Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: Manganese

CAS: **7439-96-5**

MDH has updated manganese guidance to a Health Based Value (HBV), and is removing the tiered Risk Assessment Advice. The Short-term Health-Based Value for Manganese is 100 ug/L. This value is protective of bottle-fed infants less than one year of age, the most sensitive population, as well as other populations.

MDH continues to support the U.S. Environmental Protection Agency (EPA) Lifetime Health Advisory (HA) of 300 µg/L for children older than one year of age and adults See Drinking Water Health Advisory for Manganese (https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf) (PDF).

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.083 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 145.6 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	HED/Total UF = 25/300 = 0.083 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2012
Point of Departure (POD):	25 mg/kg-d (LOAEL, Kern 2010)
Dose Adjustment Factor (DAF):	Not applicable (Insufficient data to support use of DAFs for neonatal period) (MDH, 2017) (U.S. EPA, 2011)
Human Equivalent Dose (HED):	Not applicable
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 3 for LOAEL-to-NOAEL extrapolation (due to mild effects seen at LOAEL)
Critical effect(s):	Neurological effects including increased distance traveled in open arena, decreased number of animals meeting

	learning criteria, increased learning errors, shift in goal-oriented behavior, altered dopamine receptor levels
Co-critical effect(s):	Neurological effects including increased startle response
Additivity endpoint(s):	Developmental, Nervous System

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = Not Derived (Insufficient Information)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = Not Derived (Insufficient Information)

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Group D – Not classifiable as to human carcinogenicity (U.S. EPA, 2011)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

A non-cancer Health Risk Limit (HRL) of 100 µg/L was promulgated in 1993. New guidance of 1,000 µg/L based on an updated U.S. EPA assessment was developed in 1997. A Health Based Value (HBV) of 300 µg/L based on U.S. EPA's Lifetime Health Advisory value of 300 µg/L was developed in 2008. In 2011, based on new information and risk assessment methodology, MDH reverted to recommending the 1993 HRL value of 100 µg/L for infants until guidance could be re-evaluated. In 2012, MDH again reviewed manganese and established Risk Assessment Advice (RAA) of 100 µg/L that used tiered guidance based on age instead of MDH's typical duration-specific guidance. In 2017, MDH re-evaluated the available information and updated the risk assessment methodology, which resulted in no change to the existing RAAs. In 2018, the tiered guidance methodology was removed and the guidance value was converted from RAA of 100/300 µg/L to an HBV of 100 µg/L for the short-term duration. The toxicological information available supports guidance at the level of HBV. MDH also continues to support the U.S. EPA HA of 300 µg/L for adult, infants older than one year of age, and children.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	Yes	Yes	Yes

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects observed?	No	No	Yes[1]	Yes[2]	Yes[3]

Comments on extent of testing or effects:

Note: Effects reported in dietary animal studies have limited relevance to humans because humans are known to have tightly regulated controls that limit absorption and excretion of manganese from the diet.

[1] There was some evidence of delayed fetal skeletal and organ development in offspring born to pregnant rats exposed to manganese by gavage at a dose of 33 mg/kg-day, which is similar to the critical short-term LOAEL of 25 mg/kg-day. However, these effects were not present in the same offspring when they were observed at 100 days old, so these effects may be transient. Neurodevelopmental effects are a concern following manganese exposure from drinking water during early life. Neurodevelopmental effects were selected as the basis of the short-term RfD in this assessment and are discussed in footnote 3.

[2] Some male and female reproductive effects were reported in subchronic duration rodent studies (and one developmental study) following oral exposures to manganese. The information available about these effects is very limited, which makes it difficult to establish a strong level of confidence in the results. Male reproductive effects (decreased testicular weight and increased testicular degeneration) were reported at doses 2 times to 5 times higher than the short-term critical LOAEL. Most toxicity studies did not report female reproductive toxicity. Post-implantation loss was observed in female rats as a dose slightly above the short-term critical LOAEL but this effect was not reported in other rodent studies.

[3] Neurodevelopmental effects in animals form the basis of the short-term RfD. Subtle neurodevelopmental effects (biochemical, behavioral, and cognitive changes) have been observed in neonatal rats and non-human primates following oral manganese exposure at exposure levels equal to and above the short-term critical LOAEL of 25 mg/kg-day. Manganese is well established as a neurotoxin following inhalation by humans in occupational settings with the central nervous system appearing to be the primary target for manganese toxicity.

Several epidemiology studies have suggested there could be subtle IQ and memory effects in children exposed to manganese in drinking water at concentrations >200 µg/L. Manganese has also been associated with neurological effects in adults exposed to manganese in drinking water for over 10 years at concentrations of 1,800 to 2,300 µg/L.

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