Bibliography of Selected Manganese Publications Related to Drinking Water Exposures and Infants and Children

A. Reviews, Summary Papers and Reports


Abstract: Compared to adults, children may be more highly exposed to toxic substances in drinking water because they consume more water per unit of body weight. The U.S. Environmental Protection Agency (USEPA) has developed new guidance for selecting age groups and age-specific exposure factors for assessing children’s exposures and risks to environmental contaminants. Research Aim: To demonstrate the application and importance of applying age-specific drinking water intake rates, health reference values, and exposure scenarios when assessing drinking water exposures because these approaches illustrate the potential for greater potential for adverse health effects among children. Methods: manganese, an essential nutrient and neurotoxicant, was selected as a case study and chemical of potential concern for children’s health. A screening-level risk assessment was performed using age-specific drinking water intake rates and manganese concentrations from U.S. public drinking water systems. Results: When age-specific drinking water intake rates are used to calculate dose, formula-fed infants receive the highest dose of manganese from drinking water compared to all other age groups. Estimated hazard quotients suggest adverse health effects are possible. Use of USEPA's standardized childhood age groups and childhood exposure factors significantly improves the understanding of childhood exposure and risks.


Abstract: Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants: manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethylene, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse.
Abstract: OBJECTIVE: We reviewed the scientific background for the current health-based World Health Organization (WHO) guideline value for manganese in drinking water. DATA SOURCES AND EXTRACTION: The initial starting point was the background document for the development of the WHO's guideline value for manganese in drinking water as well as other regulations and recommendations on manganese intake levels. Data referred to in these documents were traced back to the original research papers. In addition, we searched for scientific reports on manganese exposure and health effects. DATA SYNTHESIS: The current health-based guideline value for manganese in drinking water is based partly on debatable assumptions, where information from previous reports has been used without revisiting original scientific articles. Presently, preparation of common infant formulas with water containing manganese concentrations equivalent to the WHO guideline value will result in exceeding the maximum manganese concentration for infant formula. However, there are uncertainties about how this maximum value was derived. Concurrently, there is increasing evidence of negative neurologic effects in children from excessive manganese exposure. CONCLUSIONS: The increasing number of studies reporting associations between neurologic symptoms and manganese exposure in infants and children, in combination with the questionable scientific background data used in setting the manganese guideline value for drinking water, certainly warrant a re-evaluation of the guideline value. Further research is needed to understand the causal relationship between manganese exposure and children's health, and to enable an improved risk assessment.

Abstract: Objectives. Manganese (Mn) is an essential element, but overexposure can have neurotoxic effects. Methods. In this article, we review and summarize studies on exposure to Mn and nervous system impairments in children. Results. We identified 12 original articles published between 1977 and 2007. Overexposure to Mn was suspected to occur through diverse sources: infant milk formula, drinking water, industrial pollution, and mining wastes. The most common bioindicator of exposure to Mn was hair Mn content, but some studies measured Mn in blood, urine, or dentin; one study on prenatal exposure measured Mn content in cord blood. Most studies indicate that higher postnatal exposure to Mn is associated with poorer cognitive functions and hyperactive behavior. Conclusions. The limitations of the existing studies are numerous: most were crosssectional, had a modest sample size, and lacked adjustment for important confounders. Future investigations should be performed on a larger sample size and include a more detailed exposure assessment, addressing multiple sources of exposure such as food, water, and airborne particulates.

Abstract: This symposium comprised five oral presentations dealing with recent findings on Mn-related cognitive and motor changes from epidemiological studies across the life span. The first
contribution highlighted the usefulness of functional neuroimaging of the central nervous system (CNS) to evaluate cognitive as well as motor deficits in Mn-exposed welders. The second dealt with results of two prospective studies in Mn-exposed workers or welders showing that after decrease of Mn exposure the outcome of reversibility in adverse CNS effects may differ for motor and cognitive function and, in addition the issue of plasma Mn as a reliable biomarker for Mn exposure in welders has been addressed. The third presentation showed a brief overview of the results of an ongoing study assessing the relationship between environmental airborne Mn exposure and neurological or neuropsychological effects in adult Ohio residents living near a Mn point source. The fourth paper focused on the association between blood Mn and neurodevelopment in early childhood which seems to be sensitive to both low and high Mn concentrations. The fifth contribution gave an overview of six studies indicating a negative impact of excess environmental Mn exposure from air and drinking water on children's cognitive performance, with special attention to hair Mn as a potential biomarker of exposure. These studies highlight a series of questions about Mn neurotoxicity with respect to cognitive processes, forms and routes of exposure, adequate biomarkers of exposure, gender differences, susceptibility and exposure limits with regard to age.


B. More Recent Research Papers


Abstract: Recent studies of children suggest that exposure to elevated manganese (Mn) levels disrupts aspects of motor, cognitive and behavioral functions that are dependent on dopamine brain systems. Although basal ganglia motor functions are well-known targets of adult occupational Mn exposure, the extent of motor function deficits in adults as a result of early life Mn exposure is unknown. Here we used a rodent model early life versus lifelong oral Mn exposure and the Montoya staircase test to determine whether developmental Mn exposure produces long-lasting deficits in sensorimotor performance in adulthood. Long-Evans male neonate rats (n=11/treatment) were exposed daily to oral Mn at levels of 0, 25, or 50mg Mn/kg/d from postnatal day (PND) 1-21 (early life only), or from PND 1-throughout life. Staircase testing began at age PND 120 and lasted 1month to objectively quantify measures of skilled forelimb use in reaching and pellet grasping/retrieval performance. Behavioral reactivity also was rated on each trial. Results revealed that (1) behavioral reactivity scores were significantly greater in the Mn-exposed groups, compared to controls, during the staircase acclimation/training stage, but not the latter testing stages, (2) early life Mn exposure alone caused long-lasting impairments in fine motor control of reaching skills at the higher, but not lower Mn dose, (3) lifelong Mn exposure from drinking water led to widespread impairment in reaching and grasping/retrieval performance in adult rats, with the lower Mn dose group showing the greatest impairment, and (4) lifelong Mn exposure produced similar (higher Mn group) or more severe (lower Mn group) impairments compared to their early life-only Mn exposed counterparts. Collectively, these results substantiate the emerging clinical evidence in children showing associations between environmental Mn exposure and deficits in fine sensorimotor function. They also show that the objective
The quantification of skilled motor performance using the staircase test can serve as a sensitive measure of early life insults from environmental agents.


**Abstract:** BACKGROUND: Neurotoxic effects are known to occur with inhalation of manganese particulates, but very few data are available on exposure to Mn in water. We undertook a pilot study in a community in Quebec (Canada) where naturally occurring high Mn levels were present in the public water system. Our objective was to test the hypothesis that greater exposure to Mn via drinking water would be reflected in higher Mn content in hair which, in turn, would be associated with increased level of hyperactive behaviors. METHODS: Forty-six children participated in the study, 24 boys and 22 girls, 6-15 years of age (median, 11 years). Their homes received water from one of two wells (W) with different Mn concentrations: W1: mean 610 microg/L; W2: mean 160 pg/L. The Revised Conners' Rating Scale for parents (CPRS-R) and for teachers (CTRS-R) were administered, providing T-scores on the following subscales: Oppositional, Hyperactivity, Cognitive Problems/Inattention, and ADHD Index. RESULTS: Children whose houses were supplied by W1 had higher hair Mn (MnH) than those supplied by W2 (mean 6.2+/-.4.7 microg/g vs. 3.3+/-.3.0 microg/g, p = 0.025). MnH was significantly associated with T-scores on the CTRS-R Oppositional (p = 0.020) and Hyperactivity (p = 0.002) subscales, after adjustment for age, sex, and income. All children with Oppositional and Hyperactivity T-scores > 65 had MnH > 3.0 microg/g. CONCLUSIONS: The findings of this pilot study are sufficiently compelling to warrant more extensive investigations into the risks of Mn exposure in drinking water.


**Abstract:** Background: Manganese is an essential nutrient, but in excess, can be a potent neurotoxicant. Despite the common occurrence of manganese in groundwater, the risks associated with this source of exposure are largely unknown. Objectives: Our first aim was to assess the relations between exposure to manganese from drinking water and children's intellectual quotient (IQ). Secondly, we examined the relations between manganese exposures from water consumption and from the diet with children's hair manganese concentration. Methods: This cross-sectional study included 362 children ages 6 to 13 years living in communities supplied by groundwater. Manganese concentration was measured in home tap water (MnW) and children's hair (MnH). We estimated manganese intake from water ingestion and the diet using a food frequency questionnaire, and assessed IQ with the Wechsler Abbreviated Scale of Intelligence. Results: The median MnW in children's home tap water was 34 microg/L (range: 1-2700 microg/L). MnH increased with manganese intake from water consumption, but not with dietary manganese intake. Higher MnW and MnH were significantly associated with lower IQ scores. A 10-fold increase in MnW was associated with a decrease of 2.4 IQ points (95% confidence intervals: -3.9,-0.9; P < 0.01), adjusting for maternal intelligence, family income, and other potential confounders. There was a 6.2-IQ point difference between children in the lowest and highest MnW quintiles. MnW was more strongly associated with Performance IQ than Verbal IQ. Conclusions: The findings of this cross-sectional study suggest that exposure to manganese at levels common in groundwater is associated with intellectual impairment in children.

Abstract: Risk assessments of manganese by inhalation or oral routes of exposure typically acknowledge the duality of manganese as an essential element at low doses and a toxic metal at high doses. Previously, however, risk assessors were unable to describe manganese pharmacokinetics quantitatively across dose levels and routes of exposure, to account for mass balance, and to incorporate this information into a quantitative risk assessment. In addition, the prior risk assessment of inhaled manganese conducted by the U.S. Environmental Protection Agency (EPA) identified a number of specific factors that contributed to uncertainty in the risk assessment. In response to a petition regarding the use of a fuel additive containing manganese, methycyclopentadienyl manganese tricarbonyl (MMT), the U.S. EPA developed a test rule under the U.S. Clean Air Act that required, among other things, the generation of pharmacokinetic information. This information was intended not only to aid in the design of health outcome studies, but also to help address uncertainties in the risk assessment of manganese. To date, the work conducted in response to the test rule has yielded substantial pharmacokinetic data. This information will enable the generation of physiologically based pharmacokinetic (PBPK) models capable of making quantitative predictions of tissue manganese concentrations following inhalation and oral exposure, across dose levels, and accounting for factors such as duration of exposure, different species of manganese, and changes of age, gender, and reproductive status. The work accomplished in response to the test rule, in combination with other scientific evidence, will enable future manganese risk assessments to consider tissue dosimetry more comprehensively than was previously possible.


Abstract: Recent evidence suggests that low-level environmental exposure to manganese adversely affects child growth and neurodevelopment. Previous studies have addressed the effects of prenatal exposure, but little is known about developmental effects of early postnatal exposure. METHODS: We studied 448 children born in Mexico City from 1997 through 2000, using a longitudinal study to investigate neurotoxic effects of early-life manganese exposure. Archived blood samples, collected from children at 12 and 24 months of age, were analyzed for manganese levels using inductively coupled plasma mass spectrometry. Mental and psychomotor development were scored using Bayley Scales of Infant Development at 6-month intervals between 12 and 36 months of age. RESULTS: At 12 months of age, the mean (SD) blood manganese level was 24.3 (4.5)microg/L and the median was 23.7 microg/L; at 24 months, these values were 21.1 (6.2) microg/L and 20.3 microg/L, respectively. Twelve- and 24-month manganese concentrations were correlated (Spearman correlation = 0.55) and levels declined over time ([beta] = -5.7 [95% CI = -6.2 to -5.1]). We observed an inverted U-shaped association between 12-month blood manganese and concurrent mental development scores (compared with the middle 3 manganese quintiles, for the lowest manganese quintile, [beta] = -3.3 [-6.0 to -0.7] and for the highest manganese quintile, [beta] = -2.8 [-5.5 to -0.2]). This 12-month manganese effect was apparent but diminished with mental development scores at later ages. The 24-month manganese levels were not associated with neurodevelopment. CONCLUSIONS: These results suggest a possible biphasic dose-response relationship between early-life manganese exposure at lower exposure levels and infant neurodevelopment. The data are consistent with manganese as both an essential nutrient and a toxicant.

Abstract: While manganese (Mn) is essential for proper central nervous system (CNS) development, excessive Mn exposure may lead to neurotoxicity. Mn preferentially accumulates in the basal ganglia, and in adults it may cause Parkinson's disease-like disorder. Compared to adults, younger individuals accumulate greater Mn levels in the CNS and are more vulnerable to its toxicity. Moreover, the mechanisms mediating developmental Mn-induced neurotoxicity are not completely understood. The present study investigated the developmental neurotoxicity elicited by Mn exposure (5, 10 and 20 mg/kg; i.p.) from postnatal day 8 to PN27 in rats. Neurochemical analyses were carried out on PN29, with a particular focus on striatal alterations in intracellular signaling pathways (MAPKs, Akt and DARPP-32), oxidative stress generation and cell death. Motor alterations were evaluated later in life at 3, 4 or 5 weeks of age. Mn exposure (20 mg/kg) increased p38(MAPK) and Akt phosphorylation, but decreased DARPP-32-Thr-34 phosphorylation. Mn (10 and 20 mg/kg) increased caspase activity and F2-isoprostane production (a biological marker of lipid peroxidation). Paralleling the changes in striatal biochemical parameters, Mn (20 mg/kg) also caused motor impairment, evidenced by increased falling latency in the rotarod test, decreased distance traveled and motor speed in the open-field test. Notably, the antioxidant Trolox reversed the Mn (20 mg/kg)-dependent augmentation in p38(MAPK) phosphorylation and reduced the Mn (20 mg/kg)-induced caspase activity and F2-isoprostane production. Trolox also reversed the Mn-induced motor coordination deficits. These findings are the first to show that long-term exposure to Mn during a critical period of neurodevelopment causes motor coordination dysfunction with parallel increment in oxidative stress markers, p38(MAPK) phosphorylation and caspase activity in the striatum. Moreover, we establish Trolox as a potential neuroprotective agent given its efficacy in reversing the Mn-induced neurodevelopmental effects.


Abstract: Manganese (Mn) is an essential trace metal found in all tissues, and it is required for normal amino acid, lipid, protein, and carbohydrate metabolism. While Mn deficiency is extremely rare in humans, toxicity due to overexposure of Mn is more prevalent. The brain appears to be especially vulnerable. Mn neurotoxicity is most commonly associated with occupational exposure to aerosols or dusts that contain extremely high levels (>1-5 mg Mn/m(3)) of Mn, consumption of contaminated well water, or parenteral nutrition therapy in patients with liver disease or immature hepatic functioning such as the neonate. This review will focus primarily on the neurotoxicity of Mn in the neonate. We will discuss putative transporters of the metal in the neonatal brain and then focus on the implications of high Mn exposure to the neonate focusing on typical exposure modes (e.g., dietary and parenteral). Although Mn exposure via parenteral nutrition is uncommon in adults, in premature infants, it is more prevalent, so this mode of exposure becomes salient in this population. We will briefly review some of the mechanisms of Mn neurotoxicity and conclude with a discussion of ripe areas for research in this underreported area of neurotoxicity.


Abstract: Overexposure to waterborne manganese (Mn) is linked with cognitive impairment in children and neurochemical abnormalities in other experimental models. In order to characterize the threshold between Mn-exposure and altered neurochemistry, it is important to identify biomarkers that positively correspond with brain Mn-accumulation. The objective of this study was to identify Mn-induced alterations in plasma, liver, and brain metabolites using liquid/gas
chromatography–time of flight–mass spectrometry metabolomic analyses; and to monitor corresponding Mn-induced behavior changes. Weanling Sprague–Dawley rats had access to deionized drinking water either Mn-free or containing 1 g Mn/L for 6 weeks. Behaviors were monitored during the sixth week for a continuous 24 h period while in a home cage environment using video surveillance. Mn-exposure significantly increased liver, plasma, and brain Mn concentrations compared to control, specifically targeting the globus pallidus (GP). Mn significantly altered 98 metabolites in the brain, liver, and plasma; notably shifting cholesterol and fatty acid metabolism in the brain (increased oleic and palmitic acid; 12.57 and 15.48 fold change (FC), respectively), and liver (increased oleic acid, 14.51 FC; decreased hydroxybutyric acid, −14.29 FC). Additionally, Mn-altered plasma metabolites homogentisic acid, chenodeoxycholic acid, and aspartic acid correlated significantly with GP and striatal Mn. Total distance traveled was significantly increased and positively correlated with Mn-exposure, while nocturnal stereotypic and exploratory behaviors were reduced with Mn-exposure and performed largely during the light cycle compared to unexposed rats. These data provide putative biomarkers for Mn-neurotoxicity and suggest that Mn disrupts the circadian cycle in rats.


Abstract: Epidemiological studies in children have reported associations between elevated dietary manganese (Mn) exposure and neurobehavioral and neurocognitive deficits. To better understand the relationship between early Mn exposure and neurobehavioral deficits, we treated neonate rats with oral Mn doses of 0, 25, or 50 mg Mn/kg/day over postnatal day (PND) 1–21, and evaluated behavioral performance using open arena (PND 23), elevated plus maze (PND 23), and 8-arm radial maze (PND 33–46) paradigms. Brain dopamine D1 and D2-like receptors, and dopamine transporter (DAT) densities were determined on PND 24, and blood and brain Mn levels were measured to coincide with behavioral testing (PND 24, PND 36). Preweaning Mn exposure caused hyperactivity and behavioral disinhibition in the open arena, but no altered behavior in the elevated plus maze. Manganese-exposed males committed significantly more reference and marginally more working errors in the radial arm maze compared to controls. Fewer Mn exposed males achieved the radial maze learning criterion, and they required more session days to reach it compared to controls. Manganese-exposed animals also exhibited a greater frequency of stereotypic response strategy in searching for the baited arms in the maze. These behavioral and learning deficits were associated with altered expression of the dopamine D1 and D2 receptors and the DAT in prefrontal cortex, nucleus accumbens, and dorsal striatum. These data corroborate epidemiological studies in children, and suggest that exposure to Mn during neurodevelopment significantly alters dopaminergic synaptic environments in brain nuclei that mediate control of executive function behaviors, such as reactivity and cognitive flexibility.


Abstract: Background: Evidence of neurological, cognitive, and neuropsychological effects of manganese (Mn) exposure from drinking water (WMn) in children has generated widespread public health concern. At elevated exposures, Mn has been associated with increased levels of externalizing behaviors, including irritability, aggression, and impulsivity. Little is known about potential effects at lower exposures, especially in children. Moreover, little is known regarding potential interactions between exposure to Mn and other metals, especially arsenic (As). Objectives: We conducted a cross-sectional study of 201 children to investigate associations of
Mn and As in tube well water with classroom behavior among elementary school children, 8–11 years of age, in Araihazar, Bangladesh. **Methods:** Data on exposures and behavioral outcomes were collected from the participants at the baseline of an ongoing longitudinal study of child intelligence. Study children were rated by their school teachers on externalizing and internalizing items of classroom behavior using the standardized Child Behavior Checklist-Teacher’s Report Form (CBCL-TRF). **Results:** Log-transformed WMn was positively and significantly associated with TRF internalizing \(\text{estimated } \beta = 0.82; 95\% \text{ confidence interval (CI), } 0.08–1.56; p = 0.03\), TRF externalizing \(\text{estimated } \beta = 2.59; 95\% \text{ CI, 0.81–4.37; } p = 0.004\), and TRF total scores \(\text{estimated } \beta = 3.35; 95\% \text{ CI, 0.86–5.83; } p = 0.008\) in models that adjusted for log-transformed water arsenic (WAs) and sociodemographic covariates. We also observed a positive monotonic dose–response relationship between WMn and TRF externalizing and TRF total scores among the participants of the study. We did not find any significant associations between WAs and various scales of TRF scores. **Conclusion:** These observations reinforce the growing concern regarding the neurotoxicologic effects of WMn in children.

Khan, K., G. A. Wasserman, et al. (2012). "Manganese exposure from drinking water and children's academic achievement." Neurotoxicology 33(1): 91-97. http://www.ncbi.nlm.nih.gov/pubmed/22182530. **Abstract:** Drinking water manganese (WMn) is a potential threat to children's health due to its associations with a wide range of outcomes including cognitive, behavioral and neuropsychological effects. Although adverse effects of Mn on cognitive function of the children indicate possible impact on their academic achievement little evidence on this issue is available. Moreover, little is known regarding potential interactions between exposure to Mn and other metals, especially water arsenic (WAs). In Araihazar, a rural area of Bangladesh, we conducted a cross-sectional study of 840 children to investigate associations between WMn and WAs and academic achievement in mathematics and languages among elementary school-children, aged 8-11 years. Data on As and Mn exposure were collected from the participants at the baseline of an ongoing longitudinal study of school-based educational intervention. Annual scores of the study children in languages (Bangla and English) and mathematics were obtained from the academic achievement records of the elementary schools. WMn above the WHO standard of 400mug/L was associated with 6.4% score loss (95% CI=-12.3 to -0.5) in mathematics achievement test scores, adjusted for WAs and other sociodemographic variables. We did not find any statistically significant associations between WMn and academic achievement in either language. Neither WAs nor urinary As was significantly related to any of the three academic achievement scores. Our finding suggests that a large number of children in rural Bangladesh may experience deficits in mathematics due to high concentrations of Mn exposure in drinking water.

Kim, Y., B. N. Kim, et al. (2009). "Co-exposure to environmental lead and manganese affects the intelligence of school-aged children." Neurotoxicology 30(4): 564-571. http://www.ncbi.nlm.nih.gov/pubmed/19635390. **Abstract:** Background: Exposure to environmental levels of lead (Pb) and manganese (Mn) has been associated with detrimental effects to neurodevelopment. However, little is known about the potential association between environmental levels of Pb and Mn on intelligence of children. The aims of the study were to investigate the association of community level of Pb and Mn with the intelligence of school-aged children, and to explore the implications of joint exposure to these two heavy metals. **Methods:** A cross-sectional examination of blood Pb and Mn concentrations was performed, and the intelligence quotient (IQ) was determined for 261 Korean children aged 8-11 years. **Results:** The mean blood concentrations of Pb and Mn were 1.73 microg/dL (SD=0.8; median=1.55; range=0.42-4.91) and 14.3 microg/L (SD=3.8; median=14.0; range=5.30-29.02), respectively. Both Pb and Mn showed significant linear relationship with full-scale IQ (Pb, beta=-0.174, p=0.005; Mn, beta=-0.123, p=0.042) and verbal IQ (Pb, beta=-0.187, p=0.003;
Mn, beta=-0.127, p=0.036). Blood Pb (DeltaR(2)=0.03) and Mn (DeltaR(2)=0.01) explained 4% of the variances of the full-scale IQ and 5% of the variances of the verbal IQ. When Pb and Mn levels were entered as predictive variables, additive increase in the explained variances was observed. Finally, full-scale IQ and verbal IQ of the children with blood Mn>14 microg/L showed significant association with Pb, whereas group with Mn<14 microg/L did not, suggesting effect modification between Pb and Mn. **Conclusions:** The present study suggests the presence of additive interaction and effect modification between Pb and Mn on the intelligence of school-aged children, suggesting more attention should be paid to preventing the exposure of disadvantaged children to various combinations of toxic materials.

Ljung, K. S., M. J. Kippler, et al. (2009). "Maternal and early life exposure to manganese in rural Bangladesh." *Environ Sci Technol* **43**(7): 2595-2601. http://pubs.acs.org/doi/abs/10.1021/es803143z. **Abstract:** Manganese exposure and biomarker concentrations during early pregnancy and lactation were investigated in 408 women living in an area with elevated concentrations of both arsenic and manganese in drinking water derived from wells. About 40% of the water samples had manganese concentrations above the World Health Organization's guideline value and showed a strong inverse correlation with arsenic concentrations. Water manganese was found to correlate to urine concentrations, but not to blood or breast milk concentrations. No correlations were found among manganese concentrations in urine, blood, or breast milk. Compared to other populations, manganese concentrations in both urine and blood, but not breast milk, were elevated in the Bangladeshi women and more similar to those of occupationally exposed groups. The lack of associations with water manganese is likely due to variable exposure via water and food, and differences in bioavailability, as well as a complex and/or strict regulation of intestinal manganese absorption, in turn being influenced by nutritional as well as physiological and genetic factors. The results indicate that elevated maternal manganese exposure does not necessarily lead to exposure of breast-fed infants, stressing the importance of breast feeding in high manganese areas. However, the implications of fetal exposure from elevated maternal exposure need further investigation.

Moreno, J. A., E. C. Yeomans, et al. (2009). "Age-dependent susceptibility to manganese-induced neurological dysfunction." *Toxicol Sci* **112**(2): 394-404. doi: 10.1093/toxsci/kfp220. **Abstract:** Chronic exposure to manganese (Mn) produces a spectrum of cognitive and behavioral deficits associated with a neurodegenerative disorder resembling Parkinson's disease. The effects of high-dose exposure to Mn in occupational cohorts and in adult rodent models of the disease are well described but much less is known about the behavioral and neurochemical effects of Mn in the developing brain. We therefore exposed C57Bl/6 mice to Mn by intragastric gavage as juveniles, adults, or both, postulating that mice exposed as juveniles and then again as adults would exhibit greater neurological and neurochemical dysfunction than mice not preexposed as juveniles. Age- and sex-dependent vulnerability to changes in locomotor function was detected, with juvenile male mice displaying the greatest sensitivity, characterized by a selective increase in novelty-seeking and hyperactive behaviors. Adult male mice preexposed as juveniles had a decrease in total movement and novelty-seeking behavior, and no behavioral changes were detected in female mice. Striatal dopamine levels were increased in juvenile mice but were decreased in adult preexposed as juveniles. Levels of Mn, Fe, and Cu were determined by inductively coupled plasma-mass spectrometry, with the greatest accumulation of Mn detected in juvenile mice in the striatum, substantia nigra (SN), and cortex. Only modest changes in Fe and Cu were detected in Mn-treated mice, primarily in the SN. These results reveal that developing mice are more sensitive to Mn than adult animals and that Mn exposure during development enhances behavioral and neurochemical dysfunction relative to adult animals without juvenile exposure.

Abstract: Background: Manganese neurotoxicity is well documented in individuals occupationally exposed to airborne particulates, but few data are available on risks from drinking water exposure. Objective: We examined associations of manganese exposure from water and hair manganese concentration with memory, attention, motor function, and parent-and teacher-reported hyperactive behaviors. Methods: We recruited 375 children and measured manganese in home tap water (MnW) and hair (MnH). We estimated manganese intake from water ingestion. Using structural equation modeling, we estimated associations between neurobehavioral functions and MnH, MnW, and manganese intake from water. Exposure-response relationships were evaluated using generalized additive models. Results: After adjusting for potential confounders, a standard deviation (SD) increase in log10 MnH was associated with a significant difference of -24% (95% CI: -36, -12%) SD in memory and -25% (95% CI: -41, -9%) SD in attention. The relations between log10 MnH and poorer memory and attention were linear. A SD increase in log10 MnW was associated with a significant difference of -14% (95% CI: -24, -4%) SD in memory, and this relation was nonlinear, with a steeper decline in performance at MnW above 100 µg/L. A SD increase in log10 manganese intake from water was associated with a significant difference of -11% (95% CI: -21, -0.4%) SD in motor function. The relation between log10 manganese intake and poorer motor function was linear. There was no significant association between manganese exposure and hyperactivity. Conclusion: Exposure to manganese in water was associated with poorer neurobehavioral performances in children, even at low levels commonly encountered in North America.


Abstract: Background: Several reports indicate that drinking water arsenic (WAs) and manganese (WMn) are associated with children's intellectual function. Very little is known, however, about possible associations with other neurologic outcomes such as motor function. Methods: We investigated the associations of WAs and WMn with motor function in 304 children in Bangladesh, 8-11 years of age. We measured As and Mn concentrations in drinking water, blood, urine, and toenails. We assessed motor function with the Bruininks-Oseretsky test, version 2, in four subscales-fine manual control (FMC), manual coordination (MC), body coordination (BC), and strength and agility-which can be summarized with a total motor composite score (TMC). Results: Log-transformed blood As was associated with decreases in TMC (β = -3.63; 95% confidence interval (CI): -6.72, -0.54; p < 0.01), FMC (β = -1.68; 95% CI: -3.19, -0.18; p < 0.05), and BC (β = -1.61; 95% CI: -2.72, -0.51; p < 0.01), with adjustment for sex, school attendance, head circumference, mother's intelligence, plasma ferritin, and blood Mn, lead, and selenium. Other measures of As exposure (WAs, urinary As, and toenail As) also were inversely associated with motor function scores, particularly TMC and BC. Square-transformed blood selenium was positively associated with TMC (β = 3.54; 95% CI: 1.10, 6.0; p < 0.01), FMC (β = 1.55; 95% CI: 0.40, 2.70; p < 0.005), and MC (β= 1.57; 95% CI: 0.60, 2.75; p < 0.005) in the unadjusted models. Mn exposure was not significantly associated with motor function. Conclusion: Our research demonstrates an adverse association of As exposure and a protective association of Se on motor function in children.
Abstract: Manganese (Mn) is an essential element for humans, animals, and plants and is required for growth, development, and maintenance of health. Mn is present in most tissues of all living organisms and is present naturally in rocks, soil, water, and food. High-dose oral, parenteral, or inhalation exposures are associated with increased tissue Mn levels that may lead to development of adverse neurological, reproductive, or respiratory effects. Manganese-induced clinical neurotoxicity is associated with a motor dysfunction syndrome commonly referred to as manganism. Because Mn is an essential element and absorption and excretion are homeostatically regulated, a reasonable hypothesis is that there should be no adverse effects at low exposures. Therefore, there should be a threshold for exposure, below which adverse effects may occur only rarely, if at all, and the frequency of occurrence of adverse effects may increase with higher exposures above that threshold. Lowest-observed-adverse-effect levels (LOAELs), no-observed-adverse-effect levels (NOAELs), and benchmark dose levels (BMDs) have been derived from studies that were conducted to evaluate subclinical neurotoxicity in human occupational cohorts exposed to Mn. Although there is some uncertainty about the predictive value of the subclinical neuromotor or neurobehavioral effects that were observed in these occupational cohort studies, results of the neurological tests were used in risk assessments to establish guidelines and regulations for ambient air levels of Mn in the environment. A discussion of the uncertainties associated with these tests is provided in this review. The application of safety and uncertainty factors result in guidelines for ambient air levels that are lower than the LOAELs, NOAELs, or BMDs from occupational exposure studies by an order of magnitude, or more. Specific early biomarkers of effect, such as subclinical neurobehavioral or neurological changes or magnetic resonance imaging (MRI) changes, have not been established or validated for Mn, although some studies attempted to correlate certain biomarkers with neurological effects. Pharmacokinetic studies with rodents and monkeys provide valuable information about the absorption, bioavailability, and tissue distribution of various Mn compounds with different solubilities and oxidation states in different age groups. These pharmacokinetic studies showed that rodents and primates maintain stable tissue Mn levels as a result of homeostatic mechanisms that tightly regulate absorption and excretion of ingested Mn and limit tissue uptake at low to moderate levels of inhalation exposure. In addition, physiologically based pharmacokinetic (PBPK) models are being developed to provide for the ability to conduct route-to-route extrapolations, evaluate nasal uptake to the central nervous system (CNS), and determine life-stage differences in Mn pharmacokinetics. Such models will facilitate more rigorous quantitative analysis of the available human pharmacokinetic data for Mn and will be used to identify situations that may lead to increased brain accumulation related to altered Mn kinetics in different human populations, and to develop quantitatively accurate predictions of elevated Mn levels that may serve as a basis of dosimetry-based risk assessments. Such dosimetry-based risk assessments will permit for the development of more scientifically refined and robust recommendations, guidelines, and regulations for Mn levels in the ambient environment and occupational settings.


Abstract: Exposure to manganese via inhalation has long been known to elicit neurotoxicity in adults, but little is known about possible consequences of exposure via drinking water. In this study, we report results of a cross-sectional investigation of intellectual function in 142 10-year-old children in Araihazar, Bangladesh, who had been consuming tube-well water with an average concentration of 793 microg Mn/L and 3 microg arsenic/L. Children and mothers came to our
field clinic, where children received a medical examination in which weight, height, and head circumference were measured. Children's intellectual function was assessed on tests drawn from the Wechsler Intelligence Scale for Children, version III, by summing weighted items across domains to create Verbal, Performance, and Full-Scale raw scores. Children provided urine specimens for measuring urinary As and creatinine and were asked to provide blood samples for measuring blood lead, As, Mn, and hemoglobin concentrations. After adjustment for sociodemographic covariates, water Mn was associated with reduced Full-Scale, Performance, and Verbal raw scores, in a dose-response fashion; the low level of As in water had no effect. In the United States, roughly 6% of domestic household wells have Mn concentrations that exceed 300 microg Mn/L, the current U.S. Environmental Protection Agency lifetime health advisory level. We conclude that in both Bangladesh and the United States, some children are at risk for Mn-induced neurotoxicity.


**Abstract:** Recently, epidemiologic studies of developmental neurotoxicology have been challenged to increase focus on co-exposure to multiple toxicants. Earlier reports, including our own work in Bangladesh, have demonstrated independent associations between neurobehavioral function and exposure to both arsenic (As) and manganese (Mn) in school-aged children. Our earlier studies, however, were not designed to examine possible interactive effects of exposure to both As and Mn. To allow investigation of possible synergistic impact of simultaneous exposures, we recruited a new sample of 299 8-11 year old children, stratified by design on As (above and below 10μg/L) and Mn (above and below 500μg/L) concentrations of household wells. When adjusted only for each other, both As and Mn in whole blood (BAs; BMn) were significantly negatively related to most WISC-IV subscale scores. With further adjustment for sociodemographic features and ferritin, BMn remained significantly associated with reduced Perceptual Reasoning and Working Memory scores; associations for BAs, and for other subscales, were expectably negative, significantly for Verbal Comprehension. Urinary As (per gram creatinine) was significantly negatively associated with Verbal Comprehension scores, even with adjustment for BMn and other contributors. Mn by As interactions were not significant in adjusted or unadjusted models (all p's>0.25). Findings are consistent with other reports documenting adverse impact of both As and Mn exposure on child developmental outcomes, although associations appear muted at these relatively low exposure levels.


**Abstract:** The patient's family bought a home in a suburb, but the proximity of the house to wetlands and its distance from the town water main prohibited connecting the house to town water. The family had a well drilled and they drank the well water for 5 years, despite the fact that the water was turbid, had a metallic taste, and left an orange-brown residue on clothes, dishes, and appliances. When the water was tested after 5 years of residential use, the manganese concentration was elevated (1.21 ppm; U.S. Environmental Protection Agency reference, < 0.05 ppm). The family's 10-year-old son had elevated manganese concentrations in whole blood, urine, and hair. The blood manganese level of his brother was normal, but his hair manganese level was elevated. The patient, the 10-year-old, was in the fifth grade and had no history of learning problems; however, teachers had noticed his inattentiveness and lack of focus in the classroom. Our results of cognitive testing were normal, but tests of memory revealed a markedly below-average performance: the patient's general memory index was at the 13th percentile, his verbal memory at the 19th percentile, his visual memory at the 14th percentile, and his learning index at
the 19th percentile. The patient's free recall and cued recall tests were all 0.5-1.5 standard deviations (1 SD = 16th percentile) below normal. Psychometric testing scores showed normal IQ but unexpectedly poor verbal and visual memory. These findings are consistent with the known toxic effects of manganese, although a causal relationship cannot necessarily be inferred.