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Review Article

Neurobehavioral Deficits and Parkinsonism in Occupations with Manganese Exposure: A Review of Methodological Issues in the Epidemiological Literature

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ABSTRACT

Exposure to manganese (Mn) is associated with neurobehavioral effects. There is disagreement on whether commonly occurring exposures in welding, ferroalloy, and other industrial processes produce neurologically significant neurobehavioral changes representing parkinsonism. A review of methodological issues in the human epidemiological literature on Mn identified: (1) studies focused on idiopathic Parkinson disease without considering manganism, a parkinsonian syndrome; (2) studies with healthy worker effect bias; (3) studies with problematic statistical modeling; and (4) studies arising from case series derived from litigation. Investigations with adequate study design and exposure assessment revealed consistent neurobehavioral effects and attributable subclinical and clinical signs and symptoms of impairment. Twenty-eight studies show an exposure-response relationship between Mn and neurobehavioral effects, including 11 with continuous exposure metrics and six with three or four levels of contrasted exposure. The effects of sustained low-concentration exposures to Mn are consistent with the manifestations of early manganism, i.e., consistent with parkinsonism. This is compelling evidence that Mn is a neurotoxic chemical and there is good evidence that Mn exposures far below the current US standard of 5.0 mg/m^3 are causing impairment.

1. Introduction

Although the manganese (Mn) literature provides a relatively consistent body of evidence, there are inconsistencies and concerns that bear exploration. One concern is the significance of early neuropsychological effects and subtle impairment. Another is whether these effects are manifestations of parkinsonism. Other areas of contention include aspects of study design, analysis, bias, and inference. This review focuses on the literature reflecting these concerns and then summarizes current findings.

2. Neurological effects

2.1. Neuropsychological testing

Neuropsychological examinations can identify subtle and subclinical effects such as memory loss or increased anxiety [1,2]. Neurobehavioral testing began in the early 1960s based on experimental and clinical psychology and neuropsychology, and was used to identify developing impairment and prevent further deterioration [3]. Tests encompassing diverse neuropsychological and neurophysiological domains have been used to describe effects of pesticides, lead (Pb), solvents, and mercury (Hg) in the workplace and the general environment [4,5]. An attempt was made in 1983 to standardize studies of neurotoxicants at a conference arranged by the World Health Organization (WHO) and National Institute for Occupational Safety and Health [6,7]. They recommended a battery of seven neurobehavioral tests known as the WHO Neurobehavioral Core Test Battery (WHO-NCTB), and although these did not become the gold standard for neuropsychological assessment and have mostly not been adopted by psychological test publishers in the United States or elsewhere, they are among the most frequently used tests in the study of neurotoxic disorders. Many of these tests have been characterized in normal populations

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including age and sex dependence. Interpretation of individual findings may be difficult [8] and their relevance to clinical disease uncertain, but they can identify group differences [2,9–12]. Innovation and efforts at consensus on standardization have continued [2,13]. Health Canada [14] has grouped neurofunctional tests into the following broad categories: (1) effects on motor function and reaction time; (2) effects on cognition, memory, attention, and sensory function; and (3) subjective symptoms and mood. In reviewing 18 studies of Mn effects, Zoni et al [2] identified 64 tests in 14 domains, which include: reaction time, eye-hand coordination, hand dexterity, tremor or steadiness, motor batteries, cognitive functions, memory, mood, neurosensory functions, and neurological endpoints. Standardized neurological examinations such as the Unified Parkinson's Disease Rating Scale [15,16] (UPDRS) are also used, although, in some cases, neurobehavioral tests appear to be reliable substitutes [17]. Use of neuropsychological and behavioral outcomes in large epidemiologic studies and in risk assessments has been examined [9,18–20] with emphasis on the distributional implications of small average decrements in performance even in the absence of a defined clinical syndrome or known mechanistic basis. Small changes in scores on standardized tests have been shown to be important, at the population level, for real-life functions and capabilities. [21]

2.2. Effects observed with Mn

Cognitive, psychological, motor, and sensory effects have been observed in welders with relatively low Mn exposures [22–28]. These findings are consistent with assessments in other Mn-exposed populations such as battery production [8,29], ferromanganese production [30–33], and ore processing [34,35]. Although symptoms and deficits vary, workers with elevated exposures commonly reported headache, weakness, memory loss, sleep disturbance, irritability, anxiety disorders, and gait disturbance. These effects have been associated with Mn deposition in the brain as measured with magnetic resonance imaging (MRI) in otherwise normal industrial populations [25]. Early neuropsychological deficits have been clearly associated with chronic conditions such as headache, muscle weakness, or memory loss [8,22,26,28,30,33,34,36–42]. Aside from quality-of-life issues, these conditions may impair work performance and safety. Some investigators reject these findings [43–45]. Citing methodological problems in cross-sectional studies, Jankovic [43] denies the value of neuropsychological testing for assessing adverse exposure effects and considers some published reports with positive findings to be negative, such as those of Myers et al [46] and Bowler et al. [47] Olanow [45] in the legal arena has dismissed as insignificant "preclinical" effects in Mn-exposed welders. This review will address these contentions.

2.3. Idiopathic Parkinson disease and Mn

Controversy remains about whether Mn-exposed workers have increased risk of developing idiopathic Parkinson disease (PD) [48,49] and whether the associated neurobehavioral and neurological signs and symptoms constitute early manifestations of manganism [50]. Racette et al [51] reported welders have PD onset at an earlier age than others, precipitating considerable interest in Mn exposures. They examined 15 patients with movement disorder and welding experience and concluded that parkinsonism associated with welding is not clinically distinct from PD (although patients with atypical PD features had been excluded from their series) [52]. Although they argued that there were no manifestations of manganism in the welders, others disagreed [53]. It is unclear how much Mn exposure the 15 welders experienced. There were no blood-Mn determinations; only two of the 15 welders were evaluated with positron emission tomography (PET), showing evidence of diminished dopamine uptake as in PD. Finding a younger age at PD onset in welders is difficult to interpret. Perhaps welders report motor deficits sooner (at a younger age) than others as it affects their ability to work (manipulating a device with precise hand-arm control). Older workers, when asked their occupation, may be likely to say they are retired [54]. Some of the PD cases could have had an overlay of early manganism symptoms resulting in earlier detection of PD. An age-adjusted relative risk of PD in welders was not calculable in the study design by Racette et al [51]. Other studies examining a Mn-PD link have been largely negative or did not rule out manganism [55–62], although bias from the healthy worker effect may have been present (see below). In a recent study of dopamine uptake using PET scans, Criswell et al [63] compared three groups ($n = 20$ per group): normal volunteers, asymptomatic welders, and patients with PD. The welders had elevated blood Mn levels (mean: 20.7 μg/L), elevated pallidal index indicating Mn deposition in the brain, and elevated UPDRS scores despite being asymptomatic. Similar to the patients with PD, the welders had significant reductions in dopamine uptake but exhibited a distinct pattern. Compared with patients with PD, they showed a larger dopamine uptake deficit in the caudate region of the brain and a smaller effect in the anterior and posterior putamen, which the authors suggest could provide a physiological basis for observed cognitive and behavioral abnormalities associated with Mn exposure.

3. Issues in study design

3.1. Litigation series

As occurred with asbestos and benzene, litigation regarding occupational Mn exposure has stimulated epidemiological investigation. Bowler et al [47] described a relatively large litigation case series of welders and a comparison group consisting primarily of individuals randomly selected from telephone directories. The source population and case identification procedure were not described. No specific welding fume exposure measurements in air or biomarkers were available except for the duration of welding years (mean = 24.9 years). Participants, 76 welders and 42 controls, were evaluated for symptoms and administered multiple neurobehavioral batteries in a blind fashion. Welders did not perform as well as controls on verbal learning, working memory, cognitive flexibility, visuomotor speed, and motor efficiency. Welders also had poorer emotional status, impaired color vision, and increased prevalence of illnesses and psychiatric symptoms. Symptoms and neurobehavioral deficits were correlated in the welders. Statistically significant negative associations were reported between duration in welding and verbal learning, auditory span, working memory, cognitive flexibility, and motor efficiency. Lees-Haley (who was hired by the defense in welding rod litigation) et al [44] dispute the findings of Bowler (who has worked for welding plaintiffs) et al [47], claiming that the ambiguous case derivation limits etiologic inference. Thus, the Bowler case series could merely represent a selection of prevalent movement disorder or other neurobehavioral outliers from a large welder source population that has a typical, expected distribution of these outcomes. However, if that were the origin of these cases, one would expect that PD would predominate among those presenting with movement disorders. Goldman et al [56] observed in a series of 2072 consecutive parkinsonism cases that 90% were PD. Tanner [60], in a similar clinical series of 519 parkinsonism cases, classified 97% as PD. However, Bowler et al [47] identified no cases of PD for exclusion (believed not to be Mn-related; personal communication). Self-selection by welders on

the nonspecific neuropsychological outcomes studied is even less plausible than on movement disorders. The Bowler case series provides descriptive detail on likely Mn effects in a welder population but does not permit quantitative estimates of excess risk.

Bowler et al [64] evaluated a second litigation case series from an uncharacterized regional population of welders in the southeastern United States [65]. Forty-seven welders reported adverse mental, medical, or neurological effects (15 were excluded due to unavailability, illness, incomplete testing, poor vision, or potential malingering) and were compared with 42 controls (four exclusions; same controls as used in Bowler et al [47]). All participants were administered an extensive array of neuropsychological tests by trained neuropsychologists. A neurological examination by a board-certified movement disorder specialist in neurology included the UPDRS rating scale, Part III, the motor subtest. The welders showed pronounced deficits in motor skills, visuomotor tracking, information processing, working memory, verbal skills, and mood indicators. This study, like the previous case series [47], had potential selection bias preventing estimation of relative risk. However, the neurological evaluation identified only a few possible cases of PD. Thirteen symptomatic workers previously untreated for parkinsonism were evaluated for levodopa responsiveness and none showed the strong levodopa response expected for PD cases. [65]

Rohling and Demakis [66] compared the two case series by Bowler et al [47,64] and reported that the estimated neuropsychological effect sizes and the patterns of effects within each study were different, concluding that the two studies do not support a common pattern of neuropsychological impairment attributable to Mn exposure. Rohling and Demakis [66] required two unsupported assumptions: (1) that the studies had the same valid designs for quantitative etiologic inference; and (2) that the exposure experience (duration, air concentrations, types of welding), was similar. Moreover, the Rohling and Demakis analyses reveal considerable consistency in deficits in the Bowler studies, although the series by Bowler et al [64] exhibited systematically higher levels of deficit. Given that the two series represent uncharacterized self-selection of workers lacking documented Mn-exposure histories, the two groups would not be expected to show the same levels of impairment.

Although modest enhancements in study design and reporting could improve the quality of some litigation-derived analyses, Bowler et al [47,66] provide descriptive support for the association of neurological effects and Mn exposure in two typical welder populations. A third litigation-related series by Bowler et al [27,36] consisted of a cross-sectional assessment of workers on a bridge-welding project where no important selection bias could have been present. [67]

Another litigation series consisted of 20,000 union welders screened for neurologic abnormalities but the source population was not adequately described [68]; 248 cases (1.2%) of PD were found along with 583 cases (2.9%) of manganism. In an apparently random sample of 37 of the manganism cases, measurements of tremor indices were distinctly different from the published norms for healthy controls: tremor intensity was elevated fivefold. Bias from selective recruitment of welders with movement disorders was probably at most modest because the prevalence of PD in the general population >60 years is 1.5–2%; the mean age of the screened welders was 55 years so that the expected prevalence in the screened population would be somewhat lower, as observed (1.2%).[68] Litigation series could be quite informative if information that would enable an upper-bound estimate of selection bias were reported. For example: How were participants solicited? How many could have participated?

3.2. Healthy worker effect

In occupational epidemiology, inappropriate comparison populations can introduce healthy worker effect (HWE) bias [69,70]. Respiratory disease outcomes are especially vulnerable to this bias as they relate to fitness-to-perform work [70]; neurobehavioral deficits is another area where effect on work-fitness could generate an important HWE. Evidence for the HWE in neurological outcomes is apparent in several studies of Mn effects. Park et al [55] examined by interview a large Korean PD case series in relation to occupation. With the diagnosis made at five clinics beginning in 2001, 367 incident cases of PD agreed to participate (participation rate not reported; an unknown number of all other forms of parkinsonism were excluded). In a case-control design, incident cerebrovascular controls were identified in the same clinics. After controlling for age, education, sex, and smoking, occupations in manufacturing showed a negative association with PD [odds ratio (OR) = 0.56, 95% confidence interval (CI) = 0.34–0.92] suggesting selection away from such work by workers at risk for PD, or, substantially elevated cerebrovascular disease in those occupations. The associations of PD with occupations tied to Mn exposure (welders, welding rod manufacturing, Mn mining, and smelters; OR = 0.42, 95% CI = 0.22–0.81) or in transportation occupations (OR = 0.20, 95% CI = 0.06–0.71) were even smaller. Agricultural work and professional occupations exhibited elevated risks of PD as has been observed elsewhere [57,60,71–74]. It is unlikely that a variation in rates of cerebrovascular disease alone could explain these results. Instead, they suggest a strong HWE with respect to PD in many occupations and imply that a similar confounding bias would be operating for other forms of parkinsonism. The study was uninformative on the question of early manganism in Mn-exposed workers as this and other forms of non-PD parkinsonism were excluded.

Fryzek et al [75] linked the Danish National Register of Patients (hospital admission and outpatient records) with a cohort from stainless and mild steel metal manufacturers in order to study welding and parkinsonism. Standardized hospital admission ratios (SHR) were calculated. For all welding department workers the SHR for PD was 1.0 (95% CI = 0.7–1.5) and for actual welders it was 0.9 (95% CI = 0.4–1.5), exhibiting a possible deficit as observed by Park et al. [55] Fored et al [76] conducted a population-based (gainfully employed) assessment of the incidence of parkinsonism and related movement disorders among welders in Sweden by linking hospital discharge diagnoses with census data. Among almost 50,000 welders and flame cutters, there was a slight deficit in PD incidence [relative risk (RR) = 0.89, 95% CI = 0.79–0.99], replicating the observations of Park et al [55] and Fryzek et al [75] and suggesting that the welder workforce in general has favorable neurological status and thus would be subject to the HWE.

Marsh and Gula [59] were commissioned to analyze “idiopathic Parkinson’s disease, parkinsonism or a related neurological disorder,” at three Caterpillar heavy equipment manufacturing plants, using medical insurance claims. They classified workers as ever or never performing welding work (including “electrode” or resistance welding as well as other “fabrication” jobs that may not confer Mn exposures). The outcome of primary interest selected by the investigators was PD [International Classification of Diseases, Ninth Revision (ICD-9): 332.0]. Using two sets of matched controls (10:1), the investigators observed ORs for incident cases of PD of 0.76 (95% CI = 0.26–2.19) and 0.81 (95% CI = 0.29–2.25), respectively. For prevalent cases, they observed ORs of 0.82 and 0.97, respectively. Thus, compared to other workers, the group including welders had a less-than-expected association with PD, further supporting the concern over bias arising from the HWE in

occupational studies of neurological outcomes in groups with special skills.

Ellingsen et al [28] studied workers with at least 1 year of employment as a welder at two large shipbuilding and machine manufacturing enterprises in St. Petersburg, Russia. In addition, 27 from a case series of 37 workers compensated for welding-related manganism (a compensable occupational disease in Russia) from a St. Petersburg clinic were examined. Welders in groups with increasing Mn exposure exhibited substantially lower performance on Digit Symbol and Finger Tapping than referents, and welders as a group had nonsignificantly elevated symptoms, but performed better on hand steadiness. As the authors observed, hand steadiness, an attribute of considerable importance to welders, may exhibit healthy worker bias (or perhaps worker skill bias), which would tend to confound comparisons with nonwelders and cause an underestimation of Mn effects.

For a mortality study of neurodegenerative disease deaths in the United States during 1985–1999, Stampfer [61] used the Cause of Death database of the US National Center for Health Statistics and observed adjusted mortality odds ratios for PD of 0.85 (95% CI = 0.77–0.94) and 0.83 (95% CI = 0.78–0.88) in welders, using two definitions of welding occupations [61]. This supports the presence of a significant HWE among welders. An even stronger effect was observed in welders for motor neuron disease (amyotrophic lateral sclerosis, OR = 0.71, 95% CI = 0.56–0.89), a chronic condition that clearly would affect welders' ability to work.

Neurobehavioral studies of skilled workers using the general population as a reference are likely to be subject to healthy worker biases because skilled welders may require above average visuomotor skills. If the HWE were as large as 10% for neurobehavioral outcomes in welders (i.e., for an adverse outcome, RR = 0.9 in the absence of Mn exposure), and if the proportion of welders exposed to levels of Mn associated with deficits that have been observed (i.e., above 0.3 mg/m^3 Mn) were as small as 2%, then very high RRs (RR > 5, from 0.02 × RR × 0.90 = 0.10) in the group exposed above 0.3 mg/m^3 would be required prior to when the RR of welders in the aggregate would exceed 1.0, and much higher relative risks in the exposed (>30) would be needed to achieve an elevated RR of 1.5 in the aggregate. The likely presence of HWE in large surveillance-type studies and in others using general reference populations could obscure important associations in occupational studies of environmental etiologic agents.

3.3. Statistical power

Several published studies have had limited statistical power to address a Mn association with non-PD parkinsonism. Among welders in the Danish study of Fryzek et al [75] (comprising 22% of the study population), there were 11 cases of PD and only four cases of other parkinsonism or related neurodegenerative disorders (including two cases of dystonia—altered muscle tone and mobility). Without actual Mn exposure data, this study would have very limited statistical power for detecting an excess of non-PD parkinsonism in welders. In the population-based hospital discharge study of Swedish welders by Fored et al [76], there were 383 incident cases of parkinsonism of which 353 cases were of PD (92%) and 30 cases (7.8%) were of other parkinsonism: extrapyramidal and movement disorders (n = 26) and dystonia (n = 4). An analysis of RR for non-PD parkinsonism with welding was not reported but could have had limited power because of: (1) the HWE observed there for all movement disorders (RR = 0.91), and (2) the absence of type-of-welding information at the individual level, which would help identify high-exposure groups. Furthermore, cases likely to result in hospitalization would have relatively advanced parkinsonism, whereas Mn-related disease may be inherently self-limiting because significant impairment would lead to termination of employment as welders. A statistically nonsignificant elevation was observed for the four welders in whom dystonia was diagnosed (RR = 1.42), a manifestation of manganism.

In the clinical series of Goldman et al [56], 90.5% of 2249 movement disorder cases had a diagnosis of PD, including the three cases whose primary lifetime employment was welding. The expected number of non-PD parkinsonism among those welders would have been 0.29 [=(1-0.905) × 3]; therefore the study had minimal power to detect an excess of non-PD parkinsonism in welders. In the clinical series of 519 movement disorder cases by Tanner [60], 97% were PD and 41 of 519 were ever welders (a much higher proportion − by a factor of 60 − than in Goldman et al [56], where longest-duration occupation was used). In this case-control design, there was no association of parkinsonism with ever-welding (OR = 1.01), implying that about 97% of both welders and nonwelders with parkinsonism had a diagnosis of PD and that the number of non-PD parkinsonism cases expected among the 41 welders was about 1.2 [=(1–0.97) × 41], implying that this study also had limited statistical power for addressing the manganism hypothesis. However, if a 10% HWE were present (less likely for "ever-welders"), then there would be a relative risk of 1.01/0.9 = 1.12 for parkinsonism in welders, and if there was no excess of PD in welders, then the 12% excess risk would correspond to a considerably higher relative risk for non-PD parkinsonism in welders. Thus, several studies of neurological impairment in welders that have been reported and cited as "negative" had limited statistical power, which should be explicitly acknowledged.

3.4. Exposure and model specification

Some studies used analytical strategies that were not favorable toward identifying a true association of Mn with neurological deficits. Kim et al [23] studied neurobehavioral performance in 121 workers involved in welding, steel alloy production, and welding rod manufacturing in Korea. Three groups defined by current total airborne Mn concentrations were compared: "unexposed" (<0.01 mg/m^3), low (0.01–0.10 mg/m^3), and high (>0.10 mg/m^3). All three groups had elevated blood-Mn (MnB) with the levels increasing with Mn exposure but not statistically significantly. Regression models were fit for diverse neurobehavioral outcomes using all predictors and risk factors as independent variables including Mn (air), Mn (blood), Mn (urine), and MRI scores for Mn deposition in the brain. Finger Tapping deficits were significantly associated with airborne Mn but the trends for Finger Tapping, Digit Span, Digit Symbol, Pursuit Aiming, and Simple Reaction Time across levels of exposure were not significant. These models may not have been optimal for estimating the Mn exposure response because including other causal-path variables in the model [Mn (blood), MRI scores] could have reduced exposure effect-estimates. Abnormal neurological signs (tremor, muscle rigidity, bradykinesia, or postural instability) were observed in 9.1% (two cases) of the "unexposed" comparison group, which also had elevated MnB levels (11.9 μg/L), suggesting that some individuals in the unexposed group had significant prior exposure to Mn.

Myers et al [46] conducted a cross-sectional neurobehavioral study comparing South African ferroalloy smelter workers with workers in electrical fittings manufacturing not exposed to Mn. The plant process areas were classified in three levels of current inhalable Mn exposure: high > 2.0 mg/m^3 (n = 201), medium 0.1–2.0 mg/m^3 (n = 201), and low < 0.1 mg/m^3 (n = 107). The mean Mn in blood was 12.5 μg/L in the ferroalloy workers versus 6.4 μg/L in the electrical workers, and the mean Mn (urine) was 10.5 μg/L versus 0.96 μg/L, respectively. Statistically significant declining performance scores were observed with cumulative exposure classified

categorically in regression models for Digit Symbol, Digit Span, Santa Ana dexterity, reaction time, and Finger Tapping tests. Although the parameter estimate for a linear effect on Digit Span was highly significant ($p = 0.001$), most of the outcomes did not exhibit statistically significant linear trends, perhaps because much of the performance decline had already occurred within the lowest cumulative exposure category, resulting in a nonlinear relationship over the observed range of cumulative exposure. For example, with the Santa Ana dexterity test most of the deficit with increasing cumulative exposure had occurred by 1.3 mg/m^3–years, in the lowest exposure category. A metric like the square-root of cumulative exposure could have been more appropriate. Large differences in comparisons using internal versus external controls suggest either that there was residual confounding in spite of age, education, and home language being controlled, or that the processes thought to have low exposure and used to define the internal referent group may have had important Mn exposures, as suggested in the Santa Ana dexterity, Benton, and Digit-symbol regression results. A composite score of clinical abnormalities was significantly elevated comparing the medium- and high-exposure workers with the low exposure group (one or more abnormalities: OR = 3.7, 95% CI = 1.1,13), and a significant trend of the clinical abnormalities score across quartiles of MnB was also observed. However, these investigators concluded that there was "little convincing evidence for a continuum of effects…" related to Mn [46], and reviews of this study have inexplicably interpreted it as negative. [43,49] Further examination of the neurobehavioral exposure responses in this population confirmed the nonlinearity of the responses but the investigators focused more on fortuitous and inappropriate linear estimates than on characterizing and interpreting the nonlinear response as strong evidence for a substantial Mn effect. [77]

In the litigation series of 20,000 screened welders [68] where there was minimal likelihood of strong selection bias and statistically significant increased tremor intensity, regression models using 37 welders were fit on age, as a surrogate for cumulative Mn exposure. The trends were not significant. A more powerful analysis would have incorporated into the model as fixed intercepts the expected age-specific values for tremor derived from population norms.

Some studies investigating whether Mn exposures that cause PD have indirectly or inadvertently addressed the association with non-PD parkinsonism. Park et al [58] investigated PD in 24,963 blue-collar workers and 13,597 white-collar workers employed for at least 12 months at two Korean shipyards, linking records to the national medical insurance database. Study participants were classified as: (1) welders, (2) cutting, grinding, fitting, and finishing, and (3) other (painting, plating, drilling, maintenance). The geometric mean for air samples ($n = 165$) in welders was 0.88 mg/m^3 Mn and in cutters, fitters, etc. it was 0.10 mg/m^3 ($n = 41$). A neurologist identified only nine new PD cases (ICD-10: G20) among the 115 workers with 475 insurance claims coded as ICD10: G20–G26 (extrapyramidal and movement disorders). The crude (not age-adjusted) rates of PD were very close comparing the blue- and white-collar populations but using Cox regression adjusting for age, the investigators estimated the relative risk for PD among the blue-collar workers to be 4.19 (95% CI = 0.96–18.3), statistically significant as a one-tailed test. Based on the exposure classification, however, the high exposure group (welders, two cases; RR = 1.96) and the low exposure group (painters, maintenance, etc., four cases; RR = 3.65) were not significantly different (although the parameterization of the model is not entirely clear). With small numbers of exposed cases this study is not informative on whether welding with Mn exposures is a risk factor for PD. However, the large number of non-PD parkinsonism cases identified ($n = 106$; 92% of 115 parkinsonism cases) is in sharp contrast to studies based on hospitalization or tertiary clinic series where PD dominates the parkinsonism picture [56,60] and suggests excess movement disorders in these shipyard workers. Analysis of these 106 non-PD cases in relation to past exposure would have been quite revealing.

In the Marsh and Gula [59] study of welders in heavy equipment manufacturing, no PD excess was observed. Due to concern that misdiagnosis could occur, the investigators defined a second expanded group of cases to include "other degenerative diseases of the basal ganglia" and "essential or other specified forms of tremor" (ICD-9: 333.0 and 333.1, respectively). With the expanded case definition, slightly larger ORs were observed. The investigators did not analyze separately the non-PD parkinsonism cases used to expand their definition, which are some of the specific forms of parkinsonism in which manganism might be coded. However, one can ascertain the numbers of these case incidents among welders ($n = 26$) and nonwelders ($n = 12$) by comparing Tables 2 and 4 in Marsh and Gula [59] and calculating an OR (disregarding matching) to obtain OR = 1.69 (95% CI = 0.81–3.6). A more accurate, adjusted estimate would result from a matched analysis (not possible with the data reported). This result suggests that welding-(Mn)-related parkinsonism is present in this population and might be evident in analyses using estimates of cumulative or recent (5 year) Mn exposure. Implemented as a test for welding and PD, this study has been interpreted as negative.

From a mortality analysis of US welders, Stampfer [61] concluded that there were no elevations among welders for neurodegenerative conditions. However, in this study, which did not account for a HWE, presenile dementia was marginally significantly elevated (above a baseline of 0.9) and deaths among welders due to other diseases of the basal ganglia were elevated by 16–25% but based on small numbers. A key issue in assessing welding as a risk factor for mortality, of course, is identifying the general health consequences of manganism at a moderate level of progression, possibly arrested by termination of exposure.

4. Summary of neurobehavioral findings

The literature prior to 2000 documenting health effects in workers exposed to Mn in mining, ferroalloy production, welding, and manufacturing using standardized neuropsychological or neurobehavioral endpoints has been reviewed [78]. More recent reviews include Antonini et al [48], Santamaria et al [49], McMillan [79], Zoni et al [2], and Greiffenstein and Lees-Haley [80] (meta-analysis). The epidemiologic studies of Mn-exposed workers that address the association of Mn exposure with various health effects related to the nervous system, are displayed in Table 1 [8,22–35,37–42,46,82–84]. Some studies focus on neurobehavioral test endpoints, others on symptoms, but many address both. The observed Mn exposure levels are often below 0.2 mg/m^3.

Twenty-eight published reports have contrasted likely or definitely Mn-exposed workers with generally comparable groups of unexposed industrial workers (Table 2) [8,22–35,37–42,46,58,59,67,68,81–88]. These reports use diverse outcomes, exposure assessments, and study designs, making them difficult to rank on weight of evidence; they are displayed here beginning with those having a continuous Mn exposure metric followed by those with categorical exposure classifications in order of diminishing number of exposure strata. Statistically significant performance deficits or symptom excesses among the Mn-exposed workers have been observed in almost all studies. In some cases the comparison groups may have had some significant past or current Mn exposure, which would diminish the estimated Mn-effect [22,24,34,37,39,41,42,82]. Eleven of these studies observed statistically significant trends with continuous measures of Mn exposure or MnB using correlations, multiple regression, or logistic regression procedures. Seventeen studies relied on categorical comparisons, 11

Table 1
Manganese study populations with neurobehavioral effects: Mean airborne exposure concentrations (in chronological order)

Study	Work	*n*	Total Mn, mg/m^3		
			am	gm (med)	Range/SD
Roels et al 1987 [8]	MnO/salts pdn	141	1.33	0.94	0.07–8.61
Wang et al 1989 [41]	Ferroalloy	68 24 8*	–	–	0.10 0.50–1.50 28.8*
Iregren 1990 [81]	Foundry	30	0.25†	(0.14)	0.02–1.40
Sjogren et al 1990 [82]	Welding	–	–	–	–
Roels et al 1992 [29]	MnO/battery	92	1.78	0.95	0.05–10.8
Chia et al 1993 [34]	Ore crushing	–	0.70	–	–
Mergler et al 1994 [30] Bouchard et al 2007 [40]	Ferro/silico Mn	115	1.19	0.23	1.05‡
Kim et al 1994 [39]	Ferroalloy	90	–	0.60	2.3§
Chia et al 1995 [35]	Ore crushing		1.59	–	–
Lucchini et al 1995 [31]	Ferroalloy - Med - High	 19 20	–	 0.12 0.27	 0.07–0.62 0.12–0.65
Sjogren et al 1996 [22]	Welding	68	–	–	–
Lucchini et al 1997 [32]	Ferroalloy	35	–	(0.44)	0.26–0.75
Lucchini et al 1999 [33]	Ferroalloy	61	0.18	0.05	0.01–1.49
Gibbs et al 1999 [83]	Electrolytic Mn	75	0.18†	0.11	–
Jin et al 1999 [38]	Welding		2.10†	–	0.005-9.3
Kim et al 1999 [23]	Welding	23 76	–	–	0.01–0.10 >0.10
Moon et al 1999 [24]	Welding	60	0.17	0.15	1.7§
Deschamps et al 2001 [37]	Pigments	139	2.05	–	0.50–10.2
Sinczuk-Walczal et al 2001 [84]	Battery welding	75	0.39	0.15	0.54
Myers et al 2003 [46]	Ferroalloy	509	0.82†	–	1.04
Beuter et al 2004 [85]	Ferroalloy	10	–	–	–
Kim et al 2005 [25]	Welding (auto, steel, ship) smelter welding rod mfr	111	–	0.50	3.7§
Yuan et al 2006 [26]	Welding (machine manufacturing)	68	0.14	–	0.04–0.20
Wang et al 2006 [42]	Welding	82	0.25	–	0.10–0.50
Bowler et al 2007 [27]	Welding (bridge)	48	0.19	0.14	2.3§
Ellingsen et al 2008 [28]	Welding	96	–	0.12	0.007–2.3

am, arithmetic mean; gm, geometric mean; med, median; SD, standard deviation.
* Exposures of 30 min. per day during electrode maintenance.
† Inhalable dust.
‡ 75th percentile.
§ Geometric SD.

with a binary contrast (exposed vs. unexposed groups) and six with tests of trend across Mn exposures classified into two or three levels based on duration of welding, estimated cumulative exposure, or current exposure level (Table 2).

Case-control and cross-sectional studies of workers exposed to Mn in several occupations have identified psychomotor and motor function effects as well as cognitive effects [8,22–28,30–35,38,39,41,42,46,81,82,85]. These results are relatively consistent across all studies. The frequently observed findings on neurobehavioral test associations (e.g., finger tapping, eye-hand coordination, Digit Symbol, Digit Span, Santa Ana Dexterity) demonstrate that these deficits can be readily measured using standardized tests in these Mn-exposed populations. Although symptoms and deficits vary, common symptoms include headache, weakness, slowed movement, memory loss, sleep disturbance, irritability and anxiety disorders, loss of libido, and gait disturbance.

Table 2
Summary of investigations observing statistically significant associations between Mn exposure status and motor, cognitive, or symptom outcomes (in order of type of exposure response and year of publication)

Study/work	n	P	I	M	C	D	R	Hand-eye coordination, motor/postural	Cognitive, mood, autonomic/other	Symptom	Exposure response
Continuous exposure metric											
Roels et al, 1987 [8] MnO/ Mn salts pdn	141	Ch	1	1	0	0	1	Eye-hand coordination Hand steadiness Simple Reaction Time Tremor (fingers) Rigidity (neck, trunk)		Fatigue Irritability	CONT; CAT[2]
Roels et al, 1992 [29] MnO/battery	92	Mf	1	1	0	0	1	Eye-hand coordination Hand steadiness Visual Reaction Time Tremors			CONT; CAT[4]
Lucchini et al, 1995 [31] ferroalloy	19 20	Fe	1	1	1	1	1	Finger Tapping	Addition Symbol Digit Digit Span		CONT; CAT[3]
Lucchini et al, 1997 [32] ferroalloy	35	Fe	1	1	1	0	1	Aiming Pursuit II			CONT; CAT[2] (increased olfactory acuity with inc. Mn(U))
Sinczuk-Walczal et al, 2001 [84] battery/welding	75	Wl	1	0	0	0	1			Irritability Paresthesia Sleepiness	CONT; CAT[2]
Myers et al, 2003 [46] ferroalloy	509	Fe	1	1	1	1	1	Santa Ana Dexterity	Digit Symbol Digit Span Benton Visual Retention		CONT; CAT[3]
Kim et al, 2005 [25] welding (mfr), smelter, welding rod mfr	111	Wl Mf	1	1	1	0	1	Factor: psychomotor	Factor: affect, factor: attention-memory		CONT (structural equation model)
Wang et al, 2006 [42] welding		Wl	1	1	1	1	1	Simple Reaction Time	Digit Span total, forward, backward	Anger-hostility Fatigue-inertia Headache Dizziness Concentration Weakness	CONT; CAT[2] (Pb confounded)
Park et al, 2006 [67] Park et al, 2009 [86] welding	48 44	Wl	–	–	–	–	–		Working Memory Index Verbal IQ Stroop Color-word		CONT (duplicates Bowler, 2007)
Bowler et al, 2007 [27] welding	43	Wl	1	1	1	0	1	Tremors	Executive function Verbal learning Working memory Concentration and sequencing Immediate memory	Fatigue Sleep disturbance Depression Anxiety Numbness	CONT; CAT[2]
Ellingsen et al, 2008 [28] welding (shipyard, heavy machinery)		Wl	1	1	1	1	1	Finger Tapping	Digit Symbol	NCTB Q16	CONT; CAT[2]
Wastensson et al, 2011 [87]	17	Wl	1	1	0	0	1	Pegboard			CONT; CAT[2]
Categorical exposure metric in four levels											
Wang et al, 1989 [41] ferroalloy	68 24 8	Fe	1	1	1	0	0	Bradykinesia Rigidity Gait abnormality Weakness	Dislike of talking	Fatigue Loss of libido	CAT[4]
Sjogren et al, 1990 [82] welding	–	Wl	1	0	1	0	0			NCTB Q16: nervous system symptoms	CAT[4]

(*continued on next page*)

Table 2 (*continued*)

Study/work	n	P	I	M	C	D	R	Hand-eye coordination, motor/postural	Cognitive, mood, autonomic/other	Symptom	Exposure response
Mergler et al, 1994 [30] Bouchard et al, 2007 [40] ferro/silico Mn	38	Fe	1	1	1	0	0	Luria Total Score Finger Tapping Graphomotor Nine Hole Steadiness	Profuse sweating Memory loss	Agitation Anxiety Fatigue Nightmare POMS [11]	CAT[2] (matched) CAT[4] (matched)
Jin et al, 1999 [38] welding	na	Wl	1	1	1	0	0	Pursuit Aiming Finger Tapping Santa Ana Dexterity	Inability to concentrate	Muscle symptoms Neurological symptoms	CAT[4]
Lucchini et al, 1999 [33] ferroalloy	61	Fe	1	1	1	1	0	Finger Tapping disequilibria tremors	Addition Digit Symbol Digit Span	Irritability	CAT[4]
Categorical exposure metric in three levels											
Kim et al, 1999 [23] welding	23 76	Wl	1	1	1	1	0	Pursuit Aiming Finger Tapping, Santa Ana Dexterity	Digit Symbol Digit Span		CAT[3]
Park et al, 2006 [58] welding		Wl	–	–	–	–	–		Parkinson disease, parkinsonism		CAT[3] (vicarious finding*)
Categorical exposure metric in two levels											
Iregren, 1990 [81] foundry	30	Fe	1	1	1	1	0	Finger Tapping Simple Reaction Time	Digit Span		CAT[2]
Chia et al, 1993 [34] ore crushing	–	Or	1	1	1	1	0	Pursuit Aiming	Benton Visual Retention Digit Symbol	20 of 37 adverse symptoms insomnia	CAT[2] (motor speed, visual scanning, visuomotor performances)
Kim et al, 1994 [39] ferroalloy	145 49 90	Fe	1	1	0	0	0	Difficulty writing		Reduced libido	CAT[2,2]
Chia et al, 1995 [35] ore crushing	–	Or	1	1	0	0	0	Postural sway (eyes closed)			CAT[2] (two postural stability parameters)
Sjogren et al, 1996 [22] welding	68	Wl	1	1	1	0	0	Finger Tapping Pegboard Luria Nebraska (items 2, 22)	NCTB Q16: inability to concentrate memory loss	NCTB Q16: depression	CAT[2]
Moon et al, 1999 [24] welding	60	Wl	1	1	1	0	0	Tremors Gait disturbance	Amnesia General weakness Speech disturbance		CAT[2]
Gibbs et al, 1999 [83] electrolytic Mn	75	Ch	0	0	0	0	0	Reaction time Gait disturbance	Memory loss	Sleep disturbance	CAT[2]; CONT (no effects on individual measures but 5/7 show nonsignificant deficits)
Deschamps et al, 2001 [37] pigments	30	Ch	1	0	0	0	0	Asthenia		Headache Sleep disturbance	CAT[2]
Beuter et al, 2004 [85] ferroalloy	10	Fe	1	1	0	0	0	Postural tremor			CAT[2] (tremor parameters)
Yuan et al, 2006 [26] welding (machine mfr)	68	Wl Mf	1	1	1	1	0	Pursuit Aiming reaction time (improved)	Digit Span Digit Symbol	Depression-dejection Tension-anxiety Vigor-activity Fatigue-inertia	CAT[2]
Marsh et al, 2006 [59] heavy equip mfr		Wl	–	–	–	–	–		Parkinson's disease, parkinsonism		CAT[2] (vicarious finding*)

Table 2 (*continued*)

Study/work	n	P	I	M	C	D	R	Hand-eye coordination, motor/postural	Cognitive, mood, autonomic/other	Symptom	Exposure response
Chang et al, 2009 [88] ship building	43	Wl	1	1	1	1	0	Finger Tapping Pegboard tremors Hand coordination	Digit Symbol Digit Span Stroop Complex figure		CAT[2] ; CONT (on pallidal index)
Sanchez-Ramos et al, 2011 [68] welding: shipyard, refinery	37	Wl	1	1	0	0	0	Tremors			CAT[2]
TOTALS			28	25	19	10	11				

C, cognitive outcomes (1 = yes, 0 = no); Ch, chemical; D, Digit Symbol/Digit Span deficits (1 = yes, 0 = no); Exposure response, a reasonably well-designed comparison, using either continuous (CONT) or categorical [CAT (levels)] models of exposure response; Fe, ferroalloy; I, Include as positive study (1 = yes, 0 = no); M, motor outcomes (1 = yes, 0 = no); Mf, manufacturing; n, size of study group; NCTB, Neurobehavioral Core Test Battery, developed by WHO, with symptom questionnaire (Q16); Or, ore processing; P, Process; POMS, Profile of Mood States; R, continuous exposure metric showing exposure response (X-R) (1 = yes, 0 = no); Wl, welding.

* Proposed interpretation of published data regarding parkinsonism other than Parkinson's disease.

An exposure-response relationship was observed for subclinical neurobehavioral effects in several welder studies [23,25–28,38,42,82] and also in nonwelder Mn-exposed workers [8,29,31–33,46,81]. The association of these effects with Mn deposition as measured with MRI and the pallidal index in otherwise normal industrial populations [25] adds further support that these are associated with Mn exposure.

Motor effects were identified using neurobehavioral tests in 25 reports, including tests of simple reaction time, eye-hand coordination including Santa Ana dexterity, Finger Tapping, pursuit and the Luria motor tests, and measures of tremor and sway (Table 2). Cognitive effects were reported in 19 studies, including 10 using the standardized Digit Symbol and Digit Span tests. Of the 28 studies reporting an association between occupational exposure to Mn and neurobehavioral deficits or symptoms/signs of parkinsonism, 14 involved welders and nine involved high-temperature metallurgical processes producing a plausibly similar respirable Mn-containing fume.

One published study with individual Mn exposure data and a comparable comparison group of unexposed workers failed to observe statistically significant deficits in neurobehavioral performance [83]. A slowing in median reaction time was significantly associated with age but nonsignificantly associated with cumulative Mn exposures over the past month, year, or lifetime. The Mn exposures in that study were quite low and mostly nonrespirable (mean total = 0.18 mg Mn/m^3; mean respirable = 0.066 mg Mn/m^3), and possibly negatively confounded by shift work (the comparison population had more shift work, observed by these investigators to be associated with neurobehavioral deficits).

4.1. Study limitations

There are limitations in many of the etiologic studies on welders and other occupations exposed to Mn. Most are cross-sectional in design and thus are vulnerable to survivor bias (e.g., workers with developing symptoms and deficits more likely to leave employment). Some studies with external reference populations exhibited HWE bias. Methodological details are sometimes lacking, particularly on the selection and participation of study populations; past exposures and work histories were not usually known and in many cases there is limited information on current exposures. In studies where exposure response was estimated, study limitations such as HWE, survivor bias, or exposure misclassification would be unlikely to cause false associations and would cause underestimation of true associations and exposure response.

4.2. Confounding exposures

Confounding exposures may exist during welding or furnace operations, such as carbon monoxide (CO), aluminum, Pb, and heat stress, all of which could affect neurobehavioral performance in cross-sectional research [12]. CO is a neurotoxicant at very high levels, as in acute CO poisoning cases. In a series of 65 cases of severe CO poisoning, frequently resulting in loss of consciousness or coma, one or more signs or symptoms of parkinsonism were present in 80% of cases, typically developing days or weeks after recovery from coma [89]. In a series of eight patients evaluated at a Baltimore hyperbaric oxygen treatment center for chronic CO poisoning, usually caused by defective appliances, nervous system deficits were very evident but at least partially reversible [90]. Sustained exposures at levels exceeding 200 ppm were suspected but not documented. Symptoms associated with CO exposure concentrations of 100–200 ppm include headache, nausea, and mental impairment [91]. However, CO in most welding and other Mn environments is not generally elevated above levels commonly present in industry (e.g., 25 ppm). Park et al [67] reported that peak values for continuously monitored CO levels in bridge welders working in confined spaces were below 20 ppm in almost all intervals. In a study of Taiwanese smelter workers where substantial neurological impairment was observed, the average CO levels at the offending furnace were 25–60 ppm, including levels at the top of the furnace where exposures were brief [41]. Other metals with known or potential neurotoxic effects such as Pb, copper, cadmium, and aluminum are usually absent in mild or stainless steel welding activities with Mn exposures. One of the 25 studies with positive findings reported possible confounding by lead but blood levels were low (geometric mean = 11.7 μg/dL Pb) [42]. Thus, other metal and especially CO exposures are unlikely to be conferring important confounding bias in the Mn studies discussed here.

5. Contrarian reviews

Greiffenstein and Lees-Haley [80] conducted a meta-analysis of 19 studies examining Mn and neuropsychological effects in the published literature, based on the following assumptions or meta-analytic procedures: (1) setting to null rather than excluding any effect not statistically significant that was lacking sufficient statistical detail to calculate an effect size (four studies; the goal of meta-analyses is to statistically combine effects with known uncertainty); (2) discounting associations with an effect size smaller than that of the potential confounder, education (years), in comparing

Table 3
Comparison of adverse neurobehavioral effect magnitudes for neurotoxic metals: fractional score change*

Study	Finger tapping	Symbol digit	Digit symbol	Digit span	Peg board	Trail-B	Hand steadiness	Santa ana	Wisconsin total error
Mercury (per mg/m^3-yr of cumulative exposure)									
Ngim et al, 1992 [100]	0.291	0.582	–	0.885	0.185	1.277	–	–	–
Liang et al, 1993 [101]	0.146	0.431	–	–	–	–	–	–	–
Piikivi et al, 1989 [99]	0.096	0.188	–	0.127	–	–	–	–	–
Lead (per measures based on bone/blood lead)									
Stewart et al, 1999 [97] †	0.029	0.024	–	0.052	0.017	–	–	–	–
Chia et al, 1997 [102] ‡	–	–	0.244	–	0.159	0.496	–	0.089	–
Barth et al, 2002 [103] ‡	–	–	0.025	–	–	–	–		0.307
Lindgren et al, 1996 [104] §	0.018		0.022	0.036	0.016	0.065	–	–	–
Manganese (per mg/m^3-y of cumulative exposure)									
Lucchini et al, 1995 [31]	0.095	0.374	–	0.227	–	–	–	–	–
Ellingsen et al, 2008 [28]	0.016	–	0.026	0.036	0.004	–	0.125	–	–
Wastensson et al, 2012 [87]	0.0005	–	–	–	0.023	–	–	–	–
Mergler et al, 1994 and Baldwin et al, 2008 [30,105]	0.011	0.004	–	0.010	–	0.036	0.089	–	–
Lucchini et al, 1999 [33]-high	0.017	0.039	–	0.028	–	–	–	–	–
Lucchini et al, 1999 [33]-mid	0.058	0.144	–	0.183	–	–	–	–	–
Kim et al, 1999 [23]-high	0.072	–	0.225	0.151	–	–	–	0.042	–
Kim et al, 1999 [23]-low	0.438	–	1.206	0.369	–	–	–	–	–
Iregren, 1990 [81]	0.029	–	–	0.035	–	–	–	–	–
Yuan et al, 2006 [26]	–	–	0.079	0.053	–	–	–	–	–
Chang et al, 2009 [88]	0.034	–	0.040	0.084	0.040	–	–	–	–

* Calculated as: (1) for discrete analyses, difference in score between exposed and unexposed group divided by control group score and by average cumulative exposure, or (2) for regression-based results, estimated effect at 1 mg/m^3-year divided by intercept or nominal baseline normal score.
† Using normal baseline levels and based on average observed community tibial bone lead levels.
‡ Based on change per 250 μg/dL–year of cumulative lead blood level.
§ Based on change per 250 μg/dL–year of cumulative lead blood level comparing two groups: 268 versus 1227 μg/dL–year Pb (mean lead = 26.1 vs. 52.8 μg/dL, respectively).

exposed versus unexposed workers (a severe restriction); (3) using as few as two studies in the meta-analyses for specific outcomes, usually less than five (14 outcomes out of 26), and never more than 10; (4) assuming homogeneity of exposure attributes and of time courses of exposures across studies; (5) excluding analyses relying on internal comparisons, e.g., with continuous exposure classification; and (6) disregarding issues of reversibility or adaptive changes. Using this approach a meta-analytic summary of the diverse studies analyzed could be uninformative. Even with these restrictions, 15 of 26 tests meta-analyzed showed statistically significant summary effects sizes with Digit Span having the strongest association. Nonetheless the authors conclude that "the data did not support a theory of preclinical ('early') neuromotor or cognitive dysfunction."

Santamaria et al [49] reviewed the available literature on case reports and epidemiologic investigations of welders. They concluded that although manganism has been observed in highly exposed workers, the "weight of evidence to date is not sufficient to conclude that welders are at an increased risk of neurotoxicity from exposure to Mn during the welding process." Their review did not acknowledge limitations in the reportedly negative studies of Myers et al [46], Fryzek et al [75], and Fored et al [76], or point out the evidence of positive effects in those studies; it did not examine the central issue of Mn associations with non-PD parkinsonism. Santamaria et al [49] misidentified some of the populations being studied by Bowler et al [47]: these populations had no connection with the bridge welders [27,36,67]. Although authors of the various studies reporting positive findings discussed limitations in these studies, the reviewers made no attempt to assess the likely impact on inferences drawn. Santamaria et al [49] did not focus on the subset of studies with adequate comparison populations and reasonable exposure assessment. The medical significance or importance of subclinical findings was not addressed. These critiques do not rise to the level of serious challenge to the association of parkinsonism with Mn exposures currently present in specific industries.

6. Significance of Mn-attributable deficits

The history of Pb exposure is illuminating. Initial concerns focused on severe Pb poisoning resulting from high Pb exposure levels, whereas current concerns are for chronic low-level effects and multiple endpoints [92]. Pb is now widely recognized as both an environmental and occupational hazard requiring detailed

regulation. With advancing research, recommended allowable exposure levels continue to decline. [93,94] Progress in understanding the long-term Pb hazard has been driven by neurobehavioral outcomes, especially cognitive, and has been aided by development of sensitive measures of past exposure. For example X-ray fluorescence (XRF) from bone (tibia) provides a superior measure of cumulative Pb exposure over blood levels reflecting more recent exposures. [95]

The approximate potency of Mn relative to the neurotoxic metals, Pb and Hg, can be inferred from published studies. In an extensive study of 543 former workers from a plant manufacturing tetraethyl lead, average air concentrations were 62 μg/m^3 Pb [96]. The mean tibial lead current in 1990 was 14.4 μg/g and the tibial level estimated for the date last exposed ("peak" level) was 23.7 μg/g [97]. Statistically significant decrements in performance on a variety of neurobehavioral tests were associated with tibial lead (current and peak), such as for vocabulary, memory, finger-tapping, Purdue pegboard, and the Stroop test.[93] In a population-based sample from Baltimore, MD, USA, where the current tibial lead level averaged 18.8 μg/g, persistent deficits in eye-hand coordination, executive functioning, and verbal memory and learning were associated with tibial lead levels [98]. A Finnish population of chloralkali workers with average mercury exposures of 25 μg/m^3 was compared with wood-processing workers [99]. Increased symptoms of sleep disorders, fatigue, and confusion were reported by the chloralkali workers and there was a nonsignificant possible effect of shift work. The chloralkali workers performed significantly better on a test of eye-hand coordination, suggesting that the comparison group may not have been appropriate (e.g., possible musculoskeletal injury). A group of 98 dentists in Singapore, estimated to have average Hg exposures of 16.7 μg/m^3, was compared to university staff with no known Hg exposure. Statistically significant performance deficits were associated with cumulative exposure for 15 of 24 tests including finger tapping, symbol-digit, digit span, visual recall, and logical memory [100]. When compared to workers from an embroidery plant, 88 fluorescent lamp manufacturing workers in China with an average mercury exposure of 33 μg/m^3 had significantly worse performance on finger tapping, mental arithmetic, two-digit searches, switching attention, and visual reaction time. [101] Thus, the neurobehavioral effects observed in working populations at air concentrations of perhaps 60 μg/m^3 Pb or 17–33 μg/m^3 Hg are roughly comparable to effects reported in Mn populations exposed in the range of 50–500 μg/m^3 Mn (Table 1).

A direct comparison of findings from studies of different neurotoxic metals is difficult because: (1) the sets of neurobehavioral tests used vary widely, (2) details on test scoring are not always provided, and (3) exposure history is often poorly described. In the case of Pb, outcomes are commonly presented as z-scores, not actual test means, and biomarkers of exposure based on bone or blood are often used as predictors rather than environmental levels; however, some published studies provide an estimate of average cumulative blood Pb concentration. Diverse test results can be crudely compared by calculating a fractional change in score per mg/m^3-year of exposure (corresponding to 5 year at 0.2 mg/m^3) or, in the case of Pb, per 250 μg/dL-yr (corresponding to 5 year at 50 μg/dL Pb in blood). Fractional change, here, is defined as the difference in mean score comparing an exposed and unexposed group, divided by the unexposed group mean and by the average cumulative exposure for the exposed group. The distributions of fractional scores across neurobehavioral outcomes do not markedly differ among Hg, Pb, and Mn; fractional scores for the three metals are within a factor of 10 (Table 3) [23,26,28,30,31,33,81,87,88,97,99–105]. For all three metals, another source of variability in this table is the source or form of the exposure. In the case of Mn, both welding and electric furnaces are contributing. For Hg and Pb, both organic and inorganic forms are analyzed. This comparison assumes a linear exposure response that is particularly suspect for a substance such as Mn under homeostatic regulation.

Based on published work, including the 28 studies reporting neurobehavioral effects associated with exposure, Mn should be included in the group of substances including Pb, organic and inorganic Hg, and solvent mixtures associated with consistent patterns of neurobehavioral effects [10,12,106]. Alessio et al [106] reviewed the neurobehavioral effects of long-term exposure to low-level Mn, Pb, and Hg, recommending precautionary measures to prevent more severe health effects in the population. Martin [107] concluded that further investigation is needed but current neuropsychological and clinical evidence justifies preventive action to reduce the adverse effects of Mn exposure.

Support for this conclusion is not universal. This may in part reflect the dichotomy between the conflicting demands of individual clinical evaluation and public health population-inference and prevention. Clinical decision-making is typically based on a single individual (worker) with little or no knowledge of coworker status. Population studies have the benefit of potentially detailed simultaneous assessment of multiple risk factors, including exposure history, and sensitive testing procedures. Important deficits that are readily discernible at the population level disappear into the fog of normal variability at the individual level.

7. Discussion

The available weight of evidence supports the following conclusions:

(1) Neurobehavioral changes, such as performance decrements on standardized neuropsychological tests and adverse symptoms, have been consistently reported in studies of welders and other workers with known or likely sustained exposures to respirable Mn. Workers with these Mn exposures are at risk for developing neurological effects.
(2) These effects are consistent with signs of early manganism.
(3) Although some research has suggested that Mn exposures confer increased risk of PD (which might include accelerated onset or detection), and may perturb dopamine metabolism, this has not yet been established.
(4) Statistically significant adverse neurobehavioral effects have been reported at airborne concentrations below 0.2 mg/m^3 Mn. [24,26–28,31,33]

The development of regulations to limit Mn exposures for neurobehavioral effects would coordinate well with other regulatory health objectives. For example, in stainless steel welding, which typically entails Mn exposures, hexavalent chromium exposures also need to be controlled (for lung cancer risk), and in most welding there are often surface coatings or contaminants that are pyrolyzed and aerosolized with anticipated adverse effects. Nitrogen oxides and ozone, causing welding-associated respiratory effects, would also be controlled with engineered solutions to control Mn exposure.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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References

[1] Lezak MD. Neuropsychological assessment. 3rd ed. New York (NY): Oxford University Press; 1995.
[2] Zoni S, Albibi E, Lucchini R. Neuropsychological testing for the assessment of manganese neurotoxicity: a review and a proposal. Am J Ind Med 2007;50: 812–30.
[3] Iregren A. Using psychological tests for the early detection of neurotoxic effects of low level manganese exposure. Neurotoxicol 1994;15:671–8.
[4] Dick RB, Ahlers H. Chemicals in the workplace: incorporating human neurobehavioral testing into the regulatory process. Am J Ind Med 1998;33: 439–53.
[5] Gullion CM, Eckerman DA. Field testing. In: Annau Z, editor. Neurobehavioral toxicology. Baltimore (MD): The Johns Hopkins University Press; 1986. p. 288–330.
[6] Johnson BL, editor. Prevention of neurotoxic illness in working populations. Chichester (UK): John Wiley and Sons; 1987.
[7] Letz R. Use of computerized test batteries for quantifying neurobehavioral outcomes. Environ Health Perspect 1991;90:195–8.
[8] Roels H, Lauwerys R, Buchet JP, Genet P, Sarhan MJ, Hanotiau I, DeFays M, Bernard A, Stanescu D. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am J Ind Med 1987;11:307–27 erratum Am J Ind Med 1987; 12: 119–20.
[9] Fiedler N, Feldman RG, Jacobson J, Rahill A, Wetherell A. The assessment of neurobehavioral toxicity: SGOMSEC Joint Report. Environ Health Perspect 1996;104:179–91.
[10] Anger WK. Neurobehavioural tests and systems to assess neurotoxic exposures in the workplace and community. Occup Environ Med 2003;60:531–8.
[11] Anger WK, Rohlman DS, Storzbach D. Human behavioral neurotoxicology: workplace and community assessments. In: Rom WN, editor. Environmental and occupational medicine. 4th ed. New York (NY): Lippincott Williams and Wilkins; 2006.
[12] Lucchini R, Albini E, Benedetti L. Neurobehavioral science in hazard identification and risk assessment of neurotoxic agents – what are the requirements for further development? Int Arch Occup Environ Health 2005;78:427–37.
[13] Rohlman DS, Lucchini R, Anger WK, Bellinger DC, van Thriel C. Neurobehavioral testing in human risk assessment. Neurotoxicol 2008;29:556–67.
[14] Human Health Risk Assessment for Inhaled Manganese. Draft. water, air & climate change bureau. Health Canada; March 2008.
[15] Fahn S, Elton RL. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease. Florham Park (NJ): Macmillan Healthcare Information; 1987. p. 153–63.
[16] Goetz GC, LeWitt PA, Weidenman M. Standardized training tools for the UPDRS activities of daily living scale: newly available teaching program. Mov Disord 2003;18:1455–8.
[17] Steenland K, Dick R, Fine L. Agreement between clinical examination and quantitative tests of neurologic function among 384 subjects. Am J Ind Med 2001;39:361–8.
[18] Hattis D, Glowa J, Tilson H, Ulbrich B. Risk assessment for neurobehavioral toxicity: SGOMSEC joint report. Environ Health Perspect 1996;104:217–26.
[19] Bellinger DC. Perspectives on incorporating human neurobehavioral end points in risk assessments. Risk Anal 2003;23:163–74.
[20] Bellinger DC. What is an adverse effect? A possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity. Environ Res 2004;95:394–405.
[21] Bellinger DC. Interpretation of small effect sizes in occupational and environmental neurotoxicology: individual versus population risk. Neurotoxicol 2007;28:245–51.
[22] Sjogren B, Iregren A, Frech W, Hagman M, Johansson L, Tesarz M, Wennberg A. Effects on the nervous system among welders exposed to aluminum and manganese. Occup Environ Med 1996;53:32–40.
[23] Kim KS, Kim Y, Jin Y, Kim E, Yang JS, Kwon KR, Kim JW, Roh J, Moon YH. Factors associated with psychoneurobehavioral outcomes in workers exposed to manganese. Korean J Occup Environ Med 1999;11:213–28.
[24] Moon DH, Son BC, Kang DM. Manganese exposure and its health hazards of welders. Korean J Occup Environ Med 1999;11:476–91.
[25] Kim E, Kim Y, Cheong HK, Cho S, Shin YC, Sakong J, Kim KS, Yang JS, Jin YW, Kang SK. Pallidal index on MRI as a target organ dose of manganese: structural equation analysis. Neurotoxicol 2005;26:351–9.
[26] Yuan H, He S, He M, Niu Q, Wang L, Wang S. A comprehensive study on neurobehavior, neurotransmitters and lymphocyte subsets alteration of Chinese manganese welding workers. Life Sci 2006;78:1324–8.
[27] Bowler RM, Roels HA, Nakagawa S, Drezgic M, Diamond E, Park R, Koler W, Bowler RP, Mergler D, Bouchard M, Smith D, Gwiazda R, Doty RL. Dose–effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. Occup Environ Med 2007;64:167–77.
[28] Ellingsen DG, Konstantinov R, Bast-Pettersen R, Merkurjeva L, Chashchin M, Thomassen Y, Chashchin V. A neurobehavioral study of current and former welders exposed to manganese. Neurotoxicol 2008;29:48–59.
[29] Roels HA, Ghyselen P, Buchet JP, Ceulemans E, Lauwerys RR. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 1992;49:25–34.
[30] Mergler D, Huel G, Bowler R, Iregren A, Belanger S, Baldwin M, Tardif R, Smargiassi A, Martine L. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res 1994;64:151–80.
[31] Lucchini R, Sellis L, Folli D, Apostoli P, Mutti A, Vanoni O, Iregren A, Alessio L. Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure. Scand J Work Environ Health 1995;21:143–9.
[32] Lucchini R, Bergamaschi E, Smargiassi A, Festa D, Apostoli P. Motor function, olfactory threshold, and hematological indices in manganese-exposed ferroalloy workers. Environ Res 1997;73:175–80.
[33] Lucchini R, Apostoli P, Pierrone C, Placida D, Albini E, Migliorati P, Mergler D, Sassine M-P, Palmi S, Alessio A. Long term exposure to low levels of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicol 1999;20:287–98.
[34] Chia SE, Foo SC, Gan SL, Jeyaratnam J, Tian CS. Neurobehavioral functions among workers exposed to manganese ore. Scand J Work Environ Health 1993;19:264–70.
[35] Chia SE, Gan SL, Chua LH, Foo SC, Jeyaratnam J. Postural stability among manganese exposed workers. Neurotoxicol 1995;16:519–26.
[36] Bowler RM, Nakagawa S, Drezgic M, Roels HA, Park RM, Diamond E, Mergler D, Bouchard M, Bowler RP, Koller W. Sequelae of fume exposure in confined space welding: a neurological and neuropsychological case series. Neurotoxicol 2007;28:298–311.
[37] Deschamps FJ, Guillaumot M, Raux S. Neurological effects in workers exposed to manganese. J Occup Environ Med 2001;43:127–32.
[38] Jin Y, Kim Y, Kim KS, Kim E, Cho YS, Shin YC, Chai C, Choi Y, Lee SH, Moon YH. Performance of neurobehavioral tests among welders exposed to manganese. Korean J Occup Environ Med 1999;11:1–12.
[39] Kim JY, Lim HS, Cheong HK, Paik NW. A study of manganese exposure and health hazards among manganese manufacturing workers. Korean J Occup Environ Med 1994;6:98–112.
[40] Bouchard M, Mergler D, Baldwin M, Panisset M, Bowler R, Roels H. Neurobehavioral functioning after cessation of manganese exposure: a follow-up after 14 years. Am J Ind Med 2007;50:831–40.
[41] Wang JD, Huang CC, Hwang YH, Chiang JR, Lin JM, Chen JS. Manganese induced parkinsonism: an outbreak due to an unrepaired ventilation control system in a ferromanganese smelter. Br J Ind Med 1989;46:856–9.
[42] Wang X, Yang Y, Wang X, Xu S. The effect of occupational exposure to metals on the nervous system function in welders. J Occup Health 2006;48:100–6.
[43] Jankovic J. Searching for a relationship between manganese and welding and Parkinson's disease. Neurology 2005;64:2021–8.
[44] Lees-Haley PR, Greiffenstein MF, Larrabee GJ, Manning EL. Methodological problems in the neuropsychological assessment of effects of exposure to welding fumes and manganese. Clin Psychol 2004;18:449–64.
[45] Olanow CW. Manganese-induced parkinsonism and Parkinson's disease. Ann NY Acad Sci 2004;1012:209–23.
[46] Myers JE, Thompson ML, Ramushu S, Young T, Jeebhay MF, London L, Esswein E, Renton K, Spies A, Boulle A, Naik I, Iregren A, Rees DJ. The nervous system effects of occupational exposure on workers in a South African manganese smelter. Neurotoxicol 2003;24:885–94.
[47] Bowler RM, Gysens S, Diamond E, Booty A, Hartney C, Roels HA. Neuropsychological sequelae of exposure to welding fumes in a group of occupationally exposed men. Int J Hyg Environ Health 2003;206:517–29.
[48] Antonini JM, O'Callaghan JP, Miller DB. Development of an animal model to study the potential neurotoxic effects associated with welding fume inhalation. Neurotoxicol 2006;27:745–51.
[49] Santamaria AB, Cushing CA, Antonini JM, Finley BL, Mowat FS. State-of-the-Science Review: does manganese exposure during welding pose a neurological risk? J Tox Environ Health Part B 2007;10:417–65.
[50] Levy BS, Nassetta WJ. Neurologic effects of manganese in humans: a review. Int J Occup Environ Health 2003;9:153–63.
[51] Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO, Perlmutter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. Neurology 2001;56:8–13.
[52] Racette BA, Perlmutter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology [letter to the editor]. Neurology 2001;57: 1739–49.
[53] Sadek AH, Schulz PE. Welding-related parkinsonism: clinical features, treatment, and pathophysiology [letter]. Neurology 2001;57:1738–9.
[54] Ravina B, Siderowf A, Farrar J, Hurtig H. Welding-related parkinsonism: clinical features, treatment, and pathophysiology [letter]. Neurology 2001; 57:936–7.
[55] Park J, Yoo CI, Sim CS, Kim HK, Kim JW, Jeon BS, Kim KR, Bang OY, Lee WY, Yi Y, Jung KY, Chung SE, Kim Y. Occupations and Parkinson's disease: a multi-center case-control study in South Korea. Neurotoxicol 2005;26:99–105.
[56] Goldman SM, Tanner CM, Olanow CW, Watts RL, Field RD, Langston JW. Occupation and parkinsonism in three movement disorder clinics. Neurology 2005;65:1430–5.

[57] Park RM, Schulte PA, Bowman JD, Walker JT, Bondy SC, Yost MG, Touchstone JA, Dosemeci M. Potential occupational risks for neurodegenerative diseases. Am J Ind Med 2005;48:63–77.
[58] Park J, Yoo CI, Kim JW, Yi Y, Shin YC, Kim DH, Kim Y. A retrospective cohort study of Parkinson's disease in Korean shipbuilders. Neurotoxicol 2006;27:445–9.
[59] Marsh GM, Gula MJ. Employment as a welder and Parkinson disease among heavy equipment manufacturing workers. J Occup Environ Med 2006;48:1031–46.
[60] Tanner CM. Occupational and environmental causes of Parkinsonism. Occup Med 1992;7:503–13.
[61] Stampfer MJ. Welding occupations and mortality from Parkinson's disease and other neurodegenerative diseases among United States men, 1985-1999. J Occup Environ Hyg 2009;6:267–72.
[62] Firestone JA, Lundin J, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth WT, Checkoway H. Occupational factors and risk of Parkinson's disease: a population-based case–control study. Am J Ind Med 2010;53:217–23.
[63] Criswell SR, Perlmutter JS, Videen TO, Morlein SM, Flores HP, Birke AM, Racette BA. Reduced uptake of [^{18}F]FDOPA PET in asymptomatic welders with occupational manganese exposure. Neurology 2011;76:1296–301.
[64] Bowler RM, Gysens S, Diamond E, Nakagawa S, Drezgic M, Roels HA. Manganese exposure: neuropsychological and neurological symptoms and effects in welders. Neurotoxicol 2006;27:315–26.
[65] Koller WC, Lyons KE, Truly W. Effect of levodopa treatment for parkinsonism in welders. A double-blind study. Neurology 2004;62:730–3.
[66] Rohling ML, Demakis GJ. Potential neuropsychological profiles in welders occupationally exposed to manganese: an examination of effect size patterns. J Clin Expl Neuropsychol 2007;29:813–22.
[67] Park RM, Bowler RM, Eggerth DE, Diamond E, Spencer KJ, Smith D, Gwiadza R. Issues in neurological risk assessment for occupational exposures: The Bay Bridge Welders. Neurotoxicol 2006;27:373–84.
[68] Sanchez-Ramos J, Reimer D, Zesiewicz T, Sullivan K, Nausieda PA. Quantitative analysis of tremors in welders. Int J Environ Res Public Health 2011;8:1478–90.
[69] Monson RR. Observations on the healthy worker effect. J Occup Med 1981;28:425–33.
[70] Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. Epidemiology 1994;5:189–96.
[71] Park RM, Maizlish NA, Punnett L, Moure-Eraso R, Silverstein MA. A comparison of PMRs and SMRs as estimators of occupational mortality. Epidemiology 1991;2:49–59.
[72] Semchuk PhD KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 1992;42:1328–35.
[73] Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 1998;50:1346–50.
[74] Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Checkoway C. Pesticides and risk of Parkinson disease; a population-based case-control study. Arch Neurology 2005;62:91–5.
[75] Fryzek JP, Hansen J, Cohen S, Bonde JP, Llambias MT, Kolstad HA, Skytthe A, Lipworth L, Blot WJ, Olsen JH. A cohort study of Parkinson's disease and other neurodegenerative disorders in Danish welders. J Occup Environ Med 2005;47:466–72.
[76] Fored CM, Fryzek JP, Brandt L, Nise G, Sjogren B, McLaughlin, Blot WJ, Ekbom A. Parkinson's disease and other basal ganglia or movement disorders in a large nationwide cohort of Swedish welders. Occup Environ Med 2006;63:135–40.
[77] Thompson ML, Myers JE. Evaluating and interpreting exposure–response relationships for manganese and neurobehavioral outcomes. Neurotoxicology 2006;27:147–52.
[78] Toxicological profile for manganese (update). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry: Atlanta (GA) 2000.
[79] McMillan G. Is electric arc welding linked to manganism or Parkinson's disease? Toxicol Rev 2005;24:237–57.
[80] Greiffenstein MF, Lees-Haley PR. Neuropsychological correlate of manganese exposure: a meta-analysis. J Clin Exp Neuropsychol 2007;29:113–26.
[81] Iregren A. Psychological test performance in foundry workers exposed to low levels of manganese. Neurotox Teratol 1990;12:673–5.
[82] Sjogren B, Gustavsson P, Hogstedt C. Neuropsychiatric symptoms among welders exposed to toxic metals. Br J Ind Med 1990;47:704–7.
[83] Gibbs JP, Crump KS, Houck DP, Warren PA, Mosley WS. Focused medical surveillance: a search for subclinical movement disorders in a cohort of U.S. workers exposed to low levels of manganese dust. Neurotoxicol 1999;20:299–314.
[84] Sinczuk-Walczal H, Jacubowski M, Matczak W. Neurological and neurophysiological examinations of workers occupationally exposed to manganese. Int J Occup Med Environ Health 2001;14:329–37.
[85] Beuter A, Lambert G, MacGibbon B. Quantifying postural tremor in workers exposed to low levels of manganese. J Neurosci Methods 2004;139:247–55.
[86] Park RM, Bowler RM, Roels HA. Exposure-response relationship and risk assessment for cognitive deficits in early welding-induced manganism. J Occup Environ Med 2009;51:1125–36.
[87] Wastensson G, Sallsten G, Bast-Pettersen R, Barregard L. Neuromotor function in ship welders after cessation of manganese exposure. Int Arch Occup Environ Health 2012;85:703–13.
[88] Chang Y, Kim Y, Wood ST, Song H-J, Suk Hwan Kim SK, Lee H, Kwon YJ, Ahn JH, Park SJ, Chung IS, Jeong KS. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. Neurotoxicology 2009;30:555–63.
[89] Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. Occupation and risk of parkinsonism: a multicenter case-control study. Arch Neurol 2009;66:1106–13.
[90] Myers RAM, DeFazio AP, Kelly MP. Chronic carbon monoxide exposure: a clinical syndrome detected by neuropsychological tests. J Clin Psychol 1998;54:555–67.
[91] NIOSH alert: preventing carbon monoxide poisoning from small gasoline-powered engines and tools. Cincinnati (OH): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 1996. DHHS (NIOSH) Publication No. 96–118.
[92] National Toxicology Program. Research Triangle Park (USA) [Internet]. [cited 2012 Jul 5]. Available from: http://ntp.niehs.nih.gov/go/36443.
[93] Schwartz BS, Hu H. Adult lead exposure: time for change. Environ Health Perspect 2007;115:451–4.
[94] Bellinger DC. The Protean toxicities of lead: new chapters in a familiar story. Int J Environ Res Public Health 2011;8:2593–628.
[95] Shih RA, Hu H, Weisskopf MG, Schwartz B. Cumulative lead dose and cognitive function in adults: a review of studies that measured both blood lead and bone lead. Environ Health Perspect 2007;115:483–92.
[96] McGrail MP, Stewart W, Schwartz BS. Predictors of blood lead levels in organolead manufacturing workers. J Occup Environ Med 1995;37:1224–9.
[97] Stewart WF, Schwartz BS, Simon D, Bolla KI, Todd AC, Links J. Neurobehavioral function and tibial and chelatable lead levels in 543 former organolead workers. Neurology 1999;52:1610–7.
[98] Bandeen-Roche K, Glass TA, Bolla KI, Todd AC, Schwartz BS. Cumulative lead dose and cognitive function in older adults. Epidemiology 2009;20:831–9.
[99] Pikivi L, Hanninen H. Subjective symptoms and psychological performance of chlorine-alkali workers. Scand J Work Environ Health 1989;15:69–74.
[100] Ngim CH, Foo SC, Boey KW, Jeyaratnam J. Chronic neurobehavioral effects of elemental mercury in dentists. Br J Ind Med 1992;49:782–90.
[101] Liang YX, Sun RK, Sun Y, Chen ZQ, Li LH. Psychological effects of low exposure to mercury vapor: application of a computer-administered neurobehavioral evaluation system. Environ Res 1993;60:320–7.
[102] Chia SE, Chia HP, Ong CN, Jeyaratnam J. Cumulative blood lead levels and neurobehavioral test performance. Neurotoxicology 1997;18:793–803.
[103] Barth A, Schaffer AW, Osterode W, Winker R, Konnaris C, Valic E, Wolf C, Rüdiger HW. Reduced cognitive abilities in lead-exposed men. Int Arch Occup Environ Health 2002;75:394–8.
[104] Lindgren KN, Masten VL, Ford DP, Bleecker ML. Relation of cumulative exposure to inorganic lead and neuropsychological test performance. Occup Environ Med 1996;53:472–7.
[105] Baldwin M, Bouchard M, Larribe F, Mergler D. Past occupational exposure to airborne manganese in a manganese alloy plant. J Occup Environ Hygiene 2008;5:426–37.
[106] Alessio L, Campagna M, Lucchini R. From lead to manganese through mercury: mythology, science, and lessons for prevention. Am J Ind Med 2007;50:779–87.
[107] Martin CJ. Manganese neurotoxicity: connecting the dots along the continuum of dysfunction. Neurotoxicol 2006;27:347–9.