

Web Publication Date: August 2020

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 µg/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 \(PDF\)](https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf) (https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf)

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

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

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

$$= \frac{(0.083 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 143 \text{ rounded to } \mathbf{100 \text{ µg/L}}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

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. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR) - MRLs. (2009). Minimal Risk Levels for Hazardous Substances (MRLs). Retrieved from <https://www.atsdr.cdc.gov/mrls/mrllist.asp>

Agency for Toxic Substances and Disease Registry (ATSDR) - Toxicological Profiles. Toxicological Profile Information Sheet. Retrieved from <https://www.atsdr.cdc.gov/toxprofiledocs/index.html>

- Agency for Toxic Substances and Disease Registry (ATSDR). (2009). Draft Toxicological Profile for Manganese. Retrieved from <http://www.atsdr.cdc.gov/toxprofiles/tp151.pdf>
- Andersen, M. E., Dorman, D. C., Clewell, H. J., 3rd, Taylor, M. D., & Nong, A. (2010). Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment. *J Toxicol Environ Health A*, 73(2), 217-234. doi:918613622
- Aschner, J. L., & Aschner, M. (2005). Nutritional aspects of manganese homeostasis. *Mol Aspects Med*, 26(4-5), 353-362. doi:S0098-2997(05)00038-5
- Aschner, M., Erikson, K. M., & Dorman, D. C. (2005). Manganese dosimetry: species differences and implications for neurotoxicity. *Crit Rev Toxicol*, 35(1), 1-32.
- Bouchard, M., Laforest, F., Vandelac, L., Bellinger, D., & Mergler, D. (2007). Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. *Environ Health Perspect*, 115(1), 122-127.
- Bouchard, M. F., Sauve, S., Barbeau, B., Legrand, M., Brodeur, M. E., Bouffard, T., . . . Mergler, D. (2010). Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water. *Environ Health Perspect*. doi:10.1289/ehp.1002321
- Brenneman, K. A., Cattley, R. C., Ali, S. F., & Dorman, D. C. (1999). Manganese-induced developmental neurotoxicity in the CD rat: is oxidative damage a mechanism of action? *Neurotoxicology*, 20(2-3), 477-487.
- California Environmental Protection Agency-OEHHA Toxicity Criteria Database. Retrieved from <http://www.oehha.ca.gov/risk/ChemicalDB/index.asp>
- California Environmental Protection Agency - OEHHA Cancer Potency Values. (2005). OEHHA Toxicity Criteria Database.
- Chandra, S. V., Shukla, G. S., & Saxena, D. K. (1979). Manganese-induced behavioral dysfunction and its neurochemical mechanism in growing mice. *J Neurochem*, 33(6), 1217-1221.
- Claus Henn, B., Ettinger, A. S., Schwartz, J., Tellez-Rojo, M. M., Lamadrid-Figueroa, H., Hernandez-Avila, M., . . . Wright, R. O. (2010). Early postnatal blood manganese levels and children's neurodevelopment. *Epidemiology*, 21(4), 433-439.
- Collipp, P. J., Chen, S. Y., & Maitinsky, S. (1983). Manganese in infant formulas and learning disability. *Ann Nutr Metab*, 27(6), 488-494.
- Davis, C. D., Zech, L., & Greger, J. L. (1993). Manganese metabolism in rats: an improved methodology for assessing gut endogenous losses. *Proc Soc Exp Biol Med*, 202(1), 103-108.
- Dorman, D. C., Struve, M. F., Vitarella, D., Byerly, F. L., Goetz, J., & Miller, R. (2000). Neurotoxicity of manganese chloride in neonatal and adult CD rats following subchronic (21-day) high-dose oral

exposure. *J Appl Toxicol*, 20(3), 179-187. doi:10.1002/(SICI)1099-1263(200005/06)20:3<179::AID-JAT631>3.0.CO;2-C

- Ericson, J. E., Crinella, F. M., Clarke-Stewart, K. A., Allhusen, V. D., Chan, T., & Robertson, R. T. (2007). Prenatal manganese levels linked to childhood behavioral disinhibition. *Neurotoxicol Teratol*, 29(2), 181-187. doi:S0892-0362(06)00114-0
- Golub, M. S., Hogrefe, C. E., Germann, S. L., Tran, T. T., Beard, J. L., Crinella, F. M., & Lonnerdal, B. (2005). Neurobehavioral evaluation of rhesus monkey infants fed cow's milk formula, soy formula, or soy formula with added manganese. *Neurotoxicol Teratol*, 27(4), 615-627. doi:S0892-0362(05)00055-3
- Hafeman, D., Factor-Litvak, P., Cheng, Z., van Geen, A., & Ahsan, H. (2007). Association between manganese exposure through drinking water and infant mortality in Bangladesh. *Environ Health Perspect*, 115(7), 1107-1112. doi:10.1289/ehp.10051
- He, P., Liu, D. H., & Zhang, G. Q. (1994). Effects of high-level-manganese sewage irrigation on children's neurobehavior. *Zhonghua Yu Fang Yi Xue Za Zhi*, 28(4), 216-218.
- Health Canada Guidelines for Canadian Drinking Water Quality. Guidelines for Canadian Drinking Water Quality. Retrieved from http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/index-eng.php#tech_doc
- Institute of Medicine (IOM). (2001). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. In Food and Nutrition Board (Ed.). Washington, D.C.: National Academy Press.
- Kern, C. H., Stanwood, G. D., & Smith, D. R. (2010). Prewaning 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
- Kim, Y., Kim, B. N., Hong, Y. C., Shin, M. S., Yoo, H. J., Kim, J. W., . . . Cho, S. C. (2009). Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. *Neurotoxicology*, 30(4), 564-571. doi:S0161-813X(09)00075-8
- Kondakis, X. G., Makris, N., Leotsinidis, M., Prinou, M., & Papapetropoulos, T. (1989). Possible health effects of high manganese concentration in drinking water. *Arch Environ Health*, 44(3), 175-178.
- Malecki, E. A., Radzanowski, G. M., Radzanowski, T. J., Gallaher, D. D., & Greger, J. L. (1996). Biliary manganese excretion in conscious rats is affected by acute and chronic manganese intake but not by dietary fat. *J Nutr*, 126(2), 489-498.
- Menezes-Filho, J. A., Bouchard, M., Sarcinelli Pde, N., & Moreira, J. C. (2009). Manganese exposure and the neuropsychological effect on children and adolescents: a review. *Rev Panam Salud Publica*, 26(6), 541-548. doi:S1020-49892009001200010

- Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. Support document relating to Health Risk Limits for Groundwater Rules. Retrieved from <https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2>
- Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from <https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf>
- Narayanaswamy, M., & Piler, M. B. (2010). Effect of maternal exposure of fluoride on biometals and oxidative stress parameters in developing CNS of rat. *Biol Trace Elem Res*, 133(1), 71-82. doi:10.1007/s12011-009-8413-y
- National Toxicology Program (NTP). (1993). Toxicology and Carcinogenesis Studies of Manganese (II) Sulfate monohydrate (CAS No. 10034-96-5) in F344/N Rats and B6C3F Mice (Feed Studies) Retrieved from http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr428.pdf
- Pappas, B. A., Zhang, D., Davidson, C. M., Crowder, T., Park, G. A., & Fortin, T. (1997). Perinatal manganese exposure: behavioral, neurochemical, and histopathological effects in the rat. *Neurotoxicol Teratol*, 19(1), 17-25. doi:S0892036296001857 [pii]
- Reichel, C. M., Wacan, J. J., Farley, C. M., Stanley, B. J., Crawford, C. A., & McDougall, S. A. (2006). Postnatal manganese exposure attenuates cocaine-induced locomotor activity and reduces dopamine transporters in adult male rats. *Neurotoxicol Teratol*, 28(3), 323-332. doi:S0892-0362(06)00035-3
- Rodriguez-Agudelo, Y., Riojas-Rodriguez, H., Rios, C., Rosas, I., Sabido Pedraza, E., Miranda, J., . . . Santos-Burgoa, C. (2006). Motor alterations associated with exposure to manganese in the environment in Mexico. *Sci Total Environ*, 368(2-3), 542-556. doi:S0048-9697(06)00255-5
- Santamaria, A. B., & Sulsky, S. I. (2010). Risk assessment of an essential element: manganese. *J Toxicol Environ Health A*, 73(2), 128-155. doi:918612614 [pii]
- Santos-Burgoa, C., Rios, C., Mercado, L. A., Arechiga-Serrano, R., Cano-Valle, F., Eden-Wynter, R. A., . . . Montes, S. (2001). Exposure to manganese: health effects on the general population, a pilot study in central Mexico. *Environ Res*, 85(2), 90-104. doi:10.1006/enrs.2000.4108
- Syracuse Research PhysProp Database. Retrieved from <http://www.syrres.com/what-we-do/databaseforms.aspx?id=386>
- Tran, T. T., Chowanadisai, W., Crinella, F. M., Chicz-DeMet, A., & Lonnerdal, B. (2002a). Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status. *Neurotoxicology*, 23(4-5), 635-643. doi:S0161-813X(02)00091-8

- Tran, T. T., Chowanadisai, W., Lonnerdal, B., Le, L., Parker, M., Chicz-Demet, A., & Crinella, F. M. (2002b). Effects of neonatal dietary manganese exposure on brain dopamine levels and neurocognitive functions. *Neurotoxicology*, 23(4-5), 645-651. doi:S0161-813X(02)00068-2
- U.S. Environmental Protection Agency - IRIS. Integrated Risk Information Systems (IRIS) A-Z List of Substances. Retrieved from <http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList>
- U.S. Environmental Protection Agency - National Center for Environmental Assessment. Retrieved from http://cfpub.epa.gov/ncea/cfm/archive_whatsnew.cfm
- U.S. Environmental Protection Agency - Office of Drinking Water. (2011). 2011 Edition of the Drinking Water Standards and Health Advisories. Retrieved from http://water.epa.gov/action/advisories/drinking/drinking_index.cfm#dw-standards
- U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose. Retrieved from <http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf>
- U.S. Environmental Protection Agency - Regional Screening Tables. Mid-Atlantic Risk Assessment - Regional Screening Table. Retrieved from [http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/Generic Tables/index.htm](http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/Generic%20Tables/index.htm)
- U.S. Environmental Protection Agency - Toxicity and Exposure Assessment for Children's Health (TEACH). Retrieved from <https://archive.epa.gov/region5/teach/web/html/index.html>
- U.S. Environmental Protection Agency (EPA). (2004). Drinking Water Health Advisory for Manganese. Retrieved from https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf
- U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from <https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3>
- U.S. Geological Survey - Health-Based Screening Levels. Retrieved from <https://cida.usgs.gov/hbsl/apex/f?p=104:1>
- Wasserman, G. A., Liu, X., Parvez, F., Ahsan, H., Levy, D., Factor-Litvak, P., . . . Graziano, J. H. (2006). Water manganese exposure and children's intellectual function in Araihasar, Bangladesh. *Environ Health Perspect*, 114(1), 124-129.
- Wasserman, G. A., Liu, X., Parvez, F., Factor-Litvak, P., Ahsan, H., Levy, D., . . . Graziano, J. H. (2011). Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology*, 32(4), 450-457. doi:S0161-813X(11)00056-8
- Woolf, A., Wright, R., Amarasiriwardena, C., & Bellinger, D. (2002). A child with chronic manganese exposure from drinking water. *Environ Health Perspect*, 110(6), 613-616. doi:sc271_5_1835

- World Health Organization - Guidelines for Drinking-Water Quality. (2008). Retrieved from http://www.who.int/water_sanitation_health/publications/gdwq3rev/en/
- World Health Organization (WHO). (2004). Manganese in drinking water - background document for development of WHO *Guidelines for drinking-water quality*. Retrieved from http://www.who.int/water_sanitation_health/dwq/chemicals/manganese.pdf
- Yoon, M., Schroeter, J. D., Nong, A., Taylor, M. D., Dorman, D. C., Andersen, M. E., & Clewell, H. J., 3rd. (2011). Physiologically Based Pharmacokinetic Modeling of Fetal and Neonatal Manganese Exposure in Humans: Describing Manganese Homeostasis during Development. *Toxicological Sciences: an official journal of the Society of Toxicology*, 122(2), 297-316. doi:10.1093/toxsci/kfr141
- Zota, A. R., Ettinger, A. S., Bouchard, M., Amarasingwardena, C. J., Schwartz, J., Hu, H., & Wright, R. O. (2009). Maternal blood manganese levels and infant birth weight. *Epidemiology*, 20(3), 367-373. doi:10.1097/EDE.0b013e31819b93c0