Final Report of the Drexel Advisory Group on Ambient Water Quality and Manganese

Richard J Hamilton MD, MBA
Patrick Gurian PhD
Christopher Sales PhD
Hiba Choudry BS

June 7, 2022

Manganese is an essential nutrient with toxicity that depends on dose and route

Manganese is an essential element that is found in all tissues and is required for normal growth and metabolism. Manganese is also a known neurotoxin and is the cause of a Parkinson's-like disease called "manganism". This disease is the result of manganese deposition into central nervous system (CNS) structures such as the basal ganglia, cerebellum and other brain structures. Manganism is characterized by cognitive slowing, rigidity, bradykinesia, resting tremor, gait instability, masked faces, dystonia, hypophonia, hypokinesia, and postural instability. Patients may exhibit a "cock walk" gate in which the patient walks on the balls of the feet with the ankle extended due to abnormal motor functions in the brain. Symptoms of manganism may reverse if exposure is removed quickly. Psychological disturbances are often seen and manifest as hallucinations and psychosis, commonly called "manganese madness". Progression can result in irreversible neurologic disability. Evidence demonstrates that low-dose exposures to manganese can lead to subclinical neurologic symptoms without overt manganism such as decreased cognitive abilities, decreased reaction time, poor hand-eye coordination, and postural instability. Childhood exposure to toxic doses of manganese can lead to cognitive impairment, attention deficit, hyperactivity, aggressiveness, and memory loss. (Barceloux 1999).

Manganism is most typically the result of inhalational or intravenous exposure to high levels of manganese. Occupations such as welding, mining, or battery manufacturing can exposure workers to high concentrations of manganese in the air. Manganese is inhaled and absorbed through the lungs and results in rapid distribution to the central nervous system through the blood stream. The United States

Environmental Protection Agency (EPA) has well-established health-based reference concentrations for inhalational exposure to manganese. Intravenous drug users who inject manganese-contaminated drugs or individuals who are getting intravenous parenteral nutrition with high levels of manganese have also demonstrated CNS deposition of manganese and manganism. (Keen1999).

However, manganese is also an essential nutrient and demonstrates an "essentiality" U-shaped dose response curve when exposure is via ingestion. (Douron 2010). "Essentiality" U-shaped dose response curves differ from classic toxicology dose response curves because they demonstrate adverse events with deficiency, improved health with adequate intake, and toxicity with excess. Hormesis dose response curves differ from essentiality or toxicology dose response curves in that no deficient state exists. Low levels of the substance improve health, and adverse events occur with toxic doses. The essentiality dose response curve is an important concept to understand when developing a reference dose (RfD) for manganese. Deficiency is rare because it is a ubiquitous element in our diet, and human physiology is highly adapted to absorb manganese. Dietary manganese is found in water, tea, legumes, nuts, leafy vegetables and fruits such as pineapple. (Aschner 2000, Chen 2015, Finley 1999). Interestingly, pineapple juice is so rich in manganese that it can be ingested and used as a negative contrast agent when performing a magnetic resonance imaging (MRI) scan of the gallbladder. (Mohabir 2020).

Many constituents of a vegetarian diet (e.g., tannins, oxalates, phytates, fiber, calcium, and phosphorous) have been found to inhibit manganese absorption from the digestive tract presumably by forming insoluble complexes with manganese in the gut.

Thus, a diet consisting of food high in manganese content may not result in an increase in manganese retention.

Sufficient quantities of manganese are required for human health. Using data from the National Research Council (1973), Schroeder (1966), and the World Health Organization (WHO) (1989), the EPA selected a dietary manganese intake of 10 mg per day as representing the upper limit of adequate intake and the no observed adverse effect level (NOAEL) for oral dietary manganese. Deficiency in manganese causes bone demineralization, growth retardation, skin rashes, hair deep pigmentation, alteration of liver function, impairment of fertility, and abnormal carbohydrate and fat metabolism. Individuals deficient in iron demonstrate an increase in manganese absorption.

Manganese toxicity via the oral route is distinctly unusual because: 1) well-developed homeostatic mechanisms exist in the gastrointestinal tract to regulate manganese absorption and excretion 2) certain constituents in food inhibit absorption as previously discussed 3), the Secondary Maximum Contaminant Level (SMCL) of 0.050 mg/L keeps most regulated drinking water below concerning concentrations, and 4) water with manganese levels greater than 0.100 mg/L has a visually detectable brown or black appearance, stains laundry and plumbing, and imparts a metallic taste. Most individuals find these aesthetic qualities objectionable and will subsequently reduce their water intake or lodge complaints with water authorities at even lower levels than 0.100 mg/L. (PWD 2021)

Manganese is absorbed from the small intestine and transported into the liver via specific mechanisms for manganese uptake. Homeostasis of tissue and serum manganese level is maintained by well-controlled excretion via the biliary tract.

Manganese is essential to many biochemical pathways and the activation of enzymes. Most notable is manganese superoxide dismutase, which is an important component for reducing oxidative free radicals. Adequate dietary intake is thought to be between 1.8 and 2.3 mg per day for adults. (Institute of Medicine (IOM) 2001). Once in the bloodstream, manganese easily passes through the blood brain barrier and deposits into brain tissues, especially the basal ganglia and globus pallidus. (Lidsky 2007). Manganese deposition in the brain correlates significantly with clinical symptoms. (Bouabid 2016). Patients who have dysfunction of their liver or bile are at higher risk of manganese toxicity and accumulation due to impaired elimination. (Butterworth 1995, Hauser 1994, Spahr 1996, Hauser 1994, Chen 2015, Crossgrove 2004, Erikson 2007, O'Neal 2015, Schroeter 2012, Yoon 2011).

Toxic effects from high levels of manganese in drinking water were first established in a report by Kawamura et al (1941). They reported severe neurological symptoms in 25 people who drank well water contaminated with manganese from dry cell batteries for 2 to 3 months. The concentration of manganese in the water was between 14 and 28 mg/L.

In conclusion, manganese has the potential to behave as a toxic substance in the body under various circumstances. Thus, it is appropriate that manganese is added to § 93.8c Table 5 (Water Quality Criteria for Toxic Substances).

Methods for establishing RfDs, health advisory levels and regulatory limits of a toxin

The methods for establishing RfDs have been well-established by the EPA. An RfD is an estimated dose to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs are used by the EPA and states to develop health advisory levels for drinking water, Maximum Contaminant Levels (MCLs) for drinking water and Ambient Water Quality Criteria (AWQC). The methods for developing health advisory levels, MCLs, and AWQCs have also been well-established by the EPA.

According to the EPA, health advisories provide information on contaminants that can cause human health effects, are known or anticipated to occur in drinking water, and lack a regulatory standard (i.e., MCL). EPA's health advisories are non-enforceable and non-regulatory and provide technical information to states agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination.

In contrast to health advisories, MCLs are enforceable, regulatory limits established to ensure diseases and toxins are either removed from, or reduced to, acceptable levels in drinking water prior to consumption. While these values are primarily health-based, the EPA can also consider non-health-related factors, such as economics and treatability, when establishing drinking water MCL values.

While health advisories and MCLs protect finished drinking water, AWQC and ambient water quality standards describe the desired condition of a waterbody (e.g., streams, lakes and other waterbodies). When establishing AWQC for the protection of

human health, the EPA and states must satisfy the requirements of the federal Clean Water Act. States typically follow the EPA's methodologies for developing criteria, including the 2000 Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (EPA-822-B-00-004). The EPA recommends inclusion of the drinking water exposure pathway in this methodology for the following reasons: 1) drinking water is a designated use for surface waters under the Clean Water Act, 2) although rare, some public water supplies in the United States still provide drinking water from surface water sources without treatment, 3) it can be difficult and expensive to remediate surface waters, and 4) surface waters should not be so contaminated that the burden of achieving health objectives is shifted away from those responsible for pollutant discharges and placed on downstream users to bear the costs of upgraded or supplemental water treatment.

These methods for deriving RfDs to calculate AWQC and other health-based goals and standards start with determining a point of departure (POD) on a toxicologic dose response curve established from experimental or observational data in humans, preferentially, or alternatively in animal models. The point of departure is defined as the point on that curve that corresponds to either the recognized lowest observed adverse effect level (LOAEL) or the NOAEL. From this point of departure, uncertainty factors are applied to derive an RfD. Standard EPA methodologies, as described above, are then used to determine health advisory levels and other regulatory-based safe levels.

When appropriate, the NOAEL or LOAEL approach is being replaced with the use of software to analyze the original data and avoid the difficulties of selecting a POD. This statistical analysis identifies a dose or concentration that produces a

predetermined change in the response rate of an adverse effect. This predetermined change in response is called the benchmark response (BMR). The default BMR is a 5% or 10% change in the response rate of an adverse effect relative to the response of the control group depending on whether response data is continuous or quantal (dichotomous). From there, a benchmark dose (BMD) is extrapolated to derive a RfD.

Experience shows that calculating the RfD via multiple methods (NOAEL, LOAEL, BMR) builds confidence in the final determination. (USEPA 2000, 2015). The PODs and RfDs are then used in the derivation of AWQC. AWQC are derived using the 2000 EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health with the 2015 updated exposure input values (body weight, drinking water intake, and fish consumption) and PA Chapter 93 regulations. The following rubric will be used to compare PODs and oral RfDs (Figure 1). AWQC for manganese are derived as a final step using the target population selected by PA DEP (Figure 2).

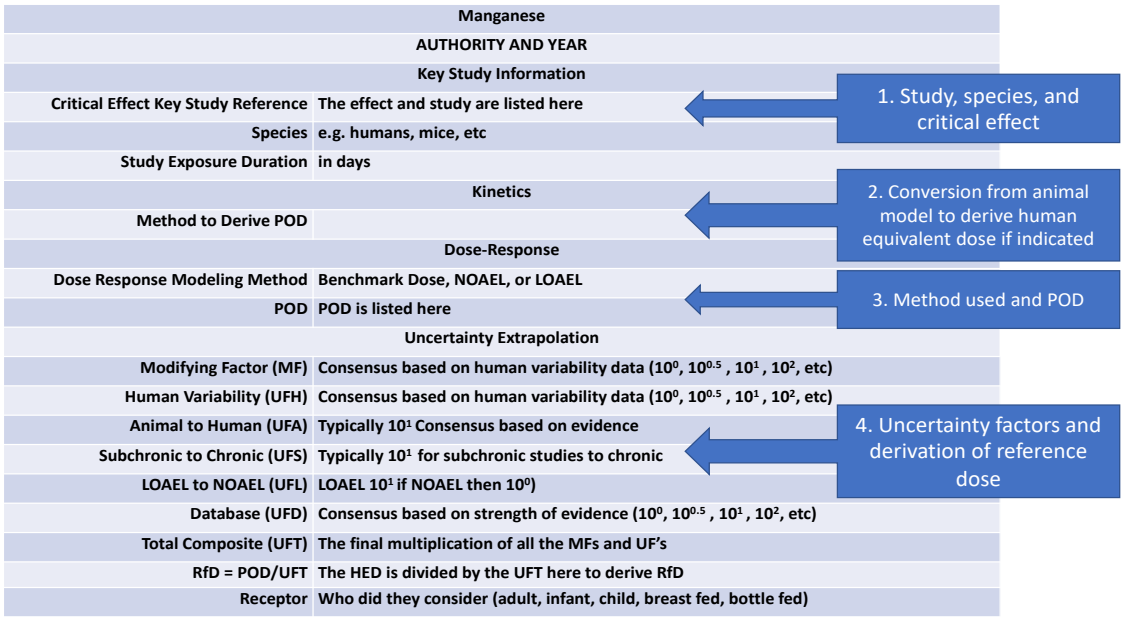

Figure 1: Rubric for determining POD and RfD

Exposure	
Drinking Water Intake (DWI) L/day	Consumption in liters a day per EPA (2.4L for adult 1 L for child typical)
Body Weight (Kg)	80 kg adult
Fish Intake (FI) kg/day	0.022 kg/day
Bioaccumulation Factor (BAF)	1 (no bioaccumulation for Mn)
Relative Source Contribution (RSC)	Contribution from water (by convention 20%, higher if target is child or infant or derived from water study)
Ambient Water Quality Criteria AWQC (mg/L)	AWQC = RfD x RSC x BW / (DWI + (FI x BAF))
Additional Information	
Reference	

5. Exposure calculation using 2015 EPA standards and final derivation of AWQC

Figure 2: Rubric for deriving the AWQC

Establishment of RfDs, health advisories and water quality standards for manganese as an essential nutrient with toxicity

In the case of manganese, a POD for oral exposure through water has been difficult to derive because of the 1) quality and observational nature of the evidence for toxicity via ingestion of water, 2) the difficulties with parsing out the retention rate and toxicity of manganese in water versus food, and 3) the lack of reliable biomarker for manganese toxicity. (Crossgrove 2004, USEPA 1994). Nonetheless, sufficiently robust data exists to establish the intersection between essentiality and toxicology dose response curves to establish an RfD for food ingestion by finding the upper limit of essentiality. This concept is described in Figure 3. (Douron 2010).

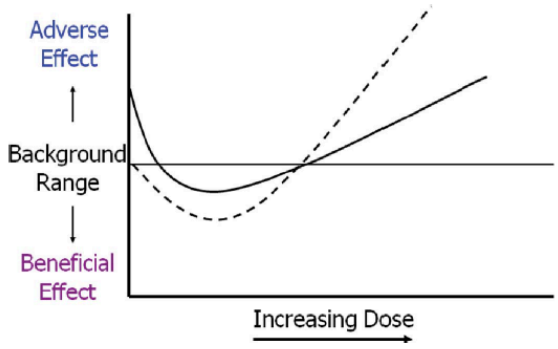

FIGURE 1. General form of the essentially (—) and hormesis (---) curves. The *y* axis shows increasing adverse effects going up the page, increasing beneficial effects going down the page, and a background range of effects in between these two. The *x* axis shows increasing dose.

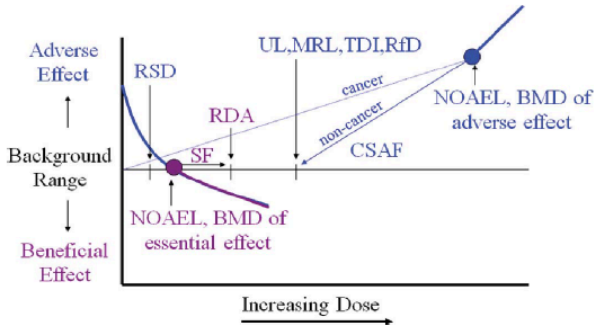

FIGURE 2. The current approach to the essentiality problem: separate groups that may or may not talk to one another develop "safe" levels. See text for explanation of acronyms.

Figure 3: Deriving a POD from essentiality curves (Douron 2010)

In 1993, this concept of essentiality guided the EPA in selecting a dietary manganese intake of 10 mg per day as representing the upper limit of adequate and the NOAEL for dietary manganese from food. (USEPA 1993) Normalizing for 70 kg adult, this resulted in the oral RfD of 0.143 mg/kg/day. (Figure 4) At that time, the EPA chose not to set a health advisory or develop a human health-based water quality criterion recommendation for manganese since a secondary maximum contaminant level (SMCL) of 0.050 for nuisance characteristics was already in place.

Manganese	
US EPA 1993	
Key Study Information	
Critical Effect Key Study Reference	NAS Food and Nutrition Board (NRC. 1989). Schroeder et al. (1966), and WHO (1973), a dietary manganese intake of 10 mg/day has been chosen to represent an upper limit of adequate daily intake chronic oral human NOAEL.
Species	Human adults
Study Exposure Duration (days)	in days
Kinetics	
Method to Derive POD	POD = (upper limit of adequate daily intake chronic oral human / BW) = (10 mg/day) / (70 kg) = 0.143 mg/kg/day
Dose-Response	
Dose Response Modeling Method	NOAEL as upper limit of adequate intake of dietary Mn
POD	0.143 mg/kg/day
Uncertainty Extrapolation	
Human Variability (UFH)	1
Animal to Human (UFA)	1
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	1
Database (UFD)	1
Total Composite (UFT)	1
POD = RfD (mg/kg/day)	0.143 mg/kg/day dietary Mn
Receptor	adults

Figure 4: USEPA derivation of POD and RfD (USEPA 1993, USEPA 1995)

In 1995, the EPA revised the oral RfD recommendation for manganese in its IRIS database to include a modifying factor of 3 when manganese is ingested in water or soil. (USEPA 1995) There were four reasons for this change: 1) concern over increased uptake of manganese from water in fasted individuals, 2) endpoints in the Kondakis (1989) study and the derivation of lower reference doses from that data (see below), 3) high levels of manganese in infant formulas that would be exacerbated by manganese in drinking water, and 4) concern for increased neonatal absorption and enhanced uptake in the brain of neonates. (Figure 5)

Manganese	
EPA 2004	
Key Study Information	
Critical Effect Key Study Reference	NAS Food and Nutrition Board (NRC. 1989). Schroeder et al. (1966), and WHO (1973), a dietary manganese intake of 10 mg/day has been chosen to represent an upper limit of adequate daily intake chronic oral human NOAEL.
Species	Adult humans
Study Exposure Duration (days)	years
Kinetics	
Method to Derive POD	POD = (upper limit of adequate daily intake chronic oral human / BW) = (10 mg/day) / (70 kg) = 0.143 mg/kg/day
Dose-Response	
Dose Response Modeling Method	NOAEL as upper limit of adequate intake of dietary Mn
POD	0.143 mg/kg/day
Uncertainty Extrapolation	
Modifying Factor	3 ($10^{0.5}$) to account for drinking water derivation from dietary POD
Human Variability (UFH)	1
Animal to Human (UFA)	1
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	1
Database (UFD)	1
Total Composite (UFT)	1
RfD = POD/UFT	0.047 mg/kg/d for oral exposure Mn
Receptor	adults

Figure 5: USEPA 2004 derivation of POD and RfD for manganese

The modifying factor of 3 has created a great deal of discussion and controversy. The controversy was no less in 1994 at the Proceedings Workshop on the Bioavailability and Oral Toxicity of Manganese. (EPA 1994). At the time, there was no high-quality evidence to fully clarify the concern that enhanced absorption occurred in the fasted state. Discussion at that conference further suggested that the water RfD is a separate endpoint from the dietary RfD because of the wide variability of manganese in the diet, especially for those individuals that ingest amounts approaching or exceeding the NOAEL of 10 mg/day. Arguments were made that vegetarians, tea drinkers, and children drinking infant formulas may consume enough manganese to account for the need for a separate RfD in water. The conference concluded that further study was warranted. (USEPA 1994)

Nonetheless, the endpoints in the Kondakis study clearly point to a lower threshold for critical effects when exposure to manganese occurs through water consumption, even if the reasons are not entirely clear. Furthermore, high levels of manganese in infant formula are a concern, but so is the variability of dietary manganese. In particular, vegetarians and tea drinkers especially typically consume manganese at or above the RfD. Hence, manganese in water would be considered an additive burden.

Establishment of RfDs for manganese based on available drinking water studies

In the original effort in 1993, instead of deriving the reference dose from food, the EPA used one observational study to derive a specific RfD and health advisory recommendation for manganese in water. (USEPA 1993).

Kondakis (1989) studied the health effects of manganese concentration and drinking water and three villages in Peloponnese's Greece. A random sample of men and women above the age of 50 were included in the study with 90% participation. The authors studied three different villages with varying manganese concentration in their well water. The villages had similar diets, and samples of the vegetables in each area showed similar manganese content. Unfortunately, dietary manganese was not measured. Area A had the lowest manganese well water concentration ranging from 0.004 to 0.015 mg/L, area B ranged from 0.020 mg/L to 0.253 (average 0.167 mg/L), and area C ranged from 1.800 to 2.300 mg/L (average 1.95 mg/L). The authors evaluated the patients for neurologic symptoms using a neurologic score and found that as the manganese level in the water increased, the neurologic scores and the

concentration of manganese in the hair increased. The authors concluded that elevations of manganese above 0.050 mg/L in drinking water may be harmful to health.

The EPA used this study to establish a NOAEL and LOAEL using the arithmetic mean of the range of manganese concentrations in Area B and Area C respectively. (USEPA 1993) Thus, they set the NOAEL and LOAEL at 0.167 mg/L and 1.950 mg/L respectively. They further used the adult body weight and drinking water consumption exposure inputs from that time (70 kg and 2 liters) and derived an RfD NOAEL of 0.005 mg/kg-day and RfD LOAEL 0.006 mg/kg-day, respectively.

From the NOAEL, a drinking water health advisory level recommendation of 0.200 mg/L was derived, but never published as a final recommendation due to the SMCL being more stringent. This advisory level recommendation would be the same even if the exposure inputs were updated to include EPA's 2015 recommendations for average adult body weight, fish consumption intake (22 grams/day), and daily drinking water intake. (Figure 6 and Figure 7)

Manganese	
US EPA 1993	
Key Study Information	
Critical Effect Key Study Reference	Kondakis Mn water in Greek villages; Accumulation of Mn and possible neuro impairment; NOAEL of 0.167 mg/L from average Mn concentration in wells of village with no observed effects
Species	Human adults
Study Exposure Duration (days)	10 years
Kinetics	
Method to Derive POD	POD = (0.167mg/L) x (2 L/d) / (70 kg) = 0.0048 mg/kg-day ~ 0.005 mg/kg/d
Dose-Response	
Dose Response Modeling Method	NOAEL of 0.167 mg/L
POD	0.005 mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	1
Animal to Human (UFA)	1
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	1
Database (UFD)	1
Total Composite (UFT)	1
RfD = POD/UFT	0.005 mg/kg/d drinking water
Receptor	adults

Figure 6: US EPA (USEPA 1993) derivation of RfD from water studies using NOAEL.

Manganese	
US EPA 1993	
Key Study Information	
Critical Effect Key Study Reference	Kondakis Mn water in Greek villages; Accumulation of Mn and possible neuro impairment; LOAEL of 1.95 mg/L
Species	Human adults
Study Exposure Duration (days)	10 years
Kinetics	
Method to Derive POD	POD = (average Mn concentration/water intake)/BW = (1.95 mg/L) x (2 L/d) / (70 kg) = 0.056 mg/kg-day ~ 0.060 mg/kg/d
Dose-Response	
Dose Response Modeling Method	LOAEL of 1.95 mg/L
POD	0.060 mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	1
Animal to Human (UFA)	1
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	10
Database (UFD)	1
Total Composite (UFT)	1
RfD = POD/UFT	0.006 mg/kg/d drinking water
Receptor	adults

Figure 7: US EPA (USEPA 1993) derivation of RfD from water studies using LOAEL.

A long-term drinking-water study in a northern rural area of Schleswig-Holstein, Germany (Vieregge 1995) found no neurological effects of manganese when subjects drank well water for 10 to 40 years that was “at least” 0.300 mg/l when compared to

individuals who drank water with “at most” 0.050 mg/L. No significant differences in the Columbia University Rating Scale for Parkinson’s disease were found in either cohort although the 0.050 mg/L group had lower blood manganese levels. Subjects of both groups were randomly selected and matched with respect to age, sex, nutritional habits and drug intake. Although the highest level of well water reported was 2.16 mg/L, the mean or standard deviation of the manganese concentration was not reported. The authors concluded that lowering the manganese concentrations below 0.050 mg/L was not warranted. Importantly, they did not suggest that the health advisory level increase.

The Minnesota Department of Health derived a RfD of 0.083 mg/kg-d to protect bottled-fed infants less than one year of age. (Minnesota Department of Health 2020). They relied on a LOAEL identified by Kern (2010) with the critical effect as neurodevelopmental and neurotransmitter changes.

Manganese	
Minnesota Department of Health	
Key Study Information	
Critical Effect Key Study Reference	Kern, C. H., Stanwood, G. D., & Smith, D. R. (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. doi:10.1002/syn.20736
Species	Neonatal rats
Study Exposure Duration (days)	14 days
Kinetics	
Dose conversion to Internal Serum Level	none (dose study)
Method to Derive Human Equivalent Dose	Not applicable (Insufficient data to support use of DAFs for neonatal period) (MDH, 2017) (U.S. EPA, 2011)
Dose-Response	
Dose Response Modeling Method	LOAEL
POD	25 mg/kg-d (LOAEL, Kern 2010)
HED = POD x DAF	HED = 25 mg/kg/d x 1 (Dose Adjustment Factor = 1)
Uncertainty Extrapolation	
Modifying Factor	Not used
Human Variability (UFH)	10
Animal to Human (UFA)	10
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	3 (only mild effects at LOAEL)
Database (UFD)	1
Total Composite (UFT)	300
RfD = POD/UFT	POD/Total UF = (25mg/kg-d)/300 = 0.083 mg/kg-d
Receptor	Bottle fed infants

Figure 8: Minnesota Department of Health derivation of RfD using Kern (2010)

Health Canada (2019) and WHO (2021) also used the Kern study and selected the same POD but applied a standard UFL (LOAEL to NOAEL conversion) of 10 for LOAEL to calculate a UFT (Total Composite Uncertainty Factor) of 1000. Each authority subsequently derived an RfD of 0.025 mg/kg-d for bottle fed infants as the target population. (Figure 9)

Manganese	
WHO 2021 and Health Canada 2019	
Key Study Information	
Critical Effect Key Study Reference	Kern, C. H., Stanwood, G. D., & Smith, D. R. (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. doi:10.1002/syn.20736
Species	Neonatal rats
Study Exposure Duration (days)	14 days
Kinetics	
Method of Administered Dose conversion to Internal Serum Level	none (dose study)
Method to Derive Human Equivalent Dose	Not applicable (Insufficient data to support use of DAFs for neonatal period) (MDH, 2017) (U.S. EPA, 2011)
Dose-Response	
Dose Response Modeling Method	LOAEL
POD	25 mg/kg-d (LOAEL, Kern 2010)
POD x DAF = HED	Dose Adjustment Factor = 1 HED = 25 mg/kg/d
Uncertainty Extrapolation	
Modifying Factor	Not used
Human Variability (UFH)	10
Animal to Human (UFA)	10
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	10
Database (UFD)	1
Total Composite (UFT)	1000
RfD = POD/UFT	POD/Total UF = (25mg/kg-d)/1000 = 0.025 mg/kg-d
Receptor	Bottle fed infants

Figure 9: WHO (2021) and Health Canada (2019) derivation of RfD using Kern (2010)

Recent work by Yoon (2019), sponsored and funded by the Afton Chemical Corporation, developed a physiological base pharmacokinetic model (PBPK). Given the known neurotoxicity of manganese and its predilection for concentrating in the basal ganglia, concentrations in the globus pallidus are considered the critical effect. In these studies, Yoon concluded that globus pallidus manganese concentrations would remain fairly constant for manganese in drinking water concentrations of up to 0.3 ppm (0.300

mg/L) for the toddler and child age groups. Figure 2 and Figure 6 from that study clearly demonstrate manganese concentrations in the globus pallidus of bottle-fed infants exceed that of breast-fed infants as the water level increases from the EPA Lifetime Health Advisory of 0.300 mg/L to 0.580 mg/L (95^{th} percentile of the drinking water in Iowa according to the National Inorganics and Radionucleotide Study).

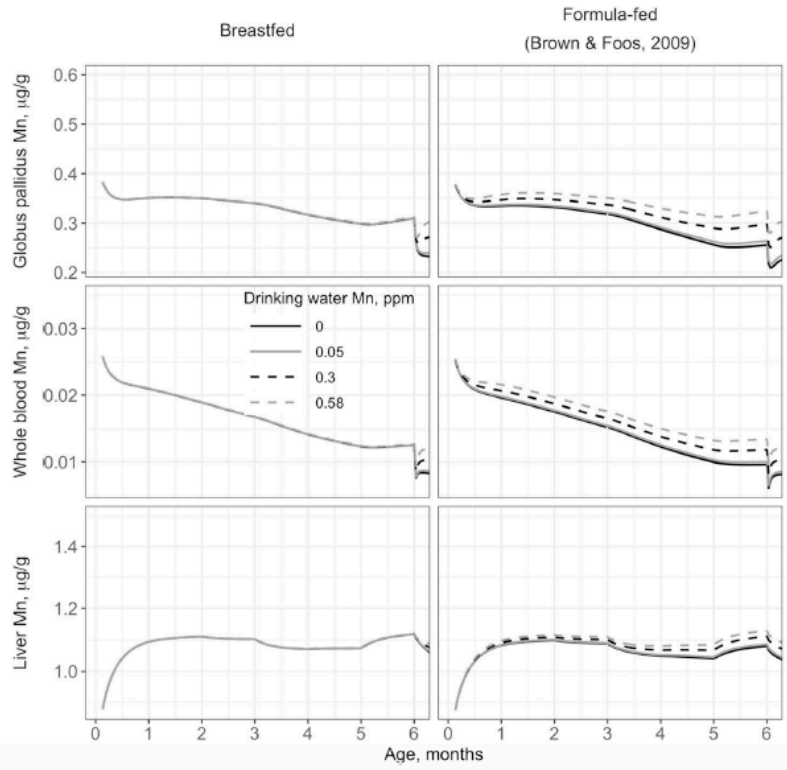

Fig. 2. Time course of tissue Mn concentration in infants with or without drinking water Mn exposure. Simulated Mn concentrations in globus pallidus (top row), whole blood (second row), and liver (bottom row) are shown for ages 0–6 months, for scenarios of breastfed infant (left column) and formula-fed infant (right column), for maternal (for breastfed infant-scenarios) and infant (for formula-fed infant scenarios) drinking-water concentrations of 0, 0.05, 0.3, and 0.58 ppm (lines in each panel). The formula-fed infant is fed with formula containing Mn based on the Brown and Foos (2009) scenario. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

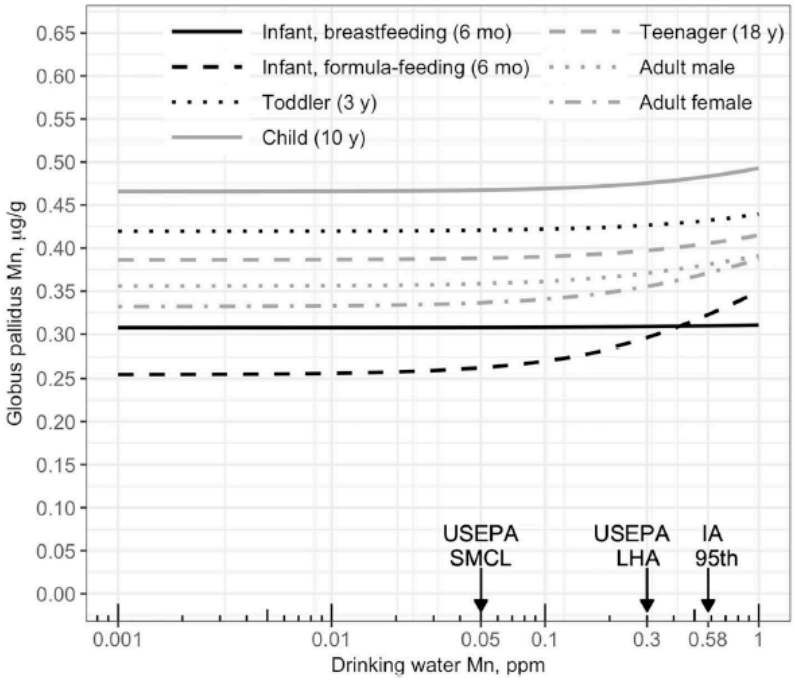

Fig. 6. Changes in globus pallidus Mn with a range of drinking-water Mn concentrations.
Simulations were performed with a range of drinking water concentrations (horizontal axis, $\log_{10}$ scale) for 7 different age scenarios (solid and dashed curves). Arrows pointing to the x-axis mark the drinking-water Mn concentrations highlighted in Fig. 4 and Fig. 5 (0.05, 0.3, and 0.58 ppm), which are based on US EPA's Secondary Maximum Contaminant Level (SMCL) for Mn based on taste & staining considerations, US EPA's lifetime health advisory value (LHA), and the 95th percentile of the drinking-water concentration in Iowa (US EPA's National Inorganics and Radionuclides Survey, 2003), respectively.

Figure 9. Figure 2 and Figure 6 from Yoon 2019

The authors concluded that the impact of adding drinking water exposure to daily manganese exposure via dietary intake and ambient air inhalation in children is not greater than the impacts in adults, even at a drinking water concentration of 0.580 mg/L. Their data (summarized in Figure 9) clearly indicates that globus pallidus concentrations increase in adults, children, toddlers, and infants above the EPA Lifetime Health Advisory Level of 0.300 mg/L.

Finally, Kullar (2019) pooled combined analysis data from Bouchard (2011) from June 2007 to June 2009 (375 children from the province of Quebec) and Bouchard (2018) from between April 2012 and April 2014 (children from the province of New Brunswick). In this study, the authors used the Bayesian Benchmark Dose Analysis System to compute weight-averaged median estimates for the benchmark concentration (BMC) of manganese in water and the lower bound of the credible interval (BMCL), based on seven different exposure-response models. The BMCL for manganese in drinking water associated with a decrease of 1% Performance IQ score was 0.078 mg/L.

Manganese	
Kullar 2019	
Standard / Guidance	HA
Media Type	DW
Threshold Level (mg/L) or (PPT)	0.080 - 0.400 mg/L
Key Study Information	
Critical Effect Key Study Reference	Kullar 2019 Benchmark concentration analysis to estimate water manganese levels associated with pre-defined levels of cognitive impairment in children, i.e. drop of 1%, 2% and 5% in Performance IQ scores. Data from two studies conducted in Canada were pooled resulting in a sample of 630 children (ages 5.9–13.7 years) with data on tap water manganese concentration and cognition, as well as confounders. Bayesian Benchmark Dose Analysis System to compute weight-averaged median estimates for the benchmark concentration (BMC) of manganese in water and the lower bound of the credible interval (BMCL), based on seven different exposure-response models.
Species	Children age 5.9 to 13.7
Study Exposure Duration (days)	years
Kinetics	
Method of Administered Dose conversion to Internal Serum Level	
Method to Derive Human Equivalent Dose	Human study so POD = HED
Dose-Response	
Dose Response Modeling Method	benchmark concentration (BMC) of manganese in water and the lower bound of the credible interval (BMCL)
POD	IQ decrease of 1% = 0.133 mg/L (BMCL, 0.078 mg/L); IQ decrease of 2%, this concentration was 0.266 mg/L (BMCL, 0.156 mg/L) IQ decrease of 5% it was 0.676 mg/L (BMCL, 0.406 mg/L).
POD x DAF = HED	Dose Adjustment Factor = 1

Figure 10: Kullar 2019 Benchmark Concentration analysis

Derivation of AWQC

In accordance with the 2000 EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, using the 2015 updated exposure input values (body weight, drinking water intake, and fish consumption) and Pennsylvania Chapter 93 regulations, DEP derived an AWQC for manganese of 0.3 mg/L. Since manganese is currently not known to significantly bioaccumulate in fish, a bioaccumulation factor of 1 was assumed.

$AWQC_{Mn}$ = RfD x RSC x (BW ÷ [DWI + (FI x BAF)])
Where:
RfD = 0.05 mg/kg-day
Relative Source Contribution Adults (RSC) = 0.2
Body Weight (BW) = 80 kg
Drinking Water Intake (DWI) = 2.4 L
Fish Intake (FI) = 0.022 kg/day
Bioaccumulation factor (BAF) = 1
$AWQC_{Mn}$ = 0.05 mg/kg-day x 0.2 x (80 ÷ [2.4 + (0.022 kg/day x 1)])
$AWQC_{Mn}$ = 0.3 mg/L

This derivation by the PA DEP follows the methodology accurately. Using the range of RfDs established by authorities around the world and the same methodology and target population (adults) as PA DEP, the following range of AWQCs would be derived. (Table 1)

Agency/Year	RfD mg/kg-d	AWQC mg/L
USEPA 1993 NOAEL Dietary MN	0.143	0.945
USEPA 1993 NOAEL Water	0.006	0.040
USEPA 1993 LOAEL Water	0.005	0.033
USEPA 2004	0.047	0.310
Health Canada 2019	0.025	0.165
Minnesota DOH 2020	0.083	0.548
WHO 2021	0.025	0.165

Table 1: RfD derived by various authorities and resulting AWQC

In conclusion, the RfD of 0.047 mg/kg-d and the $AWQC_{Mn}$ of 0.300 mg/L derived by the PA DEP is consistent with other organizations and authorities. Notable, a lower $AWQC_{Mn}$ would be derived if PA DEP considered bottle fed infants the target population, and the RSC was adjusted upward accordingly.

Water Treatment Discussion

Two alternative points of compliance for the manganese water quality criterion are under consideration in the PA DEP's analysis of its water quality standards. The first alternative, consistent with Act 40 of 2017, moves the point of compliance to the point of all existing or planned surface potable water supply withdrawals. The second alternative, consistent with the Clean Streams Law, is to maintain the existing point of compliance in all surface waters (i.e., at the point of discharge). The Commonwealth of Pennsylvania currently enforces the EPA's SMCL of 0.05 mg/L for public water supply systems. Thus, the question is whether manganese is most appropriately removed at the source, or at the point of potable water supply withdrawal with public water supply systems required to treat higher intake levels of manganese in order to meet the 0.05 mg/L SMCL for drinking water.

While qualitative, several factors nevertheless merit discussion. First, manganese is an element and hence cannot be destroyed by any chemical treatment processes. The treatment processes under consideration are concentration and separation processes. If a given level of concentration is to be achieved, it is inherently beneficial to start with a more concentrated solution. Mining and industrial effluents would have concentrated manganese which then become diluted with the surface waters of the Commonwealth upon discharge. The argument that manganese can only

be removed from concentrated effluent discharges at great expense and environmental impact but can be readily and cheaply be removed when present in dilute form in the huge volumes of water treated for public water supplies is strained. In some cases, unit operations already employed by public water supply systems in their treatment plants may have some efficacy for manganese removal, but Kohl and Medlar caution (2006) “Although manganese removal can be achieved incidentally by a unit process, if the process is not designed and operated for it, then there will be occasions that manganese control is lost.” Burdening public water supply systems with additional manganese cannot be assumed to be easy or cheap to remedy.

While conventional drinking water treatment processes do not remove soluble manganese to a great extent, a variety of manganese concentration and separation processes are available and have been applied economically for decades to achieve the very low manganese concentrations needed to comply with the 0.05 mg/L SMCL.

One reason soluble manganese is not well removed by conventional water treatment processes is that manganese is not readily oxidized by the most common oxidant used by these plants, chlorine, at pH values typical of treatment. Tobiason et al. (2016) report that oxidation of manganese by chlorine is not effective until pH 9, which is well above the range in which most water supply treatment plants operate. Thus, the equation given on page 15 of the Tetra Tech report, which shows the oxidation of manganese by chlorine, while not incorrect, would not occur to a substantial degree under typical water treatment conditions per Tobiason et al.

Tetra Tech’s point regarding the need for large pH adjustments to remove manganese from coal mine drainage can also be confirmed as applicable in some

cases relating to manganese removal from water in general. Duarte et al. (2015) present a pC-pH diagram for Mn(II) in a hydroxide system (that is, no carbonate present) with a minimum solubility around pH 12. This confirms that substantial pH adjustment would be needed in a low carbonate system. However, carbonate plays a key role, as Buamah et al. (2008) note that manganese(II) solubility is controlled by magnesium carbonate. Buamah et al. use the Phreeqc water chemistry model to investigate solubility of Mn(II) under different pH and alkalinity values and find that solubility drops to less than 0.5 mg/L at pH 8 given a bicarbonate concentration of about 150 mg/L (Figure 1 of Buamah et al.). Figures provided by Tetra Tech indicate pH, lime, and manganese concentrations but do not address carbonate concentrations, making it difficult to assess how alternative water chemistries might impact manganese removal versus pH.

The challenges of manganese removal noted above can be addressed by the use of alternative oxidants, such as potassium permanganate, which effectively convert the reduced, soluble manganese to oxidized, insoluble manganese which can be removed by conventional filtration systems. Another option is to remove the Mn(II) without oxidation by manipulating pH and carbonate concentrations so as to reduce the solubility of Mn(II). Tobiason et al. (2016) describe how lime-soda precipitative softening can effectively remove manganese without the need for oxidation. Lime increases the pH and soda ash addition increases the carbonate concentration which, as described above, decreases Mn(II) solubility at high pH. This combination of lime and soda ash would be expected to be more effective than the addition of lime alone based on the Phreeqc modeling of Buameh et al. (2008) that is described above. Softening by lime

and soda ash addition is widely practiced. (MRWA 2022) Difficulties with simultaneous removal of aluminum and manganese from coal mine drainage are noted in Tetra Tech's comments and clearly warrant careful consideration with respect to conventional drinking water treatment processes. Aluminum salts are widely used as a water treatment additive and at favorable pHs can precipitate readily. Wang et al. (2005) discuss recarbonation as an option to re-adjust pH towards a more neutral value. While clearly such an additional step has cost implications, it is feasible and widely practiced. Site specific consideration of water chemistry is likely needed to find effective treatment options but in general, one can state that feasible options for manganese removal have been in full-scale use for many decades and that removal of pollutants by precipitation is most effective when the pollutant is concentrated in a waste stream rather than widely dispersed in the environment.

These processes all consume non-negligible amounts of energy both directly in the form of electricity use by pumps, aerators, etc. and indirectly through the considerable amount of fossil fuels currently embedded in the chemicals used in water treatment processes. The same argument applied to the economics of treatment also applies to the environmental impacts of treatment, that is to remove a given quantity of manganese it is preferable to do so before widely dispersing the manganese in the environment. Pumping and aeration electricity use (a proxy for both cost and environmental impact) would scale with the amount of water present, not the amount of manganese, and hence treating the manganese before it is dispersed into the environment is preferred. Given current water treatment and energy infrastructure, essentially any effort to protect the water environment and drinking water supplies can

be cast as having negative impacts on greenhouse gas emissions. The solution is not to forgo protecting the environment and human health but rather to gradually decarbonize our water treatment and energy infrastructures. The decarbonization of electricity is feasible and has been studied extensively (for example see, Foti et al. 2016, Sepulvida et al. 2018). The electrification of water treatment processes is an active area of research (https://profiles.stanford.edu/mauter?releaseVersion=9.6.0) with options such as electro-coagulation and membrane treatment already well characterized and feasible.

Economic impacts to public water supply treatment

Control of manganese concentrations in drinking water involves source water management as well as treatment processes for removal of manganese from water. Although manganese removal from water can be accomplished by a variety of physical, chemical, and biological processes, a major factor in selection and design of a treatment process to remove manganese are the characteristics of the source water, including the concentration and form of manganese, along with other key water quality parameters (e.g., pH, alkalinity, organic carbon, iron levels, hardness). Since there are so many variables that can influence manganese removal, it is not trivial to estimate changes in treatment costs (or savings) due to the modification of regulations relating to manganese in surface waters.

Comments by the Pennsylvania Coal Alliance suggest that the only treatment method being considered by the mining sector prior to discharge is that of alkaline addition. It is unclear, however, if alkaline addition would be sufficient to remove manganese from drinking water. From a series of bench-scale tests conducted for a

study by Ballantyne et al. (2002) that considered different alternative methods for reducing manganese levels in the District Municipality of Muskova MacTier treatment plant in Ontario, Canada, it was found that alkaline conditions at pH values over 10 did not improve manganese removal in their conventional treatment process.

In order to provide a more thorough estimation of potential costs (or savings) associated with any changes in the regulation of manganese, the discussion needs to account not only for alkaline addition but also the other alternative treatment processes that exist to specifically remove manganese from surface water and wastewater (Kohl 2006, Tobiason 2016). For example, the Pennsylvania Coal Alliance estimates that if the 0.3 mg/L manganese limit is imposed at the discharge point versus the withdrawal point, a maximum potable water treatment savings would be realized of less than $0.007 per 1,000 gallons of water treated at the treatment plant. The Reading Area Water Authority, which provides water for about 125,000 residents from a 40 million gallons per day (mgd) drinking water plant, estimates that if compliance is moved to the withdrawal point versus the discharge point, it would cost them operationally $15.8 million over 20 years, plus $540,000 per years in increased treatment chemical costs, and $6,530 annually for increased monitoring. This roughly translates to an increase in operational costs of $0.09 per 1,000 gallons water treated, a $0.097 increase relative to the Pennsylvania Coal Alliance.

Kohl and Medlar (Kohl 2006) studied the capital cost for manganese removal water treatment and found that costs vary by design flow (mgd), finished water concentration goal (0.010 to 0.050 mg/L), influent concentration (typically assumed to be 0.500 mg/L), and treatment method (conventional gravity settling, direct filtration,

greensand, and membrane filtration), as well as financing structure and cost recovery. The authors produced a variety of estimates in capital costs that range from $750,000/mgd to $2 million/mgd for manganese control. This figure is in the range quoted by the Pennsylvania American Water Company (PAWC) response, although PAWC does not specify the model that they employed. They extrapolate a cost of $1.5 million/mgd across aggregate capacity of the eight (8) identified plants in the range of 40 mgd for a total cost of $40-60 million range. In addition, there were anticipated 5-10 percent ($700,000 - $1.4 Million) annual increase in chemical costs or monitoring. A more thorough critique and comparison of the methodology employed by the Pennsylvania Coal Alliance and the Reading Water Authority is needed to determine the accuracy and validity of their cost estimates.

The comments by PAWC state that their drinking water treatment plants would be significantly challenged by increased levels of raw water manganese and thus would need to make capital investments to alter their plants to specifically treat for manganese removal. Regardless if an existing potable water supply treatment plant is considered to employ “conventional treatment,” in a survey conducted by Kohl and Medlar (2006), it was discovered that utilities that did not have specific treatment in place to control manganese were not able to handle variable or intermediate manganese loadings and therefore manganese would pass through the treatment system into the distribution system, with a ratio of maximum manganese to average manganese concentration greater than 7.5:1 resulting in manganese issues, suggesting that the concern by PAWC, as well as the Reading Area Water Authority, is also a concern for other utilities in the state of Pennsylvania. These fluctuations in finished water quality typically result

in customer complaints that are costly to manage. Case studies show that many consumers will experience episodic dissatisfaction with water quality even at the SMCL of 0.050 mg/L. Public water systems typically use a value of 0.02 mg/L total manganese as a target that reasonably balances benefits to the cost of producing water at a low manganese concentration. For example, the Philadelphia Water Department (PWD) has established an even lower internal goal for treated drinking water of 0.015 mg/L. In 2020, they reported average manganese levels in the treated water of 0.55 parts per billion (PPB) (i.e., 0.00055 mg/L) with a range of 0 to 0.95 PPB. (PWD 2021), which is well below their treated drinking water target of 0.015 mg/l.

Unregulated water sources

For most Pennsylvanians, the impact of elevated levels of manganese in surface waters would be experienced as an increase in the cost of treatment to deliver the state-enforceable SMCL of 0.050 mg/L for public drinking water. However, it is important to note that Pennsylvania has the second highest number of private residential wells of any state in the Nation with approximately 1 million wells. These wells serve between 2.4 and 3.5 million residents who depend on groundwater for their domestic water supply. (Clune 2019, PSE 2016). If Bradford County, PA is an appropriate example, 30% of private residential wells may contain greater than 0.050 mg/L of manganese. (Clune 2019) Roughly 6% of Pennsylvanians are below the age of 6 - which equates to 43,200 children currently affected by manganese in well water above the SMCL of 0.050 mg/L.

Although private residential wells are not regulated by the Commonwealth of Pennsylvania, manganese contamination of residential wells does occur either via

natural or anthropogenic geological process or from surface water influence, and homeowners are encouraged to routinely test their groundwater sources and provide treatment if the water quality does not meet regulatory standards. With drinking water and surface water recommendations (i.e., health advisories, MCLs, and water quality standards) for manganese becoming more stringent based upon current knowledge of manganese toxicity rather than strictly esthetic concerns, private well owners may be more likely to test their groundwater for manganese and install treatment systems for manganese removal if groundwater concentrations exceed current recommendations. Private well owners are responsible for the quality of their own water. Testing costs are approximately $100 per household. Individual whole home water filtration and treatment systems for iron and manganese cost in the range of $500 to $2000 depending on the complexity of the system. Filter replacement costs range from $40 to $100 annually. (Kohl 2006, Brandhuber 2013, PSE). The economic burden for removal of manganese from these private wells falls on the individual, but across the state it would substantially add to the economic burden of clean water.

Socioeconomic impacts and cost of care

Lidsky (2007) suggested that the heavy metal, lead, forms a paradigm for understanding the impact of heavy metals in the diet on socioeconomic burden. Gould (2009) demonstrated that each IQ point loss from lead toxicity represents a loss of $25,000 in present discounted value of lifetime earnings (inflation adjusted USD 2022). Assume for the moment that the lead paradigm is true for manganese when levels in the body exceed those necessary for adequate health and that manganese levels increase in private wells, including those under the influence of surface waters,

sufficiently to decrease the IQ by 1% of 43,200 potentially exposed children who consume well water. This would represent a loss of lifetime earnings of $1billion dollars for this group. Children receiving drinking water from surface water sources that lack appropriate treatment systems could also be affected. While unfiltered surface water sources are uncommon, they do still occur in Pennsylvania. The economic burden to Pennsylvanians becomes obvious when this is added to the loss of tax revenue at a flat 15% rate, increased cost of education, social programs, and law enforcement associated with communities with diminished earning capacity.

Summary

In conclusion, RfDs of manganese have been informed by studies that clearly demonstrate adverse effects of elevated levels of manganese in drinking water. Multiple authorities on the matter have continued to revise previous RfDs downward. The PA DEP recommendation for $AWQC_{Mn}$ of 0.300 mg/L (300 ug/L) is consistent with current EPA RfD recommendations for manganese and scientifically sound.

To summarize, our recommendation is to maintain the existing point of compliance in all surface waters (i.e., at the point of discharge). Furthermore, it is appropriate to adopt a numeric water quality criterion, designed to protect human health, for manganese, a toxic substance. Scientific evidence supports the conclusion by the PA DEP that the $AWQC_{Mn}$ of 0.3 mg/L is consistent with the goal of protecting human health from the toxicological effects of manganese in water.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). (2012). Toxicological Profile for Manganese. https://www.atsdr.cdc.gov/ToxProfiles/tp151.pdf

Aschner, M. (2000). Manganese: Brain Transports and Emerging Research Needs". Environmental Health Perspectives. 108(3): 429-432.

Barceloux D.G. ,Barceloux D. (1999) "Manganese", Journal of Toxicology: Clinical Toxicology, 37:2, 293-307, DOI: 10.1081/CLT-100102427

Beaudin, S.A., S. Nisam, and D.R. Smith (2013). "Early life versus lifelong oral manganese exposure differently impairs skilled forelimb performance in adult rats." Neurotoxicology and Teratology. 38: 36-45.

Bouabid, S., et al. (2016). "Manganese Neurotoxicity: Behavioral Disorders Associated with Dysfunctions in the Basal Ganglia and Neurochemical Transmission." Journal of Neurochemistry. 136: 677-691.

Bouchard, M.F., et al. (2007). "Hair manganese and hyperactive behaviors: pilot studies of school-age children exposed through tap water." Environmental Health Perspectives. 119(1): 138-143.

Bouchard, M.F., et al. (2011). "Intellectual Impairment in School-age Children Exposed to Manganese from Drinking Water." Environmental Health Perspectives. 119(1): 138-143.

Brandhuber P. (2013) Legacy of Manganese Accumulation in Water Systems Literature Review. HDR Engineering. Water Research Foundation https://www.waterrf.org/system/files/resource/2019-05/4314_Literature_Review.pdf

Buamah, R., B. Petrusevski, J. C. Schippers; Adsorptive removal of manganese(II) from the aqueous phase using iron oxide coated sand. *Journal of Water Supply: Research and Technology-Aqua* 1 February 2008; 57 (1): 1–11. doi: https://doi.org/10.2166/aqua.2008.078

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. 15: 923-947.

Chen, P., et. al. (2015). "Manganese homeostasis in the nervous system". Journal of Neurochemistry. 134: 601-610.

Chung, S.E., et al. (2015). “Maternal Blood Manganese and Early Neurodevelopment: The Mothers and Children’s Environmental Health (MOCEH) Study.” Environmental Health Perspectives. 123: 717-722.

Clune, J.W., and Cravotta, C.A., III, 2019, Drinking water health standards comparison and chemical analysis of groundwater for 72 domestic wells in Bradford County, Pennsylvania, 2016 (ver 1.2, May 2019): U.S. Geological Survey Scientific Investigations Report 2018–5170, 66 p., https://doi.org/10.3133/sir20185170.

Cordova, F.M., et al. (2013). “Manganese-exposed developing rats display motor deficits and striatal oxidative stress that are reversed by Trolox.” Archives of Toxicology. 87: 1231-1244.

Crossgrove, J. and W. Zheng. (2004). “Manganese toxicity upon overexposure.” NMR in Biomedicine. 17(8): 544-553.

Douron M. 2010 “U-shaped dose-response curves: implications for risk characterization of essential elements and other chemicals.” J Toxicol Environ Health A. 2010;73(2):181-6. doi: 10.1080/15287390903340450. PMID: 20077289.

Duarte, R.S., Lima, R.M.F., Leão, V.A. 2015. “Effect of inorganic and organic depressants on the cationic flotation and surface charge of rhodonite-rhodochrosite” REM: R. Esc. Minas, 68(4), 463-469, https://doi.org/10.1590/0370-44672015680019 Erikson, K.M., et al. (2007). “Manganese Neurotoxicity.” Pharmacology and Therapeutics. 113(2): 369-377.

Finley, J.W. and C.D. Davis. (1999). “Manganese deficiency and toxicity: Are high or low dietary amounts of manganese cause for concern?”. BioFactors. 10: 15-24. Fordahl, S., 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.

Foti, R., P. Gurian, J. Wen, C. Hunold, et al. Options for Achieving Deep Reductions in Carbon Emissions in Philadelphia by 2050. Drexel University. 2015. https://www.researchgate.net/publication/283503711_Options_for_Achieving_Deep_Reductions_in_Carbon_Emissions_in_Philadelphia_by_2050

Frisbie, S.H., et al. (2012). “World Health Organization Discontinues Its Drinking-Water Guideline for Manganese.” Environmental Health Perspectives. 120(6): 775-778.

Gould E. 2009. ”Childhood lead poisoning: conservative estimates of the social and economic benefits of lead hazard control”. Environ Health Perspect. 2009 Jul;117(7):1162-7. doi: 10.1289/ehp.0800408. Epub 2009 Mar 31. PMID: 19654928; PMCID: PMC2717145.

Grandjean, P, Landrigan PJ (2014). “Neurobehavioral effects of development toxicity.” Lancet Neurology. 13: 330-38.

Greger, J.L. (1998). “Dietary Standards for Manganese: Overlap between Nutritional and Toxicological Studies”, The Journal of Nutrition, Volume 128, Issue 2, February 1998, Pages 368S–371S, https://doi.org/10.1093/jn/128.2.368S

Haynes, E.N., et al. (2015). “Manganese Exposure and Neurocognitive Outcomes in Rural School-Age Children: The Communities Actively Researching Exposure Study (Ohio, USA).” Environmental Health Perspectives. 123(10): 1066-1071.

Health Canada (2019). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document—Manganese. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. (Catalogue No H144-39/2017E-PDF).

Herndon, E. M., Havig, J. R., Singer, D. M., McCormick, M. L., & Kump, L. R. (2018). Manganese and iron geochemistry in sediments underlying the redox-stratified Fayetteville Green Lake. Geochimica Et Cosmochimica Acta, 231, 50–63. https://doi.org/10.1016/j.gca.2018.04.013

https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-manganese.html
Henn, B.C., et al. (2010). “Early Postnatal Blood Manganese Levels and Children’s Neurodevelopment.” Epidemiology. 21(4): 433-439.

Holley, A.K., et al. (2011). “Manganese Superoxide Dismutase: Guardian of the Powerhouse.” International Journal of Molecular Sciences. 12: 7114-7162.

IOM 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 D.C.

Kaushal, S., et. al. (2018). “Watershed ‘chemical cocktails’: forming novel elemental combinations in Anthropocene fresh waters”. Biogeochemistry. 141:281-305.

Kawamura, R, H. Ikuta. S. Fukuzimi. et al. 1941. Intoxication by manganese in well water. Kitasato Arch. Exp. Med. 18: 145-169.

Keen CL, Ensunsa JL, Watson MH, Baly DL, Donovan SM, Monaco MH, Clegg MS. Nutritional aspects of manganese from experimental studies. Neurotoxicology. 1999 Apr-Jun;20(2-3):213-23. PMID: 10385885.

Kern, C., G. Stanwood and D.R. Smith (2010). “Pre-weaning manganese exposure causes hyperactivity disinhibition, and spatial learning and memory deficits associated with altered dopamine receptor and transporter levels.” Synapse. 64(5): 363-378.

Khan, K., et al. (2011). “Manganese Exposure from Drinking Water and Children’s Classroom Behavior in Bangladesh.” Environmental Health Perspectives. 119(10): 1501-1506.

Khan, K., et al. (2012). “Manganese Exposure from Drinking Water and Children’s Academic Achievement.” Neurotoxicology. 33(1): 91-97.

Kim, Y., et al. (2009). “Co-exposure to environmental lead and manganese affects the intelligence of school-aged children.” Neurotoxicology. 30: 564-571.

Kohl P., Medlar S. 2006. Occurrence of Manganese in Drinking Water and Manganese Control. WaterRF and AWWA: Denver CO.
https://www.waterrf.org/system/files/resource/2019-05/91147.pdf

Kondakis, X.G., N. Makris, M. Leotsinidis, M. Prinou and T. Papapetropoulos. 1989. Possible health effects of high manganese concentration in drinking water. Arch. Environ. Health. 44(3): 175-178.

Kullar SS, Shao K, Surette C, Foucher D, Mergler D, Cormier P, Bellinger DC, Barbeau B, Sauvé S, Bouchard MF. A benchmark concentration analysis for manganese in drinking water and IQ deficits in children. Environ Int. 2019 Sep;130:104889. doi:10.1016/j.envint.2019.05.083. Epub 2019 Jun 11. PMID: 31200154.

Lanphear, B.P., et al. (2015). “The Impact of Toxins on the Developing Brain.” Annual Review of Public Health. 36: 211-30.

Lidsky, T. I., Heaney, A. T., Schneider, J. S., & Rosen, J. F. (2007). Neurodevelopmental effects of childhood exposure to heavy metals: Lessons from pediatric lead poisoning. In M. M. M. Mazzocco & J. L. Ross (Eds.), Neurogenetic developmental disorders: Variations in the manifestation in childhood (pp. 335–363). Cambridge, MA: MIT Press.

Ljung, K.S., M. J. Kippler, et al. (2009). “Maternal and early life exposure to manganese in rural Bangladesh.” Environmental Science Technology 43(7): 2595-2601.
Lytle C.M., et. al. (1994). Manganese accumulation in roadside soil and plants. Naturwissenschaften. 81:509–510.

Mena, I. (1974). The role of manganese in human disease. Ann. Clin. Lab. Sci. 4(6): 487-491.

Menezes-Filho, J.A., et al. (2011). “Elevated manganese and cognitive performance in school-aged children and their mothers”. Rev Panam Salud Publication. 26(6):541-8.

Minnesota Department of Health (2020). "Health Based Guidance for Water" Health Risk Assessment Unit, Environmental Health Division 651-201-4899 Web Publication Date: August 2020 Toxicological Summary for: Manganese CAS: 7439-96-5 https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/manganese.pdf

Moreno, J.A., et al. (2009). “Neurobehavioral Function in School-Age Children Exposed to Manganese in Drinking Water”. Toxicological Sciences. 112(2):394-404.

Mohabir S, Pitcher RD, Perumal R, Goodier MDM. (2020) The efficacy of pineapple juice as a negative oral contrast agent in magnetic resonance cholangiopancreatography. S Afr J Rad. 2020;24(1), a1875. https://doi.org/10.4102/sajr.v24i1.1875

MWRA 2022. “Lime Soda-Ash Softening” https://www.mrwa.com/WaterWorksMnl/Chapter%2016%20Lime%20Softening.pdf

NARC (National Research Council). (1989) Recommended Dietary Allowances, 10th ed. Food and Nutrition Board, National Research Council, National Academy Press, Washignto DC p 230-235

Oulhote, Y., et al. (2014). “Age-Dependent Susceptibility to Manganese-Induced Neurological Dysfunction”. Environmental Health Perspectives. 122(12):1343-1350.

O’Neal, S.L and W. Zheng (2015). “Manganese Toxicity Upon Overexposure: a Decade in Review”. Current Environmental Health Reports. 2(3):315-328.

PSE Penn State Extension. (2016) “Private Water System FAQs” https://extension.psu.edu/private-water-systems-faqs. (Accessed 3/27/2022)

PWD Philadelphia Water Department 2021. “2020 Drinking Water Quality Report”. https://water.phila.gov/drops/2020-quality/

Ramachandran, M., Schwabe, K. A., & Ying, S. C. (2021, March 16). Shallow groundwater manganese merits deeper consideration. Environmental science & technology. Retrieved April 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8363073/

Richardson, L. L., & Nealson, K. H. (1989). Distributions of manganese, iron, and manganese-oxidizing bacteria in Lake Superior sediments of different organic carbon content. Journal of Great Lakes Research, 15(1), 123–132. https://doi.org/10.1016/s0380-1330(89)71466-0

Santamaria, A.B.(2008). “Manganese exposure, essentiality & toxicity”. Indian Journal of Medical Research. 128:484-500.

Schaller, T., & Wehrli, B. (1996). Geochemical-focusing of manganese in lake sediments - an indicator of deep-water oxygen conditions - aquatic geochemistry. SpringerLink. Retrieved April 15, 2022, from https://link.springer.com/article/10.1007/BF00115977

Schroeder, H. A., Balassa, J. J., and Tipton, I. H. 1966. Essential trace metals in man: manganese. A study in homeostasis. J. Chron. Dis. 19:545–571.

Schroeter, J.D., et al. (2011). “Analysis of Manganese Tracer Kinetics and Target Tissue Dosimetry in Monkeys and Humans with Multi-Route Physiologically Based Pharmacokinetic Models”. Toxicological Sciences. 120(2):481-498.

Schroeter, J.D., et al. (2012). “Application of a Multi-Route Physiologically Based Pharmacokinetic Model for Manganese to Evaluate Dose-Dependent Neurological Effects in Monkeys”. Toxicological Sciences. 129(2):432-446.

Sepulveda, N.A., Jesse D. Jenkins, Fernando J. de Sisternes, Richard K. Lester. 2018. “The Role of Firm Low-Carbon Electricity Resources in Deep Decarbonization of Power Generation,” Joule, 2, (11): 2403-2420.

Smith, M.R., et. al. (2017). “Redox dynamics of manganese as a mitochondrial life-death switch”. Biochemical and Biophysical Research Communications. 482(3):388-398.

Streifel, K., et. al. (2013). “Manganese inhibits ATP-induced calcium entry through the transient receptor potential channel TRPC3 in astrocytes”. Neurotoxicology. 34:160-166.

Tartari, G., Copetti, D., Franzetti, A., Balordi, M., Salerno, F., Thakuri, S., Leoni, B., Chiarello, G., & Cristiani, P. (2021, July 1). Manganese-mediated hydrochemistry and microbiology in a meromictic subalpine lake (Lake Idro, Northern Italy) - a biogeochemical approach. Science of The Total Environment. Retrieved April 15, 2022, from https://www.sciencedirect.com/science/article/pii/S0048969721038158#s0075

Tobiason, J.E., Bazilio, A., Goodwill, J., Mai, X., Nguyen, C., 2016. Manganese Removal from Drinking Water Sources. Curr Pollut Reports 2, 168–177. https://doi.org/10.1007/s40726-016-0036-2

USEPA Drinking Water Criteria Document for Manganese Final Draft ECAO=CIN=D008 1993 https://www.epa.gov/sites/default/files/2018-12/documents/dw-criteria-manganese.pdf

USEPA “Proceedings: Workshop on the Bioavailability and Oral Toxicity of Manganese” Omni Netherland Plaza Cincinnati, OH August 30-31,1994 Prepared for: U.S. Environmental Protection Agency Environmental Criteria and Assessment Office

Cincinnati, OH 45268
https://hero.epa.gov/hero/index.cfm/reference/download/reference_id/77043

USEPA (U.S. Environmental Protection Agency). Integrated Risk Information System Chemical Assessment Summary for Manganese (CASRN 7439-96-5). 1995 U.S. EPA Office of Research and Development, National Center for Environmental Assessment, Integrated Risk Information System Program. Washington, D.C. Accessed April 2022. https://iris.epa.gov/static/pdfs/0373_summary.pdf

USEPA (U.S. Environmental Protection Agency). 2000.Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. EPA 882-B-00-004. U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology, Washington, DC. https://www.epa.gov/wqc/human-health-water-quality-criteria

USEPA (U.S. Environmental Protection Agency). 2004 Drinking Water Health Advisory for Manganese. EPA-822-R-04-003. EPA Office of Water; Health and Ecological Criteria Division. Washington, D.C. https://www.epa.gov/sites/default/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf

USEPA (U.S. Environmental Protection Agency). 2002. “A review of the refence dose and reference concentration process”. EPA/630/P-02/002F
https://www.epa.gov/sites/default/files/2014-12/documents/rfd-final.pdf

USEPA (U.S. Environmental Protection Agency). 2015 EPA Updated Ambient Water Quality Criteria for the Protection of Human Health U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology, Washington, DC. EPA 820-F-15-001
https://www.epa.gov/wqc/human-health-water-quality-criteria-and-methods-toxics#2015

Wasserman, G.A., et al. (2006). “Water Manganese Exposure and Children’s Intellectual Function in Araihazar, Bangladesh”. Environmental Health Perspectives. 114(1):124-129.

Wasserman, G.A., et al. (2011). “Arsenic and manganese exposure and children’s intellectual function”. Neurotoxicology. 32(4):450-457.
World Health Organization (WHO). (2004). Manganese and Its Compounds: Environmental Aspects.

Wang, L.K., Wu, J.S., Shammas, N.K., Vaccari, D.A. (2005). Recarbonation and Softening. In: Wang, L.K., Hung, YT., Shammas, N.K. (eds) Physicochemical Treatment Processes. Handbook of Environmental Engineering, vol 3. Humana Press.
https://doi.org/10.1385/1-59259-820-x:199

WHO (World Health Organization) 1973. Trace Elements in Human Nutrition: Manganese. Report of WHO Expert Committee. Technical Report Service, 532, WHO, Geneva, Switzerland. P 34-36.

WHO Manganese in Drinking Water 2021 Background Document Manganese in drinking-water. Background document for development of WHO Guidelines for drinking-water quality Geneva: World Health Organization; 2021 (WHO/HEP/ECH/WSH/2021.5). Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/350933/WHO-HEP-ECH-WSH-2021.5-eng.pdf?sequence=1&isAllowed=y

Yoon, M., et al. (2011). "Physiologically Based Pharmacokinetic Modeling of Fetal and Neonatal Manganese Exposure in Humans: Describing Manganese Homeostasis during Development". Toxicological Sciences. 122(2): 297-316.

Yoon M, et al (2109). "Updating physiologically based pharmacokinetic models for manganese by incorporating rapid association/dissociation processes in tissues." Toxicol Appl Pharmacol. 2019 Jun 1;372:1-10. doi: 10.1016/j.taap.2019.04.006. Epub 2019 Apr 9. PMID: 30978397.

Zaw, M., & Chiswell, B. (1999, April 16). Iron and manganese dynamics in Lake Water. Water Research. Retrieved April 15, 2022, from https://www.sciencedirect.com/science/article/pii/S0043135498003601