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Aluminum Dust Exposure and Evidence for Impairment of Cognitive Function:

A Critical Review and Gaps Analysis of "Systematic Review of Occupational Aluminum Exposure and Adverse Health Conditions (Final Report)"*

* 2017 Report of Intrinsik to the Workplace Safety and Insurance Board of Ontario

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*Version two of the report corrected formatting errors and added several lines on p. 13 that elaborated on findings of test scores in the 1988 and 1994 rounds of the Northern Ontario Miner's Health Survey. No changes were substantive.

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Executive Summary

This review was undertaken under contract to the Occupational Health Clinics for Ontario Workers (OHCOW). The terms of reference were to conduct a critical review of Intrinsik's 2017 Systematic Review of Occupational Aluminum Exposure and Adverse Health Conditions (Final Report), submitted to the Workplace Safety & Insurance Board (WSIB) of Ontario. The present report is not a comprehensive review of the use of McIntyre Powder as a prophylaxis against silicosis or of aluminum toxicity in general.

There are only three studies in the scientific literature that pertain to McIntyre Powder as such: 1. McDonald et al.'s A mortality study of Alzheimer's disease and aluminum exposure through inhalation of McIntyre powder in Cornish Tin Miners (1996); 2. Peters et al.'s Long-term effects of aluminum dust inhalation (2013); and 3. Rifat et al.'s Effect of exposure of miners to aluminum powder (1990). The principal drawbacks common to all three studies are lack of exposure data and the weak relationship of elevated mortality to any excess of Alzheimer's disease. The McDonald et al. report is deficient in reporting and presents only a conclusion about mortality with no supporting data and therefore cannot be assessed other than to observe that it was conducted by members of a well-recognized research group. The Peters et al. study appears to have been competently performed and reported but presents only mortality data. Despite the insensitivity of the endpoint, these data are suggestive of an adverse effect but not conclusive. Of the three, the Rifat et al. study is the only one that is both relevant to aluminum dust exposure and incidence of neurocognitive effects, methodologically robust, and ultimately informative. It includes a determination of neurobehavioral performance using robust and accepted testing methods as well as results from an otherwise uninformative mortality study. Rifat et al. also performed a follow-up study on the same population.

Brendan McDonald of the MRC Schizophrenia Research Group of the Department of Neuropathology at Radcliffe Infirmary (Oxford's principal teaching hospital) conducted a cohort mortality study in collaboration with the epidemiology group within the Health and Safety Executive in Merseyside. Only the abstract is available, from a conference on Alzheimer's disease in 1996, and it lacks basic information (such as sample size and risk estimates), concluding only with an unsupported assertion that no elevation was found in mortality from diseases associated with cognitive impairment. It is concluded that this study was uninformative rather than negative.

Peters et al. at the Western Australian Institute for Medical Research and the School of Population Health at the University of Western Australia conducted a cohort mortality study of male gold miners in Kalgoorlie, Western Australia, who had ever worked underground and were traced from 1961 to 2009. The study used internal comparisons and the Australian general male population as an external comparison population. When miners who underwent aluminum prophylaxis were compared with those who did not, the aluminum-treated workers had higher mortality from cardiovascular disease (1.38, 1.21−1.57 v. 1.26, 1.12−1.41) but were at a lower risk of death from cerebrovascular disease (1.30 1.00–1.70 v. 1.43 1.16−1.78). Neither difference is statistically significant at 95%, suggesting vascular disease is not a confounding factor. Mortality assigned to Alzheimer's disease was higher among workers who had received McIntyre Powder prophylaxis

(1.38, 0.69−2.75 v. 0.89, 0.44−1.78), although the difference did not achieve conventional statistical significance due to small numbers. The exposure-response relationship analyzed by hazard ratio again did not achieve conventional statistical significance despite an overall hazard ratio of 2.79 (0.88 – 8.82) and upper bound risk estimates on the order of 9 and 14 with increasing exposure from none to 10+ years, showing a monotonic rise with duration of exposure but again failing to achieve statistical significance. The Peters et al. study is highly suggestive of a biologically significant effect that simply fails to achieve statistical significance for mortality from Alzheimer's disease because of low power.

The initial Rifat study strongly suggests a neurological effect consistent with an association between exposure and the prevalence of neurological signs consistent with dementia, but this was not apparent on follow-up. Because of the strong and detailed protocol of the initial study and complications in the sample frame and tracing of study subjects in the follow-up study, it is evident that the follow-up study is underpowered (i.e. lacks the power to detect a true elevation) and more likely subject to bias than the initial study. For this reason, the initial "positive" study commands more confidence than the follow-up study and should be given weight.

The Intrinsik Report, as a document, is poorly focused, simplistic, and relies too heavily on a fundamental misapplication of the Hill criteria.

Background to the Issue and the Review

This review was undertaken in response to a request by the Occupational Health Clinics for Ontario Workers, Inc. (OHCOW) for the specific task of reviewing and identifying gaps in the Systematic Review of Occupational Aluminum Exposure and Adverse Health Conditions (Final Report), which was prepared by Intrinsik for the Workplace Safety and Insurance Board of Ontario (WSIB) and delivered 28 April 2017. This report will hereafter be known as the McIntyre Powder Report because it addresses the potential health effects of McIntyre Powder, a proprietary aluminum powder used in the past as a prophylaxis against silicosis in miners in Ontario and elsewhere. OHCOW requested the report be reviewed for scientific accuracy, methodological issues, and gaps. The present report is not a comprehensive review of the use of McIntyre Powder as a prophylaxis against silicosis or of aluminum toxicity in general.

This contract was cost-shared. In other words, because the topic is of professional interest and value to the consultant as well as OHCOW, the contractor absorbed approximately 50% of the total cost of conducting the work, in the form of an offset for professional services. To assist in the analysis, a biostatistician (Dr. Tsui Ying Kau) was engaged to review the Rifat study for which data were published and to calculate the power of each to detect the differences reported. (This was not done by Intrinsik.)

Evaluation of the Evidence

There are only three studies in the scientific literature that pertain to McIntyre Powder as such: 1. McDonald et al.'s A mortality study of Alzheimer's disease and aluminum exposure through inhalation of McIntyre powder in Cornish Tin Miners (1996); 2. Peters et al.'s Long-term effects of aluminum dust inhalation (2013); and 3. Rifat et al.'s Effect of exposure of miners to aluminum powder (1990). These studies have both common and individual limitations, as noted in the subsections below.

The principal drawbacks common to all three studies are lack of exposure data and the weak relationship of elevated mortality to any excess of Alzheimer's disease. The McDonald et al. report is deficient in reporting and presents only a conclusion about mortality with no supporting data and therefore cannot be assessed other than to observe that it was conducted by members of a well-recognized research group. The Peters et al. study appears to have been competently performed and reported but presents only mortality data. Despite the insensitivity of the endpoint, these data are suggestive of an adverse effect but not conclusive. Of the three, the Rifat et al. study is that only one that is both relevant to aluminum dust exposure and incidence of neurocognitive effects, methodologically robust, and ultimately informative. It includes a determination of neurobehavioral performance using robust and accepted testing methods as well as results from an otherwise uninformative mortality study.

McDonald et al. (1996): Abstract of Cornwall Miners

This study, led by Brendan McDonald of the MRC Schizophrenia Research Group of the Department of Neuropathology at Radcliffe Infirmary (Oxford's principal teaching hospital), was

conducted in collaboration with the epidemiology group within the Health and Safety Executive (HSE) in Merseyside. Only the abstract is available, from a conference on Alzheimer's disease in 1996.

The design of the study is that of a conventional cohort mortality study. The abstract reports that death certificates up to the end of 1992 were obtained for miners in two tin mines in Cornwall, one of which did not use McIntyre Powder and the other used it from the 1940s to 1964. There were two deaths certified as being caused by dementia (slightly less than expected) in the mine that did not use McIntyre Powder and none in the mine that did. The authors concluded, correctly, that their study does not provide evidence for an association despite the long period of observation (> 28 years) and lengthy duration of exposure (up to 24 years in some cases).

No sample size is reported for either the exposed or the comparison population. Such omission of basic information was unusual at the time, even in abstracts much older than 1996. The abstract alludes to low statistical power and hints at potential sources of misclassification bias: "…the terminology used in death certification (using a number of ICD codes) and sample size also mean that the data cannot conclusively disprove an association." When the study subjects are all diagnosed, treated, or certified similarly, information bias tends to be minimized; when the differences are large but random, they tend to wash out (i.e., random errors cancel) if the study population is large enough. In this case, however, there are strong indications that the population was small and that statistical power was low (meaning an effect that was truly present could have been missed by random error alone). Thus, unless further information can be found, the McDonald et al. study should be considered inconclusive rather than negative. Its only outcome is mortality from dementia, which is a very poor indicator of the incidence of Alzheimer's disease. McDonald is an ophthalmic neuropathologist, not an epidemiologist. He retired in 2018 and was not communicating although his associates indicate that he is alive and receiving emails. Repeated attempts to find contemporary investigators or support staff at Oxford and at the HSE who know something about this work have been unsuccessful.

It is concluded that lacking even minimal statistical data, this study is simply uninformative. The MRC Schizophrenia Research Group is well-recognized and distinguished, but dementia was not a priority interest of either the Group or Dr. McDonald himself at the time. That fact and the paucity of information in the published abstract, which was contrary to usual practice in occupational epidemiology in the 1990s, suggest that no confidence should be placed in the reported findings of this study.

Peters et al. (2013): Cohort Mortality Study of Gold Miners in Kalgoorlie, Western Australia

Investigators at the Western Australian Institute for Medical Research and the School of Population Health at the University of Western Australia conducted a cohort mortality study of male gold miners in Kalgoorlie, Western Australia, who had ever worked underground and were traced from 1961 to 2009). The study used internal comparisons and the Australian general male population as an external comparison population.

Of 1,894 miners, there were 1,577 known deaths and 42,780 person-years of observation in total. Six hundred and forty-seven miners (34.2%) were documented to have been exposed to aluminum

dust (binary: yes/no, as indicated by a stamp on a time card indicating treatment) in a survey conducted between 1961 and 1975, reporting on McIntyre dust exposure for 10-minute dosages in the change rooms in jobs held by the miners from 1951 to 1968. The dates of exposure were not reported, but treatment ended in the late 1960s. Two hundred and eighty-three miners were lost to follow up (i.e., death certificate records were not available) and were assumed to be alive for calculation purposes in the last study period in which they appeared in the survey but were omitted from analysis (numerator and denominator) after the last date of contact. The study used the standardized mortality ratio (SMR) as its risk estimate. The method of analysis was a conventional proportional hazards regression (Cox regression) that allows calculation of survival time given that a subject has survived to a specific time and analysis of the effect on survival of several variables at once: birth cohort (range 1887 to 1959), age, aluminum exposure duration (1 to 15 years, median 10), and smoking (control of which had little effect on the risk estimate—probably because smoking was highly prevalent at 85%— and so was omitted in the final analyses). There was a known bias in that aluminum prophylaxis was probably more likely to be overreported than misclassified as absent due to the miner's aversion to it. This bias was judged to be relatively small on the basis of anecdotal impressions. Therefore, the effects reported in the study are likely to be underestimates.

The results were more suggestive than striking but, because they consistently pointed in the same direction, are noteworthy. Among the 1,577 deaths, cardiovascular disease was the most common cause, as expected, and was elevated in the mining population overall (SMR 1.31, 1.20–1.43), with no reported difference between the aluminum-treated and the untreated miners. Cerebrovascular disease (mostly stroke) was elevated to the same degree overall (1.38, 1.16–1.63). A total of 16 cases of Alzheimer's disease were reported overall (1.08, 0.66–1.76). Mortality from pneumoconiosis was highly elevated (16.1, 12.8–20.2). Thus, this population has a statistically significant elevated risk of background respiratory disease and vascular disease overall. Comparing miners who underwent aluminum prophylaxis with those who did not, the aluminum-treated workers had higher mortality from cardiovascular disease (1.38, 1.21–1.57 v. 1.26, 1.12–1.41) but a lower risk of death from cerebrovascular disease (1.30, 1.00–1.70 v. 1.43 1.16–1.78); neither difference is statistically significant at 95%. This suggests that vascular disease is not a confounding factor.

Mortality assigned to Alzheimer's disease, however, was noticeably higher among workers who had received McIntyre Powder prophylaxis (1.38, 0.69 −2.75 v. 0.89, 0.44 −1.78), although the difference did not achieve conventional statistical significance of 95% (5% likely to be replicated by chance alone). With only 16 cases (8 in each group), the difference may not be statistically significant, but at 160%, the magnitude of the elevation remains highly suggestive and potentially biologically significant. Convergent evidence in the data for an association came the exposure-response relationship analyzed by hazard ratio, again not achieving conventional statistically significance despite an overall hazard ratio of 2.79 (0.88 – 8.82) and upper bound risk estimates on the order of 9 and 14 with increasing exposure from none to 10+ years, showing a monotonic rise with duration of exposure but again failing to achieve statistical significance.

The power of the Peters et al. study to detect the difference in mortality observed (1.38, 0.69−2.17), with as many as 647 exposed subjects, given the confidence interval reported, is calculated at < 10%. As a practical interpretation, this means the Peters et al. study would be expected to miss

(i.e., fail to identify) the association between McIntyre Powder exposure and death from Alzheimer's disease 9 out of 10 times. This means that the study would be much more likely to miss a true difference at that level than it would be to detect one. The power to detect a difference in mortality from Parkinson's disease is also low, around 60%, meaning that it would detect a true difference 6 out of 10 times if it were present, which is better than for Alzheimer's disease but not much better than even odds. Thus, the study by Peters et al., as well conceived as it may have been for other outcomes, demonstrates very low power to indicate a difference. The Peters et al. study would have required 11 observed cases to achieve conventional statistical significance. For mortality from neurocognitive disorders, therefore, the study by Peters et al. is simply uninformative for this type of disorder. It is, however, highly suggestive for other outcomes studied.

The authors concluded that "our results show a tendency towards a possible association between aluminum dust exposure and an increased risk of mortality from cardiovascular disease and dementia of the Alzheimer's type." The Intrinsik review minimizes this conclusion and counts the study, essentially, as negative. Viewed more critically, however, Peters et al. can be considered positive in the sense that it strongly suggests a biologically significant effect: a substantial increase and an exposure-response relationship, evident despite its low power and the intrinsic bias of an insensitive outcome measure missing a true association.

The Peters et al. study is therefore best considered to be highly suggestive of a biologically significant effect that simply fails to achieve statistical significance for mortality from Alzheimer's disease because of low power.

Rifat et al. (1990): Northern Ontario Miners Health Survey

Dr. S.L. Rifat conducted the most comprehensive and detailed study on McIntyre Powder and cognitive changes for her PhD thesis at the University of Toronto. With three collaborators, she published her findings in The Lancet, one of the few most highly visible medical publications in the world, which immediately brought the work to worldwide attention.

The Lancet paper describes two distinct components to her study: 1. a conventional cohort mortality study, which yielded unremarkable findings for death from neurocognitive disease, and 2. an outcomes study (described in the paper as a "morbidity prevalence study") that compared performance on standard neurobehavioral tests with unexposed controls, which yielded highly significant findings. The findings from two study components will be discussed separately. Both study components drew subjects from a cohort of 6,604 Ontario hard rock miners born between 1918 and 1928 and entering the occupation between 1940 and 1959, who were identified from a sampling frame of 29,000 underground miners with records of having been examined in one of three clinics in Ontario between 1955 and 1979. The records of these examinations allowed identification of 2,424 miners for whom records of the McIntyre prophylactic program on at least one occasion indicated that they had been exposed to McIntyre Powder during the preceding year, leaving 4,180 presumed unexposed.

A stratified sample paired exposed and unexposed miners, 308 pairs, matched on year of entry and total time underground. In addition, Rifat et al. studied a non-overlapping (i.e. no names were

duplicated) random sample of 1,353 miners (631 exposed, 722 unexposed). Of 63 miners who were sampled in both protocols (but only retained in the random sample), 49 were exposed and 14 were unexposed.

Six hundred and forty-seven miners (63%) completed the interview out of 1,027 who were successfully traced, 15% of whom had died (19% exposed and 13% unexposed). The testing was performed in 1988 and 1989.

Exposure to McIntyre Powder ranged from 6 months to 36 years. The extent to which miners might have sought to avoid exposure is unknown because study staff intentionally avoided discussing attitudes or understanding of the prophylaxis program with subjects in order to avoid biasing the response.

The Ontario cohort was simply unique, and there will be no duplication or replication of this study. Use of McIntyre Powder in other countries was less intense, for shorter periods, and less well documented than in Ontario. Because the global population of miners treated with McIntyre Powder is advanced in age and will soon approach extinction, there is no possibility that this study could be repeated on another cohort with similar characteristics.

Cohort Mortality Study Component

Of the miners traced and determined to be alive or dead, there is no significant difference in mortality. Unfortunately, Rifat et al. did not provide a standardized mortality ratio or other risk estimates, and generally minimized the conclusions from the mortality study, which was not unreasonable to do so considering the power of mortality study component in Rifat et al. to detect a difference in death from Alzheimer's disease at a magnitude similar to that shown in Peters et al. was less than 10%, meaning that the mortality study component would have missed a true excess about 9 times out of 10.

The reported percentage of subjects who were deceased among those cohort subjects successfully traced (about 75% of both exposure groups) was 19.2% for the exposed and 13.6% for the unexposed. This discrepancy was not commented on in either The Lancet article or the University of Toronto thesis but would yield a proportionate mortality of 1.40 (for both the random and stratified samples), which might be significant depending on the distribution. This calculation does not usually accurately approximate the standardized mortality ratio under normal circumstances, but in this case, the two groups were documented to be similar in age distribution. The comparison can therefore be taken to suggest (but not prove) a mortality differential with exposed miners dying sooner than their unexposed coworkers.

Autopsy results were known for 28 deaths, only one of which revealed a cause related to the central nervous system (from Parkinson's disease). The autopsy reports were not available for the team to review.

Rifat et al. did not view this as a finding, given all the caveats, but rather as a background characteristic of the population and a check that would have assisted in the interpretation of survivorship bias in the event that there had been no difference in cognitive impairment (i.e.,

negative result). Their focus was not on mortality, and to collect cause of death information was apparently an obstacle.

Outcomes Study Component

Outcomes were obtained in 1988. Of those 1,027 subjects who were traced, 647 completed all modalities of the examination protocol. Alive, and accessible to the investigators, 40 were excluded because of a medical history of stroke, head injury, or other disorder involving the brain and cognition. This left 261 exposed and 346 unexposed miners in the study cohort.
Since mortality was about the same for exposed and unexposed miners (although not reported in detail) and was not much different between groups, it is unlikely that failure to trace was linked to exposure and outcome. The more important variable, the percentage that refused to participate, was relatively low at 10%.

The successive levels of recruitment and exclusion may have introduced bias in the subjects available to perform the test, but there is no evidence available to confirm or rule out selection bias. The most likely direction of such bias would be to reduce the prevalence of impairment in both exposure groups, rather than introducing a differential bias. It is more likely that such individuals who refused to participate would have a greater rather than lesser prevalence of impairment that made them experience discomfort or impeded their cooperation with the study. If so, it is unlikely that the difficulty maintaining the cohort introduced significant bias, although it may have reduced the power of the study from the ideal.

There were a significant number of refusals (about 10%) among the 514 surviving miners who were successfully traced, roughly equal in both exposure groups. Reasons for refusal were not documented, and so it is unknown whether there was a higher prevalence in impairment among subjects who refused, but there is no evidence for this either. Three hundred and twenty-three subjects completed the interview and all three tests, including 42 of the matched pairs. As a consequence, the analysis was performed only at the group level and not by pairs. (This would not be expected to introduce a significant bias. Had the matching pairs been maintained, the power would have been higher.)

Analysis of detailed information on medical condition was deemed unproductive because of uncertainties over reliability. Rifat in her thesis (p. 163) also noted qualitative evidence that miners overall were seemingly reluctant to seek medical attention compared to other populations and thus to be aware of or treated early for chronic conditions. This would suggest, without quantitative confirmation, that prevalence estimates of neurological impairment are likely to be underestimates and supports the decision not to rely on medical histories from subjects or their surrogates.
Risk estimates were adjusted for age, years underground, age at the time of interview, education, elevated blood pressure, history of head injury resulting in loss of consciousness, and interviewer notation of subject characteristics (hearing impairment, visual impairment, visible tremor, and evident cooperation). Adjustment made only minor differences in risk estimates. The investigators reported no change in risk estimates when occupational history other than mining, personal medical history, family history (of dementia), and alcohol consumption were factored into the model, and so these variables were dropped.

Miners who could be traced (an obvious potential source of bias) were interviewed at home regarding their medical history for neurological disorders. Among the exposed miners, one had a "probable" diagnosis of Alzheimer's disease and three carried the diagnosis of Parkinson's. Only one unexposed miner had a diagnosis of neurological disorder, which was "probable" Alzheimer's disease. However, these numbers signify very low power for this analysis and are too small to calculate a stable risk estimate.

Miners who could be traced were also administered standardized and well-accepted screening (not diagnostic) tests of cognitive function at the time of the interview. Tests included the Mini-Mental State Examination (a test of general cognitive function that is dependent on memory and heavily used in research and clinically), the Ravens Coloured Progressive Matrices test (a heavily used nonverbal test of reasoning ability, quantified as g, for "general intelligence" heavily used in education), and the Symbol Digit Modalities Test (a screening test for impaired cognitive function heavily used clinically). The cutoff points for these tests, especially the Mini-Mental State Examination, were deemed inappropriately high, because these tests were designed for functional impairment in nursing home populations with higher levels of impairment than would be observed in subjects living independently or with family in their community. Cutoff scores derived from population studies were used instead of the clinical guidance suggested with the test kit. For the purposes of analysis, the scores on the three tests were added and the sum was treated as the outcome variable.

The study found that exposed miners showed a clear difference in summed scores, with a difference of 4.2 (adjusted for age, time underground, and other relevant variables) to 6.3 (unadjusted) points, which was highly significant ($p \leq 0.001$). Another measure, the proportion showing impairment on at least one test (range about 0.14), was similarly significant ($p \leq 0.0002$). Furthermore, there was a clear inverse association between proportion impaired and duration of exposure to McIntyre Powder, yielding a highly significant test for trend ($p = 0.0001$).
Given the study design and large numbers (despite attrition of the cohort) Rifat et al. were able to achieve high power, > 0.99 for both outcome measures (unadjusted) and 0.84 to detect differences in proportion with impaired cognitive function in the two highest exposure levels (adjusted). (For purposes of planning studies, power > 0.80 is usually the practical goal.)

Notwithstanding that some miners reported overstating their age at the beginning of their career to get hired, there was no evidence that this was significant in biasing the overall results or of differential bias between the exposed and unexposed groups. This is partly explained by the observation that most participants fell into a narrow age range of about 60 – 70 years at the time they were studied and that there was no suggestion of significant or differential anomalies in educational level attained. Immigrant status did not show a consistent effect.

The findings of the outcomes component of the study is therefore unequivocal. In this uniquely documented cohort, there is a strong, robust, and unconfounded inverse association between exposure to McIntyre Powder and performance on reliable, robust tests of neurocognitive function.

Obviously, no epidemiological study is free of limitations and drawbacks. However, the study by Rifat et al. does not show an obvious fatal flaw or reason to suspect bias or confounding sufficient

to produce spurious results.

Statistically, the outcomes study component is very strong, with a power of 99% to detect the difference in mean sum scores at the reported level and > 93% to detect the proportion impaired. Such levels of power are unusual for "rare" diseases (in the statistical sense) in occupational medicine.

Rifat et al. proposed a series of follow-up studies and suggested documenting accumulation of aluminum in the brain tissue of subjects, but that suggestion was not followed up.
In summary, the study component by Rifat et al. on prevalence of neurological impairment shows clearly that there is a strong and consistent association between neurocognitive impairment and exposure to McIntyre Powder.

Even the weakest element of this study component was suggestive of a difference. Notwithstanding the insensitivity of self-reported neurological diseases as an indicator of Alzheimer's disease, Rifat et al. came very close to achieving statistical significance on prevalence ($p = 0.054$). This was not true for Parkinson's disease ($p > 0.60$).

Rifat et al. Follow-Up Study: Northern Ontario Miners Health Survey

Rifat and the same coauthors conducted a follow-up study in 1994 that was never published in the scientific literature, although a copy was obtained through a Freedom of Information Act request. Dr. Rifat has suggested that there was some disagreement among the authors regarding preparation of a follow-up paper in 1996, and so the findings of the second round were never published. At the time, there were concerns about potential bias in the second, follow-up sample and this may have been a critical issue at the time. She of course did discharge her and the coauthors' responsibility to report findings from the follow-up study to the funding agency.

This was a restudy of 151 men in the exposed group and 123 in the unexposed group from the 1990 study, consisting of those who had scored below cut points on the neurocognitive study in the outcomes study component that were used to define abnormal test results (and were therefore considered to be impaired) and a sample of those who scored above the cut points (and were not). The same tests were repeated, with the addition of a neuropsychological examination.

Of the 424 men selected for study, 150 miners were lost to follow-up, approximately equally from exposed and unexposed groups. Those lost to follow up did not differ in current age, employment duration, or educational level. There was a small subgroup in both exposure categories but predominantly from the unexposed category that refused to participate in the second study after participating in the first and who reported symptoms that might reflect neurological impairment as a reason for refusing to participate. There were only three subjects lost to follow up because of death from neurological disease.

Using a complicated clinical assessment protocol that rested on the opinions of expert reviewers, the investigators determined probable diagnostic categories and determined that 4% of each exposure category appeared to show neurocognitive disorder of unknown cause (i.e., not otherwise explained). There were many cases difficult to classify, and new diagnoses had arisen since the

earlier study. Because of the nature of the diseases, clinical criteria are more reliable for Parkinson's disease than for "early dementia of Alzheimer's type" (so classified because Alzheimer's disease as such requires in-depth evaluation to confirm but disorders of dementia and cognitive impairment could be identified from the data obtained without specific diagnosis).

In the 1994 restudy, there was no difference in prevalence of presumed neurocognitive disorder between the exposed (30%) and unexposed (29%) groups; that was reported as the principal finding.

Looking more closely at subgroups, each group (exposed or unexposed) had the same rate of clinical findings characteristic of dementia (4%); nor was there a difference in 63 observed cases of neurological impairment with an attributed (known) cause. Subjects who did not test impaired on the first round of testing in 1988 did not show a decline in scores in 1994, regardless of exposure group. Within the group of subjects showing impairment, exposed subjects showed lower scores in 1988 but the biggest change was the greater decline in scores of unexposed subjects between 1988 and 1994. Five of the six exposed subjects who met the diagnostic criteria for "dementia of unknown cause" were in the highest stratum of exposure but overall there was no evidence of an exposure-response relationship in the 1994 round for duration of exposure.

Further analysis did not yield an explanation for the discrepancy, although the timing of the cases suggested that exposed subjects might have been identified with dementia earlier, in 1988, while the group of unexposed miners may have "caught up" in the ensuing 6 years, achieving similar proportions in the end. Otherwise, there was no consistent pattern suggesting migration of miners from the unimpaired group to the impaired group occurred disproportionately in the exposed group. On the other hand, there was a reported trend for increasing risk of "neurocognitive disorders of unknown causes" with increasing duration of exposure to McIntyre Powder.

The potential for selection bias is obvious in a protocol this complicated but there is no firm evidence on which to estimate direction and magnitude of bias. However, the most impaired men in either exposure group did not perform the text, which subtracted the worst-affected from both exposure groups. (This may or may not have truncated the range of scores.)

Dr. Rifat and her colleagues wrote that the null hypothesis (no difference between exposed and unexposed miners) could not be rejected.

In subsequent communications, Dr. Rifat indicated that she has confidence in the findings of impairment in the first study but is not committed to an interpretation on causation (in other words, whether aluminum exposure was the causal factor). She also indicated that she had confidence in the diagnostic classification in the follow-up study but considered the loss of subjects to follow-up and reduced power in the follow-up study to be "concerning."

Given the complexity of the analysis, the practical issue of accurately separating the dementia diagnostic categories, and the selection process that may have introduced bias into the subject pool in the second study, it is not possible to determine with any confidence whether the follow-up study contradicted the 1990 study or was simply uninformative due to circumstances. It does appear that the follow-up study had a higher vulnerability to selection bias in unknown directions

as well as lower power than the initial outcomes study. Between the two, there is necessarily greater confidence in the findings of the first round, which showed differences in prevalence of impairment.

Critique of the Intrinsik Report

The Intrinsik report presumably follows negotiated terms of reference approved or proposed by the WSIB. Some of the choices, however, may have had unintended consequences. For example, the omission of the second (1994 follow-up) Rifat study was clearly a consequence of confining the literature search to peer-reviewed publications. However, although the findings of the follow-up Rifat study are difficult to interpret, it was most likely at least internally peer reviewed at some point, and was clearly relevant and so should have been included as a special case.

The Intrinsik report casts a wide net, examining mortality and prevalence of many conditions following exposure to McIntyre Powder, and it is often difficult to see the relevance of the detailed treatment, especially given that the medical community is in agreement that aluminum exposure does not prevent silicosis and it is well known (with exhaustive research in the industry) that the hazards of the aluminum smelting industry have little to do with aluminum.

The most important outcome under consideration is clearly that of presumptive Alzheimer's disease (ICD-9 331) from neurological disorders with disparate causes and different risk factors. Alzheimer's disease is of greatest interest because of putative association with aluminum in neurofibrillary tangles in the central nervous system, although it is not clear whether accumulation of aluminum is an effect of the underlying process or a cause. Parkinson's disease (although in this case "syndrome" would be more accurate, ICD-9 332) has different risk factors, although in some cases, dementia occurs with progression.

The Intrinsik report is notable for its extensive literature review, which ranges into distant topics, and is constrained by the bluntness of available instruments for diagnosing neurocognitive disorders from death records. Mortality from dementia, in particular, is not a sensitive or reliable indicator of the prevalence of Alzheimer's disease. The report states this in several passages but then goes on treat it as if it were.

Alzheimer's disease is easily conflated with dementia from other causes in the elderly, particularly vascular dementia, which reflects common cardiovascular risk factors. Post-traumatic dementia following head trauma may also resemble Alzheimer's disease. The Intrinsik report does not put Alzheimer's disease in context, devoting less than a page to the background to the diagnosis, most of which is taken up by a large graph showing the increase in mortality in the United States from the disease with age and longitudinally between 2000 and 2010, which is irrelevant to the report.

Parkinson's disease (when the condition is primary) or syndrome (when it is the result of other factors, such as medication side effects) is a protean disease (meaning that it can appear in different guises) than can manifest itself as paralysis, a characteristic movement disorder, mouth movement, tremor, swallowing impairment, labile blood pressure, impaired speech, muscle contractions (similar to cramps), depression, and dementia. Neuroscientists have accepted for many years that there may be interactions between a genetic predisposition and environmental

causes, particularly because the syndrome can be caused by several drugs and by exposure to manganese.

Amyotrophic lateral sclerosis (ALS, ICD-9 335) is a disorder of motor neuron function that manifests as progressive paralysis. ALS is characterized by an absence of dementia in half of reported cases, and when they do occur (in about 20% of cases), they tend to mimic a specific condition called frontal temporal dementia, which is distinct from Alzheimer's disease and primarily affects language processing and rapid forgetting (impaired imprinting before short-term memory). ALS is currently thought to be a process of nerve cell death and drop-out occurring at a particularly vulnerable place in the nervous system (the anterior horn cell of the spinal cord) in response to oxidative stress on the nerve cell, which clearly includes head trauma and might include exposure to dust and chemicals. (There is, for example, a strong association between ALS and exposure to formaldehyde.) There is no obvious causal connection among these conditions, and so a negative study for one does not have implications for causation in the others.

None of these neurological diseases are a sole cause of death nor are they likely to be recorded as such on a death certificate. At best, these diseases would be recorded as underlying causes of death. The most likely cause of death for any of the three is pneumonia, reflecting inability to control secretions and immobility, and in the case of ALS, paralysis and inability to breathe. Most conscientious physicians will record the neurocognitive disease as an *underlying* cause of death if they are aware of it (death certificates are often signed by physicians who are not the treating doctor), but this reporting is variable and often overlooked. Therefore, any study of these disorders, but especially Alzheimer's disease, that relies on mortality underestimates the contribution of neurocognitive disorder as an underlying cause, will undercount the frequency of neurocognitive disease, and is likely to miss a true association.

The Intrinsik report converts the estimated exposure of 7.35 mg/m^3 over 10 minutes (from the 1992 ISDP Report) to conclude (pp. ii and 68) that it is equivalent to an 8-hour time-weighted average exposure of 1 to 15 mg/m^3. This cannot be correct, arithmetically, as an average over 8 hours cannot be higher than the average over 10 minutes of those 8 hours. Intrinsik must show its work.

More fundamentally, a 10-minute peak or short-term exposure is not physiologically equivalent to an 8-hour continuous exposure for a dust that undergoes effective clearance in the respiratory tract (as most do except asbestos, silica, and a few acutely toxic dusts that are retained). A high bolus of soluble dust is much more likely to be retained and sequestered in the lung and therefore to support elevated blood levels over a longer period of time.

Stated goals of the Intrinsik report were to "identify any subgroups of workers with occupational aluminum exposure who have an increased risk of developing adverse health conditions," to "identify exposure-response relationships," and to "determine whether a causal relationship can be established for any health conditions based on the available scientific evidence." Given the paucity of studies on neurocognitive disorders, these goals were unachievable.

The Hill Criteria (p. 64) cannot be meaningfully applied to these results because of dependence of the analysis on a single study. However, if the suggestive mortality results are taken into account

and the uninformative study is omitted, then eight of the nine Hill criteria as listed in the Intrinsik report are actually satisfied mostly by the study of Rifat et al. for the specific outcome study components, listed as follows: temporality (cause preceding effect), strength (the association for impairment is very strong), dose-response relationship (using either years of service or time spent underground, which covary), biological plausibility (given extant theories of an exposure + susceptibility model), alternative explanations (implicit in the regression model, which tested for alternative hypotheses), specificity (because the association does not hold for Parkinson's disease), and coherence (because the findings are compatible with at least some existing theories). The only Hill criteria not met by Rifat et al., because one study cannot support application of the criteria, are replicability and cessation of exposure. Replicability is partially met by the suggestive but not conclusive evidence for increased mortality from dementia, weak though they are in isolation and not voided by the discrepancies of the findings of the Rifat et al. follow-up study in 1994 compared to 1988. Cessation of exposure is not possible in this study in any event.

It should be noted that the Intrinsik report does not conform to the actual Hill criteria, as outline by Bradford Hill in 1965. The original (actual) Hill criteria were listed as follows: 1. Strength (met); 2. Consistency (partially met, with respect to the suggestive findings of the mortality studies); 3. Specificity (met); 4. Temporality (met); 5. Biological gradient (met, see dose-response relationship, above); 6. Plausibility (met); 7. Coherence (met, as above); 8. Experiment (and which Hill only stated was valuable when it occurred, and is not limited to "cessation of exposure," as implied in the Intrinsik report); and 9. Analogy (which is a weak criterion and which is omitted from the Intrinsik list, but may be considered to be met by analogy to manganese and its neurophilic toxicity).

Thus, the conclusion of the Intrinsik report that "The findings across the literature were inconsistent" does not apply to dementia of Alzheimer's disease. The conclusion of the Intrinsik report that "most of the … [Hill] criteria were not satisfied" is not true for dementia of Alzheimer's disease. Left unstated is the deeper issue that the Hill criteria is not usually so dependent a single study because it refers to a body of evidence. An even deeper issue is that the Hill criteria have been misrepresented in the Intrinsik report because they are not "criteria for causality" at all. The Hill criteria are a checklist for considering the likelihood of causation, recognizing that they are not proof of a causal association and that associations may be causal even if the criteria are incomplete or some are missing because they have not been researched or determined.

The Intrinsik report has the effect of minimizing the significance of the neurocognitive studies reported by Rifat et al., not by omission but by lack of detail and emphasis. In many passages (for example, p. 60), the report gives each of the three studies equal treatment (false equivalence) and column inches as if they were equally informative. The suggestive nature of the Peter et al. findings is nowhere noted, as are the convergent suggestive findings of the mortality study component of Rifat et al. In the same passage, the strongly positive morbidity prevalence findings of Rifat et al. are not given numbers or textual emphasis. It is easy for the casual reader to come away from the Intrinsik report failing to understand or even notice the strength of the evidence. Indeed, the findings of an association between McIntyre Powder exposure and dementia are buried in a mass of essentially irrelevant detail.

Although the WSIB may have had an interest in determining the association between McIntyre

Powder and pulmonary function, cardiovascular disease, and other outcomes, the effect of including so many outcomes obscured the single most important reason for the analysis: neurological impairment. Similarly, inclusion of irrelevant exposure situations (such as aluminum smelting, in which the relevant issues do not include aluminum exposure) obscured the paucity of analysis for the one outcome that really mattered. The final terms of reference for the Intrinsik report, by including this morass of irrelevant detail, made it more difficult to cut through to the one issue of greatest concern and had the effect of reinforcing the erroneous conclusion that evidence was weak for an effect on neurocognitive function.

On the whole, the Intrinsik report is wordy in many passages, contains much material irrelevant to the core question of neurocognitive impairment, and has significant omissions and misrepresentations, such as its inaccurate presentation of the Hill criteria. It does not go out of its way to question the validity of mortality as an indicator of neurocognitive disorders, although this outcome is highly insensitive, and its treatment of the neurobehavioral testing protocol in the Rifat et al. 1990 paper is rather basic.

Because of these deficiencies and the obfuscation introduced by including too many extraneous outcomes, it is recommended that the Intrinsik review not be used as a primary source on this topic and that instead interested parties go directly to the studies in question and read them for themselves.

Assessment of the Totality of Evidence

Given the totality of evidence, it is apparent that the strength of evidence is much higher for the neurocognitive testing results from the well-conducted and appropriate protocol reported by Rifat et al. than implied by the Intrinsik report. The ambiguous results of the 1994 follow-up study do not reduce confidence in the initial findings. Although the 1994 follow-up did not validate the 1988 round, it cannot be said to have invalidated the earlier study either. The follow-up study had lower power, and the follow-up subject pool was a residual group remaining after a number of steps may have introduced bias in unknown directions.

On the one hand, there are three nominally inconclusive mortality studies, one with inadequate reporting, and two, include the mortality component of the study of Rifat et al., that despite grossly insufficient power are at least suggestive of an effect. Mortality is an insensitive and unreliable indicator of whether either or both the frequency and severity of neurocognitive disorders are elevated. It should never be relied upon as evidence for “no effect”.

On the other hand, there is a single well-conducted study, which is well done and adequate to conclude that morbidity from neurocognitive disorders is elevated. This study, which cannot be repeated, uses much more sensitive and reliable indicators and demonstrates high power to determine significance both statistically and functionally.

The follow-up study in 1994 does not invalidate the findings of the first, from 1988, because the cohort was clearly aging, the subject pool was substantially different (through no fault of the investigators), there was evidence for a persistent association between impairment and duration of employment (although details were not reported) in one clinically-determined type (“neurological

disorders of unknown cause") but not the others, and the observed convergence of rates of dementia in the two exposure groups was explained by the "catching up" of rates in the interim period.

Thus, the weight of evidence falls on the side of there being a difference in neurocognitive function and impairment associated with increased levels of impairment among the miners treated with McIntyre Powder.

References Supplemental to Intrinsik Report

References are as given in the Intrinsik report, with the addition of the following:

Rifat, S L. Evidence Regarding Effects of Exposure to McIntyre Powder. Ph.D. Thesis. Toronto, University of Toronto, School of Graduate Studies, 1990.

Rifat, S L; Corey, P N & McLachlan, D R C. Northern Ontario Miners' Health Survey: A Summary of the Follow-Up Investigations. Toronto, Ontario Ministry of Labor on deposit with the Evidentiary Centre, Master File Number 4694. Undated.

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Biostatistician Subcontractor

Dr. Tsui Ying Kau, University of Michigan. Dr. Kau was retained on our behalf by ATL International of Gaithersburg, Maryland, and in order to avoid bias, was not informed of the nature and substance of the review project or the anticipated results. Dr. Kau conducted this work under the auspices of The Good Number Consulting Group.

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Support services, including literature search and copyreading, were provided by ATL International, Inc. of Gaithersburg, Maryland, USA under contract to Dr. Guidotti.

Consultant: Biography and Experience

Tee L. Guidotti, MD, MPH, DABT, FRCPC, FFOM, FCBOM, is an international consultant and physician-scientist with a practice in occupational and environmental health. Dr. Guidotti first became aware of the use of McIntyre Powder in 1973, as a medical student studying occupational lung diseases, particularly silicosis. He wrote a paper on the topic and subsequently has been following the issue for many years. He has been interested in silica-related lung disease throughout his medical career and has examined cases in China as well as North America. He was one of the first investigators, together with David Goldsmith, to assert on the basis of the evidence that silica is a cause of lung cancer, in 1982 at a time when conventional wisdom held that it was not.

Dr. Guidotti is registered as a specialist in occupational medicine by the College of Physicians and Surgeons of Ontario. His consultancy practice consists primarily of health-related problem-solving projects, medicolegal (expert witness) services, publishing-related activities, and medical review. He sometimes, as with this project, provides services through the sole proprietorship Occupational and Environmental Health and Medicine (O+EH&M).

Dr. Guidotti is a physician with American board certification in internal medicine, pulmonary medicine and American (ABPM board certification), Canadian (FRCPC and FCBOM), and UK (FFOM) recognition as a specialist in occupational and environmental medicine. Following the completion of his training in each of these specialties at Johns Hopkins in 1981, he has been in medical practice continuously since. Dr. Guidotti is licensed to practice medicine in the District of Columbia, Maryland, California, and registered the province of Ontario. He is a Diplomate of the American Board of Toxicology (DABT), a nonmedical credential primarily for regulatory and research toxicologists. He also holds a credential in environmental management and regulation, Qualified Environmental Professional (QEP) specializing in air pollution. For 6 months in 2015, he was Fulbright Visiting Research Chair in the Institute for Science, Society, and Policy at the University of Ottawa, studying science policy.

In June 2008, Dr. Guidotti took early retirement as Professor and Chair of the Department of Environmental and Occupational Health in the School of Public Health and Health Services, The George Washington University Medical Center, Washington DC; and Director of the Division of Occupational Medicine and Toxicology in the Department of Medicine, School of Medicine and Health Sciences, where he saw patients weekly at the Division's Occupational Medicine and Toxicology Consultation Clinic in the Department of Medicine, where he had a cross-appointment. Prior to taking that position in 1999, he was for 14 years Professor of Occupational and Environmental Medicine and Director of the Occupational Health Program in the Department of Public Health Sciences at the University of Alberta in Edmonton, Canada. There he saw patients at the Occupational Medicine Referral Clinic at the University of Alberta Hospital site, Capital Health Authority, where he was academic chair of occupational medicine and had a cross-appointment in pulmonary medicine. Prior to moving to Alberta in 1984, he was Professor of Occupational and Environmental Health at the San Diego State University Graduate School of Public Health, which was affiliated with the Rees-Stealy Medical Group (now Sharp Medicine), where he saw patients in medicine at the Occupational/Industrial Medical Clinic. Prior to that he was in residency and fellowship training in the three specialties at The Johns Hopkins Hospital,

Baltimore, with 2 years for clinical research at the National Institutes of Health in Bethesda Maryland. He attended medical school at the University of California at San Diego and went to university at the University of Southern California.

Dr. Guidotti has served as President and is a fellow of the American College of Occupational and Environmental Medicine, the American Thoracic Society, and the American Association for the Advancement of Science. He holds many other professional fellowships and awards, including the 2013 Knudsen Award (the highest award in American occupational medicine). He is the author of over 250 papers and book chapters and has produced 8 books, among them The Praeger Handbook of Occupational and Environmental Medicine (Praeger, 2010, in three volumes, solo authored), Global Occupational Health (Oxford University Press, 2011), Occupational Health Services: A Practical Approach (Routledge, 2012), and Health and Sustainability (Oxford University Press, 2015).

Dr. Guidotti has had a special interest in occupational lung disease and inhalation toxicology, including especially the pneumoconiosis, occupational asthma, and lung cancer. He has conducted research on silica and lung cancer, firefighters and cancer risk, and arc welder's lung, and he has written extensively on silicosis and coal workers' pneumoconiosis, which he first studied as a medical student on a traineeship at the Appalachian Laboratory for Occupational Safety and Health in West Virginia. In recent years, he has become interested in nanoparticles and ultrafine air pollution. He has participated in a variety of projects to develop clinical guidelines, particularly the ACOEM Practice Guidelines, with uses the methodology developed by the Cochrane Collaboration.

Consultant's Published Works Relevant to Metals Toxicology and Aluminum

Dr. Guidotti has written or coauthored over 300 peer-reviewed publications, including many original research papers in toxicology, environmental health, and occupational medicine. The papers listed below relate directly to aluminum or metals toxicology in general, the progression of silicosis, and silicosis-related disease.

Occupational Interstitial Lung Disease Guideline. [TL Guidotti was a member of the Evidence-Based Practice Panel, which had 10 members.] In: Hegman, K T, editor-in-chief. ACOEM Practice Guidelines. Westminster CO, American College of Occupational and Environmental Medicine, Reed Group Ltd., 2015, 59 pp, in press. (This is the authoritative set of practice guidelines for occupational interstitial lung disease, including pneumoconiosis and related conditions.)

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