HHS Public Access
Author manuscript
Neurotoxicology. Author manuscript; available in PMC 2015 August 28.

Published in final edited form as:
Neurotoxicology. 2014 December ; 45: 276–284. doi:10.1016/j.neuro.2014.03.015.

Respiratory manganese particle size, time-course and neurobehavioral outcomes in workers at a manganese alloy production plant

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Abstract

The progression of manganism with chronic exposure to airborne manganese (Mn) is not well understood. Here, we further investigate the findings on exposure and neurobehavioral outcomes of workers from a silico- and ferromanganese production plant and non-exposed workers from the same community in 1990 and 2004, using a variety of exposure metrics that distinguish particle size and origin within the range of respirable airborne exposures. Mn exposure matrices for large respirable particulate (Mn-LRP, dust) and small respirable particulate (Mn-SRP, fume), based on process origins, were used together with detailed work histories since 1973 (plant opening), to construct exposure metrics including burdens and cumulative burdens with various clearance half-lives. For three out of eight 1990 neurobehavioral tests analyzed with linear regression models, duration of Mn exposure was the best predictor: Luria-Nebraska Neuropsychological Battery – Motor Scale, Trail-Making B and Finger Tapping. The Luria-Nebraska Motor Scale had the strongest association ($t \sim 5.0$, $p < 10^{-6}$). For outcomes on three other tests, the duration and Mn-SRP metrics were comparable: Trail Making Test A, Cancellation H and Stroop Color-Word Test (color/word subtest). Delayed Word Recall was best predicted by Mn-SRP (based on square root or truncated air-concentrations). The Word score on the Stroop Color-Word Test was the only outcome for which Mn-LRP was the leading predictor ($t = -2.92$, $p = 0.003$), while performance on the WAIS-R Digit Span Test was not significantly predicted by any metric. For outcomes evaluated in both 1990 and 2004, a mixed-effect linear regression model was used to examine estimates of within-individual trends. Duration and Mn-SRP were associated with performance on the Luria-Nebraska Motor Scale, as well as with other outcomes that appeared to have both reversible and progressive features, including Trail Making A and B, Cancellation H and Delayed

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Conflict of interest
The authors declare that there are no conflicts of interest.

Transparency document
The Transparency document associated with this article can be found in the online version.

Word Recall. With the mixed-effect model, Digit Span exhibited a significant irreversible association with exposure duration ($t = -2.34$, $p = 0.021$) and Mn-SRP (square root; $t = -2.38$, $p = 0.019$) metrics. The strong prediction using duration of exposure is consistent with effective homeostatic regulation of tissue-level Mn in the observed exposure range of respirable Mn (<0.2 mg/m^3).

Keywords

Manganese; Burden; Fume; Half-life; Homeostasis

1. Introduction

High exposures of workers to manganese (Mn) in mining, manufacturing operations and welding can lead to manganism (Levy and Nassetta, 2003), an atypical form of parkinsonism (Guilarte, 2013). Early manganism resulting from sustained lower exposures to Mn, reported in epidemiologic studies of active workers, is characterized by reduced motor coordination, tremor, cognitive deficits and mood lability (for review see: ATSDR, 2000; Mergler and Baldwin, 1997; Zoni et al., 2007). However, relations between neurobehavioral test results and measures of exposure are inconsistent; some studies have reported diminished performance associated with blood Mn or with a cumulative index, others have only reported differences between the exposed workers and a referent group (for review see: Park, 2013). Systemic uptake of manganese occurs largely via the pulmonary route because excess Mn absorbed from the GI tract is efficiently eliminated (Andersen et al., 1999). Larger inhaled particles (>1.0 μm) are generally transported to the GI tract. Uptake of small particles containing manganese via the olfactory nerve has also been proposed (Elder et al., 2006; Fechter et al., 2002). One important question concerns the relative potency of airborne Mn in the respirable size range when present as a dust (>1.0 μm in diameter), typically from crushing operations, or as a smaller, condensation fume (≪1.0 μm in diameter) from electric furnace or welding emissions. Because manganese is an essential nutrient, it is under complex homeostatic regulation (Schroeter et al., 2011) which could influence the shape of the exposure response.

In 1990, Mergler et al. (1994) evaluated workers employed at a ferro- and silicomanganese alloy production plant with exposures to Mn dust (crushing operations) and fume (a sealed submerged arc electric furnace) that operated in Quebec, Canada beginning in 1973 and closing in 1991. After 1991 there was no comparable industrial facility in this area.

One hundred and fifteen alloy workers (95% of those eligible) and 145 community-derived referent workers were assessed using an extensive neuropsychological test battery. Exposure concentrations, at the time of the study, averaged 0.23 mg/m^3 (geometric mean, GM) for total Mn and 0.04 mg/m^3 (GM) for respirable Mn. Compared to the referents, Mn-exposed workers reported a higher prevalence of symptoms and matched-pair analyses showed deficits in motor, cognitive and emotional functioning (Mergler et al., 1994). The plant closed in 1991 and later Bouchard et al. (2007, 2008) conducted a 14-yr follow-up assessment of the Quebec alloy workers, using a reduced neuropsychological battery. The follow-up showed that the Mn-exposed workers still displayed poorer performance than controls for several motor tasks, while on other tests, differences were no longer observable with the exception of older workers who showed poorer results for certain cognitive tests compared to their referents. Exposure at this workplace was extensively analyzed by Baldwin et al. (2008) using data taken at the time of the study, as well as historical data, coupled to workers' records from the plant opening to its closure. We recently examined blood levels of Mn from the 1990 survey in relation to exposure history (applying various half-lives to exposures) and observed that air concentrations of Mn as small respirable particulates (Mn-SRP, largely fume) were much stronger predictors of blood levels than the larger respirable particulates (Mn-LRP, largely dust); duration of exposure was also a strong predictor (Park et al., in this issue). The derivation of Mn-SRP and Mn-LRP was based on process characterization and location in the plant and job titles (Park et al., in this issue). In the absence of detailed particle-size information, we assumed that Mn-LRP exposures were generally > 1.0 μm in mass median aerodynamic diameter and Mn-SRP exposures < 1.0 μm diameter.

The present investigation used the exposure assessment (Baldwin et al., 2008) and the outcome data from the study of Mergler et al. (1994) and the 14-yr follow-up study of Bouchard et al. (2007) to examine in more detail the exposure-response relationships between airborne manganese and neurobehavioral outcomes. A special focus was comparing the relative potency of manganese as large respirable particulate (Mn-LRP) vs. small respirable particulate (Mn-SRP), understanding that some small particulate has mechanical origins and some of the small particulate is present as agglomerates (Park et al., in this issue).

2. Methods

2.1. Neurobehavioral outcomes

Eight neurobehavioral outcomes that represent a range of attributes including motor and cognitive abilities were selected from the previous studies (Mergler et al., 1994; Bouchard et al., 2007). Exposure-response relations were examined for the full 1990 participant group ($n = 244$; two were excluded due to missing information on education) and for the subset of workers and community referents, who participated in both the 1990 and 2004 surveys ($n = 135$). The majority of workers terminated employment in this plant between May and October 1991 and thus had up to a year of Mn exposure following the 1990 investigation.

For a sub-sample of the study group neurobehavioral test scores were analyzed as aggregated domain z-scores for the original 1990 population restricted on age (≥30) and employment duration in the study plant (≥10 yr) in order to make the exposed and referent groups comparable with respect to age and educational level. The mean non-exposed workers' scores and standard deviations were considered as the reference value; the z-score was calculated as the observed score of the exposed and non-exposed workers minus the mean reference score, divided by the standard deviation of the reference score. The direction of score was standardized so that negative scores indicate poorer performance. The domains analyzed were: Executive Function (Stroop Color-Word Score, Trail-making Test B, Digit Span Backwards), other cognitive functions (Symbol Digit Modalities (written), Symbol

Digit Modalities (oral), Delayed Word Recall), and the Luria Nebraska Neuropsychological Test Battery Motor Scale.

2.2. Exposure history

The previously constructed exposure matrix for Mn providing estimates of total respirable particulate (Mn-TRP) in 14 time periods during 1973–1991 across 32 process-defined job groups (Baldwin et al., 2008) was used to distinguish Mn-LRP from Mn-SRP exposures based on process origin (Park et al., in this issue). The 14 periods captured changes in process including furnace modifications, maintenance shut-downs and two periods of plant closure. The available work history (Baldwin et al., 2008) consisted of the sequence of job group assignments for each worker across time, with associated dates. There was relatively little workforce turnover during 1973–1990 and some workers held numerous job assignments (more than 20). Duration of exposure to Mn exceeded 10 yr for 94% of the Mn alloy production workers population (mean = 14.4, maximum = 16.1 yr). The estimated time-weighted mean exposure of the Mn alloy production workers to respirable Mn was 0.148 mg/m^3. The mean cumulative exposures for Mn-LRP, Mn-SRP and Mn-TRP were, respectively, 0.92, 1.18 and 2.09 mg/m^3-yr (Park et al., in this issue).

2.3. Exposure metrics

In order to model neurobehavioral status, *cumulative exposure*, cum(Mn), was calculated in the usual manner as a time-weighted sum of job assignment exposures up until the date of survey participation:

$$\mathrm{cum(Mn)}=\sum_{i=t1}^{t2} X(t_i),\ \text{expressed in } \mathrm{mg/m^3 yr}$$

where $X(t_i)$ is the estimated respirable Mn concentration at time, t_i, t_1 is time of first exposure, t_2 is time of survey. Time, t_i, in this calculation, was partitioned into 10-day units. This metric is appropriate for an exposure effect that is irreversible and fast-acting. It takes no account of how much time has passed between the exposure event and measured effect.

Because excess Mn is under homeostatic control and is cleared from the body, exposure *burdens*, B(Mn), were calculated, as follows:

$$\mathrm{B(Mn)}=\sum_{i=t1}^{t2}[X(t_i)\times(0.5)^{(t_2-t_i)/T_{\mathbf{half};)}}],\ \text{expressed in } \mathrm{mg/m^3\ yr}$$

where $T_{½}$ is the half-life specifying that the burden declines with time, at a fixed proportional rate (e.g., 50% per year). With half-life approaching ∞, B_{Mn} becomes the usual cumulative exposure. This metric would also better predict outcomes that have some reversibility of adverse effect because the burden resulting from a specific exposure episode also declines with subsequent time.

Cumulative burden, cumB (Mn), is the time-weighted sum of burden over time:

$$\mathrm{cumB(Mn)}=\sum_{i=t1}^{t2}[B(i)],\ \text{expressed in mg/m}^3\,\text{yr}^2$$

as might be appropriate for an exposure resulting in tissue deposition from which toxic effects are continuing or from which progressive changes devolve (Links et al., 2001; Kriebel et al., 2007). With this metric, the effect of exposure at a point in time increases over the following observation period, even when exposure has ceased.

In order to examine dose-rate effects, some cumulative metrics summed exposure concentrations raised to the 0.5 or 2.0 power to determine whether low or high exposures contribute more or less than proportionally to subsequent effects. For example, the cumulative exposure metric with the square root of exposure intensity was:

$$\mathrm{cum(Mn)}=\sum_{i=t1}^{t2}X(t_i)^{0.5},\ \text{expressed in (mg)}^{0.5}/\text{m}^3\,\text{yr}$$

When duration of exposure was found to be a strong predictor, a saturation threshold was examined by calculating exposure metrics in which Mn-SRP concentrations are truncated above some threshold value, such as 0.1 mg/m^3. This metric could be appropriate if homeostatic mechanisms are limiting the blood or tissue excursions resulting from external exposures.

2.4. Statistical models

Eight neurobehavioral outcomes were modeled in relation to past Mn exposure with multiple linear regression using proc REG in SAS (SAS Institute, 2011). Age centered at 40 yr, and education centered at 12 yr, together with their squares, were included in models. Different exposure metrics were compared based on model R^2 and exposure term-associated *t*-statistics.

Outcome data for those workers evaluated in both 1990 and 2004 was analyzed using a mixed-effect linear regression model (proc MIXED in SAS) (SAS Institute, 2011) which permits within-worker comparison by allowing separate intercept estimates for each worker rather than assuming a uniform baseline score. The same age and education variables were included as in the previous regression models.

3. Results

3.1. Exposure-response for 1990 outcomes

Demographic characteristics of the populations analyzed are displayed in Table 1. In all cases mean ages and education attainment were quite similar between the alloy workers and referents.

The eight neurobehavioral tests previously analyzed as matched pairs (Mergler et al., 1994) or with multiple regression using an ordinal scale for exposure (Bouchard et al., 2007), all showed deficits in performance in 1990 for the exposed workers compared to community referents and all but two (Stroop Color-Word and Digit Span) were statistically significant (Table 2). The Luria Nebraska Neuropsychological Test Battery Motor Scale scores showed the strongest effect. In the present analysis, as observed previously (Bouchard et al., 2007) smaller and mostly non-significant differences remained in the 2004 assessment that involved 137 of the 244 subjects participating in 1990. Examining the 1990 performance on the Luria-Nebraska Motor Scale in relation to various exposure metrics in the present study reveals the leading role of exposure duration in predicting the deficit (Table 3). With little dependence on half-life weighting, duration exhibits a highly statistically significant adverse effect ($t \sim 5.0$, $p < 10^{-6}$). (Because of the relatively uniform distribution on employment duration, all duration metrics, with varying half-life, are highly correlated.) From a baseline of 5.96, 10 yr of Mn exposure was predicted to raise the Luria score to 7.82 (Table 4), corresponding to a 31 percent decrease in performance. For the 1990 data there is a weak suggestion of reversibility in that the burden metrics produce slightly better fitting models than cumulative exposure or cumulative burden. The Mn-LRP – dust – metric is barely significant. The Mn-SRP – fume – metric in various guises approaches the performance of duration, particularly the metric based on square root of Mn concentration, which exhibits a stronger suggestion of reversibility. The Mn-SRP metric based on exposures truncated above 25 μg/m^3 and calculated with a 5 yr half-life is even better ($t = 4.36$, $p = 10^{-5}$)(Table 3).

For Trail Making A scores, duration is again a strong predictor with evidence of reversibility ($t = 3.28$, $p = 0.001$) but Mn-SRP (truncated at 25 μg/m^3) is a comparable predictor ($t = 3.33$, $p = 0.001$) with little evidence of reversibility. Delayed Word Recall is somewhat better predicted by Mn-SRP metrics (both square root and truncated versions) than by duration with short half-lives (for burden based on square root of intensity, $t = -3.47$, $p = 0.0005$), suggesting a relatively fast reversible component (6 mo or less). For the Cancellation H test, duration is the best predictor ($t = 2.73$, $p = 0.006$) but with the Mn-SRP saturation metric (50 μg/m^3 threshold and a 2 yr burden half-life) performing almost as well ($t = 2.45$, $p = 0.01$) (Table 3).

With Trail Making B, only duration metrics significantly predict deficits for the workers, with a suggestion of reversibility (Table 3). Finger Tapping scores are also predicted only by the duration metric, with suggestions of irreversibility and progression across all exposure metrics. Unlike all other outcomes studied, performance on the Stroop Word Test was best predicted by Mn-LRP – dust – ($t = -2.92$, $p = 0.003$); duration shows little association, and the effects based on dust (or fume) indicate a progressive deterioration (Table 3). In contrast, for the Stroop Color-Word Test, the best predictors were duration with a short half-life ($t = -3.38$, $p = 0.0007$) and the truncated or square root of fume cumulative burden measure with a long half-life ($t = -3.37$, $p = 0.0007$) (Table 3).

In the analysis here of the 1990 assessment, Digit Span was not well-predicted by any of the exposure metrics examined including duration (data not shown).

For the domain *z*-scores, the results were similar. In the Luria-Nebraska Luria Motor Scale, the R^2 values were slightly higher than for the raw score, but duration of exposure was again the best predictor followed by Mn-SRP (sqrt) (Tables 3 and 5). Executive Function *z*-scores showed the same patterns as the Trail Making B scores, and Other Cognitive tests were similar to scores on Delayed Word Recall and Cancellation H, the latter exhibiting superior prediction by Mn-SRP (sqrt) in the reversible realm in both z-scores and raw score (Tables 3 and 5).

3.2. Mixed-effect models of neurobehavioral outcomes

Analyses were conducted among 135 study subjects who participated in both the 1990 and 2004 neurobehavioral assessments permitting within-worker comparisons using a mixed effect linear regression model. In this design exposure metrics will differ for the two time points only because of the half-life time weighting or because a alloy worker may have continued briefly in employment beyond the time of the first survey until the plant closed later that year. For these analyses, the Mn-SRP saturation variable was calculated with a truncation above 150 $\mu g/m^3$, the mean Mn concentration observed. All statistically significant effects were in the direction of diminished performance. For the Luria-Nebraska Motor Scale, duration was the best predictor (t = 3.98, p = 0.0001) as observed in the 1990 results, and model fit improved with 5 yr half-life weighting for duration as both burden and cumulative burden, implying both reversible and progressive changes (Table 6). The Mn-SRP metric as a burden based on square root of intensity was also a strong predictor (t = 3.64, p = 0.0004), but with suggestion only of reversibility. Trail Making A and B were poorly predicted by simple cumulative exposure without half-life weighting, but quite significantly predicted by duration with a 5 yr half-life as both burdens (t = 3.69, p = 0.0003, and t = 2.77, p = 0.0065, respectively) and cumulative burdens (t = 3.84, p = 0.0002, and t = 2.97, p = 0.0036, respectively). For scores on Trail Making A, Mn-SRP (square root), a somewhat weaker prediction but similar pattern is shown. Digit Span, which was not associated with any metric in the 1990 cross-sectional survey, was best predicted with duration (t = −2.34, p = 0.021), Mn-SRP (cumulative square root of intensity, t = −2.38, p = 0.019), and SLP (t = −2.31, p = 0.023) all without half-life weighting, suggesting simple irreversibility (Table 6).

Delayed Word Recall scores were best predicted by duration as burden (for a 5 yr half-life, t = −2.32, p = 0.022) (Table 6). Cancellation H scores was significantly predicted by duration as a burden (t = 2.66, p = 0.009) and cumulative burden (t = 2.74, p = 0.007) but not by simple cumulative duration. Finger Tapping scores were not significantly predicted by any metric although fume as a cumulative burden was marginally significant. Stroop Color-Word (word subtest) scores were better predicted by dust and fume metrics than duration, Mn-LRP being the best predictor (t = −2.58, p = 0.011) suggesting simple irreversible deterioration (Table 6). For the color/word subtest, Mn-SRP (square root) was the best predictor, slightly better than duration and also suggesting simple irreversible deterioration.

4. Discussion

4.1. Exposure metrics for homeostatically regulated substances

Because Mn is an essential nutrient, one might expect that adverse effects of chronic high airborne exposures would not be well-predicted by simple, linear cumulative exposure metrics. Extensive analyses using physiologically based pharmacokinetic (PBPK) models accounting for oral, nasal and respiratory routes of entry and accommodating numerous tissue compartments support this concern (Andersen et al., 2010; Nong et al., 2008; Schroeter et al., 2011; Teeguarden et al., 2007a,b,c). Schroeter et al. (2011) synthesizes findings from multiple animal and human studies in a PBPK model that in simulations corresponds well to empirical observations. This model includes (a) saturable storage effects, (b) asymmetric diffusion (active or energy-dependent transport) of Mn and (c) dose-dependent Mn elimination rates (apparent up-regulation of biliary elimination pathways). Early evidence of dose-dependent Mn elimination rates in men was observed by Mena et al. (1969) in active vs. inactive miners.

In a well-functioning regulatory system, with dose-dependent elimination rates, wide variation in airborne exposure concentrations could result in minor, relatively uniform excursions in excess tissue levels above some normal low set-point such that duration of exposure to respirable particles could become a reasonably predictive metric for adverse effects of exposures that do not exceed the control capability. This is what has been observed for the neurobehavioral endpoints in the Mn alloy production workers examined in the present study. The Mn-SRP metrics are considerably improved when square-root transformed to a supralinear form, or, in the extreme case, when truncated to a relatively low, fixed level. A more biologically plausible transformation might be intermediate between the two that were investigated.

PBPK investigations tend to involve steady-state conditions modeled with fixed kinetic parameters. But up-regulation and other control changes could complicate the dynamic behavior of the homeostatic systems. The response times for kinetic rate adjustments (hours, days, weeks?), etc., would need to be determined and is a largely unexplored area. The form of airborne exposure may be another complication with the available PBPK models. Doses delivered by nebulizer-generated dust aerosols of Mn, as used in some animal studies, where mass median aerodynamic diameters (MMAD) were almost 2.0 μm (Dorman et al., 2004), may not adequately represent workplace exposures to dusts and especially condensation fume with diameters $\ll 0.1$ μm in terms of deposition and transport.

4.2. Reversibility and progression

Evidence of both reversible and progressive components in their exposure metric associations were shown for scores on the Luria-Nebraska Motor Scale, Trail Making A and B, Delayed Word Recall, Cancellation H, and (weakly) for Finger Tapping. The burden and cumulative burden metrics predicting these outcomes were stronger than cumulative exposure or duration (without time weighting). It is biologically plausible that either effect could occur due to repair, adaptation and cumulative deterioration mechanisms and, if both are present, would possibly suppress a cumulative exposure association. Irreversible effects in the longitudinal analysis (better predicted by cumulative exposure than by burden or cumulative burden) were absent or statistically nonsignificant for five of the outcomes tests studied: Trail Making A and B, Delayed Word Recall, Cancellation H, and Finger Tapping.

Different optimum metric associations for the outcomes studied could merely result from random error but may reflect different pathways and mechanisms of action, or target tissues.

The Stroop Color-Word Test scores were unique in that duration was not a significant predictor and irreversible Mn-LRP was the best one, better than Mn-SRP. For some pathways, very small particulate at the nano-level may be the primary source of internal dose whereas for others, particles of any respirable size may suffice. Smaller particles may produce a more rapid uptake of Mn than larger ones, which could affect the efficacy of homeostatic control.

4.3. Digit Span and inter-individual variability

A statistically significant irreversible effect of Mn exposure for Digit Span performance was observed with a repeated measure, mixed-effect, linear model, where none was observed in the 1990 cross-sectional survey. This suggests that controlling between-individual variability is more important for this outcome, compared to the others.

4.4. Comparison with other studies

Only a few published studies have had detailed retrospective exposure assessments for respirable Mn and none have distinguished large vs. small respirable particulate. Roels et al. (1992) analyzed workers at a dry alkaline battery factory with average Mn in dust exposures of 1.78 mg/m^3 (total) and 0.30 mg/m^3 (respirable), and observed statistically significant associations between cumulative exposure to Mn dust (total and respirable) and measures of visuo-motor performance. The small-particulate composition in the Roels studies (<0.10 μm MMAD) was not known. For comparison, in the current Mn-alloy production study, where duration of exposure and, in some cases cumulative exposure to small respirable particles, were strong predictors, the average respirable Mn exposure concentration was 0.15 mg/m^3 (or 0.065 mg/m^3 as large respirable particulate), somewhat lower than in the Roels populations.

In a study of Italian Mn alloy production workers (Lucchini et al., 1999), a cumulative exposure index was the main predictor of neurobehavioral outcomes. It is noteworthy that Health Canada used this study for the reassessment of the Mn RfC, adopting a cumulative exposure index based on small respirable particulate (http://www.hc-sc.gc.ca/ewh-semt/pubs/air/manganese-eng.php). Although imprecision increased with applying estimates of respirable proportion across job tasks, the respirable cumulative exposure index was the best predictor neuropsychological deficits. Scores on the partial version of the motor scale of the Motor Scale of the Luria-Nebraska Neuropsychological Battery (items 1–5), used by Lucchini et al. (1999) and serum prolactin showed the strongest associations. Similar to the present study, results on the tests from the motor scale of the Luria-Nebraska Battery were associated with the estimated cumulative index based on respirable particulates, but not the one based on total dust.

Deschamps et al. (2001) studied pigment workers with Mn exposures of 3.24 mg/m^3 (total) and 0.057 mg/m^3 (respirable) and observed symptoms (sleep disturbance, headache) but no associations of clinical neurological effects with duration of exposure. Average exposure duration was 20 yr but Mn blood levels were not elevated compared to unexposed controls. The small proportion of exposure that was respirable (1.8%) indicates that most exposure was in large particulate and the levels of small respirable particulate were probably quite low ($\ll$0.057 mg/m^3).

Gibbs et al. (1999) investigated workers at an electrolytic manganese manufacturing plant compared with workers at a companion plant without Mn exposure. Average exposure to respirable Mn was 0.066 mg/m^3 (total Mn: 0.18 mg/m^3). Duration of Mn exposure and measures of lifetime respirable cumulative exposure (as well as that accruing in the past month or year) exhibited no significant associations with a variety of measures of hand and postural movement disorders although there was evidence of uncontrolled confounding by shift-work status: compared to controls, Mn-exposed workers had work schedules more associated with neurobehavioral deficits. Exposures at this facility as respirable dust were somewhat lower than those in the population studied here (Baldwin et al., 2008) and Mn was not present as a condensation fume; no description of the submicron Mn particulate size distribution was available.

In a study of bridge-pier welders working in confined spaces (Bowler et al., 2007, 2011), cumulative exposure to Mn in welding fume (adjusted for use of personal protective equipment) was a considerably better predictor of neuropsychological outcomes than duration of exposure (Park et al., 2009), unlike the results in the present Mn alloy production plant study. However, the average exposure level in one major group of the welders in that study was 0.34 mg/m^3, largely as welding fume (respirable), and in one 6 month period of the two yr project, the average was 0.44 mg/m^3; the overall time-averaged exposure to Mn fume for all bridge welders was 0.15 mg/m^3 (Park et al., 2009). In the study population in the present study, all but one job (furnace laborer) had average fume exposures during almost all time periods of less than 0.17 mg/m^3 and the overall time-averaged exposure to Mn SRP was 0.082 mg/m^3.

The possibility that homeostatic regulation is overwhelmed at levels above 0.2–0.3 mg/m^3 Mn as fume, and possibly dust, needs to be considered. The evidence suggests that the traditional cumulative exposure metrics may well predict neurobehavioral effects when exposures are high enough to defeat homeostatic regulation.

5. Conclusion

Adverse neurobehavioral effects of respirable exposures in this manganese-alloy production facility appear largely to depend on furnace-area emissions rather than mechanically generated dusts. These furnace emissions originate as much smaller particles and have distinct surface characteristics. Comparing predictions using metrics with diverse treatment of time since exposure suggests that there are reversible, irreversible and progressive changes with Mn exposure for selected outcomes.

Duration of exposure itself is a strong predictor of effects probably reflecting homeostatic control of Mn tissue levels for airborne exposures less than 0.2 mg/m^3 respirable Mn. The challenge for risk assessment is to identify the upper bound of internal Mn tissue levels under normal metabolic regulation, establish an exposure response in this range on external exposures, and determine if the maximum level of acceptable risk is exceeded in that range of Mn exposure. If not, then the more complex exposure response in the region of failing homeostatic regulation would need to be described.

Acknowledgments

We appreciate the time and effort put into the original study by the workers, the community referents and the employers in this Mn alloy production plant. The original study (1990–1991) was financed by the Québec Institute for Research in Occupational Health and Safety (IRSST) and the 2004 follow-up study was financed by grant #117076 from the Canadian Institutes for Health Research (CIHR), respectively. Dr. Fabrice Larribe assisted with file retrieval and documentation.

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Table 1

Demographic attributes and duration of Mn exposure in study populations.

Study population	Age in 1990	Education (yr)	Duration of Mn exposure (yr)
Full 1990 population			
Referents (*n* = 138)	43.0	10.8	0.0
Alloy workers (*n* = 106)	44.3	10.6	14.4
1990 population with z-score domains			
Referents (*n* = 124)	44.2	10.6	0.0
Alloy workers (*n* = 105)	44.3	10.6	14.4
Population studied in both 1990 and 2004			
Referents (*n* = 67)	43.0	11.1	0.0
Alloy workers (*n* = 68)	43.9	10.9	14.7

Table 2

Neurobehavioral outcomes comparing Mn-exposed and unexposed workers at 1990 and 2004 surveys, in order of decreasing statistical significance (1990).

Outcome	n_X	n_R	Difference, mean score	SE	t	p
1990[a]						
Luria Motor Scale (total)	106	138	2.84	0.54	5.24	1.6×10^{-7}
Stroop … test (color/word trial, raw)	100	136	−3.30	1.01	−3.26	0.0013
Trail Making A (s)	106	138	3.89	1.28	3.05	0.0026
Delayed Word Recall (no. words recalled)	102	106	−0.54	0.21	−2.57	0.011
Cancellation H (s)	106	138	5.18	2.04	2.54	0.012
Trail Making B (s)	106	133	8.49	3.63	2.34	0.020
Finger Tapping (mean 2 hands)	106	136	−1.40	0.70	−2.00	0.047
Stroop … test (word trial, raw)	104	136	−2.04	1.71	−1.20	0.23
Digit span score total (forward + backward)	106	138	−0.17	0.30	−0.56	0.57
2004[b]						
Luria Motor Scale (total)	68	67	1.97	0.82	2.40	0.018
Stroop … test (color/word trial, raw)	67	66	−2.70	1.46	−1.84	0.067
Trail Making A (s)	68	67	−1.29	1.89	−0.69	0.49
Delayed Word Recall (no. words recalled)	68	67	−0.35	0.25	−1.40	0.16
Cancellation H (s)	68	67	0.47	2.99	0.16	0.88
Trail Making B (s)	68	67	0.58	4.43	0.13	0.90
Finger Tapping (mean 2 hands)	68	67	0.20	1.17	0.17	0.86
Stroop … test (word trial, raw)	68	66	−3.28	2.39	−1.37	0.17
Digit span score total (forward + backward)	68	67	−0.87	0.68	−1.28	0.20

n_X – no. of alloy workers; n_R – no. of community worker referents; SE – standard error.

Regression models included linear and quadratic terms for age and education.

[a] All differences in score were in direction of diminished performance in the alloy workers.

[b] Differences in score were in direction of diminished performance for alloy workers compared to community referents except for Trail A and Finger Tapping, but most were not statistically significant.

Table 3

Selected neurobehavioral outcomes at 1990 survey in relation to Mn-exposure metrics: by multiple linear regression.

Luria Motor Scale (total)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:25)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
B(Mn)	0.25	0.2761	4.91	0.2143	1.88	**0.2421**	**3.51**	**0.2567**	**4.16**	0.2519	3.96
	0.5	0.2785	4.99	0.2155	1.98	0.2401	3.42	0.2563	4.14	0.2538	4.03
	1	**0.2792**	**5.02**	**0.2165**	**2.05**	0.2363	3.24	0.2538	4.03	0.2568	4.16
	2	0.2787	5.00	0.2160	2.02	0.2316	2.99	0.2505	3.89	0.2607	4.32
	5	0.2783	4.99	0.2141	1.87	0.2291	2.85	0.2476	3.77	**0.2618**	**4.36**
	10	0.2784	4.99	0.2131	1.78	0.2284	2.82	0.2463	3.71	0.2604	4.31
cum(Mn)	∞/0	0.2785	4.99	0.2122	1.71	0.2274	2.76	0.2443	3.62	0.2571	4.17
cumB(Mn)	1	0.2783	4.99	0.2118	1.66	0.2269	2.73	0.2430	3.56	0.2559	4.12
	5	0.2782	4.98	0.2107	1.56	0.2254	2.64	0.2405	3.44	0.2515	3.93
	10	0.2782	4.98	0.2103	1.53	0.2248	2.61	0.2395	3.39	0.2496	3.85

Trail Making A (s)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:25)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
B(Mn)	0.25	**0.2261**	**3.28**	**0.2094**	**2.35**	**0.2098**	**2.37**	**0.2188**	**2.90**	0.2205	2.99
	0.5	0.2251	3.23	0.2084	2.28	0.2066	2.16	0.2166	2.78	0.2206	3.00
	1	0.2238	3.16	0.2074	2.21	0.2008	1.70	0.2132	2.59	0.2220	3.07
	2	0.2227	3.11	0.2056	2.08	0.1975	1.39	0.2107	2.43	0.2245	3.20
	5	0.2221	3.08	0.2026	1.86	0.1973	1.36	0.2103	2.41	0.2267	3.31
	10	0.2220	3.07	0.2012	1.74	0.1976	1.40	0.2106	2.43	**0.2271**	**3.33**
cum(Mn)	∞/0	0.2219	3.07	0.1991	1.54	0.1976	1.40	0.2109	2.44	0.2267	3.31
cumB(Mn)	1	0.2216	3.05	0.1994	1.58	0.1980	1.44	0.2104	2.41	0.2264	3.29
	5	0.2216	3.05	0.1982	1.45	0.1986	1.50	0.2104	2.41	0.2251	3.23
	10	0.2216	3.05	0.1978	1.41	0.1988	1.52	0.2103	2.41	0.2244	3.19

Delayed Word Recall (number)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	*t*	R^2	*t*	R^2	*T*	R^2	*t*	R^2	*t*
B(Mn)	0.25	0.1237	−2.94	**0.0975**	**−1.60**	0.1331	−3.30	0.1365	−3.43	0.1353	−3.38
	0.5	**0.1244**	**−2.97**	0.0971	−1.57	**0.1334**	**−3.31**	**0.1378**	**−3.47**	**0.1372**	**−3.45**
	1	0.1238	−2.94	0.0958	−1.47	0.1275	−3.09	0.1343	−3.34	0.1336	−3.32
	2	0.1217	−2.86	0.0947	−1.38	0.1184	−2.71	0.1266	−3.06	0.1260	−3.03
	5	0.1182	−2.71	0.0929	−1.23	0.1103	−2.34	0.1170	−2.66	0.1153	−2.58
	10	0.1163	−2.62	0.0920	−1.14	0.1068	−2.16	0.1124	−2.44	0.1101	−2.33
cum(Mn)	∞/0	0.1142	−2.53	0.0911	−1.05	0.1019	−1.88	0.1066	−2.15	0.1043	−2.02
cumB(Mn)	1	0.1132	−2.48	0.0909	−1.03	0.1011	−1.83	0.1051	−2.07	0.1020	−1.89
	5	0.1115	−2.40	0.0902	−0.95	0.0969	−1.55	0.1006	−1.80	0.0975	−1.60
	10	0.1110	−2.37	0.0900	−0.93	0.0955	−1.45	0.0992	−1.71	0.0963	−1.51

Cancellation H (s)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:50)	
		R^2	*t*	R^2	*t*	R^2	*t*	R^2	*t*	R^2	*t*
B(Mn)	0.25	**0.1751**	**2.73**	**0.1612**	**1.84**	**0.1612**	**1.84**	**0.1664**	**2.21**	0.1630	1.97
	0.5	0.1737	2.65	0.1611	1.83	0.1611	1.83	0.1663	2.21	0.1646	2.09
	1	0.1725	2.58	0.1611	1.83	0.1607	1.80	0.1669	2.24	0.1675	2.28
	2	0.1719	2.55	0.1610	1.83	0.1602	1.76	0.1673	2.27	**0.1702**	**2.45**
	5	0.1721	2.56	0.1607	1.80	0.1601	1.75	0.1669	2.24	0.1699	2.43
	10	0.1725	2.58	0.1604	1.77	0.1599	1.74	0.1662	2.20	0.1684	2.34
cum(Mn)	∞/0	0.1730	2.61	0.1595	1.71	0.1587	1.64	0.1651	2.12	0.1659	2.18
cumB(Mn)	1	0.1730	2.61	0.1597	1.72	0.1593	1.68	0.1646	2.09	0.1653	2.14
	5	0.1735	2.64	0.1591	1.67	0.1585	1.62	0.1630	1.98	0.1625	1.94
	10	0.1736	2.65	0.1589	1.65	0.1581	1.58	0.1624	1.93	0.1614	1.86

Trail Making B (s)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	*t*	R^2	*t*	R^2	*t*	R^2	*t*	R^2	*t*
B(Mn)	0.25	**0.2407**	**2.50**	0.2221	0.74	0.2270	1.42	0.2285	1.57	0.2257	1.28
	0.5	0.2406	2.49	0.2221	0.74	**0.2288**	**1.59**	0.2294	1.66	0.2265	1.36

Trail Making B (s)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
	1	0.2400	2.45	**0.2229**	**0.88**	0.2283	1.55	**0.2297**	**1.68**	**0.2266**	**1.38**
	2	0.2392	2.40	0.2228	0.87	0.2263	1.34	0.2291	1.62	0.2263	1.34
	5	0.2388	2.38	0.2217	0.64	0.2242	1.08	0.2274	1.46	0.2246	1.13
	10	0.2389	2.38	0.2212	0.52	0.2232	0.93	0.2263	1.34	0.2235	0.98
cum(Mn)	∞/0	0.2392	2.40	0.2208	0.38	0.2218	0.66	0.2249	1.17	0.2222	0.76
cumB(Mn)	1	0.2391	2.39	0.2208	0.37	0.2218	0.67	0.2245	1.12	0.2219	0.69
	5	0.2393	2.41	0.2205	0.25	0.2209	0.43	0.2233	0.95	0.2211	0.48
	10	0.2394	2.42	0.2205	0.21	0.2207	0.34	0.2229	0.88	0.2208	0.40

Finger Tapping (mean 2 hands)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
B(Mn)	0.25	0.0894	−1.92	0.0752	−0.20	0.0772	−0.75	0.0802	−1.15	0.0770	−0.71
	0.5	0.0903	−1.99	0.0756	−0.38	0.0768	−0.66	0.0800	−1.12	0.0766	−0.76
	1	0.0915	−2.06	0.0756	−0.36	0.0767	−0.65	0.0804	−1.17	0.0774	−0.77
	2	0.0927	−2.14	0.0755	−0.34	0.0770	−0.71	0.0812	−1.25	0.0787	−0.96
	5	**0.0935**	**−2.19**	0.0758	−0.43	0.0780	−0.86	0.0824	−1.37	0.0800	−1.13
	10	**0.0935**	**−2.19**	0.0759	−0.48	0.0787	−0.97	0.0831	−1.43	0.0805	−1.18
cum(Mn)	∞/0	0.0934	−2.18	0.0762	−0.54	0.0796	−1.08	0.0841	−1.52	0.0810	−1.23
cumB(Mn)	1	**0.0935**	**−2.19**	0.0762	−0.54	0.0800	−1.13	0.0841	−1.53	0.0812	−1.26
	5	0.0932	−2.17	**0.0764**	**−0.58**	0.0813	−1.26	0.0847	−1.58	0.0814	−1.27
	10	0.0930	−2.16	**0.0764**	**−0.59**	**0.0818**	**−1.31**	**0.0849**	**−1.59**	**0.0814**	**−1.28**

Stroop Color-Word Test (word)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
B(Mn)	0.25	0.1281	−1.00	0.1408	−2.11	0.1305	−1.29	0.1313	−1.36	0.1306	−1.30
	0.5	0.1281	−1.01	0.1445	−2.34	0.1307	−1.31	0.1318	−1.42	0.1313	−1.37
	1	0.1283	−1.03	0.1464	−2.46	0.1292	−1.14	0.1319	−1.43	0.1326	−1.49
	2	0.1286	−1.07	0.1473	−2.51	0.1281	−1.01	0.1318	−1.42	0.1341	−1.62

Stroop Color-Word Test (word)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
	5	0.1289	−1.11	0.1507	−2.69	0.1297	−1.20	0.1336	−1.58	0.1367	−1.83
	10	**0.1289**	**−1.11**	0.1526	−2.79	0.1315	−1.39	0.1351	−1.71	0.1382	−1.94
cum(Mn)	∞/0	**0.1288**	**−1.10**	0.1535	−2.83	0.1341	−1.62	0.1372	−1.87	0.1399	−2.05
cumB(Mn)	1	0.1288	−1.10	0.1542	−2.87	0.1349	−1.69	0.1375	−1.89	0.1402	−2.08
	5	0.1287	−1.08	0.1551	−2.91	0.1388	−1.98	0.1396	−2.03	0.1414	−2.15
	10	0.1286	−1.07	**0.1551**	**−2.92**	**0.1405**	**−2.09**	**0.1403**	**−2.08**	**0.1417**	**−2.17**

Stroop Color-Word Test (color/word)

Cumulative Metric form	$T_{1/2}$	Duration		LRP		SRP		SRP (sqrt)		SRP (sat:100)	
		R^2	t	R^2	t	R^2	t	R^2	t	R^2	t
B(Mn)	0.25	**0.1704**	**−3.38**	0.1360	−1.35	0.1569	−2.75	0.1648	−3.13	0.1555	−2.68
	0.5	0.1686	−3.30	0.1374	−1.48	0.1550	−2.65	0.1634	−3.07	0.1540	−2.60
	1	0.1658	−3.18	0.1382	−1.55	0.1493	−2.33	0.1601	−2.91	0.1536	−2.57
	2	0.1641	−3.10	0.1400	−1.70	0.1461	−2.14	0.1582	−2.81	0.1559	−2.70
	5	0.1645	−3.12	0.1450	−2.06	0.1483	−2.27	0.1606	−2.93	0.1611	−2.96
	10	0.1651	−3.14	0.1481	−2.26	0.1509	−2.42	0.1631	−3.05	0.1640	−3.09
cum(Mn)	∞/0	0.1657	−3.17	0.1519	−2.48	0.1544	−2.62	0.1666	−3.21	0.1672	−3.24
cumB(Mn)	1	0.1656	−3.16	0.1523	−2.50	0.1550	−2.65	0.1665	−3.20	0.1674	−3.25
	5	0.1663	−3.20	0.1550	−2.65	0.1592	−2.86	0.1693	−3.33	0.1694	−3.33
	10	0.1663	−3.20	**0.1560**	**−2.70**	**0.1608**	**−2.94**	**0.1703**	**−3.37**	**0.1700**	**−3.36**

Duration – any current exposure; LRP – large respirable particulate; SRP – small respirable particulate; SRP (sqrt) – SRP based on sq. root of Mn conc.; SRP (sat:100) – SRP based on Mn conc. truncated at 100 μg/m^3; $T_{1/2}$ – half-life; R^2 – proportion of variance explained; t – t-score; B(Mn) – burden of respirable Mn; cum(Mn) – cumulative exposure to respirable Mn; cumB(Mn) – cumulative burden of respirable Mn.

Numbers of alloy workers and community referents same as in Table 1, 1990 survey.

Model predictors are linear and quadratic terms for age and education, and exposure metric.

Results in bold font represent strongest associations.

Table 4

Linear regression model for Luria Motor Scale (*T* score) on duration of Mn exposure and demographic risk factors.

var	Parameter estimate	SE of estimate	*t*	*p*-Value
Intercept	5.958	0.420	14.18	$<10^{-6}$
Age-40	0.129	0.067	1.93	0.055
$(\text{Age-40})^2$	0.005	0.005	1.03	0.31
Education-12 yr	−0.325	0.139	−2.34	0.020
$(\text{Education-12})^2$	0.048	0.028	1.70	0.091
Duration of exposure	0.187	0.037	4.99	$<10^{-6}$

Predicted Luria Motor Scale Score for 40 yr-old unexposed worker with 12 yr education = 5.96; for same worker with 10 yr exposure (no half-life imposed), predicted Luria Motor.

Score = 5.958 + 10 × 0.1865 = 7.82

Table 5

Neurobehavioral outcomes from 1990 as *z*-scores in three domains with burdens and cumulative burdens and various half-life.

Cumulative Metric form	$T_{1/2}$	Duration			LRP			SRP (sqrt)		
		R^2	*t*	*p*	R^2	*t*	*p*	R^2	*t*	*p*
Luria T z-score										
B(Mn)	0.25	0.2877	−5.00	5.7×10^{-7}	0.2289	−2.24	0.026	**0.2698**	**−4.31**	$\mathbf{1.6 \times 10^{-5}}$
	1	**0.2914**	**−5.14**	$\mathbf{2.7 \times 10^{-7}}$	0.2320	−2.45	0.015	0.2677	−4.22	2.4×10^{-5}
	5	0.2907	−5.11	3.2×10^{-7}	0.2300	−2.32	0.214	0.2624	−4.00	6.3×10^{-5}
cum(Mn)	∞/0	0.2907	−5.11	3.2×10^{-7}	0.2273	−2.13	0.034	0.2593	−3.87	0.001
cumB(Mn)	1	0.2905	−5.10	3.4×10^{-7}	0.2270	−2.11	0.036	0.2580	−3.81	0.002
	5	0.2903	−5.10	3.4×10^{-7}	0.2256	−1.99	0.047	0.2554	−3.69	0.003
	10	0.2902	−5.09	3.6×10^{-7}	0.2251	−1.95	0.052	0.2543	−3.64	0.003
Exec functions										
B(Mn)	0.25	0.2418	−3.12	0.0020	0.2154	−1.53	0.128	0.2280	−2.41	0.017
	1	0.2409	−3.08	0.0023	0.2193	−1.84	0.076	0.2260	−2.29	0.023
	5	0.2412	−3.10	0.0022	0.2227	−2.08	0.039	0.2256	−2.26	0.025
cum(Mn)	∞/0	0.2424	−3.15	0.0019	0.2244	−2.19	0.030	0.2277	−2.39	0.018
cumB(Mn)	1	0.2425	−3.16	0.0018	0.2245	−2.19	0.029	0.2276	−2.38	0.018
	5	0.2431	**−3.18**	**0.0017**	0.2247	−2.21	0.028	0.2285	−2.44	0.016
	10	0.2431	**−3.18**	**0.0017**	0.2248	−2.21	0.028	0.2287	−2.45	0.015
Other cognitive										
B(Mn)	0.25	**0.2474**	**−2.30**	**0.028**	0.2407	−1.89	0.060	**0.2503**	**−2.46**	**0.015**
	1	0.2471	−2.28	0.024	0.2433	−2.06	0.041	0.2477	−2.32	0.022
	5	0.2449	−2.15	0.033	0.2416	−1.95	0.052	0.2428	−2.02	0.044
cum(Mn)	∞/0	0.2428	−2.03	0.044	0.2397	−1.82	0.070	0.2407	−1.89	0.060
cumB(Mn)	1	0.2424	−2.00	0.047	0.2394	−1.81	0.073	0.2400	−1.84	0.067
	5	0.2414	−1.94	0.054	0.2383	−1.73	0.086	0.2388	−1.76	0.080
	10	0.2410	−1.91	0.058	0.2380	−1.70	0.090	0.2383	−1.72	0.087

Duration – any current exposure; LRP – large respirable particulate; SRP (sqrt) – SRP based on sq. root of Mn conc.; $T_{1/2}$ – half-life; B(Mn) – burden of respirable Mn; cum(Mn) – cumulative exposure to respirable Mn; cumB(Mn) – cumulative burden of respirable Mn; R^2 – proportion of variance explained; *t* – *t*-score; *p* – *p*-value. Results in bold font represent strongest associations.

Table 6

Neurobehavioral outcomes from 1990 and 2004 with best mixed effect models: duration, cumulative exposure, and burden/cumulative burden (half-life of 5 yr) metrics.

Cumulative exposure metric	X	Luria Motor scale Duration	Trail Making A (s) Duration	Trail Making B (s) Duration	Digit Span SRP(sqrt)	Delayed Word Recall Duration
B(Mn)	*t*	4.65	3.69	2.77	−1.78	−2.32
	p	<.0001	0.0003	0.0065	0.078	0.022
cum(Mn)	*t*	3.98	0.77	0.87	−2.38	−1.66
	p	0.0001	0.44	0.39	0.019	0.099
cumB(Mn)	*t*	4.43	3.84	2.97	−1.72	−2.00
	p	<.0001	0.0002	0.0036	0.088	0.048

Cumulative exposure metric	X	Cancellation H (s) Duration	Finger Tapping (2 hands) SRP(sqrt)	Stroop (word test) LRP	Stroop (color/word test) SRP(sqrt)
B(Mn)	t	2.66	−1.29	−2.17	−1.41
	p	0.0088	0.20	0.032	0.16
cum(Mn)	t	1.14	−0.11	−2.58	−2.29
	p	0.26	0.91	0.011	0.023
cumB(Mn)	t	2.74	−1.73	−2.22	−1.60
	p	0.0070	0.086	0.028	0.11

X – exposure metric; duration – any current exposure; LRP – large respirable particulate; SRP (sqrt) – small respirable particulate based on sq. root of Mn conc; B(Mn) – burden of respirable Mn; cum(Mn) – cumulative exposure to respirable Mn; cumB(Mn) – cumulative burden of respirable Mn; *t* – *t*-statistic; *p* – *p*-value. Subjects evaluated in both 1990 and 2004; *n* = 135 (68 alloy workers, 67 community referents).

Model predictors are linear and quadratic terms for age and education, and exposure metric; fit with random intercept.