2012 Health Based Guidance for Groundwater
Health Risk Assessment Unit, Environmental Health Division
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Chemical Name: Manganese (Mn)

CAS: 7439-96-5

During the 2011/2012 manganese review MDH did not derive new non-cancer guidance values for the acute, subchronic and chronic durations and did not derive a cancer guidance value.

Infant (Short-term) Non-Cancer Risk Assessment Advice (RAA_{12}) = 100 ug/L*

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.083 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 143 rounded to **100 ug/L**

Reference Dose / Concentration:	0.083 mg/kg-day (Sprague Dawley rats)
Source of toxicity value:	MDH 2012
Point of Departure:	25 mg/kg-day (LOAEL)
Human Equivalent Dose Adjustment:	Not calculated
Total uncertainty factor:	300
UF allocation:	10 for interspecies extrapolation, 10 for intraspecies variability, 3 for LOAEL-to-NOAEL extrapolation (the neurological effects observed at the LOAEL were subtle, a factor of 3 is expected to be sufficiently protective)
Critical effect(s):	Increase in the distance traveled in open arena, decreased number of animals meeting learning criteria, and an increase in learning errors, shift in goal oriented behavior, altered dopamine receptor levels
Co-critical effect(s):	Neurological effects – Increased startle response, increased manganese concentrations in the brain
Additivity endpoint(s):	Developmental (nervous system)

*This advice applies to infants less than 1 year of age that are bottle fed plain tap water or given reconstituted formula. Please refer to the MDH manganese guidance explanation webpage for more information about MDH water guidance for manganese: http://www.health.state.mn.us/divs/eh/risk/guidance/gw/manganese.html.

Child and Adult Non-Cancer Risk Assessment Advice (RAA_{12}) = 300 ug/L

This advice applies to children 1 year of age and older and adults and is based on the U.S. Environmental Protection Agency (EPA) Lifetime Health Advisory of 300 ug/L (Link to the 2004 EPA Health Advisory

for Manganese). Please refer to the MDH manganese guidance explanation webpage for more information about MDH water guidance for manganese: http://www.health.state.mn.us/divs/eh/risk/guidance/gw/manganese.html.

Volatile: Not volatile

Summary of Guidance Value History:
In 1993, MDH promulgated a HRL for manganese of 100 ug/L. In 1997, MDH developed new guidance of 1,000 ug/L based on an updated U.S. EPA assessment. In 2008, MDH developed a new Health Based Value based on EPA's Lifetime Health Advisory value of 300 ug/L, which was considered protective of infants and children at that time. In 2011, due to new information and risk assessment methodology, MDH reverted to recommending the 1993 HRL value of 100 ug/L for infants until guidance could be reevaluated. In 2012, MDH reevaluated the existing guidance and established Risk Assessment Advice (RAA_{12}) of 100 ug/L. This guidance applies to infants less than one year of age that drink tap water or reconstituted formula. MDH continues to recommend the U.S. EPA Health Advisory of 300 ug/L for children older than one year of age and adults and this advice was established as 2012 Risk Assessment Advice (RAA_{12}). For more information see: http://www.health.state.mn.us/divs/eh/risk/guidance/gw/manganese.html.

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

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

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

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 not be persistent. Neurodevelopmental effects are a concern following manganese exposure from drinking water during early life exposure. 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 appears to be the primary target for manganese toxicity (Narayanaswamy & Piler, 2010).

Several epidemiology studies have suggested there could be an association between subtle learning (IQ and memory) and behavioral (ADHD) effects in children exposed to manganese in drinking water at concentrations >200 ug/L (M. F. Bouchard, et al., 2010; He, et al., 1994; Menezes-Filho, et al., 2009; Wasserman, et al., 2006; Wasserman, et al., 2011). 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 ug/L (Kondakis, et al., 1989).

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