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Exposure-Response Relationship and Risk Assessment for Cognitive Deficits in Early Welding-Induced Manganism

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Learning Objectives

- Describe the recognized features of manganism, including comparison with Parkinson's disease and the cognitive and neurobehavioral impairments reported in welders with high manganese exposure.
- Discuss key unanswered questions related to manganese exposure in welding operations, including the optimum exposure metric, exposure-response relationship, and reversibility of effects.
- Summarize the new research findings, including exposure level associated with a risk of cause cognitive impairment, the percentage of workers likely to be affected, and uncertainties in the exposure-response and risk assessment estimates.

Abstract

Objective: *The exposure-response relationship for manganese (Mn)-induced adverse nervous system effects is not well described. Symptoms and neuropsychological deficits associated with early manganism were previously reported for welders constructing bridge piers during 2003 to 2004. A reanalysis using improved exposure, work history information, and diverse exposure metrics is presented here.* ***Methods:*** *Ten neuropsychological performance measures were examined, including working memory index (WMI), verbal intelligence quotient, design fluency, Stroop color word test, Rey-Osterrieth Complex Figure, and Auditory Consonant Trigram tests. Mn blood levels and air sampling data in the form of both personal and area samples were available. The exposure metrics used were cumulative exposure to Mn, body burden assuming simple first-order kinetics for Mn elimination, and cumulative burden (effective dose). Benchmark doses were calculated.* ***Results:*** *Burden with a half-life of about 150 days was the best predictor of blood Mn. WMI performance declined by 3.6 (normal = 100, SD = 15) for each 1.0 mg/m³ × mo exposure (P = 0.02, one tailed). At the group mean exposure metric (burden; half-life = 275 days), WMI performance was at the lowest 17th percentile of normal, and at the maximum observed metric, performance was at the lowest 2.5 percentiles. Four other outcomes also exhibited statistically significant associations (verbal intelligence quotient, verbal comprehension index, design fluency, Stroop color word test); no dose-rate effect was observed for three of the five outcomes.* ***Conclusions:*** *A risk assessment performed for the five stronger effects, choosing various percentiles of normal performance to represent impairment, identified benchmark doses for a 2-year exposure leading to 5% excess impairment prevalence in the range of 0.03 to 0.15 mg/m³, or 30 to 150 μg/m³, total Mn in air, levels that are far below those permitted by current occupational standards. More than one-third of workers would be impaired after working 2 years at 0.2 mg/m³ Mn (the current threshold limit value).* (J Occup Environ Med. *2009;51:1125–1136*)

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High exposures to manganese (Mn) in mining and ferroalloy operations can induce severe manganism.[1] This well-described syndrome has features of parkinsonism involving degradation of the basal ganglia in the extrapyramidal motor pathways of the central nervous system as well as neuropsychological and neurobehavioral effects. Early manganism resulting from brief high or sustained lower exposures to Mn has not been well described. There are important differences between Mn-induced movement disturbances and idiopathic Parkinson's disease (PD) including an awkward high-stepping gait in manganism in contrast to the typical shuffling gait in patients with PD.[1,2] In addition, tremor characteristics differ with postural intention tremor observed in manganism and resting tremor in PD. Neuronal degeneration at the level of the basal ganglia is presynaptic for PD (in substantia nigra pars compacta) and largely postsynaptic for manganism (globus palladus).[2] However, the extent to which manganism may share pathophysiology with classical PD, itself a complex and possibly multiple entity,[3] remains controversial.[2,4,5]

In arc welding, Mn exposures arise as a respirable fume from the base metal or welding rods, wire or flux containing Mn, where Mn is important for weld integrity or surface hardness. Neurological findings in case reports of welders with high Mn exposures and in case series of welders with uncharacterized Mn exposures have shown atypical parkinsonian features

of tremor and postural instability.[2,6–8] When assessed, these welder cases commonly exhibited cognitive or neurobehavioral impairment.[5,6,8–10]

In defined welder populations, a number of investigators also have observed symptoms and signs consistent with onset of manganism,[11–17] including cognitive and other neuropsychological deficits. These findings are similar to observations in populations with intermediate levels of Mn exposure to fume in ferroalloy production[18–23] or to dusts in Mn oxides or salts production,[24,25] dry-cell battery manufacture,[26] or welding rod manufacture.[10,20]

A recent review of the scientific literature concluded there is little support for concerns over Mn exposures in typical welding operations.[27] Moreover, two population-based studies using national databases in Sweden[28] and Denmark[29] have not confirmed an association between welding and PD or other forms of parkinsonism. However, the welding classifications used in these two studies were not specific to Mn exposure, statistical power was limited for non-PD parkinsonism, and the outcomes studied were largely restricted to severe cases (requiring hospitalization). Work-related conditions would be missed because loss of function would tend to terminate welding employment and exposure, and thus limit or slow progression of the disease. Evidence of a healthy worker effect in the study of Fryzek et al[29] and Fored et al[28] indicates potential bias and suggests welders in the absence of Mn exposure have neurological health status superior to that of the general or employed populations. In a series of 2072 parkinsonism cases identified at three movement disorder clinics in the United States,[30] the three welders identified were among the 1875 (90.5%) idiopathic PD cases. The statistical power for identifying a welder excess among the 197 non-PD cases (9.5%; including 85 "other secondary" or "unspecified") was very low in this population (expected number of welders was ~0.3).

Important questions on the exposure response for welding-induced manganism that will be addressed here include 1) what is the optimum exposure metric? ie, what features of the time course of exposure best predict deficits? 2) what is the exposure-response relationship using an optimum exposure metric? and 3) are Mn effects reversible? Other questions, not addressed, include 1) what is the spectrum of effects across exposed populations? and 2) how do particle size and detailed composition affect response?

The results of an evaluation of 48 welders for workers compensation using neuropsychological measures and neurological examination were previously reported.[11,12,31] These welders were constructing piers for a new San Francisco-Oakland Bay Bridge. An exploratory risk assessment using four of the neuropsychological outcomes focused on methodological issues.[32] For this study, supplemental work history was obtained by interview for most of the same bridge welders ($n = 36$) emphasizing pier configurations where welding was performed, and respiratory protection history was collected. Previously unavailable Mn air sampling data for the second half of 2004 were also obtained. The intent of this study was to examine different Mn exposure metrics for predicting neuropsychological effects and describe the exposure response for risk assessment purposes.

Materials and Methods

Study Population

The previously described welders were shown to comprise almost all members of Pile Drivers Union, Local 34, with at least several months on the bridge project during 2003 to 2004.[32] During 2 days in early 2005, each welder had been given a clinical interview, administered work and health history questionnaires, and participated in a comprehensive battery of cognitive, motor, sensory and behavioral assessments.[11,12] A neurological evaluation, a test of olfaction, spirometry, and an electrocardiogram were also performed, and blood and urine samples were drawn for analysis of Mn and other metals. Four workers from the original analyses were excluded because of insufficient work history, leaving 44 workers for the study.

Work History

To supplement the original work history that summarized overall experience on this bridge project (eg, percent of time manual welding[11]), a detailed month-by-month record of a worker's activity was elicited by interview from 36 welders in May 2006. The query distinguished working locations (piles, chambers, other confined spaces, other locations) and welding activities (automatic, manual, carbon arc, cutting torch, or other). Location was important because the records of Mn air samples specified location, and levels tended to be considerably higher in pier chambers versus pile or other locations. Workers for the most part were able to recall these details because they worked as a group in consecutive periods on a sequence of identifiable piers (eg, "8E," "9E," "10E" . . .) and could recall specific features of their work associated with specific piers. Also queried was the month when a worker began consistently using personal protective equipment (PPE) as a result of a mandatory respiratory protection policy initiated in mid-2004.

Exposure Assessment

Much of the welding was performed in confined spaces in piles (almost vertical steel tubes typically about 2 m in diameter) and in adjoining chambers constructed around the piles at the foot of the piers on the bay floor (within coffer dams to exclude bay water) (Fig. 1). Both automated and manual processes were used, predominantly flux-cored arc and shielded metal arc welding, respectively. Some carbon arc welding and torch cutting were performed.

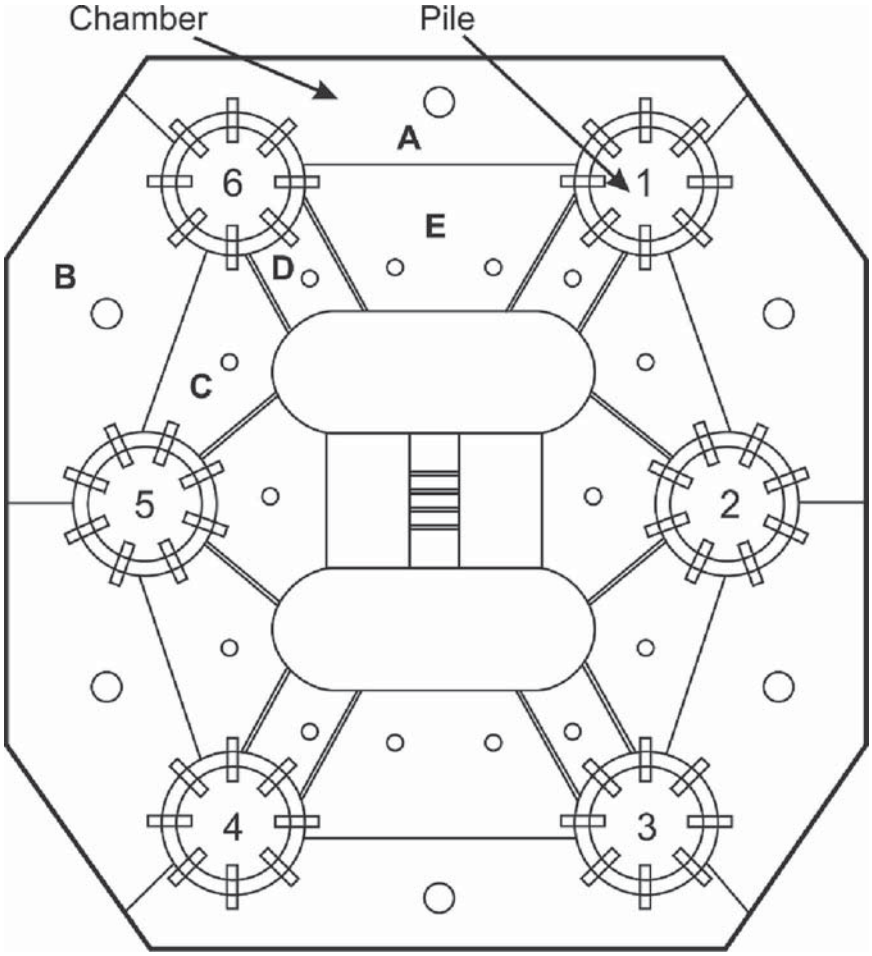

Fig. 1. Vertical view of pier footing box on bay floor showing six piles and contiguous chambers (A, B, C, D, E).

Elevated temperatures and humidity, due to the necessity of warming the structural steel with electric heaters before welding, constituted another adverse condition, possibly influencing ventilatory rate, Mn uptake, and metabolism. Because air sampling was compliance driven with special emphasis on high exposures arising from automatic welding in pier chambers, other activities had minimal or no air samples. When samples were unavailable, levels were estimated using explicit rules based on the following: 1) air concentrations in piles for automatic welding seemed to be about double the manual levels, 2) air concentrations for automatic and manual welding activities seemed to decline over time in pile locations but not chamber locations, and 3) torch cutting was assumed to have similar levels to carbon arc work. Area samples, collected only in chambers, the most confined spaces, were combined with personal samples in estimating mean Mn concentrations because most of the airborne particulate was assumed to be dispersed respirable fume. Similarly, respirable samples were included with total particulate samples for exposure estimates. Both arithmetic and geometric mean exposures were calculated.

Air sampling during 2003 to 2004 was conducted by IHI Environmental (Oakland, CA) under contract with the employer using MSA low-flow pumps and 37-mm cassettes with 0.8-μm pore size, mixed cellulose ester filters and analyzed for Mn by Galson Laboratories (East Syracuse, NY) using National Institute for Occupational Safety and Health 7300 method (inductively coupled argon plasma, atomic emission spectroscopy). Carbon monoxide levels in confined spaces were measured by employer using Industrial Scientific MG-140 that was calibrated monthly and zeroed daily.

Exposure Metrics

Cumulative exposure to Mn (cumMn) was calculated up to the time of a worker's neuropsychological evaluation using estimated process exposure levels in four 6-month periods: January to June 2003, July to December 2003, January to June 2004, and July to December 2004. As described previously,[32] adjustment was made for shift when two shifts were operating (before May 2004); exposures were higher in the afternoon shift, but that shift was 1 hour shorter. Adjustment was also made for reported hours worked per day (reference = 10 hours), days per week worked (reference = 5 days), and for job title if not welder (supervisors or support workers [$n = 5$] were assumed to have one-fourth the average exposure of welders). The end result was an estimated exposure level for each worker in each 10-day period of employment on the project.

Cumulative exposure was calculated as follows:

$$\text{cumMn}(t2) = 0.329 \times H \times D \times \sum_{i=t1}^{t2} [S_i \times X_i] \quad \text{in mg/m}^3 \times \text{mo} \qquad (1)$$

where, H is hours-worked adjustment (hours/10), D is days-worked adjustment (days per week/5), S_i = work shift adjustment; X_i = location- and activity-specific exposure level for period i, reflecting proportions of time spent in different locations and activities; $t1$ is period (10-day units) hired on project; $t2$ is period at observation; 0.329 is adjustment from 10-day units to months. For workers without the supplemental work his-

tory ($n = 8$), cumulative exposure was calculated as previously,[32] using reported proportions of work time in automatic or manual welding, or other activities, without regard to location, and a corresponding exposure matrix.

Effects that depend on the prior distribution of exposure over time might be better described with metrics that decrease or increase with time elapsed since the exposure contribution. Burden metrics were calculated as well as a cumulative burden metric, also known as "effective dose" or "area under the curve"[33] as follows:

$$\text{burden, } B\text{: } B(t2) = 0.329 \times H \times D \times \sum_{i=t1}^{t2} [S_i \times X_i \times (0.5)^{(t2-i)/T_{1/2}}] \quad \text{in mg/m}^3 \times \text{mo} \qquad (2)$$

where $T_{[1/2]}$ is the half-life (specified to be in the range 60 to 400 days), describing how the burden declines with time, at a fixed proportional rate (eg, 10% per month).

cumulative burden, cumB:

$$\text{cumB } (t2) = 0.329 \times \sum_{i=t1}^{t2} [B(i)] \quad \text{in mg/m}^3 \times \text{mo}^2 \qquad (3)$$

Cumulative burden could be an appropriate metric for an exposure that results in a persistent body burden of some entity that continues to produce cellular changes while present in the body.

Because most workers at some point began using respiratory protection, a companion exposure metric term was calculated consisting of the contribution to the exposure metric that took place after the start of respiratory protection. Dose-rate effects (variable effects of the same dose—cumulative exposure—spread over different time periods) were examined by calculating cumulative exposure with exposure intensity raised to some power: 0.3, 0.4, 0.5, 0.8, 1.0 (default), 1.2, 1.5, and 2.0.

Outcomes Analyzed

The outcomes included those used earlier[32]: Working Memory Index (WMI),[34] Rey-Osterrieth Complex Figure test,[35] Stroop color word test (STP),[36] and Auditory Consonant Trigrams test (ACT)[37] together with six additional measures from the original evaluation[11]: 1) verbal intelligence quotient (VIQ), 2) verbal comprehension index (VCI), 3) performance IQ (PIQ),[34] 4) design fluency,[38] 5) letter-number sequencing (LNS), and 6) verbal paired associates (VPA).[34]

Analysis of Exposure Response and Risk Assessment

The exposure-response relationship for untransformed outcome scores was modeled using multiple linear regression in S-Plus[39] and various exposure metrics together with education (centered; years >12), age (centered; years >40), and ethnicity (1 = white and Anglo, 0 = all other). Blood levels of Mn (MnB) were analyzed in relation to the exposure and demographic predictors. Approximate confidence intervals for half-life and dose-rate parameters were obtained using profile likelihoods[40] with −2ln (likelihood) = constant + $n \times$ ln(sum of squared error), where a) sum of squared error was obtained from multiple linear regression models fit for the series of parameter choices of half-life or dose-rate and b) n = number of workers analyzed.

Risk assessment for neurological outcomes poses questions on what constitutes impairment, whether effects are reversible,[32] and what levels of excess impairment are acceptable under established policy. The benchmark dose (BMD) method is an approach that makes explicit the underlying assumptions[41,42] and has been used for neurological outcomes.[43] It avoids limitations of earlier approaches using lowest observed adverse effect level and no observed adverse effect level based on arbitrary exposure dosing levels. The BMD method was used based on final regression models for the outcomes that exhibited statistically significant associations with an optimum Mn exposure metric. The method predicts the increase in the proportion of the population impaired with increasing exposure. Because defining impairment requires judgment, particularly when using neuropsychological performance measures, benchmark exposures were calculated using three different impairment definitions: the 1st, 5th, and 10th percentiles of performance in normal populations. Excess impairment over a 2-year period of exposure was specified in four levels corresponding to excess prevalence of 0.001, 0.01, 0.05, and 0.10.

Results

Study Population

The study population of 43 men and 1 woman was ethnically diverse: 50% white (Anglo), 34% white (Hispanic), 11% African American, and 5% other. The average age was 43 years (SD = 10), and mean education was 12.5 years (SD = 2.3). The mean duration of employment on this bridge was 16.8 months (SD = 6.4; range: 7.2 to 29.6 months; some workers started before January 1, 2003 or continued after January 1, 2005).

Mn Exposures

With the addition of air-sampling results for June to December 2004 to the previously available gravimetric data, a database of 159 airborne total Mn concentrations was available for 2003 to 2004. These consisted of area ($n = 43$) and personal ($n = 97$) samples for total Mn, as well as personal respirable Mn levels ($n = 19$) and generally were full-shift (7 to 8 hours) samples (Table 1). Excluded from this database were 21 short-term exposure level samples, generally taken to characterize high exposures, and background samples from outside the work area. Most samples were from automatic weld-

TABLE 1
Exposure Assessment: Compliance Air Sampling for Full Shift Total Mn (Milligram per Cubic Meter) and Estimated Levels, During 2003 to 2004

	January to June 2003		July to December 2003		January to June 2004		July to December 2004		All*	
	n†	Mean‡	*n*	Mean	*n*	Mean	*n*	Mean	*n*	Mean
Box/chamber										
Automatic welding	5	0.228	5	0.195	74	0.449	37	0.171	121	0.344
Manual welding		0.114		0.098		0.161		0.085		0.132
Carbon arc		0.131	6	0.134	2	0.122		0.131	8	0.131
Torch		0.131		0.134		0.122		0.131		0.131
Other		0.060		0.060	1	0.060		0.060	1	0.060
Pile										
Automatic welding	2	0.205	9	0.102	8	0.039	3	0.024	22	0.078
Manual welding	1	0.110	3	0.054	1	0.190		0.093	5	0.093
Carbon arc		0.130		0.103		0.077		0.050		0.090
Torch		0.130		0.103		0.077		0.050		0.090
Other		0.040		0.036		0.033		0.030		0.035
Other confined space										
Automatic welding		0.200		0.170		0.140		0.110		0.155
Manual welding		0.100		0.080	1	0.041		0.060	1	0.041
Carbon arc		0.070		0.065		0.060		0.055		0.063
Torch		0.070		0.065		0.060		0.055		0.063
Other		0.024		0.024	1	0.024		0.024	1	0.024

*Breathing zone ($n = 116$) and area ($n = 43$) samples; most samples ~8 hr; some half-shift samples. Short-term samples excluded ($n = 21$).

†When no samples were available (*n*: blank), means were estimated from available data (see Methods).

‡Arithmetic mean concentration (milligrams of Mn per cubic meter).

ing operations at chamber locations (121 of 159 or 76%) and most of these were during January to June 2004 (74 of 121) (Table 1). Fewer samples were collected for automatic welding in piles (22), carbon arc work in chambers (8), and manual welding in piles (5). The average Mn determination from automatic welding locations in chambers was 0.34 mg/m^3 whereas that for pile locations was 0.078 mg/m^3. The mean for manual welding in piles (based on five samples) was 0.093 mg/m^3. Inconsistencies perhaps arising from sampling strategies were apparent, for example, the mean for automatic welding in piles during January to June 2004 (0.039 mg/m^3) was less than one-tenth that of chambers in the same period (0.449 mg/m^3). The overall time-weighted average Mn exposure was 0.15 mg/m^3 and the mean cumulative exposure among welders at the time of evaluation was 2.41 mg/m^3 × month (median: 2.13; range: 0.09 to 6.02). Arithmetic means were used in analyses because of our interest in linearity of exposure response; geometric means, which are biased but more precise estimates of true exposure, produced very similar results.

Blood Mn

The mean whole blood Mn concentration assayed at the time of neuropsychological assessment was 9.6 μg/L (range: 5.1 to 15.3).[31] Mn blood levels vary widely in the general population (3 to 12 μg/L) due to dietary and metabolic differences.[44] Mn blood levels showed no dependence on education or ethnicity but declined slightly with age and significantly increased with employment duration on the bridge project ($P = 0.045$, one tailed; Table 2, model 1). Cumulative exposure was a stronger predictor of MnB (model 2), and the prediction substantially improved with adjustment for PPE usage ($R^2 = 0.310$, model 3) indicating that respirator use largely eliminated (roughly 86%) Mn exposure and that blood levels increased by about 1 μg/L for each milligram per cubic meter × month of (unprotected) cumulative exposure. Using Mn burden with a half-life of ~150 days in place of the cumulative exposure metric produced the best-fitting model ($R^2 = .348$) (Table 2, model 4; Table 3). Removing the unimportant ethnicity term produced the strongest prediction of MnB by burden ($P = 0.00045$, one tailed; data not shown). Based on the profile likelihood procedure, cumulative exposure (burden with $T_{[1/2]} = \infty$) could not be excluded as the best metric (ie, the 95% confidence interval includes the null case); the 80% confidence interval for half-life in predicting MnB was ~85 to 500 days.

Neuropsychological Outcomes

As in the earlier analysis,[32] deficits in WMI (normal ~ $N(100, SD = 15)$) were significantly predicted by Mn exposure metrics. Age and ethnicity were not significant predictors but education was (Table 4, models 1 to 4). Cumulative Mn alone was nonsignificantly associated with WMI score (Table 4, model 2), but when adjusted for PPE use, cumulative Mn accounted for a reduction in WMI score of ~3.6 for each milligram cubic meter × month of Mn ($P = 0.021$, one tailed; Table 4, model 3). The effect was somewhat stronger with the burden metric and a half-life of 275 days ($P = 0.015$, one tailed; Table 4, model 4; Table 3). Four other test scores significantly declined with Mn exposure: design fluency (DFT), VIQ, VCI, and the STP (Table 5, models 1 to 4). The model intercept for design fluency (11.95, for white or Anglo) was considerably higher than expected (population mean = 10.0) and DFT was slightly better predicted using Mn burden with a 90-day half-life ($P = 0.014$, one tailed; Table 5, model 1). The two verbal measures VIQ and VCI were best predicted with cumu-

TABLE 2
Regression Models for Whole Blood Manganese Levels (Microgram per Liter) on Duration of Employment and Cumulative Exposure ($n = 40$)

Model	β	β/SE	P*	R^2	Resid. SE	P†
1				0.217	2.39	0.067
Intercept	7.7554	4.93				
Age, centered at 40 yr	−0.0527	−1.34	0.19			
Education, centered at 12 yr	−0.0436	−0.22	0.83			
Ethnicity, 1 = white (Anglo)‡ 0 = other	−0.3757	−0.45	0.66			
Duration (mo)	0.0434	1.74	0.09			
2				0.257	2.33	0.030
Intercept	8.3143	8.07				
Age, centered at 40 yr	−0.0622	−1.65	0.11			
Education, centered at 12 yr	−0.0072	−0.04	0.97			
Ethnicity, 1 = white (Anglo), 0 = other	−0.3948	−0.49	0.63			
cum(Mn) (mg/m^3 × mo)	0.6952	2.25	0.03			
3				0.310	2.24	0.010
Intercept	8.2683	9.12				
Age, centered at 40 yr	−0.0611	−1.69	0.10			
Ethnicity, 1 = white (Anglo), 0 = other	−0.2841	−0.37	0.71			
cum(Mn)	1.0112	3.09	0.0039			
cum(Mn:PPE)§	−0.8645	−1.65	0.11			
4				0.348	2.18	0.004
Intercept	8.6533	11.02				
Age, centered at 40 yr	−0.0586	−1.63	0.11			
Ethnicity, 1 = white (Anglo), 0 = other	−0.5161	−0.71	0.48			
Burden (Mn, $T_{1/2} = 150$)	5.6836	3.43	0.0016			
Burden (Mn:PPE)	−5.5740	−2.60	0.014			

*P value from parameter Wald statistic, two tailed.
†P value for model fit from F statistic, two tailed.
‡Non-Hispanic white workers (reference = Hispanic, African American, and others).
§Exposure metrics: cumX, cumulative exposure and B, burden (milligrams per cubic meter × month).

lative burden and a 400-day half-life (respectively, $P = 0.015$, 0.016, one tailed; Table 5, models 2 and 3; Table 3). The STP, marginally statistically significant in the earlier analyses,[32] was more significant in this analysis ($P = 0.046$, one tailed; Table 5, model 4), but two other previously significant tests were no longer significant: Rey-Osterrieth Immediate Copy (Rey-O) (Table 5, model 7) and the Auditory Consonant Trigrams test (18 seconds, ACT) (Table 5, model 9). The Rey-O test had a very strong ethnicity dependence with white or Anglo workers performing 30% better than others ($P = 0.017$; data not shown). The ACT scores (normal ~ $N(0, SD = 1)$ were substantially below normal in the study population (intercept = −1.24 for white or Anglo, data not shown) but exhibited no association tendency with the metrics used. Three other tests not analyzed in the earlier analysis were poorly predicted by Mn exposure: VPA, LNS, and PIQ (Table 5, models 5, 6, and 8). Three of the five outcomes showing not significant dependence on Mn exposures (VPA, LNS, and Rey-O) exhibited the same pattern of negative

TABLE 3
Regression Model Fit (R^2) for Whole Blood Manganese (MnB) and Neurobehavioral Outcomes on Exposure Metrics, by Half-Life of Exposure Intensity Contribution to Metric (Outcomes in Decreasing Order of Maximum R^2)

		MnB†		VCI		VIQ		WMI		DFT		STP	
Model*	$T_{1/2}$	R^2	P‡	R^2	P	R^2	P	R^2	P	R^2	P	R^2	P
cumB	∞	0.263	0.0138	0.429	0.034	0.415	0.031	0.343	0.107	0.182	0.256	**0.134**	**0.093**
	400	0.280	0.0089	**0.430**	**0.032**	**0.416**	**0.030**	0.360	0.063	0.191	0.205	0.131	0.100
	150	0.294	0.0060	0.428	0.035	0.414	0.032	0.363	0.058	0.200	0.160	0.126	0.113
	75	0.304	0.0046	0.425	0.039	0.410	0.036	0.366	0.050	0.204	0.128	0.122	0.124
	60	0.306	0.0043	0.424	0.045	0.409	0.037	0.366	0.048	0.204	0.122	0.121	0.128
cumX	0/∞	0.310	0.0039	0.428	0.041	0.412	0.037	0.366	0.042	0.206	0.096	0.120	0.137
B	400	0.332	0.0022	0.409	0.080	0.393	0.069	0.373	0.030	0.224	0.051	0.107	0.249
	275	0.339	0.0018	0.402	0.106	0.386	0.090	**0.373**	**0.029**	0.231	0.043	0.102	0.332
	200	0.342	0.0018	0.394	0.142	0.379	0.124	0.369	0.032	0.238	0.037	0.101	0.439
	150	**0.348**	**0.0016**	0.386	0.207	0.369	0.190	0.358	0.048	0.245	0.033	0.100	0.636
	120	0.343	0.0019	0.380	0.276	0.363	0.251	0.349	0.067	0.251	0.032	0.102	0.781
	100	0.330	0.0029	0.379	0.308	0.362	0.294	0.340	0.096	0.257	0.031	0.107	0.968
	85	0.318	0.0044	0.377	0.361	0.360	0.351	0.331	0.135	0.260	0.034	0.111	0.905
	60	0.270	0.0192	0.378	0.398	0.360	0.413	0.311	0.313	0.257	0.046	**0.120**	**0.701**

*Exposure metrics: cumB, cumulative burden (milligrams per cubic meter × square month); cumX, cumulative exposure and B, burden (milligrams per cubic meter × month); bold indicates best model fit.
†Models adjusted for age, education, ethnicity, PPE use (see Tables 4 and 5) except for MnB: age, ethnicity, PPE use (Table 2, model 4); $T_{1/2}$ half-life, in days.
‡P: for exposure effect, two-tailed P value.

TABLE 4
Regression Models for Working Memory Index (~N(100, SD = 15) on Duration of Employment and Cumulative Exposure (n = 41)

Model	β	β/SE	P*	R^2	Resid. SE	P†
1				0.285	12.11	0.014
Intercept	88.915	11.96				
Age, centered at 40 yr	0.1501	0.75	0.46			
Education, centered at 12 yr	2.1853	2.39	0.022			
Ethnicity, 1 = white or Anglo‡, 0 = other	5.8628	1.36	0.18			
Duration (mo)	−0.0627	−0.54	0.59			
2				0.320	11.82	0.007
Intercept	91.316	18.45				
Age, centered at 40 yr	0.1502	0.78	0.44			
Education, centered at 12 yr	1.8961	2.14	0.040			
Ethnicity, 1 = white or Anglo, 0 = other	5.1818	1.28	0.21			
cum(Mn) (mg/m^3 × mo)	−2.1733	−1.46	0.15			
3				0.366	11.57	0.005
Intercept	91.291	18.84				
Age, centered at 40 yr	0.1507	0.80	0.43			
Education, centered at 12 yr	1.7117	1.95	0.059			
Ethnicity, 1 = white or Anglo, 0 = other	5.0689	1.28	0.21			
Cum(Mn)	−3.6202	−2.11	0.042			
cum(Mn:PPE)§	4.2793	1.60	0.12			
4				0.373	11.51	0.005
Intercept	91.652	19.30				
Age, centered at 40 yr	0.1542	0.81	0.42			
Education, centered at 12 yr	1.7476	2.03	0.050			
Ethnicity, 1 = white or Anglo, 0 = other	5.1358	1.30	0.20			
B(Mn:$T_{1/2}$ = 275)	−10.714	−2.28‖	0.029			
B(Mn:PPE)	10.890	1.71¶	0.10			

*P value from parameter Wald statistic, two tailed.
†P value for model fit from F statistic, two tailed.
‡Non-Hispanic white workers (reference = Hispanic, African American, and others).
§cum(Mn:PPE): cumulative exposure accruing during period with PPE use.
‖95% CI = β: −19.9 to −1.50.
¶95% CI = β: −1.56 to 23.3.

parameter estimate for the Mn metric and a positive estimate for the PPE adjustment term. Like the Rey-O, PIQ exhibited a strong ethnicity dependence.

For the five outcomes showing statistically significant association with Mn exposure, the predicted performance ranged 83% to 90% of normal at the mean value of the predicting exposure metric in the study population (Table 6) corresponding to the 17th to 36th percentiles of normal performance. At the maximum observed value of the predicting metric, the corresponding performance was 39% to 72% of normal and in the range of 2nd to 3rd percentile of normal (Table 6).

Calculating cumulative exposure allowing for variable dose-rate effects (accumulating exposure intensity raised to some power, a, but ignoring half-life) produced similar model fits but, for several outcomes and for MnB, a = 1.0 produced the best fit, corresponding to no dose-rate effect (data not shown). For MnB, the 80% confidence interval for dose-rate exponent was 0.5 to 1.5. VCI fit best with a = 1.5 whereas STP fit best with a = 0.3, but the confidence intervals were wide.

Risk Assessment

For the five outcomes showing significant declines in performance with Mn exposure (WMI, DFT, VIQ, VCI, and STP), BMDs were quite similar, varying by less than a factor of 2.0 for excess impairments (benchmark risk) of 5% or 10% (Table 7). With impairment defined as performance below the 5th percentile of normal, an additional 5% impaired would be expected with 2 years of Mn exposure at 0.045 to 0.068 mg/m^3 or 45 to 68 μg/m^3 (Table 7). Using a more broad definition of impairment (below the 10th percentile of normal), the benchmark exposures for an additional 5% impaired are 27 to 42 μg/m^3.

Using the shifts in outcome distribution associated with an exposure metric, as calculated by the BMD procedure, the excess impairment (defined as performance <5 percentiles of normal) after 2 years at 0.2 mg/m^3 total airborne Mn was estimated to be 58% (WMI), 75% (DFT), 36% (VIQ), 35% (VCI), and 43% (STP) of workers (data not shown).

Discussion

Findings

The observation of cognitive deficits with Mn exposure is consistent with previous studies reporting memory-related deficits based on digit-span performance in ferroalloy[21,23,45,46] and in welding[16,17,20,47] populations. Santamaria et al in their comprehensive review identify many of the studies reporting cognitive and other neurobehavioral effects.[27] However, no regression analysis specifically of Mn and WMI, which includes a digit-span component, has been previously reported. Digit symbol is another cognitive test that has been reported to be adversely affected by Mn exposure.[17,21,23,46–48] Regression results for verbal outcomes and executive function in other populations with Mn exposure have not been reported previously.

Limitations

Although the exposure assessment has the limitations of compliance-driven environmental monitoring, the retrospective exposure history avail-

TABLE 5
Regression Models for Outcomes on Optimum Exposure Metrics (in Order of Decreasing Statistical Significance of Exposure Metric Estimate)

	Model	β	β/SE	*P**
1				
	Design fluency, total ~N(10, SD = 3) n = 42			
	R^2 = 0.264 resid. SE = 2.62 P = 0.043†			
	B(Mn:$T_{1/2}$ = 90)	−9.7615	−2.30	0.028
	B(Mn:PPE)	8.1887	1.73	0.093
2				
	Verbal IQ ~N(100, SD = 15) n = 35			
	R^2 = 0.416 resid. SE = 11.96 P = 0.006			
	cumB(Mn:$T_{1/2}$ = 400)	−0.4934	−2.29	0.030
	cumB(Mn:PPE)	0.3552	1.05	0.30
3				
	Verbal comprehension index ~N(100, SD = 15) n = 35			
	R^2 = 0.430 resid. SE = 12.85 P = 0.004			
	cumB(Mn:$T_{1/2}$ = 400)	−0.5214	−2.25	0.032
	cumB(Mn:PPE)	0.2125	0.58	0.56
4				
	Stroop color word ~N(50, SD = 10) n = 43			
	R^2 = 0.134 resid. SE = 13.18 P = 0.354			
	cumB(Mn:$T_{1/2}$ = ∞)	−0.2042	−1.72	0.093
	cumB(Mn:PPE)	0.2033	0.89	0.38
5				
	Verbal paired associates ~N(10, SD = 3) n = 37			
	R^2 = 0.353 resid. SE = 1.68 P = 0.015			
	cumB(Mn:$T_{1/2}$ = ∞)	−0.0271	−1.38	0.18
	cumB(Mn:PPE)	0.0055	0.16	0.87
6				
	Letter−number sequencing ~N(10, SD = 3) n = 41			
	R^2 = 0.222 resid. SE = 2.84 P = 0.103			
	cum(Mn)	−0.5379	−1.28	0.21
	cum(Mn:PPE)	0.4514	0.69	0.50
7				
	Rey−Osterrieth Immediate Copy ~N(50, SD = 10) n = 44			
	R^2 = 0.319 resid. SE = 12.67 P = 0.010			
	cumB(Mn:$T_{1/2}$ = ∞)	−0.1132	−0.99	0.33
	cumB(Mn:PPE)	0.2472	1.17	0.25
8				
	Performance IQ ~N(100, SD = 15) n = 42			
	R^2 = 0.346 resid. SE = 11.88 P = 0.007			
	cum(Mn)	−1.1636	−0.66	0.51
	cum(Mn:PPE)	−1.9501	−0.72	0.47
9				
	Auditory Consonant Trigram, 18 sec ~N(0, SD = 1) n = 44			
	R^2 = 0.248 resid. SE = 0.96 P = 0.047			
	B(Mn:$T_{1/2}$ = 60)	1.4000	0.50	0.62
	B(Mn:PPE)	−1.9999	−0.68	0.50

*P value from parameter Wald statistic, two tailed.
†P value for model fit from F statistic, two tailed.

able for this study population is relatively detailed compared with other Mn-related studies or occupational studies in general. Besides possibly worst-case sampling, which could overestimate levels, many lower exposure activities were not evaluated, or only in selected periods, requiring assumptions in creating an exposure matrix. It is, however, quite certain that exposures in those areas were much lower than for automatic welding in chambers. Area and personal samples were combined (chambers only) because obtaining a systematic relationship between them was not feasible, and it was assumed that for welding fume in confined spaces, the differences between personal and area samples would be minimal. The strong prediction of blood Mn levels using the derived exposure matrix justifies some confidence in its validity. Further confidence comes from the observed substantial effect of PPE use, which is gratifying even though dust masks or full-face particulate respirators are not a preferred choice to control welding exposures, particularly in hot, humid environments. Exposure misclassification would be nondifferential (unrelated to outcomes), would be expected to attenuate the estimated exposure responses, and may have contributed to nonsignificance for several of the outcomes studied.

Welders' Mn exposure levels before this project were unknown. Their previous welding was reported in almost all cases to not involve confined spaces. Nonetheless, some neuropsychological deficits from previous work may have been present. In the opposite direction, better performance may have resulted from a healthy worker effect, as suggested by findings for parkinsonism in other welder studies.[28,29]

The results here differ from the preliminary risk assessment performed previously for these bridge welders.[32] In this study, the exposure assessment and work history were improved, and the PPE use was accounted. The current modeling of outcomes provides better control of confounding by education and cultural factors compared with the earlier analyses. The associations of WMI and STP performance with Mn and the corresponding benchmark exposures are very similar comparing the present and earlier studies whereas the effects on Rey-O and ACT performance are no longer statistically significant. The strength of the ethnicity predictor for the Rey-O (and PIQ) suggests that these tests are quite culture dependent, an effect that could possibly overwhelm an exposure association. Another difference with the earlier analysis is that four workers were excluded who, ear-

TABLE 6
Predicted Neurobehavioral Performance for Workers Not Using PPE at Study Mean and Maximum Observed Exposure Metrics

Outcome*	Exposure Metric†	Predicted Outcome at Mean or Maximum‡	Outcome as of Baseline	Outcome as % of Normal	Outcome as Percentile in Normals
Prediction at mean observed exposure metric					
WMI (B; half-life = 275)	1.03	85.8	88.6	85.8	17.2
DFT (B; half-life = 90)	0.31	8.90	85.7	89.0	35.7
VIQ (cumB; half-life = 400)	21.5	88.8	89.3	88.8	22.8
VCI (cumB; half-life = 400)	21.5	90.0	88.9	90.0	25.3
STP (cumB; half-life = ∞)	31.1	41.4	86.7	82.9	19.7
Prediction at maximum observed exposure metric					
WMI (B; half-life = 275)	2.44§	70.7	73.0	70.7	2.5
DFT (B; half-life = 90)	0.83	3.90	37.5	39.0	2.1
VIQ (cumB; half-life = 400)	56.6	71.5	71.9	71.5	2.9
VCI (cumB; half-life = 400)	56.6	71.7	70.9	71.7	2.0
STP (cumB; half-life = ∞)	87.6	29.9	62.6	59.8	2.2

*B, burden ($mg/m^3 \times mo$); cumB, cumulative burden ($mg/m^3 \times mo^2$).
†Mean (or maximum) value of exposure metric observed in study population, in $mg/m^3 \times mo$ (cumulative exposure, burden) or $mg/m^3 \times mo^2$ (cumulative burden).
‡Based on Table 4 (model 4) and Table 5 (models 1–4), for white (Anglo) workers assuming no dose-rate effect.
§Two years of continuous exposure at California OSHA PEL (0.2 mg/m^3) corresponds to 2.22, 0.88 $mg/m^3 \times mo$, respectively, for the metrics WMI, DFT, and 40.1, 40.1, and 58.3 $mg/m^3 \times mo^2$ for the metrics VIQ, VCI, and STP.

TABLE 7
Estimated Benchmark Dose Exposure Levels for Airborne Manganese (Microgram of Mn per Cubic Meter)

Population Percentile Defining Impairment	1st Percentile				5th Percentile				10th Percentile			
Benchmark risk*	0.1%	1%	5%	10%	0.1%	1%	5%	10%	0.1%	1%	5%	10%
Relative risk	1.1	2.0	6.0	11.0	1.02	1.2	2.0	3.0	1.01	1.1	1.5	2.0
WMI† (B; half-life = 275)	10	51	110	144	1	12	45	72	0.4	6	27	47
DFT (B; half-life = 90)	25	67	108	129	4	27	62	84	1	14	42	61
VIQ (cumB; half-life = 400)	16	74	151	194	2	20	67	103	1	10	40	68
VCI (cumB; half-life = 400)	14	70	146	190	2	20	68	104	1	10	42	72
STP (cumB; half-life = ∞)	2	19	76	129	1	10	45	83	0.5	8	36	68

*Attributable impairment prevalence resulting from 2-year exposure.
†Based on models in Tables 4 (model 4) and 5 (models 1–4).

lier, were included with missing aspects of their work history estimated.

The focus on Mn was supported by extensive prior findings cited above and also by low levels of potential confounding exposures such as other metals or carbon monoxide.[11,32] Iron was the major component of welding fume but is not known to cause neurological effects and actually competes with Mn for some metal transporters.[49]

Insights From Exposure Metric Half-Lives

The estimated half-life for levels of Mn in blood of ~150 days is consistent with rates from brain and bone tissue that have been reported in reviews by Andersen et al[44] (">50 days") and Kim[50] ("up to >200 days"), although the literature on this subject is sparse. Mn deposition in the brain visualized by MRI T1 signals (possible because Mn is paramagnetic) has been observed to clear within ~6 months to 1 year.[9,50] Serial MRIs in two welders over 5 months after welding cessation demonstrated continuing but diminishing Mn brain deposition.[5] Young patients with Mn toxicity arising from excess Mn in long-term parenteral nutrition had declining MRI signals that persisted >3 years.[51] The well-known existence of multiple pharmacokinetic compartments for Mn, which partly account for the differing time courses of Mn levels in blood and urine,[44] may of course render less appropriate a simple first-order burden estimator.

Although the estimates of half-life for the burden and cumulative burden metrics in predicting outcomes are very uncertain, they may provide some insight into reversible and progressive aspects of Mn effects.[33,52] For DFT, the 90-day half-life suggests that the effect parallels current Mn burden, diminishing with Mn

clearance, ie, a reversible effect; the effect may even depend on a Mn activity occurring early after exposure, resulting in a shorter half-life than for MnB itself (90 vs150 days). WMI, with a 275-day half-life, also suggests some reversibility of Mn effect that is slower than Mn clearance from the blood. On the other hand, VIQ, VCI, and STP deficits, with half-lives of 400 days or more in cumulative burdens, seem to be at least partially irreversible, progressing after Mn has largely cleared, raising the possibility that some cellular damage persists and some functional sequelae expand with time for a fixed extent of damage. This is consistent with observations by Roels et al[53] in a follow-up study of battery workers.

Risk Assessment

McClure and Odin[54] reviewed risk assessments by US EPA[55] and Crump[41] using eye-hand coordination data from Roels et al.[26] Defining impairment as the lower 5th percentile of performance in controls, they found BMDs in the range 16 to 183 $\mu g/m^3$ respirable Mn for excess risks of 1% to 10%, somewhat higher than the BMD results from this study: 10 to 104 $\mu g/m^3$ based on total Mn concentrations. Clewell et al[43] found a BMD for eye-hand coordination deficit of 155 $\mu g/m^3$ respirable Mn for a 10% excess risk above a 5% baseline versus 72 to 104 $\mu g/m^3$ total Mn estimated here. Earlier, Roels et al[26] had concluded that risk of tremor increased for a life-time cumulative exposure to respirable Mn exceeding 0.73 $mg/m^3 \times$ yr, corresponding to BMD of 147 $\mu g/m^3$ for 5 years, or 73 $\mu g/m^3$ for 10 years.

One difference with earlier risk assessments is that Mn exposure was in the form of dusts in dry-cell battery[26] or chemical manufacture[56] versus very small condensation-fume particulate in the case of bridge welders. Particle size would affect the distribution of inhaled dose that ultimately passes through the respiratory tract, from which systemic uptake of Mn occurs.[44] Size could also be important if the olfactory route of Mn uptake to the brain plays a significant role.[57,58] Differences in Mn tissue distribution have been observed in animal models with different forms of inhalation exposure.[59,60] Another difference for the bridge welders was that the working environment was often very warm and humid, which could alter respiratory rate and Mn internal dose.

Bellinger[61,62] has addressed issues regarding the public health and clinical significance of deficits in neuropsychological performance in groups or populations exposed to neurotoxicants. Small shifts in distributions not discernable in individuals can produce substantial changes in the proportions of a population that fall below some impairment threshold.[61] Standardized tests can measure performance that has been shown to reflect important real-life functions and capabilities.[62] Finally, the absence of a clearly recognized and defined disease entity does not diminish the potential significance of a pattern of symptoms and signs observed in an exposed population.[61,62]

Conclusion

The analyses reported here indicate that significant increases in the prevalence of cognitive impairment would occur over a 2-year period with Mn exposures below 100 $\mu g/m^3$ (as total dust) that is far below a) the current US OSHA permissible exposure limit[63] permitting 8-hour times-weighted average exposures of 5000 $\mu g/m^3$, or 5 mg/m^3, b) the California OSHA permissible exposure limit or ACGIH threshold limit value permitting exposures of 200 $\mu g/m^3$,[64] and c) the National Institute for Occupational Safety and Health Recommended Exposure Limit of 1000 $\mu g/m^3$. More than one-third of workers would be impaired after 2 years at the current threshold limit value. If some of these effects are irreversible or progressive, then higher excess impairment prevalence would be expected over periods longer than 2 years, implying that BMD exposure estimates would be lower. On the other hand, limitations in the exposure assessment and variability in neuropsychological performance imply uncertainty in the exposure-response and risk-assessment estimates, requiring confirmation in other populations.

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