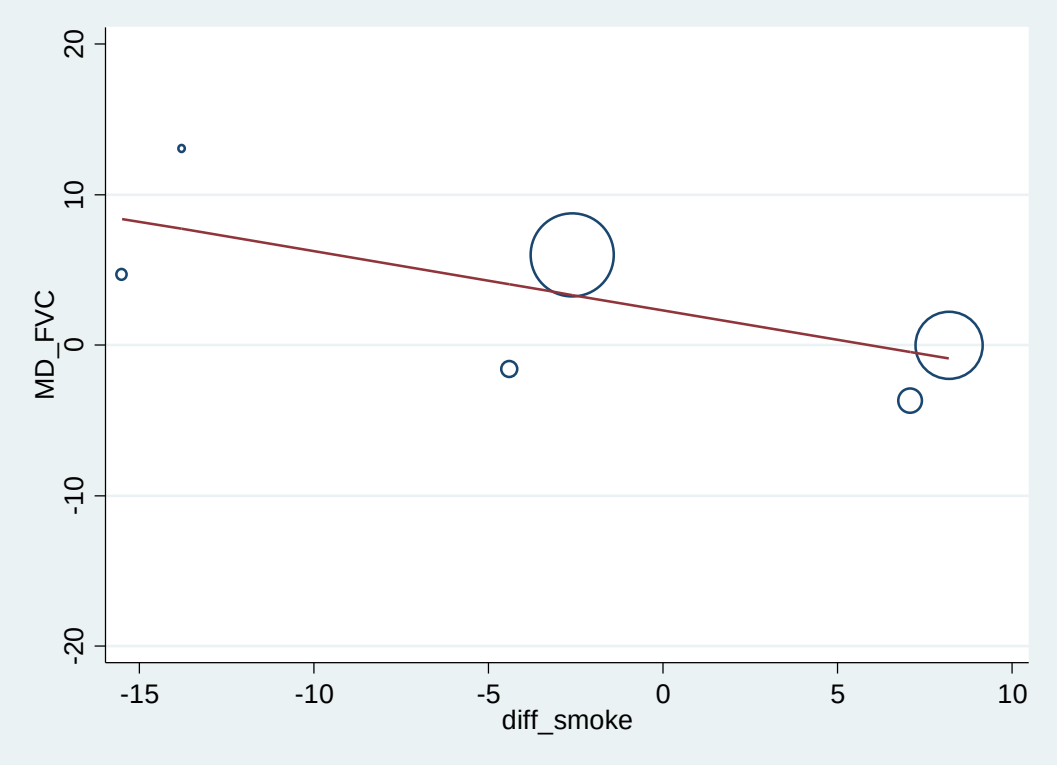
Comparison 2. Years of exposure

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   41.14
% residual variation due to heterogeneity               I-squared_res  =  85.86%
Proportion of between-study variance explained          Adj R-squared  =  50.11%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_FVC |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    YearsExp |   1.528533   .6877451     2.22   0.090    -.3809537    3.438019
       _cons |  -26.73529   9.553473    -2.80   0.049    -53.25998   -.2105921
------------------------------------------------------------------------------
```



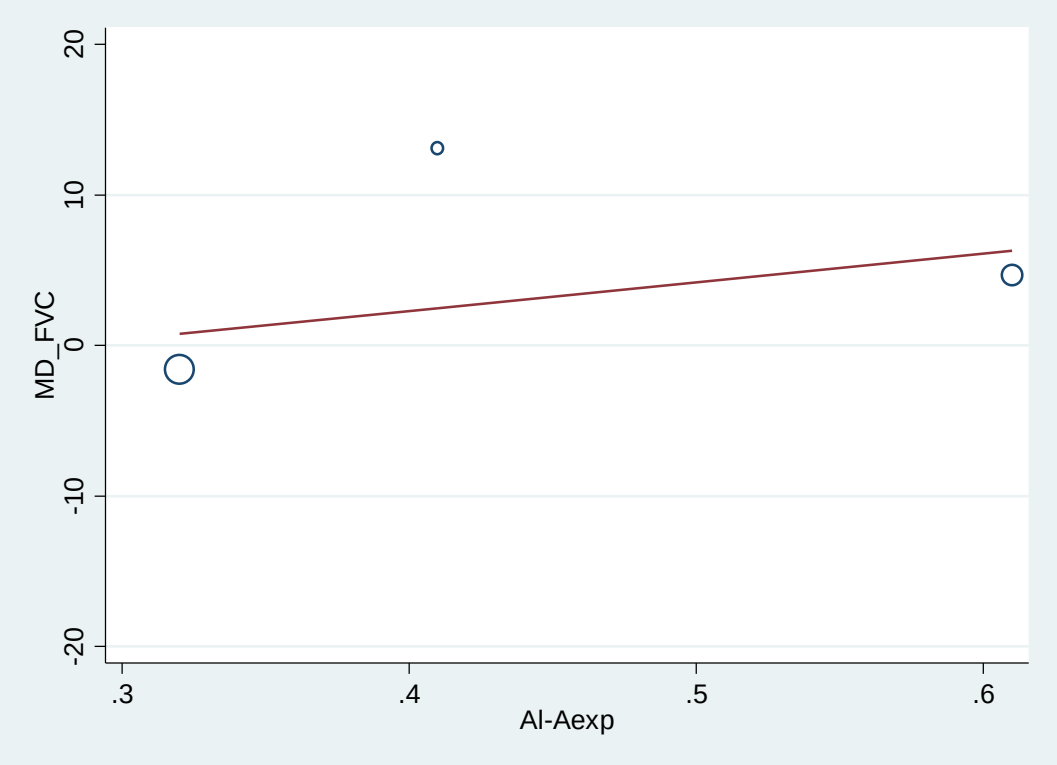
Comparison 3. Differences in Percentage smokers in studies

```
Meta-regression                                         Number of obs  =       6
REML estimate of between-study variance                 tau2           =   7.407
% residual variation due to heterogeneity               I-squared_res  =  41.59%
Proportion of between-study variance explained          Adj R-squared  =  45.17%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_FVC |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |  -.3917306    .233938    -1.67   0.169    -1.041247    .2577854
       _cons |   2.318128   1.683142     1.38   0.240    -2.355023    6.991278
------------------------------------------------------------------------------
```



Comparison 4. Level of Air aluminum

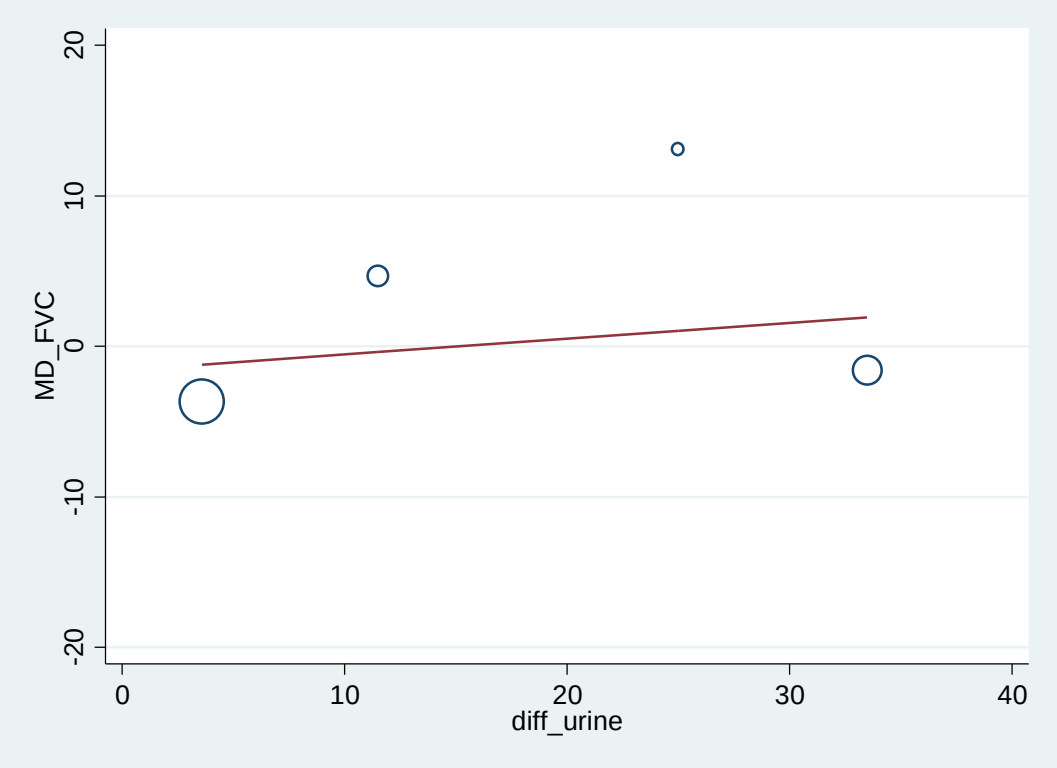
```
Meta-regression                                         Number of obs  =       3
REML estimate of between-study variance                 tau2           =   23.02
% residual variation due to heterogeneity               I-squared_res  =  22.28%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_FVC |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      AlAexp |   19.09117   35.85914     0.53   0.689    -436.5424    474.7248
       _cons |  -5.356694   16.17379    -0.33   0.796    -210.8642    200.1508
------------------------------------------------------------------------------
```



Comparison 5. Blood aluminum: Insufficient studies N=1

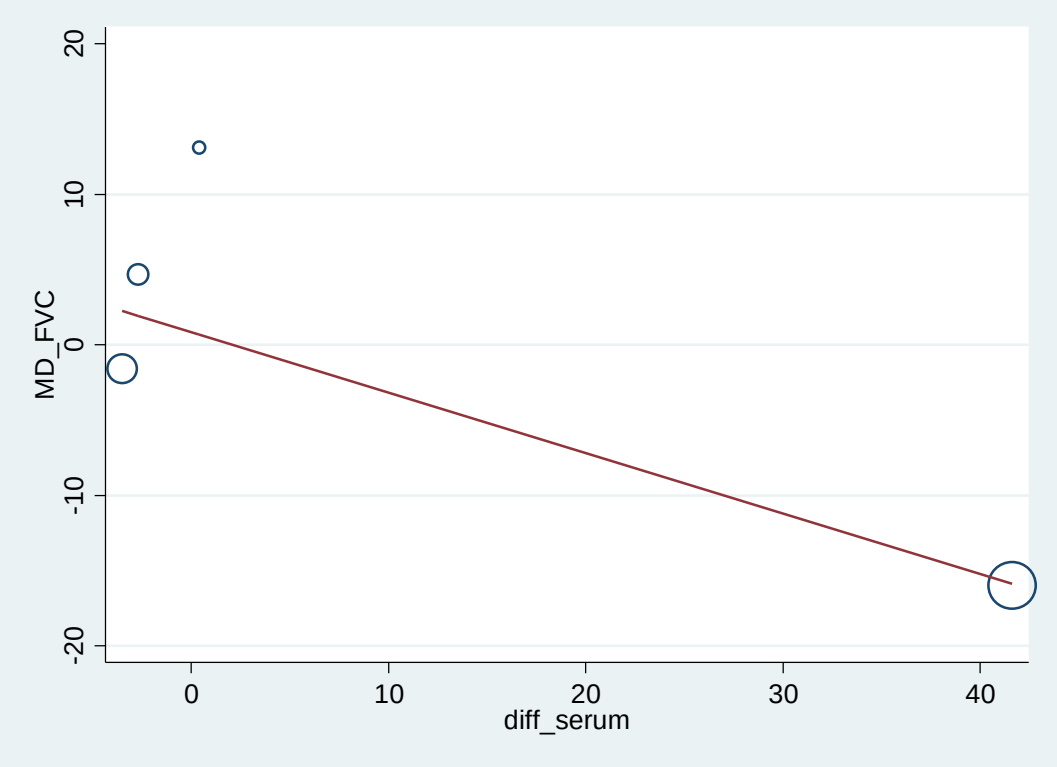
Comparison 6. Differences in Urine Aluminum concentration

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =   20.39
% residual variation due to heterogeneity               I-squared_res  =  32.27%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_FVC |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |   .1051004   .2717297     0.39   0.736    -1.064058    1.274259
       _cons |  -1.590669   5.580718    -0.29   0.802    -25.60256    22.42122
------------------------------------------------------------------------------
```



Comparison 7. Differences in Serum Aluminum concentration

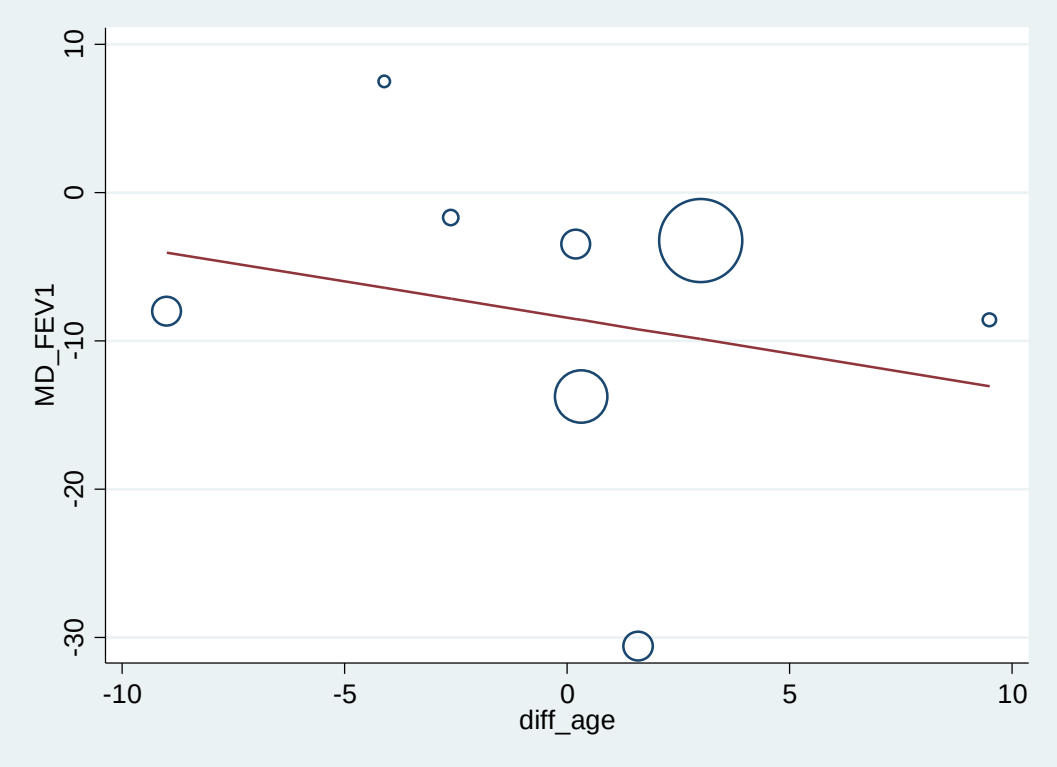
```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =   4.299
% residual variation due to heterogeneity               I-squared_res  =  12.01%
Proportion of between-study variance explained          Adj R-squared  =  96.20%
With Knapp-Hartung modification
------------------------------------------------------------------------------
      MD_FVC |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_serum |  -.4019328    .118023    -3.41   0.076     -.909745    .1058793
       _cons |   .8449947    3.61188     0.23   0.837    -14.69567    16.38566
------------------------------------------------------------------------------
```



Appendix F-2 Meta-regression of factors for ppFEV1

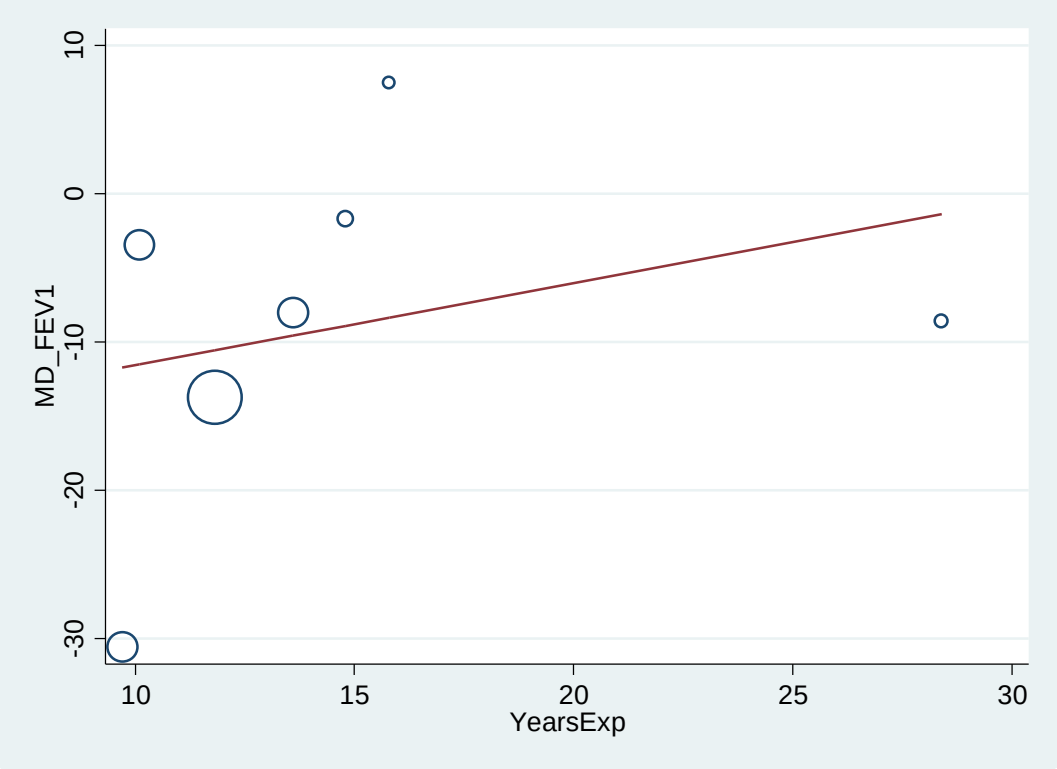
Comparison 1: Difference in age

```
Meta-regression                                         Number of obs  =       8
REML estimate of between-study variance                 tau2           =   119.2
% residual variation due to heterogeneity               I-squared_res  =  93.90%
Proportion of between-study variance explained          Adj R-squared  = -12.31%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_FEV1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    diff_age |   -.486324   .8370692    -0.58   0.582    -2.534558     1.56191
       _cons |  -8.416064    4.12982    -2.04   0.088    -18.52137    1.689242
------------------------------------------------------------------------------
```



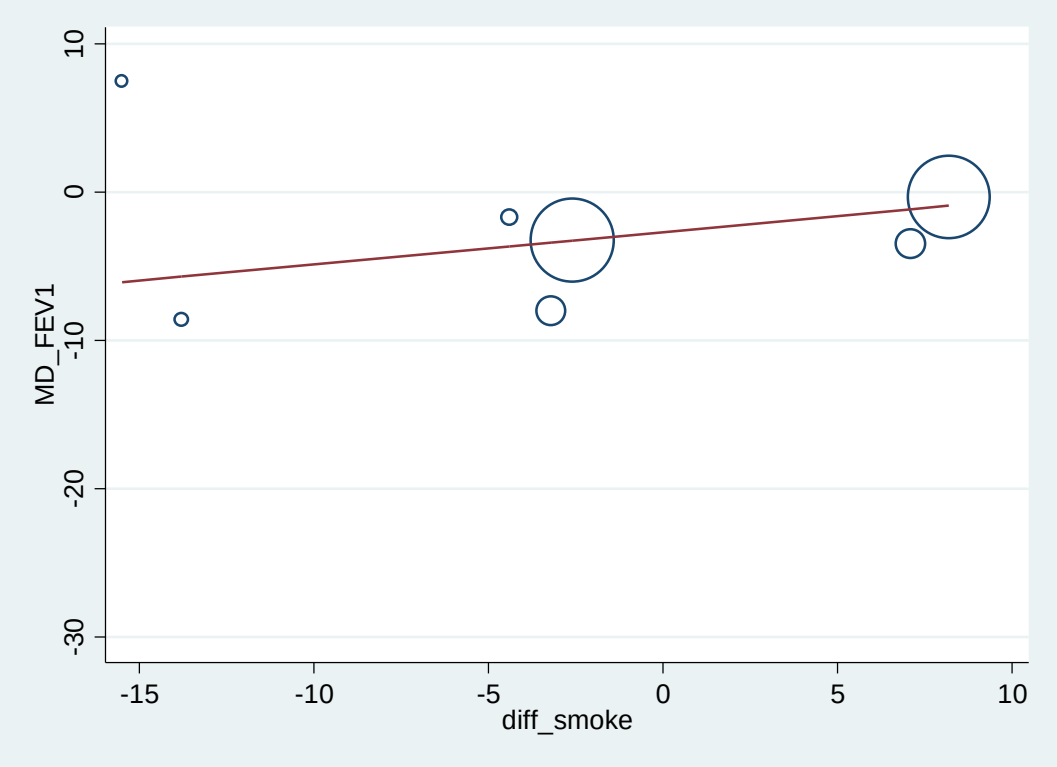
Comparison 2. Years of exposure

```
Meta-regression                                         Number of obs  =       7
REML estimate of between-study variance                 tau2           =     131
% residual variation due to heterogeneity               I-squared_res  =  90.84%
Proportion of between-study variance explained          Adj R-squared  =  -8.09%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_FEV1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    YearsExp |   .5532957   .8302917     0.67   0.535    -1.581037    2.687628
       _cons |  -17.08767   12.86371    -1.33   0.241    -50.15488    15.97953
------------------------------------------------------------------------------
```



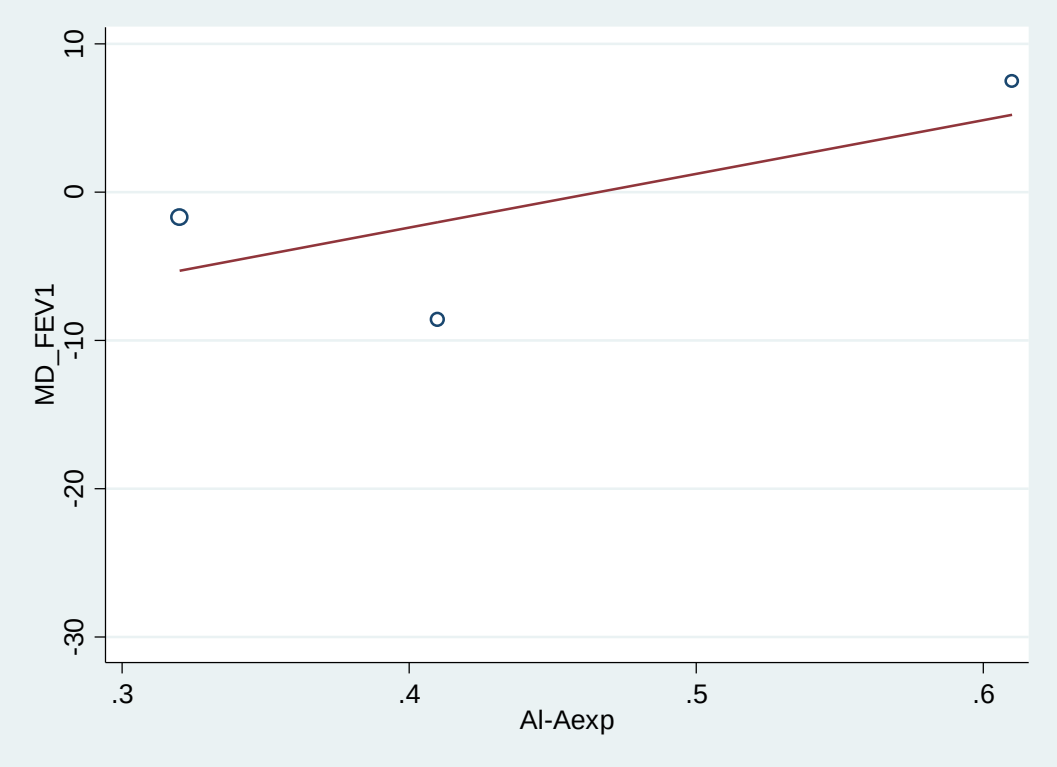
Comparison 3. Differences in smoking percentage

```
Meta-regression                                         Number of obs  =       7
REML estimate of between-study variance                 tau2           =   .1953
% residual variation due to heterogeneity               I-squared_res  =  31.48%
Proportion of between-study variance explained          Adj R-squared  =  94.82%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_FEV1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_smoke |   .2172115   .1490389     1.46   0.205     -.165905    .6003281
       _cons |  -2.685603   .9421368    -2.85   0.036    -5.107443   -.2637633
------------------------------------------------------------------------------
```



Comparison 4. Differences in air aluminum

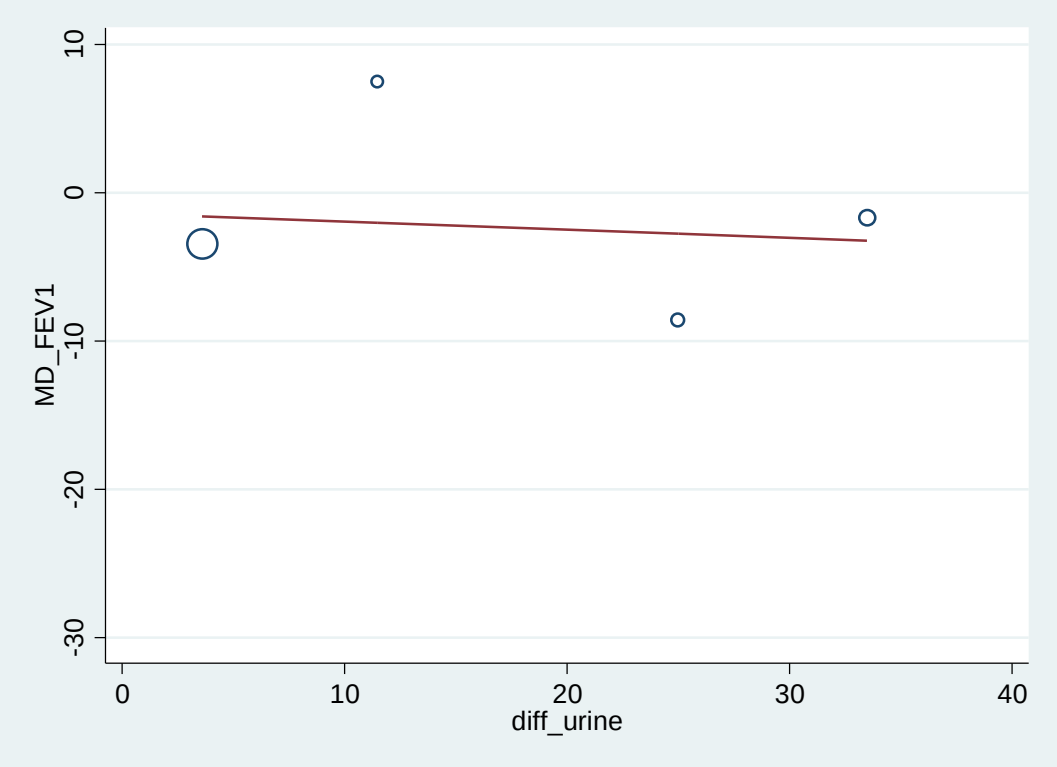
```
Meta-regression                                         Number of obs  =       3
REML estimate of between-study variance                 tau2           =   21.01
% residual variation due to heterogeneity               I-squared_res  =  34.71%
Proportion of between-study variance explained          Adj R-squared  = -95.25%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_FEV1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      AlAexp |   36.27784   37.90425     0.96   0.514    -445.3413     517.897
       _cons |  -16.90893   16.94025    -1.00   0.501    -232.1552    198.3374
------------------------------------------------------------------------------
```



Comparison 5. Difference in blood aluminum (insufficient data N=1)

Comparison 6. Difference in urine aluminum

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =   15.14
% residual variation due to heterogeneity               I-squared_res  =  32.33%
Proportion of between-study variance explained          Adj R-squared  =      .%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_FEV1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_urine |  -.0542079   .2694554    -0.20   0.859    -1.213581    1.105165
       _cons |  -1.400258   5.366901    -0.26   0.819    -24.49217    21.69165
------------------------------------------------------------------------------
```



Comparison 7. Difference in serum aluminum

```
Meta-regression                                         Number of obs  =       4
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   8.55%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
     MD_FEV1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  diff_serum |  -.6717355   .1113959    -6.03   0.026    -1.151033   -.1924375
       _cons |    -2.7277   3.600809    -0.76   0.528    -18.22073    12.76533
------------------------------------------------------------------------------
```