Comments of the Manganese Interest Group in response to the Pennsylvania Department of Environmental Protection Advanced Notice of Proposed Rulemaking: Water Quality Standard for Manganese

48 Pa.B. 605; Pa.B. Doc. No. 18-138 (Jan. 27, 2018)

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I. Introduction

On behalf of the Manganese Interest Group ("MIG"), we are pleased to submit the following comments regarding the Pennsylvania Department of Environmental Protection ("PaDEP" or "Department") advanced notice of proposed rulemaking ("ANPR") on revisions to the Water Quality Standard for Manganese. *See* 48 Pa.B. 605 (Jan. 27, 2018) (hereinafter "the Notice"). MIG is an *ad hoc* coalition of trade associations and companies interested in the scientifically sound evaluation and regulation of manganese ("Mn") and its compounds. MIG members include steel producers, metalworkers, chemical manufacturers, ferroalloy producers, and other like-minded stakeholders, many of whom operate in Pennsylvania.[1]

Manganese is an essential nutrient that is subject to strict homeostatic control in the human body. As the current U.S. Environmental Protection Agency ("EPA") Integrated Risk Information System ("IRIS") assessment for manganese states:

> Manganese is a ubiquitous element that is essential for normal physiologic functioning in all animal species. Several disease states in humans have been associated with both deficiencies and excess intakes of manganese. Thus any quantitative risk assessment for manganese must take into account aspects of both the essentiality and the toxicity of manganese.

Large amounts of Mn are naturally present in many foods consumed as a part of a normal diet, so Mn in drinking water is unlikely to add materially to the normal daily ingestion of Mn from diet. Against this backdrop, the science in the current literature concerning manganese and any potential risk it might pose as a constituent of drinking water[2] does not support amendment of the Mn water quality standard.

MIG's principal interest in the Notice is the Department's request for information concerning "[p]eer-reviewed, published toxicological studies, reports and data on human health effects resulting from exposure to Mn in water." As discussed below, while a number of studies during the last decade have examined the potential for adverse effects, particularly developmental toxicity, from exposure to Mn in water, these studies do not support a causal association. In particular:

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[1] Group members include: the American Iron and Steel Institute, the Steel Manufacturers Association, the Specialty Steel Industry of North America, the International Manganese Institute, the National Slag Association, Afton Chemical Corporation, Carpenter Technology Corp., Cliffs Natural Resources, Electralloy, Eramet Marietta, Inc., Felman Production, Inc., New Castle Stainless Plate LLC, Nucor Steel, S.H. Bell Company, Universal Stainless & Alloy Products, and U.S. Steel.

[2] The Notice states: "Manganese possesses toxic characteristics according to information available in the scientific literature and as described in the EPA Integrated Risk Information System (IRIS) database. Some studies suggest elevated levels of Mn may lead to neurological deficits in children, including poor school performance, impaired cognitive function, diminished memory, abnormal performance on neuro-behavioral tests, motor impairments, and increased oppositional or aggressive behavior and hyperactivity."

1. Results are not consistent from one study to the next. The studies do not indicate any consistent dose-response relationship, with some showing no impact, at least one showing positive effects, and some showing (mostly statistically nonsignificant) negative effects. Moreover, there is no clear pattern of association between adverse effects and within study populations or in comparison to the general population (*i.e.*, negative associations are not systematically stronger or more likely to be statistically significant in studies with higher average blood or hair Mn concentrations).

2. The studies do not use consistent biomarkers for Mn and apply different sets of tests to evaluate intellectual development from one study to the next. Unfortunately, there is not yet a validated biomarker for Mn exposure (similar to blood as a biomarker for lead exposure).

3. All of the studies openly acknowledge confounding variables that limit the strength of any causal inferences that might be made concerning the effects of Mn exposure. Environmental confounding factors such as parental education, nutrition, and exposure to other environmental pollutants, such as lead, all have been shown to statistically affect IQ. Most of the current studies were conducted in areas where effects of poverty lead to decreased education of both parents and children as well as malnutrition and exposure to other environmental pollutants. Other confounding factors such as information or selection bias, reverse causation, and effect modification, may influence the reported results and could be responsible for the inconsistencies observed among studies. Accordingly, it is impossible for these studies to establish a causal link between Mn exposure and developmental effects.

4. The cross-sectional design of most of these studies also is problematic in attempting to establish a causal relationship. In general, properly conducted prospective cohort studies are more likely to yield valid results than cross-sectional studies because exposure assessment prior to outcome assessment precludes reverse causation in prospective studies, whereas the temporal relationship between exposure and outcome is ambiguous in cross-sectional studies.

5. The results showing adverse impacts are not biologically plausible based on validated human physiologically-based pharmacokinetic ("PBPK") models for manganese inhalation and ingestion.

Any purported link between the consumption of drinking water and developmental neurotoxicity is not sufficiently robust to warrant adoption of a health effects-based Mn water quality standard. The most recent assessments of these studies by other highly respected regulatory authorities, such as the Agency for Toxic Substances Disease Registry ("ATSDR") and the Ontario Ministry of Environment ("MOE"),

reached similar conclusions. In addition, studies released subsequent to the ATSDR and Ontario assessments, suffer from the same limitations as those noted above. While ATSDR and MOE have acknowledged the existence of studies which purport to show a link between exposure to Mn in air or water and developmental neurotoxicity, those agencies also have recognized the significant scientific weaknesses inherent to those studies that foreclose causal inferences that would support the need to amend the Mn water quality standard.

In addition, several studies, including a study in rats, conducted to augment existing and validated human PBPK models for adults, pregnant and lactating women, neonates and infants, demonstrate that Mn taken into the body via ingestion of drinking water does not lead to greater tissue concentrations of Mn in critical tissues, such as the brain, than Mn ingested in food.[3] Because the amount of Mn safely consumed on a daily basis in food is very large in comparison to the U.S. Environmental Protection Agency's ("EPA's") existing lifetime health advisory value of 0.3 milligrams of Mn per liter ("mg Mn/L"), that value is protective of public health with an ample margin of safety. Accordingly, MIG respectfully maintains that current science does not warrant development of a human health-based toxics criteria for Mn in water and requests that Pennsylvania maintain the existing Mn water quality standard.

[3] The human PBPK model can be used to estimate changes in manganese tissue levels as normal dietary intake and environmental or occupational exposures to manganese in air and water change over time. It demonstrates, among other things, the existence of dose dependent triggers for the accumulation of manganese in key target tissues, such as the brain.

See Schroeter, JD; Dorman, DC; Yoon, M; Nong, A; Taylor, MD; Andersen, ME; Clewell, HJ. 2012. "Application of a multi-route physiologically-based pharmacokinetic model for manganese to evaluate dose-dependent neurological effects in monkeys." Toxicol. Sci. 129(2):432-446;

Schroeter, JD; Nong, A; Yoon, M; Taylor, MD; Dorman, DC; Andersen, ME; Clewell, HJ III. 2011. "Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multiroute physiologically based pharmacokinetic models." Toxicol. Sci. 120(2):481-498. doi: 10.1093/toxsci/kfq389;

Yoon, M; Schroeter, JD; Nong, A; Taylor, MD; Dorman, DC; Andersen, ME; Clewell, HJ III. 2011. "Physiologically based pharmacokinetic modeling of fetal and neonatal manganese exposure in humans: Describing manganese homeostasis during development." Toxicol. Sci. 122(2):297-316. doi: 10.1093/toxsci/kfr141.

II. The Purported Link Between Consumption of Drinking Water and Developmental Neurotoxicity is Not Sufficiently Robust to Warrant Development of a Human Health-Based Standard

In 2012, ATSDR updated its comprehensive "Toxicological Profile for Manganese" (hereafter "Mn Profile").[4] As part of the update, ATSDR reviewed the developmental neurotoxicity studies that have been cited as raising questions about potential adverse effects associated with ingesting Mn in drinking water. Based on its review, ATSDR ultimately concluded that the studies were not sufficiently robust for a range of reasons to allow causal inferences concerning exposure to manganese in air or water and developmental neurotoxicity. A summary of ATSDR's assessment of the studies can be found in the following table. (The parenthetical in the "Assessment" column provides the page or pages from the Mn Profile that address the studies.)

Study	Summary	Assessment
Riojas-Rodriguez et al. 2010	Air-borne manganese exposure is inversely associated with intellectual function in young school-age children.	"[M]anganese exposure from other sources (groundwater, dietary) was not considered, and association between air concentration and test results were not explored." (Page 89)
Menezes-Filho et al. (2011)	High manganese exposure, likely via air emissions from a Brazilian ferroalloy plant, had detrimental effects on cognition in children, especially in the verbal domain.	"[T]hey state that poor cognitive development in children may also be due in part to lower caregiver IQs. Additionally, this study bears the limitations of a cross-sectional design, and casual inferences cannot be made on the relationship of manganese exposure and cognitive defects." (Page 90)
Bouchard et al. (2011)	Low-level chronic exposure to manganese in drinking water is associated with intellectual impairments in children.	The study authors "acknowledged that inferences that can be drawn from the study are limited due to the cross-sectional design, and suggested that the findings should be replicated in another study." (Page 168)
Kim et al. (2009)	Shows a significant inverse association between both blood manganese and blood lead and full scale and verbal IQs.	"The results are consistent with joint toxic action of lead and manganese on full scale and verbal IQ scores in these children, but the design of the experiment is inadequate to conclude whether the joint action is additive, greater than additive, or less than additive." (Page 169)

[4] Toxicological Profile for Manganese, U.S. Department of Health and Human Services, Public Health Service Agency for Toxic Substances and Disease Registry (September 2012) available at http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=102&tid=23.

Claus Henn et al. (2010)	Results suggest a possible synergism between lead and excessive manganese to impair development of mental and psychomotor skills during the first year of life.	"The study design, however, is inadequate to discern if the possible interaction is additive or greater than additive." (Page 170)
Bouchard et al. (2007, 2011); Claus Henn et al. (2010); Farias et al. (2010); He et al. (1994); Kim et al. (2009); Wasserman et al. (2006, 2011); Zhang et al. 1995	Results from these epidemiological studies suggest the possibility that excess manganese ingestion could lead to learning or behavioral impairment in children.	"[A]n association of this sort is not sufficient to establish a cause-effect relationship because a number of other agents, including lead, might also be involved (Phil and Parkes 1977). Moreover, other potentially confounding factors (e.g., health and nutritional status) must be taken into consideration in interpreting such studies." (Pages 172-173)
Bouchard et al. (2007, 2011); Claus Henn et al. (2010); Farias et al. (2010); Wasserman et al. (2006, 2011); Brna et al. (2011); Sahni et al. (2007); Woolf et al. (2002); Riojas-Rodriguez et al. (2010); Meneze-Filho et al. (2011)	Several recent reports continue to implicate elevated manganese exposure with impaired neurodevelopment.	"Taken together, these recent studies provide added weight to the evidence for the neurotoxic potential of excessive manganese in children, but one or more of the following uncertainties preclude the characterization of causal and dose-response relationships between the observed effects and manganese exposure: (1) whether or not the observed effects were solely due to excess manganese alone or could have been influenced by other drinking water or dietary components; (2) the lack of quantitative information about manganese levels from different environmental sources (food, water, and air); and (3) the small sample sizes." (Pages 311-313)

Like ATSDR, the Ontario MOE also assessed several of the studies regarding exposure to Mn in drinking water.[5] As shown in the table below, the MOE expressed concerns similar to those stated by ATSDR. (The parenthetical in the "Assessment" column provides the page or pages from the MOE assessment that address the studies.)

Study	Summary	Assessment
Zoni et al. (2007); Ericson et al. (2007); Takser et al. (2003); Bouchard et al. (2007); Wasserman et al. (2006); He et al. (1994); Wright et al. (2006); Menezes-Filho et al. (2009)	Studies assessing the effect of Mn neurotoxicity in children reveal dose-dependent cognitive effects more consistently and at lower doses, than motor effects.	"It is important to state that in some of these studies potential confounders were not taken into consideration therefore interpretation of the results needs to proceed with caution." (Page 50)

[5] Ontario Air Standards for Manganese and Manganese Compounds, Standards Development Branch, Ontario Ministry of the Environment (June 2011) available at:

www.ebr.gov.on.ca/ERS-WEB-External/displaynoticecontent.do?noticeId=MTA2MTc3&statusId=MTY5OTM4

Ericson et al. (2007); Takser et al. (2003); Bouchard et al. (2007); Wasserman et al. (2006); He et al. (1994); Wright et al. (2006); Menezes-Filho et al. (2009); Hafeman et al. (2007); Collip et al. (1983); Zhang et al. (1995); Kim et al. (2009)	Limited epidemiological studies conducted in children alert of the possibility that the developing nervous system may be particularly susceptible to subtle yet significant adverse neurological effects.	"[T]hese studies have issues with potential confounders and thus may not render themselves to detailed dose/response analysis . . . ." (Page 101)

In addition, researchers openly acknowledge that the studies purporting to show a link between manganese exposure and effects in children "have numerous limitations":

> Studies published so far have several serious limitations, including sample size, research design, adjustment for potential confounding variables, and control of coexposure to other neurotoxicants. All reviewed studies except that of Takser and colleagues (33) were cross-sectional and had a modest sample size. Cross-sectional studies provide less convincing evidence than cohort studies in showing a potentially harmful effect.[6]

For this reason, it has been recommended that any "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."[7] (In the case of studies considering potential effects of Mn exposure on development, it is important that future research also consider information on parental professional status/level of education and general life style as these factors normally have a direct effect on intellectual performance.)

Finally, and of particular note, ATSDR's 2012 Mn Profile increased by nearly an order of magnitude the inhalation "minimal risk level" for manganese from 0.04 micrograms per cubic meter ("$\mu g/m^3$") to 0.3 $\mu g/m^3$.[8] ATSDR did so, despite the studies purporting to show developmental neurotoxicity, by removing an uncertainty factor of five that was previously applied "for potentially increased susceptibility in children based on differential kinetics in the young."[9] ASTDR determined that the PBPK model for fetuses, suckling neonates, and 3-year old children demonstrated that the additional uncertainty factor was not necessary "under normal dietary manganese exposure conditions" and that the standard uncertainty factor of ten "for human variability including possibly enhanced susceptibility of the elderly, infants, and children" was sufficient.[10]

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[6] Menezes-Filho, J.A., et al., "Manganese exposure and the neuropsychological effect on children and adolescents: a review," Rev Panam Salud Publica/Pan Am J Public Health 26(6), 2009, p. 546.

[7] *Id*. at 541.

[8] Mn Profile at 435.

[9] *Id*.

[10] *Id*.

Since release of the Mn Profile, other offices within EPA, including the Office of Air Quality Planning and Standards, have recognized the merit of ATSDR's 2012 manganese review.[11] MIG urges PaDEP to do so as well, particularly as it relates to ATSDR's treatment of the studies purporting to show developmental neurotoxicity due to exposure to Mn in air or drinking water. Like ATSDR and the Ontario MOE, PaDEP should conclude that the studies purporting to show adverse effects from exposure to Mn in water are not sufficiently robust to allow causal inferences, particularly in relation to developmental neurotoxicity. Lacking a foundation for causal inferences of adverse effects, the Mn water quality standard should not be amended at this time.

III. Several Studies Demonstrate that Manganese Consumed in Drinking Water is Not More Bioavailable than Manganese Consumed in Food

Several of the developmental neurotoxicity studies involving drinking water speculate that Mn consumed in drinking water is metabolized differently than Mn consumed in the diet and, as a result, "can lead to overload and subsequent neurotoxic effects . . . ."[12] In addition, EPA's existing lifetime health advisory ("HA") for Mn in drinking water is based, in part, on application of an uncertainty factor of three applied to the reference dose ("RfD") for Mn to account "mainly for bioavailability concerns."[13]

The bioavailability of Mn in either food or water may vary greatly depending on the specific food and the type of diet that a person consumes.[14] For instance, the presence of other elements in the diet, such as calcium, may lower the absorption of Mn.[15] However, as EPA separately has concluded based on its own investigation, the bioavailability of Mn from water is not expected to be significantly different than the

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[11] *See* "Prioritized Chronic-Dose Values, Manganese compounds" available at: http://www2.epa.gov/fera/dose-response-assessment-assessing-health-risks-associated-exposure-hazardous-air-pollutants.

[12] Bouchard, M.F. *et al*., "Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water," Environ Health Perspect 119: 138-143 (2011); *see also* Wasserman, G.A., *et al*. "Water Manganese Exposure and Children's Intellectual Function in Araihazar Bangladesh," Environ Health Perspect 114: 124-129 (2006) ("both the valence state and the bioavailability of Mn in food (oxidized Mn) and water (reduced Mn) differ, and these factors may contribute to the observed neurotoxicity of Mn from drinking water.")

[13] Drinking Water Health Advisory for Manganese, U.S. Environmental Protection Agency (EPA-822-R-04-003) (January, 2004), p. 33.

[14] Khouzam, R.L. et al., "Bioaccessibility of essential elements from white cheese, bread, fruit and vegetables," Talanta 86: 425-428 (2011).

[15] Health Effects Support Document for Manganese, U.S. Environmental Protection Agency (EPA-822-R-03-003) (February, 2003) (hereinafter "HES Document"), p. 6-3.

bioavailability of Mn from food.[16] A 2015 study designed and implemented to incorporate drinking water as a specific route of exposure in the human PBPK models for Mn noted above confirms that the bioavailability of Mn ingested via drinking water compared to diet is generally the same.[17]

The study compared the pharmacokinetic equivalency of three different oral routes of delivery of Mn in F344 rats using Mn chloride ($MnCl_2 \cdot 4H_2O$) to supplement Mn present in the control diet.[18] Across all tissues there did not appear to be a difference in tissue concentrations for increased Mn received from diet compared to increased Mn received from drinking water. <u>These results indicate that Mn consumed in drinking water will not lead to greater tissue concentrations of Mn in critical tissues, such as the brain, compared to Mn consumed in the diet</u>.

For all these reasons, the uncertainty factor of three that EPA applied in deriving the lifetime HA for Mn in drinking water is not necessary. That means, in turn, that EPA's existing lifetime HA of 0.3 mg/L is unnecessarily conservative in its derivation. Because the existing lifetime HA has been set at a very protective level, there is no need to consider reducing it any further. The likelihood that consumption of water containing Mn at the existing HA limit presents any risk to children (or adults) is extremely small.

The table below shows (a) the daily recommended intake ("DRI") of water for children of different ages, (b) the intake of Mn at the HA for Mn in drinking water, (c) the recommended daily adequate intake ("AI") for Mn (assumed to be derived from diet) for children in the same age groups, and (d) the "upper limit" ("UL")

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[16] Ruoff, W.L. (1995) "Relative bioavailability of manganese ingested in food or water." In: Proceedings: Workshop on the Bioavailability and Oral Toxicity of Manganese. Sponsored by the U.S. Environmental Protection Agency, Cincinnati, OH, August 30-31, 1994. (as cited in Manganese review 0373, U.S. Environmental Protection Agency, Integrated Risk Information System, last revised December 3, 2002, http://www.epa.gov/IRIS/subst/0373.htm).

[17] Foster, M.L. et al., "Pharmacokinetic evaluation of the equivalency of oral routes of manganese exposure in F344 rats," Toxicol Sci (2015) doi:10.1093/toxsci/kfv047.

[18] Adult male rats were allocated to control diet (10 parts per million ("ppm")), high Mn diet (200 ppm), and Mn-supplemented drinking water, or Mn gavage treatment groups. Animals in the drinking water and gavage groups were given the 10 ppm Mn diet and supplemented with Mn in drinking water or once-daily gavage to provide a daily Mn intake equivalent to that seen in the high-Mn diet group. Mn chloride was used to represent a worst-case scenario as it is expected to be better absorbed than other species of Mn in drinking water (as well as Mn in some types of food) (*see* HES Document at 6-3 to 6-5). Rats were anesthetized following 7 and 61 exposure days, and samples of bile and blood were collected. Rats were then euthanized and striatum, olfactory bulb, frontal cortex, cerebellum, liver, spleen, and femur samples were collected for chemical analysis. Hematocrit was unaffected by Mn exposure. Liver and bile Mn concentrations were elevated in all treatment groups on day 61 (relative to controls). Increased cerebellum Mn concentrations were seen in animals from the high Mn diet group (day 61, relative to controls). No additional statistically significant increases in brain Mn tissue concentrations were seen in the high Mn diet or high Mn water groups at 7 or 61 days compared to the control animals. Increased (relative to all treatment groups) femur, striatum, cerebellum, frontal cortex, and olfactory bulb Mn concentrations also were seen following gavage suggesting that dose rate is an important factor in the pharmacokinetics of oral Mn.

recommended daily intake for each age group, where applicable. The source of the information contained in the table is *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001)* and *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2005)*, both established by the Institute of Medicine at the National Academy of Sciences.[19]

Life Stage	H_2O DRI(L)	Mn Intake at Existing HA (mg)	AI (Diet) (mg)	HA Mn + AI (mg)	UL (mg)
0-6 Mo	0.7	0.21	0.003	0.213	ND
7-12 Mo	0.8	0.24	0.6	0.84	ND
1-3 yr	1.3	0.39	1.2	1.59	2.0
4-8 yr	1.7	0.51	1.5	2.01	3.0
9-13 yr (M)	2.4	0.72	1.9	2.62	6.0
9-13 yr (F)	2.1	0.63	1.6	2.23	6.0
14-18 yr (M)	3.3	0.99	2.2	3.19	9.0
14-18 yr (F)	2.3	0.69	1.6	2.29	9.0

In all cases where a UL has been established, the combined intake of Mn from food and water at the HA level is safely below the UL. In the case of infants, EPA has separately noted that the U.S. National Research Council has established an "Estimated Safe and Adequate Daily Dietary Intake" ("ESADDI") of Mn of 0.6 mg/day for infants up to 6 months and 1 mg/day for infants up to 12 months.[20] The table above shows that the combined intake of Mn from food and water is safely below the ESADDIs for infants, even when Mn in drinking water is at the HA limit.

IV. Conclusion

As explained in these comments, any purported link between the consumption of Mn in water and adverse health effects, primarily developmental toxicity, is not sufficiently robust to warrant amendment of the Mn water quality standard. In addition, Mn taken into the body via ingestion of water is not more bioavailable than Mn ingested in food. Because the amount of Mn safely consumed on a daily basis in the diet is very large in comparison to EPA's existing lifetime HA value of 0.3 mg Mn/L, that value is protective of public health with an ample margin of safety. Accordingly, MIG respectfully requests that the Department decline to amend the Mn water quality standard on the basis of human health effects.

MIG appreciates the opportunity to provide comments on the Department's review of the Mn water quality standard. If you have any questions concerning these comments, please contact Joseph Green, counsel to MIG, at 202.342.8849 or JGreen@KelleyDrye.com.

[19] Available at www.nap.edu.

[20] Manganese TEACH Chemical Summary (Last revised 10/29/2007) available at: https://archive.epa.gov/region5/teach/web/html/teachsummaries.html.