February 26, 2018

Submitted Via eComment System
Jessica Shirley, Director
Policy Office
Pennsylvania Department of Environmental Protection
Rachel Carson State Office Building
Harrisburg, PA 17105-2063

Re: Water Quality Standard for Manganese
Advance Notice of Proposed Rulemaking
48 Pa. Bull. 605 (Jan. 27, 2018)

Dear Ms. Shirley:

On behalf of Citizens for Pennsylvania's Future (PennFuture) and its members, I submit this letter and the attached information in response to the "Water Quality Standard for Manganese; Advance Notice of Proposed Rulemaking" (ANPR). 48 Pa. Bull. 605 (Jan. 27, 2018). The ANPR seeks information to support the development of regulations as required by Section 6 of the Act of October 30, 2017, P.L. ___, No. 40, § 6 (Act 40), which is codified at 71 P.S. § 510-20(j).

PennFuture is a public interest membership organization dedicated to leading the transition to a clean energy economy in Pennsylvania and beyond. PennFuture strives to protect our air, water and land, and to empower citizens to build sustainable communities for future generations. One focus of PennFuture's work is to improve and protect water resources and water quality across Pennsylvania through public outreach and education, advocacy, and litigation.

1. Studies of Human Health Effects

One specific category of information sought by the ANPR is "[p]eer-reviewed, published toxicological studies, reports and data on human health effects resulting from exposure to Mn [manganese] in water." 48 Pa. Bull. at 606. In response, PennFuture provides copies of two documents containing bibliographies of published studies concerning the effects of manganese in drinking water on infants and children.

The first document, titled "Bibliography of Selected Manganese Publications Related to Drinking Water Exposures and Infants and Children," was prepared in October 2014 by the Massachusetts Department of Environmental Protection (MassDEP) Office of Research and Standards. It lists more than two dozen publications and provides an abstract for most of them. That document remains posted on MassDEP's web page at

Northeast: 425 Carlton Road Suite 1 Mount Pocono, PA 18344
Southeast: 1429 Walnut Street Suite 400 Philadelphia, PA 19102
Central: 610 North Third Street Harrisburg, PA 17101
Southwest: 200 First Avenue Suite 200 Pittsburgh, PA 15222
Website: www.pennfuture.org

http://www.mass.gov/eea/docs/dep/water/drinking/alpha/i-thru-z/mangrefs.pdf.[1] A copy of the document is attached to this letter as **Attachment A**. Please note that the first source cited in this bibliography – the Agency for Toxic Substances and Disease Registry's (ATSDR's) 2009 Draft Toxicological Profile for Manganese – was finalized in 2012 and is available at https://www.ncbi.nlm.nih.gov/books/NBK158872/pdf/Bookshelf_NBK158872.pdf.

The second document is a cover letter dated April 6, 2015 and attached comments submitted by the Association of State Drinking Water Administrators (ASDWA) to the U.S. Environmental Protection Agency (EPA) on the draft Fourth Contaminant Candidate List (CCL4) under the federal Safe Drinking Water Act. *See* 80 Fed. Reg. 6076 (Feb. 4, 2015).[2] ASDWA's cover letter and comments are attached to this letter as **Attachment B**. Included therein, in comments provided by the Massachusetts Drinking Water Program, is a listing of 19 publications titled "Selected Bibliography of Post 2011 Manganese Publications Related to Drinking Water Exposures and Infants and Children," which overlaps slightly with MassDEP's similarly-titled 2014 list.

2. Protection of Other Water Supply and Recreational Uses

Pennsylvania's specific water quality criterion for manganese is a maximum instream concentration of 1.0 milligram per liter (mg/l) as total recoverable. 25 Pa. Code § 93.7(a) & Table 3. The critical water use the manganese criterion is designed to protect is Potable Water Supply (PWS). *Id*. "Potable Water Supply" is defined as use of water for drinking and other domestic purposes "after conventional treatment," *id.* § 93.3, which in turn is defined as coagulation followed by filtration and disinfection. *Id*. § 93.1. As stated in the ANPR, "a PWS water quality criterion must be set at a level to provide acceptable drinking water after conventional treatment." 48 Pa. Bull. at 606.

Pennsylvania's current manganese criterion was intended to ensure that drinking water regulated under federal or Pennsylvania Safe Drinking Water Acts contains an acceptable concentration of manganese. Specifically, the maximum instream concentration of 1.0 mg/l was selected to ensure that, after conventional treatment (modified to include the addition of potassium permanganate in the coagulation stage), finished drinking water would contain a concentration of manganese no higher than 0.05 mg/l. (Schoener, K., "Rationale Document – Manganese" (March 15, 1979)). This maximum acceptable concentration of 0.05 mg/l, which is the secondary maximum contaminant level (SMCL) under the safe drinking water program, *see* 25 Pa. Code § 109.202(b)(1), (2); 40 C.F.R. § 143.3; 44 Fed Reg. 42195, 42198 (July 19, 1979), is designed to avoid adverse taste or palatability impacts, as well as staining of household fixtures and laundry.

Currently, the instream manganese criterion of 1.0 mg/l is governed by the general rule requiring the criterion to be achieved at least 99% of the time throughout all surface waters. *See* 25 Pa. Code § 96.3(c); *see also id*. § 93.4(a) & Table 2. Through its reference to the exception

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[1] All links provided in this letter were last visited on February 23, 2018.

[2] As recommended by both ASDWA and the Commonwealth of Massachusetts, EPA's final regulatory determination for CCL4 included manganese. *See* 81 Fed. Reg. 81099, 81108-09, 81112 (Nov. 17, 2016).

found in 25 Pa. Code § 96.3(d), Section 6 of Act 40 requires the Environmental Quality Board (Board) to propose a regulation that would change the "point of compliance" by providing that the PWS-based manganese criterion must be met at least 99% of the time only "at the point of all existing or planned surface potable water supply withdrawals." 25 Pa. Code § 93.6(d).

The ANPR correctly raises the issue of how this change in the point of compliance for the current, PWS-based manganese criterion may affect other water supply and recreational water uses that are designated as statewide protected uses under Pennsylvania's water quality standards. *See* 25 Pa. Code §§ 93.3 (Table 1); 93.4(a) & Table 2. The ANPR states that "[w]hile the current [manganese] standard was developed specifically for PWS protection, it has also provided protection for these other designated uses." 48 Pa. Bull. at 606. The ANPR specifically seeks "[i]nformation related to the water quality needs or potential impacts to other water supply and recreational users that may be exposed to Mn levels *greater than 1.0 mg/l* in surface waters." *Id*. (emphasis added).

Implicit in the ANPR's framing of this request is the assumption that the current instream criterion of 1.0 mg/l *adequately* protects the other water supply and recreational uses, and that those other uses may be adversely impacted only if instream concentrations of manganese *exceed* 1.0 mg/l.

This assumption is called into question, however, by reports concerning the impacts of manganese on livestock watering. The Penn State Extension reports that the same effects on palatability that provide part of the support for the drinking water SMCL of 0.05 mg/l may inhibit dairy cattle from ingesting sufficient amounts of water if it contains a manganese concentration higher than 0.05 mg/l:

> Experience in Pennsylvania has shown that aesthetic pollutants like iron, manganese and hydrogen sulfide, are the most common water-related causes of problems with dairy herds. These pollutants cause tastes or odors that result in reduced water intake and milk production
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> * * *
>
> Iron and manganese are very common pollutants that can occur naturally in groundwater or from nearby mining activities. Both cause severe staining and a metallic taste to water resulting in reduced water intake and reduced milk production. Iron levels above 0.3 mg/L and manganese concentrations exceeding 0.05 mg/L are sufficient to cause unpleasant tastes in water that may cause reduced water intake and milk production.

Penn State Extension, "Interpreting Drinking Water Tests for Dairy Cows" (available at https://extension.psu.edu/interpreting-drinking-water-tests-for-dairy-cows). *See also* Beede, D. "Evaluation of Water Quality and Nutrition for Dairy Cattle" (2006), p. 8 ("In general, a concentration [of manganese] greater than 0.05 ppm is thought to affect water intake because of the off-taste it imparts.") (available at https://msu.edu/~beede/dairycattlewaterandnutrition.pdf).

Professor Beede's 2006 paper goes on to discuss the varieties of treatment that may be available to remove manganese from a dairy's water supply. (*Id*., at 15-18). Importantly, however, unlike the definition of "Potable Water Supply," the definition of "Livestock Water Supply" (LWS) in Pennsylvania's water quality standards – "Use by livestock and poultry for drinking and cleansing" – does not presuppose that the surface water withdrawn will be treated before being used. 25 Pa. Code § 93.3. Thus, in evaluating whether an instream criterion for manganese is needed to protect the statewide use of LWS, the Department and the Board must assume that the water will be provided to the animals without treatment.

This example illustrates the broader point that the Department, in considering whether to recommend a new instream criterion (or criteria) for manganese to protect other water supply and recreational water uses, and the Board, in determining whether to propose such a criterion, should not assume that the existing, PWS-based criterion of 1.0 mg/l adequately protects the other water uses. Instead, the Department and the Board should remain open to the possibility that an instream concentration of manganese *below* 1.0 mg/l is necessary to protect one or more of those additional water uses.

Thank you for your consideration of these comments and the accompanying information. Please feel free to contact me at 717-214-7925 if you have any questions.

Sincerely,

/s/ Kurt J. Weist

Kurt J. Weist
Senior Attorney
Harrisburg Office

ATTACHMENT A

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

A. Reviews, Summary Papers and Reports

ATSDR (2009). Draft Toxicological Profile for Manganese. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/tp151.pdf

Brown, M. T. and B. Foos (2009). Assessing Children's Exposures and Risks to Drinking Water Contaminants: A Manganese Case Study. Human and Ecological Risk Assessment: An International Journal **15**(5): 923-947. http://www.tandfonline.com/doi/full/10.1080/10807030903153030.
Abstract: Compared to adults, children maybe 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.

Grandjean, P. and P. J. Landrigan (2014). "Neurobehavioural effects of developmental toxicity." The Lancet Neurology **13**(3): 330-338. http://www.thelancet.com/journals/laneur/issue/current?tab=past
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, dichlorodiphenyltrichloroethane, 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.

Institute of Medicine (2001). DIETARY REFERENCE INTAKES FOR Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC, National Academy Press. http://books.nap.edu/openbook.php?record_id=10026

Ljung, K. and M. Vahter (2007). Time to re-evaluate the guideline value for manganese in drinking water? Environ Health Perspect **115**(11): 1533-1538. http://www.ncbi.nlm.nih.gov/pubmed/18007980
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.

Menezes-Filho, J. A., M. Bouchard, et al. (2009). Manganese exposure and the neuropsychological effect on children and adolescents: a review. Rev Panam Salud Publica 26(6): 541-548. http://www.ncbi.nlm.nih.gov/pubmed/20107709
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.

Roels HA, et al. Manganese exposure and cognitive deficits: A growing concern for manganese neurotoxicity. Neurotoxicology (2012), http://dx.doi.org/10.1016/j.neuro.2012.03.009
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.

US EPA (2004). Drinking Water Health Advisory for Manganese. EPA-822-R-04-003, US EPA, Office of Water, Health and Ecological Criteria Division. http://www.epa.gov/ogwdw/ccl/pdfs/reg_determine1/support_cc1_magnese_dwreport.pdf

B. More Recent Research Papers

Beaudin, S. A., S. Nisam, et al. (2013). "Early life versus lifelong oral manganese exposure differently impairs skilled forelimb performance in adult rats." Neurotoxicol Teratol **38C**: 36-45. http://www.ncbi.nlm.nih.gov/pubmed/23623961.

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

quantification of skilled motor performance using the staircase test can serve as a sensitive measure of early life insults from environmental agents.

Bouchard, M., F. Laforest, et al. (2007). Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ Health Perspect **115**(1): 122-127. http://www.ncbi.nlm.nih.gov/pubmed/17366831
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: WI: 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 WI 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.

Bouchard, M. F., S. Sauve, et al. (2011). Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water. Environ Health Perspect **119**: 138-143. http://www.ncbi.nlm.nih.gov/pubmed/20855239
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.

Boyes, W. K. (2010). "Essentiality, toxicity, and uncertainty in the risk assessment of manganese." J Toxicol Environ Health A **73**(2): 159-165. http://www.ncbi.nlm.nih.gov/pubmed/20077286.

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, methylcyclopentadienyl 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.

Claus Henn, B., A. S. Ettinger, et al. (2010). "Early postnatal blood manganese levels and children's neurodevelopment." Epidemiology **21**(4): 433-439. http://www.ncbi.nlm.nih.gov/pubmed/20549838.

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.

Cordova, F. M., A. S. Aguiar, Jr., et al. (2013). "Manganese-exposed developing rats display motor deficits and striatal oxidative stress that are reversed by Trolox." Arch Toxicol **87**(7): 1231-1244. http://www.ncbi.nlm.nih.gov/pubmed/23385959

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.

Erikson, K. M., K. Thompson, et al. (2007). Manganese neurotoxicity: a focus on the neonate. Pharmacol Ther **113**(2): 369-377. http://www.ncbi.nlm.nih.gov/pubmed/17084903
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.

Fordahl, S., P. Cooney, et al. (2012). "Waterborne manganese exposure alters plasma, brain, and liver metabolites accompanied by changes in stereotypic behaviors." Neurotoxicology and Teratology **34**(1): 27-36. http://www.ncbi.nlm.nih.gov/pubmed/22056924.
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.

Kern, C. H., G. D. Stanwood, et al. (2010). Preweaning manganese exposure causes hyperactivity, disinhibition, and spatial learning and memory deficits associated with altered dopamine receptor and transporter levels. Synapse **64**(5): 363-378. http://www.ncbi.nlm.nih.gov/pubmed/20029834
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.

Khan, K., P. Factor-Litvak, et al. (2011). Manganese Exposure from Drinking Water and Children's Classroom Behavior in Bangladesh. Environmental Health Perspectives **119**(10): 1501-1506. http://www.ncbi.nlm.nih.gov/pubmed/21493178
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 [estimated β = 0.82; 95% confidence interval (CI), 0.08–1.56; p = 0.03], TRF externalizing (estimated β = 2.59; 95% CI, 0.81–4.37; p =0.004), and TRF total scores (estimated β = 3.35; 95% 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 exposurefrom 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.

Oulhote Y, Mergler D, et al. (2014). "Neurobehavioral Function in School-Age Children Exposed to Manganese in Drinking Water " Environ Health Perspect. Advance publication 26 Sept., 2014.http://dx.doi.org/10.1289/ehp.1307918.

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.

Parvez, F., G. A. Wasserman, et al. (2011). Arsenic Exposure and Motor Function among Children in Bangladesh. Environmental Health Perspectives **119**(11): 1665-1670. http://www.ncbi.nlm.nih.gov/pubmed/21742576

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 [$\beta = -3.63$; 95% confidence interval (CI): -6.72, -0.54; $p < 0.01$], FMC ($\beta = -1.68$; 95% CI: -3.19, -0.18; $p < 0.05$), and BC ($\beta = -1.61$; 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 ($\beta = 3.54$; 95% CI: 1.10, 6.0; $p < 0.01$), FMC ($\beta = 1.55$; 95% CI: 0.40, 2.70; $p < 0.005$), and MC ($\beta= 1.57$; 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.

Santamaria, A. B. and S. I. Sulsky (2010). Risk Assessment of an Essential Element: Manganese. Journal of Toxicology & Environmental Health: Part A **73**(2/3): 128-155. http://www.ncbi.nlm.nih.gov/pubmed/20077284

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

Wasserman, G. A., X. Liu, et al. (2006). Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect **114**(1): 124-129. http://www.ncbi.nlm.nih.gov/pubmed/16393669

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.

Wasserman, G. A., X. Liu, et al. (2011). Arsenic and manganese exposure and children's intellectual function. Neurotoxicology **32**(4): 450-457. http://www.ncbi.nlm.nih.gov/pubmed/21453724

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 10mug/L) and Mn (above and below 500mug/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 socio-demographic 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.

Woolf, A., R. Wright, et al. (2002). A Child with Chronic Manganese Exposure from Drinking Water. Environ Health Perspect **110**(6). http://www.ncbi.nlm.nih.gov/pubmed/12055054

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

ATTACHMENT B

April 6, 2015

Docket EPA-HQ-OW-2012-0217
Water Docket
Environmental Protection Agency
Mail Code: 2822T
1200 Pennsylvania Ave., NW.
Washington, DC 20460

To Whom it May Concern:

In response to the notice in the *Federal Register* of February 4, 2015 (80 FR 6076), the Association of State Drinking Water Administrators (ASDWA) is offering comments to the U.S. Environmental Protection Agency (EPA) on the draft Fourth Contaminant Candidate List (CCL4). ASDWA is the professional Association that represents the collective interests of the drinking water programs in the states, territories, Navajo Nation, and District of Columbia responsible for implementation of the Safe Drinking Water Act (SDWA). The regulatory determinations that will ultimately be made on the contaminants on this list can significantly impact the future activity of state drinking water programs as they implement the SDWA. The path to future regulatory decisions begins with this list and the contaminants that are included need to be carefully evaluated. We therefore ask you to consider these comments as you finalize CCL4.

ASDWA continues to support the regulatory process (CCL, UCMR, Regulatory Determination, 6 year review) set forth in the 1996 amendments to the SDWA. We especially appreciate and encourage continued strong coordination between the CCL and UCMR processes. It is a science-based process that makes regulatory determinations only after considering health effects, occurrence and determining that a regulation can improve public health protection. We believe that the process, when supported with adequate data, is vastly preferable to regulating based on arbitrary target numbers or focusing on contaminants with high media profiles -- but where regulation may not supported by reliable data. We also appreciate, and actively contribute to, the public participation opportunities at each stage of the regulatory process. Such an open and transparent process is essential to developing regulations that are both scientifically credible and implementable.

Comments on the Contaminants on the Draft List:

We support EPA's process for developing the CCL4 which carries forward those contaminants from CCL3 where there have not yet been regulatory determinations made. Available data on the CCL3 contaminants have already shown that there could be some potential public health

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impact in drinking water from these contaminants and it makes sense to continue to evaluate them until a final decision can be made. However, the CCL should not be a permanent home for contaminants. Once there is adequate data to support a decision, either to regulate or not to regulate, those contaminants should be removed so the focus can shift to other contaminants where more information is needed. It also makes sense to continue to look for potential additions to the list by asking the public for recommendations and reviewing contaminants previously dropped due to a negative regulatory determination. We support the decision to include manganese in the CCL4, since there have been several studies on the adverse neurotoxic effects of high manganese (> 400 ug/L) in drinking water (see additional comments by Minnesota). We also believe EPA has adequate justification for adding nonylphenol to the CCL, based on new health effects and occurrence data.

The state of Massachusetts provided detailed comments in support of a few of the contaminants on CCL4, including 1,4-dioxane, chlorate, manganese, perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS) and methyl tertiary butyl ether (MTBE). In addition, Minnesota provided detailed comments on other contaminants on the list – viruses, *Legionella*, and manganese. These state comments not only support the inclusion of the contaminants in the CCL but provide information that can support future inclusion in the UCMR and subsequent regulatory decisions. We have attached those comments in separate pages because of their length. The attachment also includes comments from the state of Washington relative to possible future CCLs. Although we understand that the time for officially recommending new contaminants has passed, the state of Washington did propose some additional contaminants that EPA should consider for the CCL. ASDWA is passing along these recommendations for your consideration and action at the appropriate time. Finally, we are attaching a March 23, 2015 letter from the Ohio EPA which recommends including saxotoxin and its associated isomers, as well as euglenophycin to the CCL4 – and expanding the evaluation of microcystin-LR to include all commonly occurring microcystin conginers. We commend those recommendations for your consideration.

In closing, ASDWA is pleased to provide input on the draft CCL4 and appreciates the Agency's consideration of our comments. We also ask that you pay particular attention to the more detailed data provided by individual states on this subject. Please contact me at 703-812-9507 or jtaft@asdwa.org if we can provide additional information or if any clarification of these comments is needed.

Sincerely,

James D. Taft
Executive Director

Attachment

Detailed Comments on CCL4 Contaminants from Massachusetts:

Massachusetts' Drinking Water Program would like to comment on six of the chemicals listed in the draft CCL 4 list of chemicals: 1,4-dioxane, chlorate, manganese, perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS) and methyl tertiary butyl ether (MTBE).

1,4-dioxane:

Many states first became aware of the potential for 1,4-dioxane to impact drinking water resources from monitoring around older landfills where escaping leachates were mixing with surrounding groundwaters. While often a private well issue, there are cases where public water supply groundwater wells are or were being or are potentially impacted by 1,4-dioxane from that type of source. More recently, with improved monitoring, states are getting a better picture of the potential for this chemical to be present in public water supplies. We urge that EPA retain 1,4-dioxane on its CCL 4 list for several reasons: 1) it has been a widely used as a solvent and organic solvent stabilizer in the past. It has also been a component of many home personal care products; 2) the US EPA has a recent toxicological evaluation of 1,4-dioxane and toxicity values which could serve as the basis for national drinking water exposure limits and which presently are the basis of some state's drinking water guidance values (e.g., Massachusetts: available at http://www.mass.gov/eea/agencies/massdep/water/drinking/standards/1-4-dioxane.html); 3) early data returns from Unregulated Monitoring Rule (UCMR) 3 monitoring programs show somewhat frequent, low level 1,4-dioxane concentrations. For example, one New England member state, Massachusetts, has had 75 positive detections of 1,4-dioxane with an average concentration of 0.14 ug/L and maximum of 0.41 ug/L after about 2/3 of its UCMR3 monitoring returns have been received. EPA's leadership on following this chemical through its drinking water standards development process will be most beneficial to states because setting and implementing a drinking water exposure limit for 1,4-dioxane presents challenges to each and every state. A health-based exposure limit derived from current IRIS toxicity values yields a very low concentration in water. There is a good EPA analytical method for quantitating down in this concentration range. Much of the monitoring data coming in to some programs is in the same concentration range. It is not clear what type of water treatment can be used to address 1,4-dioxane and what associated costs might be. This is a compound that has been in wide use in personal care products, however we understand that reformulations are lowering the 1,4-dioxane contents of some of these products.

Chlorate:

Chlorate is a presently unregulated oxidant (and chlorite) produced in drinking water systems that disinfect water using chlorine dioxide. Chlorine dioxide is a strong oxidant that is fairly unstable and readily decomposes to sodium chlorite (its main degradation product), chloride and to a lesser extent, chlorate under oxidant demand conditions. Chlorite and chlorate may also be produced in drinking waters disinfected with sodium hypochlorite. As the sodium hypochlorite

slowly decomposes, and more is added to maintain chlorine residual, the chlorate level of the water also increases (WHO, 2005).

We are recommending that chlorate be retained on the CCL 4 list for toxicity and exposure potential considerations. By far the largest source of exposure of Americans to this compound is as a disinfectant byproduct through drinking water.

Chlorate, chlorite and chlorine dioxide have similar types of effects and potencies, primarily associated with disruption of the thyroid and pituitary gland. Alterations in thyroid hormone levels can lead to changes in somatic growth, brain development and be manifested in neuropsychological developmental deficits. Exposures to all of these compounds are also associated with hematological changes.

Chlorine dioxide and chlorite have the same IRIS oral reference doses (0.03 mg/kg/d) for neurodevelopmental endpoints. A case can be made for a similar value for chlorate. Each RfD value translates into an associated drinking water concentration of 0.8 mg/L. This numerical value is presently codified as an MCLG for chlorite (MCL is actually 1.0 mg/L based on practicality considerations) and MRDLG for chlorine dioxide.

The individual drinking water exposure concentration limits for chlorine dioxide and chlorite neglect to consider co-exposures from the other compounds producing similar effects. Because chlorine dioxide, chlorite *and* chlorate produce similar effects, have the same RfD, and are to a certain extent interconvertible, the limit of acceptable daily exposure represented by the reference dose should apply to the total exposures from all three. It would make more sense to limit total exposures to all 3 compounds to the protective concentration of any one, rather than to allow 3 independent exposures up to this same level, essentially allowing exposures three times the protective level for the same endpoint.

This approach would be in keeping with the US EPA's 2010 announced New Approach to Protecting Drinking Water and Public Health to "address contaminants as groups rather than one at a time so that enhancement of drinking water protection can be achieved cost-effectively" (http://water.epa.gov/lawsregs/rulesregs/sdwa/dwstrategy/index.cfm).

This recommendation is also very similar to the recommendation made by the U.S. EPA in their 1983 document, "Trihalomethanes in Drinking Water: Sampling, Analysis, Monitoring and Compliance, EPA 570/9-83-002", in which it states, "If chlorine dioxide is used [as a disinfectant], the total oxidant (i.e., chlorine dioxide, chlorite and chlorate) residual should be kept below 1.0 mg/L…"

EPA's leadership on this issue is needed to provide clear, health-protective guidance on oxidant exposures in drinking water systems while crafting eventual guidance which balances the health benefits

Manganese:

Massachusetts Department of Environmental Protection in their letter of June 22, 2012 to the docket (**Docket ID No. EPA-HQ-OW-2012-0217**), nominated manganese for inclusion on the CCL 4 list. Since that time there has been additional information supporting their comments that we wish to bring to your attention.

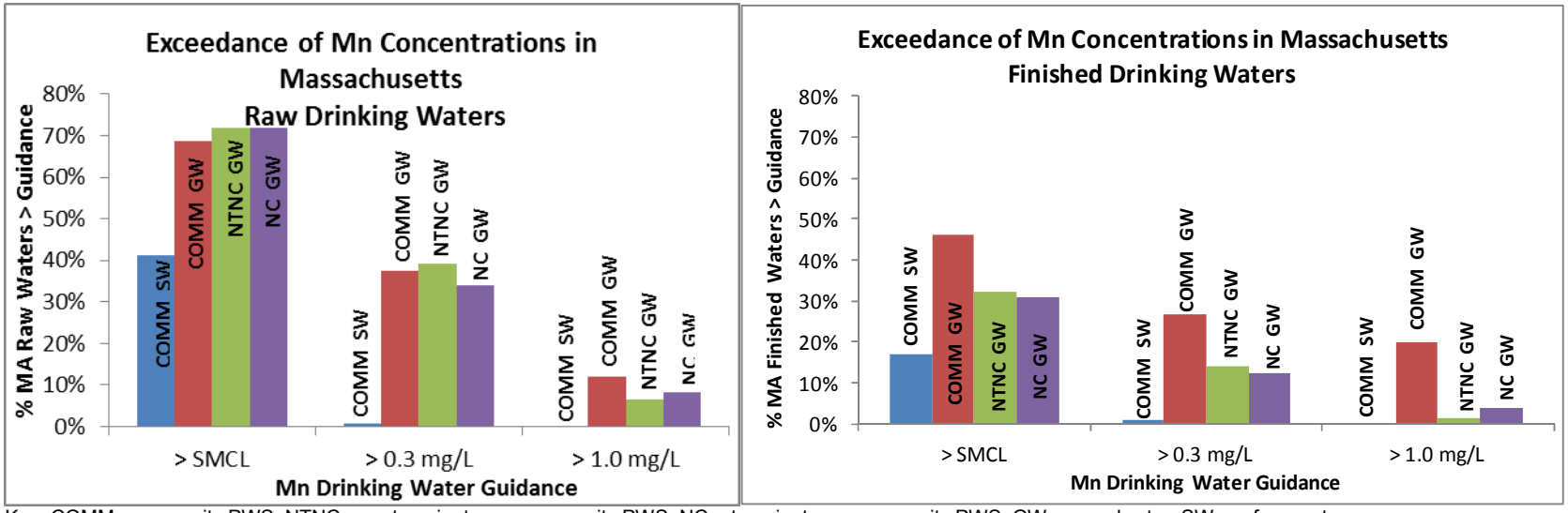
There have been a number of additional studies concerning the possible link between drinking water manganese exposures and neurodevelopmental deficits in school age children. Other studies with arsenic exposures in drinking water have also considered manganese exposure issues and bear examination. There have also been some large scale natural occurrence studies. These are listed in the attachment to this letter. We recommend that they be evaluated by EPA as part of a consideration about regulating manganese on a national scale. At a minimum, the toxicity and epidemiology studies should serve as a part of an updated evaluation of the toxicity of manganese from drinking water exposures which would serve to support updated Health Advisory values.

Massachusetts has recently undertaken an initiative to make its public water suppliers and their customers more aware of the existing US EPA Health Advisory values for manganese and the health implications of having exposures greater than those guidelines. A monitoring requirement for manganese was also a part of the initiative so that suppliers would know the manganese status of their systems. A preliminary summarization of that data is included in Table 1 and Figure 1 to illustrate the occurrence of manganese in raw and finished water of different categories of public drinking water supplies of that state.

Note that from these data, a significant number of the samples had manganese concentrations greater than the US EPA lifetime Health Advisory level of 0.3 mg/L. That advisory also includes a warning to not use water with that much manganese longer than 10-days for infants. The summarized sampling data indicate that approximately 35-40% of raw groundwater samples used by these public water suppliers exceed this limit and about 12-26% of finished water samples do.

Table 1. Summary Statistics for Manganese Concentrations in PWS in Northeast State 2013-2015.

SYSTEM TYPE	WATER TYPE	n	MIN (mg/L)	MAX (mg/L)	Median (mg/L)	75th %ile (mg/L)	95th %ile (mg/L)	% > SMCL	% > 0.3 mg/L	% > 1.0 mg/L
COMMUNITY	SURFACE RAW	141	ND	0.48	0.04	0.10	0.20	41.13	0.71	0.00
	SURFACE FINISHED	522	ND	0.81	0.01	0.03	0.11	17.05	1.15	0.00
	GROUNDWATER RAW	922	ND	3.58	0.17	0.48	1.60	68.55	37.42	12.04
	GROUNDWATER FINISHED	3620	ND	2.40	0.01	0.09	0.38	46.10	26.63	19.81
NTNC	GROUNDWATER RAW	303	ND	2.40	0.21	0.57	1.12	71.95	39.27	6.60
	GROUNDWATER FINISHED	731	ND	2.67	0.01	0.10	0.66	32.01	14.09	1.50
NC	GROUNDWATER RAW	132	ND	5.38	0.16	0.43	1.39	71.97	34.09	8.33
	GROUNDWATER FINISHED	1458	ND	8.65	0.01	0.09	0.72	30.80	12.21	3.98



Key: COMM=community PWS; NTNC=non-transient, non-community PWS; NC = transient non-community PWS; GW=groundwater; SW=surface water

Figure 1. Frequencies of Exceedances of Manganese Concentration Exposure Limits in Community Water Systems (Raw and Finished Water)

MTBE:

This compound has been of concern to states for many years, particularly when it was used widely as a gasoline additive in the United States and still as a legacy contaminant. States have urged EPA for many years (both through comment to the Docket on various CCL lists and in interactions with EPA at meetings of the Federal-State Toxicology and Risk Analysis Committee) to issue toxicological guidance for MTBE to help them deal with MTBE contamination issues. Yet EPA has failed to take a definitive position on the appropriate toxicity value (s) to use when assessing health risks from exposures to MTBE and for identifying a protective drinking water concentration. For these reasons, we urge EPA to retain MTBE on its CCL 4 list.

Perfluorooctanoic Acid (PFOA) and Perfluorooctanesulfonic Acid (PFOS):

These two perfluorinated compounds have been coming to states' attentions more recently as a result of early data returns from the UCMR 3 sampling program. The undesirable toxicological and environmental fate characteristics of these compounds have been summarized by Post *et al.* (2012). While some uses and production of these compounds have been reduced or curtailed, they nevertheless continue to be problematic from a drinking water perspective given their persistence in the environment. We are pleased to see the continued presence of these two compounds on the fourth CCL list after they were on the third list. We urge EPA to continue to keep them in their process for eventual drinking water regulation as addressing their presence in public water supply source or finished waters they will present some serious challenges to states. This is because toxicological evaluations presently in progress by EPA suggest that eventual health-based drinking water limits for these compounds could be very low, with the often attendant implication that presence equates to unacceptable risk. In addition, states will need assistance identifying effective treatment methods for these compounds.

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Detailed Comments on CCL4 Contaminants from Minnesota:

Viruses:

Several studies have indicated that viruses are present in approximately 25% of groundwater drinking water sources. What we need to know is how to target drinking water protection efforts to the sources that are vulnerable to virus contamination. It is recommended for EPA to: Work on developing/refining a method for testing multiple microbes that is faster and less expensive than current methodologies. A method that requires a reasonable sample volume (<100 L) and gives a good indication of overall microbial quality would be ideal. Dead-end ultrafiltration is currently the technology of choice for sampling many microbes, and a standardized methodology could be developed around this technology. Updating laboratory protocols/certification for qPCR and other methods also needs to be a priority.

If EPA continues occurrence sampling, it is recommended to be more strategic in choosing sample sites with known well construction information and to "ground-truth" geology, climatological factors (rainfall) and contamination source data so that any occurrence data are more useful. The sample site should be standardized to untreated source water. If only annual samples are possible, the month following the highest average monthly precipitation should be sampled.

Legionella:

The current scientific consensus is that *Legionella* is something that can be present in source water and distribution systems, and that sampling for Legionella is less useful than assuming Legionella could be present and managing building water systems accordingly to minimize risk. We would want to know EPA's plan and purpose for any Legionella sampling. It seems the question is how Legionella should be managed and should it be by the water utility, building owners, or both? Clarifying the regulatory connections will be important going into the future.

Manganese:

We write today in support of your decision to include manganese in the CCL4. Manganese occurrence in Minnesota groundwater is widespread. Many Minnesotans may be exposed at levels that present a health risk. About 20% of groundwater samples tested in Minnesota contained manganese above the USEPA Health Advisory level of 300 µg/L. Approximately half of all ground water samples tested in the last 20 years contained manganese above the Minnesota health based guidance value of 100 µg/L.

Although many consider manganese to be only a nuisance, the evidence supports that exposure to manganese can present a health threat. Bouchard et al. (2011) and Oulhote et al. (2014) have published studies showing neurological effects in children exposed to levels as low as 100 µg/L. Although these studies have some shortcomings, they are supported by the animal evidence. Kern and colleagues (2010) clearly showed neurological effects in young rats after exposure to manganese. Taken together, these three studies raise the alarm that manganese may be causing neurological deficits in young children that are exposed.

The occurrence data, combined with the health effect information, clearly shows that there is a case for monitoring and regulating manganese in drinking water. Including manganese in the CCL4 is the first step in protecting infants and children from the deleterious effects of manganese.

Comments from Washington on Future CCLs:

1. The list of Cyanotoxins should be revised to include Saxitoxin. See https://www.nwtoxicalgae.org/StateSummary.aspx. In Washington State, we conducted a review of the health risk of saxitoxin in 2011 with involvement of experts outside the agency. See http://www.doh.wa.gov/Portals/1/Documents/4400/332-118-CylindroSax%20Report.pdf. As noted in this document, this cyanotoxin has drinking water health advisories in the 1.0 to 3.0 ug/L range due to its acute neurotoxic effects. Given the acute nature of this toxin and its occurrence in recreational water bodies in Washington State, it merits inclusion in the CCL for future consideration along with the currently listed cyanotoxins.
2. Based on a EPA presentation to the National Drinking Water Advisory Council (NDWAC) in November 2014, the list of unregulated carcinogenic VOCs for potential future regulation includes 1,1,2,2-Tetrachloroethane (CASRN 79-34-5). This contaminant should be listed on the CCL if it still under consideration for the potential cVOC group.
3. DCPA and DCPA acid metabolites should be restored in the next Contaminant Candidate List. Since the EPA removed DCPA from the CCL2 in 2008 (http://www2.epa.gov/ccl/regulatory-determination-2-support-documents-dacthal-mono-acid-mtp-and-di-acid-tpa-degradates) Washington has measured the metabolites, MTP and TPA, in both private and public ground water supplies. The Washington State Department of Agriculture and the Washington State Department of Health have found that concentrations have exceeded the health advisory limit in two areas of the state. See http://agr.wa.gov/FP/Pubs/docs/103-410DacthalReport2014.pdf and http://iaspub.epa.gov/tdb/pages/contaminant/contaminantOverview.do. Because DCPA persists in the environment and we have discovered levels in drinking water above the health advisory limit, we recommend its inclusion in the CCL.