HHS Public Access

Author manuscript

Neurotoxicology. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Neurotoxicology. 2018 January ; 64: 159–165. doi:10.1016/j.neuro.2017.08.003.

Manganese and neurobehavioral impairment. A preliminary risk assessment☆

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Abstract

Similar patterns of cognitive and motor deficits have been widely reported from manganese exposures in welding, metallurgical and chemical industry workers. A risk assessment was performed based on studies reported in the literature, extending some earlier work, and deriving new estimates of exposure response and excess risk. Many investigations of manganese neurological effects in humans have insufficient information to derive an exposure response; however, findings from a chemical manufacturer, two smelter and two welder populations permitted application of the benchmark dose procedure for continuous end-points. Small particles and aggregates of condensation fume (condensing vaporized metal, <0.1 μm in diameter) appear to have a higher potency per unit mass than larger particles from dusts (>1.0 μm). Consideration was given to long-term effects of continuous low exposures that instead of producing increasing toxicity attain a steady-state condition. Impairment was defined as excursions beyond the 5th percentile in a normal population and the concentrations of manganese predicted to result in 1% excess prevalence of impairment over different time periods were calculated. Over five years, exposures resulting in 1% excess prevalence of impairment (for purposes of discussion) were in the vicinity of 10 μg/m^3 for manganese fume and 25 μg/m^3 for larger particle dusts. These levels are below current recommendations for occupational limits on manganese exposure in the United States.

Keywords

Manganese; Neurobehavioral; Risk assessment; Smelter; Steady state; Welding

☆Most of this work was presented September 25–28, 2016, at *Manganese Health Effects on Neurodevelopment and Neurodegenerative Diseases*, Icahn School of Medicine, New York City.

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Conflict of interest

the authors report no conflicts of interest in this work

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

1. Introduction

Blood levels of manganese (Mn), an essential nutrient, are heavily regulated to accommodate widely varying food intake and interacting iron metabolism. The routine physiologic control of Mn is mostly exercised in the gastrointestinal tract and liver, while inhaled manganese appears to be much less well managed (Andersen et al., 1999). The metabolic control of Mn has been examined in detail using physiologically based pharmacokinetic (PBPK) models (Ramoju et al., 2017).

There is considerable epidemiological evidence of homeostatic Mn regulation. Quebec smelter workers showed a negative dose-rate effect where increasing air levels of Mn produced less than proportional increases in a) blood levels (Park et al., 2014a) and b) neurobehavioral effects (Park et al., 2014b). For the neurobehavioral end-points examined in Quebec smelter workers, such as those measured by the Luria Motor scale, recent duration of exposure (e.g., prior five years) was as good as, or superior to, the corresponding recent Mn cumulative exposure metric in predicting impairment using a detailed retrospective exposure assessment. In South African smelter workers, a strong attenuation of neurobehavioral effects with increasing cumulative Mn exposure suggests a role for homeostatic controls (Myers et al., 2003b; Thompson and Myers, 2006). While in humans there is a dose-response relationship with duration of exposure to airborne Mn at physiologically-regulated blood levels, lower exposure concentrations are also potentially hazardous. These considerations argue against a special role for short-term high exposures, although delays in physiological regulatory responses to rapidly changing exposure levels could become important in uptake and distribution.

In response to the growing large body of evidence concerning neurobehavioral impairment resulting from manganese occupational and ambient environmental inhalation exposures, several risk assessments have been conducted using epidemiologic data collected on welders and other Mn-exposed worker populations. Benchmark dose (BMD) analyses were applied using the Roels et al. (1992) data from alkaline battery workers and from a cohort of bridge welders (Bowler et al., 2006). Summaries of these risk assessments are presented here. In addition, studies of smelter workers in Quebec (Mergler et al., 1994) and South Africa (Myers et al., 2003b), and welding trainees (Laohaudomchok et al., 2011) provided additional opportunities for risk assessment. This work assembles risk estimates from the studies with sufficient retrospective exposure assessment and evaluation of neurobehavioral outcomes to support a quantitative risk assessment. Summary estimates of risk are presented along with discussion of issues unique to neurobehavioral end-points in protecting workers as previously raised by Park et al. (2006).

1.1. Benchmark dose calculations for risk assessment

BMD analyses require defining an impairment threshold for the outcome under study. This is often the 5th percentile of poor performance in a normal or unexposed population (used for the present analysis) or impairment quantified as a standardized or other evaluation score determined by clinical consensus. Also required is specification of a maximum acceptable increment in the attributable risk of impairment (Bailer et al., 1997; Crump, 1995), usually ranging from 0.1% to 10%. Considerations of homeostatic regulation imply that cumulative

exposure may not be an optimum metric in linear models of exposure response (Clewell et al., 2003; Park et al., 2014a, 2014b; Thompson and Myers, 2006). Other metrics related to body burdens of Mn have been used in estimating dose-response for neurobehavioral outcomes (Park et al., 2014a). In addition this risk assessment considers recent Mn exposures, defined as exposures in the prior 5 years, as a possible appropriate metric. However, most plausible metrics are correlated (e.g., cumulative exposure or burdens with various half-lives) and most population observations have been for relatively short time periods (compared to a 45 year working lifetime) making the choices of an appropriate metric and model specifications difficult for predicting long-term effects. One important possibility with some empirical support is that, for a given fixed low Mn exposure concentration, a steady-state or maximal response is attained after some time interval much less than 45 years. In the Quebec smelter study, there was weak support favoring burden metrics with half-lives on the order of a few years suggesting that impairment reflected relatively recent exposure, not cumulative exposure over a lifetime (Park et al., 2014b). The PBPK model simulation work of Ramoju et al. (2017) observed attainment of steady-state Mn concentrations in the globus pallidus after about 1 year at airborne concentrations of 300 $\mu g/m^3$ in battery manufacturing workers. In this situation, it would be inappropriate to linearly extrapolate an observed response based on cumulative exposure over several years to a 45 year working life. All of the risk assessments utilizing battery worker data reported by McClure and Odin (1998) used average *current* Mn exposure intensity as the predicting metric, implicitly assuming a steady state response, attained in this case over a 5 year period.

1.2. Published risk assessments

Lucchini et al. (1999) produced an estimate of the *lowest observable adverse effect level* (LOAEL) for Mn-induced neurobehavioral deficits in ferroalloy workers. The 97.7 $\mu g/m^3$ LOAEL was based on the mean cumulative exposure and mean duration (11.5 years) of the mid-level exposed subpopulation. This estimate was dependent on choices made in stratifying the population on exposure (Bailer et al., 1997; Clewell et al., 2003). It was also affected by the history of rapidly declining Mn air concentrations in this industry (2 to 5 fold reductions over 10 years), raising the possibility of irreversible effects sustained from earlier higher exposures. Roels et al. (1992) conducted a semi-quantitative risk assessment on their data of alkaline battery production workers and low-exposed chemical workers. They concluded that a lifetime integrated exposure of 1200 $\mu g/m^3$-yr respirable Mn resulted in “slight neurofunctional changes in a significant proportion of exposed subjects.” In this study population with an average duration of exposure of 5.3 years, the lifetime integrated exposure level corresponded to an average level of 225 $\mu g/m^3$.

McClure and Odin (1998) conducted a BMD analysis of, and summarized previous work on, the Roels et al. (1992) data on eye-hand coordination. The exposure metric used was a worker’s lifetime average air concentration of either total or respirable Mn. The average exposure levels for respirable Mn corresponding to maximum acceptable levels of increased risk of impairment were calculated making various exposure-response modeling assumptions (Table 1). There was considerable agreement across investigators and modeling approaches in estimating the benchmark dose for a 10% additive increase in risk of eye-hand coordination impairment above the 5th percentile threshold in relation to respirable Mn. The

estimates ranged from 113 to 183 μg/m^3 (McClure and Odin, 1998). BMD estimates were also reported for additive excess risk levels of 5% down to 0.1% using three modeling strategies. Increased variability in risk estimates at the lower exposure concentrations was observed. For example, for a 0.5% risk increment in impaired eye-hand coordination, the BMDs ranged from 8 to 67 μg/m^3.

Clewell et al. (2003) calculated BMDs across three neurobehavioral endpoints in the Roels et al. (1992) data: eye-hand coordination, visual reaction time and hand steadiness. Estimates of current exposures associated with 10% increments were 155, 400 and 520 μg/m^3, respectively, with an average BMD of 357 μg/m^3. Clewell et al. (2003) also analyzed data from a low-exposed population of chemical manufacturing workers (Gibbs et al., 1999) across five endpoints using different modeling approaches for a total of 13 estimates based on current exposure. The BMD results for a 10% impairment increment ranged from 275 μg/m^3 (reaction time) to 3980 μg/m^3 (tap time, continuous). Several of the outcomes were unable to be analyzed due to negative associations. The mean lower 95% confidence limit for the five endpoints (averaging models within endpoints) was 190 μg/m^3, about the same as that calculated by Roels et al. (1992).

Park RM et al. (2006) conducted an exploratory risk assessment for neurobehavioral outcomes in welders working in confined spaces during construction of bridge piers originally reported by Bowler et al. (2007). Park et al. (2009) subsequently conducted a risk assessment of the same workers using more detailed work histories and a more complete exposure assessment (Table 2). Neurobehavioral assessment data were available for more than 80% of the welders employed for up to 2 years on this bridge construction project involving work in confined spaces. Exposures were estimated from compliance sampling including 116 mostly full-shift or half-shift personal breathing zone samples and 43 area samples. The bridge welders showed statistically significant negative performance associations with burden or cumulative burden metrics over a 2 year period in five of 10 measures examined: Design Fluency (one-tailed p-value = 0.014, for exposure metric regression coefficient), Working Memory (WAIS III) (p = 0.015), Verbal IQ (p = 0.015), Verbal Comprehension (p = 0.016) and Stroop Color-Word (p = 0.045). The BMD estimates for a 5% increase in impairment ranged from 27 to 151 μg/m^3 using the 1st, 5th and 10th percentile of normal to define impairment (Park et al., 2009) (Table 2). The deficits observed in these standardized neurobehavioral tests in bridge welders corresponded to significant levels of symptoms: 63% of welders had clinical depression on the Beck Depression Inventory (BDI), and 80% had clinical elevation in anxiety (Bowler et al., 2007).

2. Materials and methods

2.1. Description of published studies used for new assessments

From the Mergler et al. (1994) study of Quebec smelter workers three neurobehavioral end-points (Luria Motor Scale, Trail Making A and Trail Making B) were used for BMD excess risk calculations [Table 3]. The original response data, as T-scores, were available and the exposure metrics used were those with the best statistical model fit in estimating the exposure response (Park et al., 2014b); these were burden metrics with half-lives based on estimated exposure levels of “small” respirable Mn. Applying the estimated exposure

response for a series of constant exposure levels over a 45 year working life using a benchmark dose procedure as described previously (Park et al., 2006) yielded corresponding risk estimates for the Luria Motor and Trail Making outcomes.

From the South African smelter workers study of Myers et al. (2003b) published regression model findings for both cognitive and motor outcomes in relation to cumulative Mn exposure provided a basis for risk assessment. The calculation of BMD estimates depended on normative data (expected means and standard deviations) for the reported outcomes which were provided by the study investigators [personal communication, Dr. Jonny Myers, 10/16/16]. For several of the outcomes the investigators observed the exposure response to be non-linear with an initial rapid change at low levels of cumulative exposure (Myers et al., 2003b; Thompson and Myers, 2006). The present risk assessment used the exposure response reported in the lowest cumulative exposure stratum (<1.3 mg/m^3–yr) which is closer than the higher strata to worker exposure levels of concern. Applying the reported regression estimates of exposure response for the eight outcomes analyzed for the South African smelter workers in the benchmark dose procedure produced risk estimates for 45 year exposures.

From the San Francisco bridge welders study, in addition to the five cognitive outcomes on which a published risk assessment was based (Park et al., 2009), eight other outcomes, all motor-related, were evaluated using regression results provided by the original investigators [personal communication, Drs. Vihra Gocheva and Rosemarie Bowler, 10/28/16] (Table 4). The regression analyses predicted motor outcomes in relation to cumulative Mn exposure (over the 2 year project), controlling for age, years of education and race, and corresponding risk estimates were calculated as previously performed for the five cognitive outcomes.

In a study of welding trainees from a Boston-area union (Laohaudomchok et al., 2011) response time, finger tapping, handwriting stability and Profile of Mood States (POMS) were evaluated. Response time was measured using the Continuous Performance Test [CPT, Neuro-behavioral Evaluation System 3; (Letz, 2000; Letz et al., 2003)]. Using linear regression those investigators found a significant increase in response time with welding exposure (β= 0.71 ms/(mg/m^3-h), SE_β = 0.22). For the calculation of excess risk here, it was assumed that the CPT is approximately normally distributed in the general population and that the population standard deviation (SD) (unavailable) was close to that observed in the trainee group (e.g., 57 ms) although, in the latter, there could be additional variance due to the exposure effect. The population was exposed for only 1–5 years and excess risk was calculated for only a 15 year period rather than the usual working lifetime of 45 year because of the uncertainty on long-term cumulative effects (Table 4). The finger-tapping exposure-response regression result was very imprecise in this welder population with low exposures (median: 12.9 $\mu g/m^3$ $PM_{2.5}$ Mn) despite a statistically significant overall group performance deficit on finger tapping, and the handwriting and POMS outcomes posed challenges in terms of background rates, normal variability and defining impairment; these outcomes were not included in this risk assessment.

2.2. Alternate risk assessment assumptions

Taking into account possible reversible components and attainment of steady-state levels of impairment with constant low exposure, the estimated fixed concentrations conferring 1% excess risk were calculated for the two smelter and the two welder populations corresponding to five rather than 45 years of exposure. For the chemical worker study, the exposure metric was average airborne concentration (not cumulative) and the duration of employment was about 5 years; therefore the reported risks were for the equivalent of 5-year cumulative exposures.

2.3. Data analysis

All calculations were performed in SAS (SAS, 1999) using macros constructed for specific benchmark dose estimations.

3. Results

From the Quebec smelter study, excess risks of 5% or 1% for the Luria Motor Scale corresponded to 45 year constant exposures of 21 or 5.5 μg/m^3, respectively, for impairment defined as scores departing more than 1.64 SD from the mean (Table 3). The selected exposure metric used for Luria Motor Scale calculations assumed that the Mn blood burden had a half-life of 5 years and a linear dependence on exposure intensity that was truncated above 25 μg/m^3(to address homeostasis); excess risk was evaluated at age 65 at which point the maximum burden would have occurred. The mean exposure averaged over time for this smelter population was 82 μg/m^3 (Park et al., 2014a). For the Trail Making A and B outcomes, 1% excess risk over 45 years corresponded to Mn exposures of 2.5 and 7.0 μg/m^3 (Table 3). In the South African smelter study for an excess risk of 1%, the estimated 45 year exposures over eight outcomes ranged 4–12 μg/m^3 inhalable Mn (Table 4). These estimates assumed that the exposure response observed in the low cumulative exposure stratum can be used to predict an accumulating risk over 45 years. For the motor outcomes in the bridge welder study, risks of 1% accruing from a 2 year period corresponded to Mn exposures ranging 13–89 μg/m^3 (Table 4; discrepancy between Tables 2 and 4 for the outcomes reported in Park et al. (2009) arises because the SD used to define impairment in Table 2 was derived from the regression residual standard error while in Table 4 the normative score SD was utilized). In the apprentice welders, increased response times (by 1.64 SD) with an excess risk of 1% corresponded to a 15 year exposure to 1.0 μg/m^3 Mn (PM 2.5) (Tables 3 and 4).

3.1. Five year steady-state risk assessment

For the Belgian battery chemical workers, whose average duration of exposure was about 5 years, the 5-year risks corresponding to different levels of *current* exposure were those previously calculated (McClure and Odin, 1998). From the findings in the South African smelter study (Myers et al., 2003b) excess risks for cumulative exposures over 5 years were calculated in the same manner as for 45 years yielding substantially higher Mn levels for 1% excess risk (by a factor of 45/5) (Table 4). Similarly, estimates were calculated for the Quebec smelter workers, based on 5-year steady state exposures (Park et al., 2014b). For the San Francisco bridge welders, the estimates of exposure for 2-year (observed employment

duration on bridge piers at time of study) and 5-year effects were calculated based on reported cognitive outcome regression results (Park et al., 2009). For outcomes predicted by Mn burdens with small half-lives, e.g., the Design Fluency with 90 day half-life, the exposure levels causing a specified impairment over 2 or 5 years would be similar. For the bridge welder results on motor performance, the non-dominant hand findings were used because they were consistently stronger and displayed higher statistical significance. (The smaller effects in the dominant hand may represent a) neurological compensation or b) higher vulnerability of less used pathways in the brain [personal communication, Dr. Vihra Gocheva, 11/1/16]). Finally the 1% excess prevalence of impaired response time in apprentice welders (Laohaudomchok et al., 2011), calculated over 5 years gave an estimate of 2.9 $\mu g/m^3$ Mn (Table 4).

Over 5 years, 1% excess risk of impairment appears to result from lower exposures to welding fume compared to the Belgian chemical and South African smelter exposures with larger airborne particulate (Table 4); in the South African smelter study, inhalable air sampling was conducted across homogeneous exposure zones covering raw material handling, electric furnace operation and crushing of cast manganese (Myers et al., 2003a). In the case of the Quebec smelter workers, the exposure metric used was “small respirable” particles derived from location proximity to electric furnace operation which produce a Mn fume with very small particle size. The 1% excess risk Mn concentrations for the Quebec smelter workers were similar to the welding populations. Although the dust-exposed workers, for which higher Mn concentrations were predicted for 1% excess risk, were evaluated primarily for motor-related effects, in the welding populations both motor and cognitive end-points appear to have similar responses, at lower concentrations.

4. Discussion

4.1. Reversibility and other concerns

In considering an exposure limit for occupational exposure to manganese, several issues must be addressed relating to neurobehavioral impairment: acceptable risk, metabolic regulation of this essential dietary nutrient, and the derivation of appropriate exposure-response relationships. Neurobehavioral health effects that are adverse and measurable and would qualify as clinical impairment, such as depression, anxiety, memory loss or motor deficits, are appropriate end-points for consideration. Although the research literature provides clear evidence of adverse neurobehavioral effects of sustained low air Mn concentrations (<0.2 mg/m^3), there are important unknowns such as a) the extent to which irreversible, cumulative changes are occurring, b) role of particle size, c) particle chemical form and solubility. Some apparent reversibility may actually be instances of complex compensation or accommodation imposing other burdens or adverse consequences (Martinu and Monchi, 2013; Mohr et al., 2016). Several investigations have examined aspects of reversibility (Bouchard et al., 2007a, 2007b, 2008; Bowler et al., 2011; Huang et al., 1998; Josephs et al., 2005). Some reversibility was observed by Bouchard et al. (2007a) in all three areas: neuromotor, cognitive and psychiatric outcomes. Reversibility, here, pertains to behavioral manifestations and may not reflect reversal of underlying neurological damage.

One issue is how workers should be protected from exposures resulting in reversible impairment, when experienced over periods less than a working lifetime.

This risk assessment examines end-points that could be interpreted as assessing both acute and chronic effects. No attempt was made to distinguish these, and the 5 year attainment period utilized tends to capture both acute and chronic contributions.

Risk assessment ultimately requires choosing a target excess risk. For illustration purposes, a target risk of 1% was selected. The risk assessments for multiple neurobehavioral end-points are summarized in Table 4, presenting the reported or calculated cumulative effects of Mn exposure and equivalent estimates based on 5 year steady-state responses. These estimates of airborne Mn exposure concentrations represent levels at which a 1% excess risk of impairment is expected where impairment is defined on the 5th percentile in the normal population or at 1.64 SD from normal. If there were irreversible and cumulative effects from Mn exposure, then the estimated steady state related exposures in Table 4 would represent upper bounds for the maximum allowable exposure. If there are only reversible effects and a steady-state is attained after 2 years, for example, then higher corresponding Mn levels would result, as displayed for the San Francisco bridge welders (Table 4).

4.2. Implications for risk management

For end-points evaluated in relation to small respirable Mn particulate, as for condensation fume, the exposure levels predicting 1% excess impairment ranged 2.9–35 μg/m^3, and all but one were less than 17 μg/m^3. For end-points evaluated for large Mn particulate, as in dusts, the exposure levels predicting 1% excess impairment ranged 16–106 μg/m^3 (as both respirable and inhalable particulate), and all but one were greater than 30 μg/m^3. Thus respirable exposures associated with 1% excess risk of adverse neurobehavioral effects correspond to concentrations of approximately 10 μg/m^3 for Mn fume exposure (welding and electric furnace operations), and 25 μg/m^3 for Mn dust (without fume, all other operations generating airborne Mn particulate). A somewhat higher level for larger particulate, e.g., 30–40 μg/m^3, would correspond to inhalable Mn (as reported in Myers et al., 2003b).

For Mn fume this is a factor of 2.0 lower than the *threshold limit value* (TLV) presented by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH, 2013) for “respirable particulate matter.” Also specifying a two-tier occupational exposure limit, the ACGIH established a maximum level of 100 μg/m^3 for “inhalable particulate matter” which would include dusts above the 10 μm range, from non-welding and non-electric furnace operations, and which is a factor of 4 higher than the 1% excess risk dust levels shown here (a factor of 3 for inhalable Mn). At other target excess risks, e.g., 5% or 0.5%, the corresponding Mn exposures would be essentially proportional to the 1% risk estimates.

4.3. Summary

This risk assessment utilized estimates of exposure response derived from epidemiological analyses of occupationally manganese-exposed populations. It extended some earlier work while calculating new estimates of exposure response and excess prevalence of impairment. Impairment was defined as excursions beyond the 5th percentile in a normal population.

Small particles and aggregates of condensation fume (condensing vaporized metal, <0.1 μm in diameter) appeared to have a higher potency per unit mass than larger particles from dusts (>1.0 μm) providing further support for a two-tiered approach previously adopted by ACGIH for establishing exposure limits to protect against adverse neurobehavioral effects. In considering an exposure limit, several issues were addressed relating to neurobehavioral impairment: acceptable risk, metabolic regulation of this essential dietary nutrient, and the derivation of appropriate exposure-response relationships for health effects that may be partially reversible, may attain maximal levels after prolonged exposures at moderate concentrations, and are responsive to homeostatic regulation. Although future investigations will enhance understanding of the mechanisms of Mn induced neurobehavioral effects, the currently available knowledge is sufficient for progress in risk assessment of public health significance.

Acknowledgments

Helpful comments were provided by Harvey J. Clewell III, Robert Dick, Donald Eggerth, and Sudha Pandalai. Supplemental data and findings were provided by Jonny Myers, Donna Mergler, and Vihra Gocheva and Rosemarie Bowler.

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Table 1

Risk assessments for manganese and impaired eye-hand coordination, using Roels et al. (1992) data, assuming impairment at fifth percentile of performance in population for various levels of manganese-attributable excess risk.

	Benchmark Dose, μg/m^3, respirable Mn				
	Risk Increment, per 1000				
	100	**50**	**10**	**5**	**1**
	10%	**5%**	**1%**	**0.5%**	**0.1%**
Crump Continuous One Hit	113				
Crump Continuous Linear Mean Fcn	149				
EPA Quantal Linear	110				
SRC Polynomial	160	81	16	8	1.6
EPA Log-logistic	176				
SRC Log-logistic	183	138	82	67	45
Crump Quantal Weibull	179				
Clewell Weibull[a]	155				
EPA Weibull	170				
SRC Weibull	176	119	49	33	14

Abbreviations: EPA = U.S. Environmental Protection Agency; Fcn = function; SRC = Syracuse Research Corporation (McClure and Odin, 1998).

[a]Clewell et al. (2003). Source: McClure and Odin (1998) unless otherwise noted.

Table 2

Estimated benchmark dose exposure levels for airborne manganese (μg/m3 Mn) in Bay Bridge welders.

	Population Percentile Defining Impairment											
	1st percentile				5th percentile				10th percentile			
Benchmark Risk (per 1000)[a]	1	10	50	100	1	10	50	100	1	10	50	100
Relative Risk	1.1	2.0	6.0	11	1.02	1.2	2.0	3.0	1.01	1.1	1.5	2.0
WMI (B; half-life = 275 da)	10	51	110	144	1	12	45	72	0.4	6	27	47
DFT (B; half-life = 90 da)	25	67	108	129	4	27	62	84	1	14	42	61
VIQ (cumB; half-life = 400 da)	16	74	151	194	2	20	67	103	1	10	40	68
VCI (cumB; half-life = 400 da)	14	70	146	190	2	20	68	104	1	10	42	72
STP[2] (cumB; half-life = ∞)	2	19	76	129	1	10	45	83	0.5	8	36	68

Abbreviations: B = Mn burden; cumB = cumulative Mn burden; DFT = Design Fluency; STP = Stroop Color Word Test; VCI = Verbal Comprehension Index; VIQ = Verbal Intelligence Quotient; WMI = Working Memory Index.

[a]Risk resulting from a two-year exposure, calculated using 5th percentile estimated from regression residual standard error.

Source: Park et al. (2009), Table 7.

Table 3

Risk assessments from Quebec smelter and welder apprentice studies: Mn airborne concentrations corresponding to excess risk of impairment defined as 1.64 SD departure from population mean.

Excess risk	Mn concentrations (μg/m^3)			
Per 1000	Quebec smelter workers			Apprentice welders CPT-response time[4]
	Luria Motor Scale[1]	Trail making A[2]	Trail making B[3]	
200	60	28	>200	11
100	37	17	>200	6.6
50	21	10	113	3.9
20	10	4.7	25	1.9
10	5.5	2.5	7.0	1.0
5	2.8	1.3	1.9	0.5
2	1.2	0.6	0.3	0.2
1	0.6	0.3	0.1	0.1

CPT = continuous performance test (response time).

[1] Park et al. (2014b) (45 yr from age 20; burden of saturation dose >= 25 with 5 yr Thalf; small respirable Mn).

[2] Park et al. (2014b) (45 yr from age 20; burden of saturation dose >= 25 with 10 yr Thalf; small respirable Mn).

[3] Park et al. (2014b) (45 yr from age 20; burden of sqrt of dose with 1 yr Thalf; small respirable Mn).

[4] Laohaudomchok et al. (2011) (500 h/yr; 15 yr from age 20 to 35; cumulative PM 2.5 Mn).

Table 4

Risk assessments based on 5% (or 1.64 SD) impairment definition and for 1% increase in impairment, for reported or cumulative effect and with 5-year equivalent steady-state.

Population (Mn sampling fraction, duration for calculation, n)	end-point (Mn metric, half-life)	Mn exposures conferring 1% excess risk	
		Reported or calculated cum. effect μg/m^3	For 5 year steady-state equiv.
Belgian battery factory, 1992 [a] (respirable, 5 yr, n = 92)	Eye-hand, Polynomial (curX)	16	16
	Eye-hand, Log-logistic (curX)	82	82
	Eye-hand, Weibull (curX)	49	49
South African smelter, 2003 [b] (inhalable, 45 yr, n = 509)	Santa Ana pegboard (cumX)	3.5	32
	Benton visual retention (cumX)	5.8	52
	Digit span (forward and back) (cumX)	6.4	58
	Digit-symbol (cumX)	12	106
	Reaction time (cumX)	5.4	48
	Finger tapping, endurance (cumX)	7.8	70
	Finger tapping, dom. (cumX)	4.4	40
	Finger tapping, non-dom. (cumX)	9.5	84
Quebec alloy smelter, 2014 [c] (small respirable, 45 yr, n = 106)	Luria Motor (B, 5 yr)	5.5	11
	Trail Making A (B, 10 yr)	2.5	8.5
	Trail Making B (B, 1 yr)	7.0	7.3
San Fran. bridge welders, 2009 [d] (respirable, 2 yr, n = 44)	Working Memory Index (B, 275 da)	12	9.8
	Design Fluency Test (B, 90 da)	6.6	6.6
	Verbal Intelligence Quotient (cumB, 400 da)	14	3.5
	Verbal Comprehension Index (cumB, 400 da)	13	3.2
	Stroop Color Word Test, (cumB, >20 yr)	15	2.5
	WAIS-III Processing Speed Index (cumX)	40	16
	Digit symbol coding (cumX)	21	8.6
	Trail Making A (T) (cumX)	89	35
	Finger tapping, non-dom. (T) (cumX)	33	13
	Grooved pegboard, non-dom. (T) (cumX)	23	9.1
	Dynamometer, non-dom. (T) (cumX)	22	8.8
	Santa Ana pegboard, dom. (z) (cumX)	13	5.4
	Santa Ana pegboard, non-dom. (z) (cumX)	16	6.3
Apprentice welders, 2011 [e] (PM 2.5, 15 yr, n = 46)	Reaction time, CPT (cumX)	1.0	2.9

curX – current Mn exposure B – Mn burden (half-life, yr) cumB – cumulative Mn burden (half-life, yr).

cumX – cumulative Mn exposure X – Mn, respirable unless indicated otherwise T – standardized T-score.

[a] McClure and Odin (1998).

[b] Myers et al. (2003b) with normative data.

[c] Park et al. (2014b).

[d] Park et al. (2009) (for motor outcomes (using regression results, on cumX): personal communication, V. Gocheva and R. Bowler, 10/28/16).

[e] Laohaudomchok et al. (2011) (500 h/yr; from age 20 to 35).