Toxicological Summary for: Manganese

CAS: 7439-96-5

The 2011/2012 MDH manganese review established age-specific rather than duration specific (e.g., short-term, subchronic, and chronic) non-cancer guidance values.

Infant (Short-term) Non-Cancer Risk Assessment Advice (nRAA) = 100 µg/L

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

\[
= \left( \frac{0.083 \text{ mg/kg-d}}{0.285 \text{ L/kg-d}} \right) \times 0.5 \times (1000 \text{ µg/mg}) \\
\]

\[
= 145.6 \text{ rounded to } 100 \text{ µg/L} \\
\]


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-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 and increased manganese concentrations in brain tissue

Additivity endpoint(s): Nervous System

1This advice applies to infants less than one 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
Child and Adult Non-Cancer Risk Assessment Advice (nRAA) = 300 µg/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 µg/L. See Drinking Water Health Advisory for Manganese (https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_manganese_dwreport_0.pdf) (PDF). Please refer to the MDH manganese guidance explanation webpage for more information: Manganese: Tiered Health Based Guidance for Water (http://www.health.state.mn.us/divs/eh/risk/guidance/gw/manganese.html).

Cancer Risk Assessment Advice (cRAA) = 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 new 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, due to 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 re-evaluated the existing guidance and established Risk Assessment Advice (RAA) of 100 µg/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 µg/L for children older than one year of age and adults, and in 2012 this advice was established as a RAA. In 2017, MDH re-evaluated the existing RAAs. The values did not change as a result of the evaluation and the incorporation of MDH’s most recent risk assessment methodology.

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.

<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effects observed?</td>
<td>Endocrine</td>
<td>Immunotoxicity</td>
<td>Development</td>
<td>Reproductive</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>----------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>No</td>
<td>Yes&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
<td>Yes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

**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.

<sup>1</sup> 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 33mg/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 exposure. Neurodevelopmental effects were selected as the basis of the short-term RfD in this assessment and are discussed in footnote 3.

<sup>2</sup> 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.

<sup>3</sup> 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 an association between subtle learning (IQ and memory) and behavioral (ADHD) 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:**


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


U.S. Environmental Protection Agency - National Center for Environmental Assessment. Retrieved from [http://cfpub.epa.gov/ncea/cfm/archive_whatsnew.cfm](http://cfpub.epa.gov/ncea/cfm/archive_whatsnew.cfm)


