Manganese in drinking-water

Background document for development of WHO Guidelines for drinking-water quality

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Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters ...”, including those related to the safety and management of drinking-water.

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International standards for drinking-water. It was revised in 1963 and 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects, reviewing selected microorganisms, was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006, and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2017.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation relating to aspects of protection and control of drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other information to support the GDWQ, describing the approaches used in deriving guideline values, and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks to human health from exposure to that chemical in drinking-water was prepared. The draft health criteria document was submitted to a number of scientific institutions and selected experts for peer review. The draft document was also released to the public domain for comment. Comments were carefully considered and addressed, as appropriate, taking into consideration the processes outlined in Policies and procedures used in updating the WHO guidelines for drinking-water quality and the WHO Handbook for guideline development.

The revised draft was submitted for final evaluation at expert consultations.

During preparation of background documents and at expert consultations, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents; the International Agency for Research on Cancer; the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues; and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO website and in the current edition of the GDWQ.
Acknowledgements

The background document on manganese in drinking-water for the development of the World Health Organization (WHO) *Guidelines for drinking-water quality* (GDWQ) was initially prepared by Dr Ruth Bevan, independent consultant, United Kingdom, and was finalized by Dr Jane MacAulay and Ms Andrea Cherry, Health Canada, Canada, under the coordination of WHO as described further below.

The work of the following experts was crucial in the development of this document and others in the second addendum to the fourth edition:

- Dr M Asami, National Institute of Public Health, Japan
- Dr RJ Bevan, independent consultant, United Kingdom
- Mr R Carrier, Health Canada, Canada
- Dr J Cotruvo, Joseph Cotruvo & Associates and NSF International WHO Collaborating Centre, United States of America
- Dr D Cunliffe, South Australian Department of Health, Australia
- Dr L d’Anglada, Environmental Protection Agency, United States of America
- Dr A Eckhardt, Umweltbundesamt (Federal Environment Agency), Germany
- Professor JK Fawell, Cranfield University, United Kingdom
- Dr A Hirose, National Institute of Health Sciences of Japan
- Dr A Humpage, University of Adelaide (formerly South Australian Water Corporation), Australia
- Dr P Marsden, Drinking Water Inspectorate, United Kingdom
- Professor Y Matsui, Hokkaido University, Japan
- Dr E Ohanian, Environmental Protection Agency, United States of America
- Professor CN Ong, National University of Singapore, Singapore
- Dr J Strong, formerly Environmental Protection Agency, United States of America
- Dr E Testai, National Institute of Health, Italy

The draft text was discussed at the expert consultations for the second addendum to the fourth edition of the GDWQ, including on 28–30 March 2017, 13–14 July 2018 and 2 March 2021. The final version of the document takes into consideration comments from both peer reviewers and the public, including P Aggett, Emeritus University of Central Lancashire, United Kingdom; C Alzamora, International Manganese Institute, France; V Bhat, formerly NSF International, United States of America; P Brandhuber, Brandhuber Water Quality & Treatment, United States of America; H Costa, Departamento da Qualidade, Portugal; J Donohue, Environmental Protection Agency, United States of America; JO Falkingham, Virginia Tech, United States of America; J Hunt, Drinking Water Inspectorate, United Kingdom; WR Knocke, Virginia Tech, United States of America; B Lampe, NSF International, United States of America; D Lee, PUB, Singapore; L Lejon, Flemish Agency for Care and Health, Belgium; O Loebel, European Federation of National Association of Water Services, Belgium; C Nishida, WHO, Switzerland; S Robjohns, Public Health England, United Kingdom; L Rogers, WHO, Switzerland; J Tobiason, University of Massachusetts Amherst, United States of America; and M Valeke, Institut National de Santé Publique du Québec, Canada.

The coordinator was Ms J De France, WHO. Strategic direction was provided by Mr B Gordon, WHO. Dr E Petersen and Dr S Madsen provided liaisons with the Joint FAO/WHO Expert Committee on Food Additives and the Joint FAO/WHO Meeting on Pesticide Residues. Dr R Brown and Ms C Vickers, WHO, provided liaisons with the International Programme on Chemical Safety. Dr M Perez contributed on behalf of the WHO Radiation Programme. Dr A Faragher, Biotext, Australia, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document are greatly appreciated.
**Acronyms and abbreviations**

<table>
<thead>
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<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>bw</td>
<td>body weight</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GV</td>
<td>guideline value</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population</td>
</tr>
<tr>
<td>MMT</td>
<td>methylcyclopentadienyl manganese tricarbonyl</td>
</tr>
<tr>
<td>Mn</td>
<td>manganese</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>particulate matter less than or equal to 2.5 μm in diameter</td>
</tr>
<tr>
<td>PM&lt;sub&gt;10&lt;/sub&gt;</td>
<td>particulate matter less than or equal to 10 μm in diameter</td>
</tr>
<tr>
<td>PND</td>
<td>postnatal day</td>
</tr>
<tr>
<td>TDI</td>
<td>tolerable daily intake</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

Manganese is an essential element that originates in the environment as a result of natural and anthropogenic sources. Oral exposure of the general population to manganese occurs primarily through food; however, manganese may also be present in drinking-water in varying amounts. Higher levels can occur as a result of industrial discharges, and under acidic or reducing conditions that are found in groundwater and in some lakes and reservoirs.

A number of epidemiological studies have identified associations between neurotoxic effects in children and increased exposure to manganese in drinking-water. Although limitations in these studies preclude their use for quantitative risk assessment, the findings support the choice of neurotoxicity as a key end-point of concern. The health risk assessment for manganese in drinking-water is based on studies in rats orally exposed to manganese that report neurotoxic effects consistent with those observed in the epidemiological studies.

A provisional health-based guideline value (pGV) of 80 µg/L is established for total manganese, based on identified health considerations for bottle-fed infants. Although infants have been identified as the most susceptible subpopulation, the pGV is also applicable to the general population as a whole. The health-based GV is considered provisional because of the high level of uncertainty in the overall assessment (as reflected in a composite uncertainty factor of 1000). As part of the hazard assessment phase of water safety planning, water sources should be assessed to determine if manganese is present. Where manganese is present at concentrations close to the pGV or the water is treated to remove manganese, routine monitoring should be conducted post-treatment. Several methods for removing manganese are available, including oxidation/filtration, adsorption/oxidation, softening/ion exchange and biological filtration. Selection of the appropriate treatment system for manganese removal depends on the form of manganese (dissolved or particulate) present in the source water. In general, treatment methods used for manganese rely on a combination of processes (e.g. oxidation, adsorption, filtration) to remove both the dissolved and particulate forms.

In cases where meeting the pGV is technically or financially unfeasible, incremental improvement is encouraged. Risks to infants arising from exceedance of the pGV may be mitigated by following the World Health Organization recommendation for exclusive breastfeeding, or by using an alternative safe source of drinking-water to prepare formula.
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1 General description

1.1 Identity

Manganese is a transition metal and one of the most abundant metals in Earth’s crust, frequently co-occurring with iron. It is a component of more than 100 minerals but is not found naturally in its pure (elemental) form (ATSDR, 2012). Manganese can exist in 11 oxidation states; the most environmentally and biologically important manganese compounds are those that contain Mn(II), Mn(III), Mn(IV) or Mn(VII). Manganese can form a large variety of complexes by combining with other elements such as oxygen, sulfur and chlorine, and with carbonates and silicates (Stokes & NRCC, 1988; ATSDR, 2012). Some of these compounds are listed in Table 1.1.

**Table 1.1. Some manganese compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Abstracts No.</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manganese(II) chloride</td>
<td>7773-01-5</td>
<td>MnCl₂</td>
</tr>
<tr>
<td>Manganese(II, III) oxide (manganese tetroxide)</td>
<td>1317-35-7</td>
<td>Mn₃O₄ (MnO₃MnO₃)</td>
</tr>
<tr>
<td>Manganese dioxide</td>
<td>1313-13-9</td>
<td>MnO₂</td>
</tr>
<tr>
<td>Potassium permanganate</td>
<td>7722-64-7</td>
<td>KMnO₄</td>
</tr>
<tr>
<td>Sodium permanganate</td>
<td>10101-50-5</td>
<td>Na₂MnO₄</td>
</tr>
<tr>
<td>Manganese sulfate</td>
<td>7785-87-7</td>
<td>MnSO₄</td>
</tr>
</tbody>
</table>

Source: ATSDR (2012).

1.2 Physicochemical properties

The physical and chemical properties of manganese and manganese compounds vary substantially (Table 1.2). These characteristics determine environmental behaviour and fate, exposure potential, and the toxicological impact of each compound or dissolved ion.

**Table 1.2. Physicochemical properties of manganese and manganese compounds**

<table>
<thead>
<tr>
<th>Property</th>
<th>Mn</th>
<th>MnCl₂</th>
<th>Mn₃O₄</th>
<th>MnO₂</th>
<th>KMnO₄</th>
<th>MnSO₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point (°C)</td>
<td>1244</td>
<td>650</td>
<td>1564</td>
<td>loses oxygen at 535 °C</td>
<td>decomposes at &lt;240 °C</td>
<td>700</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>1962</td>
<td>1190</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Decomposes at 850 °C</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>7.21–7.44</td>
<td>2.98</td>
<td>4.86</td>
<td>5.03</td>
<td>2.70</td>
<td>3.25</td>
</tr>
<tr>
<td>Water solubility (g/L at 20°C)</td>
<td>0.001</td>
<td>799</td>
<td>virtually insoluble</td>
<td>virtually insoluble</td>
<td>≥64</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Sources: * ATSDR (2012); † European Chemicals Agency (2021).

1.3 Organoleptic properties

The taste threshold for dissolved Mn(II) has been estimated as 75.4 mg/L (50% population threshold). Dissolved Mn(II) is colourless and is visually undetectable at concentrations as high as 506 mg/L (maximum tested). In contrast, particulate Mn(IV) can be visually detected at a
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congestion of 0.005 mg/L. Estimates of the taste threshold of particulate Mn(IV) are confounded by discoloration of the water by these compounds but have been reported to be >0.05 mg/L (Sain, Griffin & Dietrich, 2014).

When manganese is not adequately removed during treatment, soluble Mn(II) compounds may undergo oxidation (e.g. as a result of disinfection or other treatment processes), forming manganese oxides, which can cause discolored water and staining of laundry and fixtures. This is supported by numerous studies of drinking-water systems that have reported that manganese concentrations above 0.02 mg/L cause complaints about discolored water, staining of plumbing fixtures and laundry, and general dissatisfaction with the water quality (Sly, Hodgkinson & Arunpairojana, 1990; Sommerfield, 1999; Casale, LeChevallier & Pontius, 2002; Kohl & Medlar, 2006; Tobaison et al., 2008). An extensive review of the literature conducted by Kohl & Medlar (2006) indicated that manganese can be deposited in distribution systems as manganese oxides even when the concentration leaving the treatment plant is as low as 0.02 mg/L.

1.4 Major uses and sources

Manganese is used principally in the manufacture of iron and steel alloys. Manganese compounds are also used in fertilizers, livestock feeding supplements, fungicides, varnishes and pottery glazes (IPCS, 1999; ATSDR, 2012; International Manganese Institute, 2014). Manganese dioxide and other manganese compounds are used in products such as dry-cell batteries, glass and fireworks.

Potassium and sodium permanganate are common oxidants used for cleaning, bleaching and disinfection. Permanganate can be added during water treatment to remove iron and manganese, and improve taste and odour (IOM & National Research Council, 1982; ATSDR, 2012; Health Canada, 2019). Manganese can also be present as an impurity in coagulants (principally ferric-based coagulants) used in drinking-water treatment. Water treatment media with manganese oxide surfaces are used in some locations for potable water treatment (ATSDR, 2012) to remove iron and manganese. Manganese that accumulates on these media during the treatment process can be released into treated water when filters are improperly operated.

An organomanganese compound, methylcyclopentadienyl manganese tricarbonyl (MMT), can be used at low concentrations1 as an octane-enhancing agent in unleaded petrol in some countries; in Canada, its use declined sharply after 2004 following voluntary action by Canadian petroleum refiners (Lynam et al., 1999; Walsh, 2007; Health Canada, 2019).

Manganese occurs naturally in many surface water and groundwater sources. Manganese in surface water and groundwater can result from natural leaching (e.g. from rock and soil weathering) and anthropogenic activities (e.g. industrial discharges, mining, landfill leaching) (Stokes & NRCC, 1988; Kohl & Medlar, 2006; Ljung & Vahter, 2007; ATSDR, 2012). The species of manganese in soil are dependent on the pH of the soil and/or the water, the reduction potential of the water and, to a lesser extent, soil mineralogy, oxidative microbial activity and organic matter content.

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1 Equivalent to 8.3 mg manganese/L in USA.
The main sources of particulate manganese in ambient air are industrial activities, including iron and steel production, burning of MMT-containing petrol, operation of power plants and coke ovens, and mining operations (creating dust). Manganese can also be released into the atmosphere during volcanic eruptions and forest fires, and from ocean spray and soil erosion (Stokes & NRCC, 1988; IPCS, 1999; US EPA, 2004).

1.5 Environmental fate

In water, the transport and partitioning of manganese depend on the chemical form present and its solubility, which is determined by pH, oxidation–reduction potential and characteristics of the available anions. Manganese can occur in particulate, colloidal and dissolved forms in surface water. The dissolved form (Mn(II)) is most common in groundwater, given that low levels of dissolved oxygen favour reduction of Mn(IV) to dissolved Mn(II). Most manganese salts are soluble in water to some extent (ATSDR, 2012; Health Canada, 2019). Manganese levels and retention in soils depend on the organic content and cation exchange capacity of the soil (ATSDR, 2012).

In air, manganese can exist as suspended particulate matter, which is removed largely by gravitational settling.

2 Environmental levels and human exposure

2.1 Water

Manganese occurs naturally in many surface water and groundwater sources, from dissolution of manganese oxides, carbonates and silicates in soil and rock. Anthropogenic activities (industrial discharges, mining and landfill leaching) can also be a source of manganese contamination of water (Stokes & NRCC, 1988; Kohl & Medlar, 2006; Ljung & Vahter, 2007).

When reducing conditions are present in groundwater, higher concentrations of dissolved manganese are favoured; up to 1300 µg/L in neutral groundwater and 9600 µg/L in acidic groundwater have been reported (ATSDR, 2012). Manganese levels tend to be lower in flowing rivers and streams because of the presence of dissolved oxygen, which limits the amount of manganese that is dissolved. Surface water supplies such as lakes and reservoirs can, however, become seasonally stratified, which causes the lower sections of the water body to become anoxic. This allows release of dissolved Mn(II) into the water column from manganese oxides that are present in sediments at the bottom of the water body (Civardi & Tompeck, 2015). Less commonly, elevated manganese concentrations can also occur in stream sources. The concentration is dependent on stream-flow conditions and the water sources feeding the stream (Brandhuber et al., 2013; Health Canada, 2019). Higher manganese levels in water bodies with higher dissolved oxygen are usually associated with industrial pollution.

Manganese concentrations in seawater are reported to range from 0.4 to 10 µg/L (ATSDR, 2012), with an average of about 2 µg/L. Levels in fresh water typically range from 1 to 200 µg/L. Manganese has been detected in about 97% of surface water sites in the United States of America at a median concentration of 16 µg/L (US EPA, 2002; ATSDR, 2012). ATSDR (2012) reported that a river water survey in the USA found dissolved manganese levels ranging from <11 to >51 µg/L. Since 1991, the National Water-Quality Assessment Project of the United States Geological Survey has gathered limited data on manganese from representative study basins around the USA, starting in 1991. Combined, these data indicate
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a median manganese level of 16 µg/L in surface waters, with 99th percentile concentrations of 400–800 µg/L (Leahy & Thompson, 1994; USGS, 2001; US EPA, 2003).

Overall, the detection frequency of manganese in groundwater in the USA is high (approximately 70% of sites), as a result of the ubiquity of manganese in soil and rock. Groundwater in the USA contains median manganese levels of 5–150 µg/L (ATSDR, 2012).

The National Water-Quality Assessment Project data indicate that the 99th percentile level of manganese is generally higher in groundwater (5600 µg/L) than in surface waters, but the median level is lower in groundwater (5 µg/L) than in surface waters (16 µg/L) (USGS, 2001; US EPA, 2003). In contrast, maximum average annual concentrations were reported to be 3000 µg/L for groundwater and 500 µg/L for surface water for 179 treatment plants located across North America (Kohl & Medlar, 2006). However, the median values for groundwater and surface waters were similar and below 100 µg/L.

In the USA, the National Inorganic and Radionuclide Survey collected data from 989 community public water systems served by groundwater in 49 states between 1984 and 1986. Manganese was detected in 68% of systems, with a median concentration of 10 µg/L. Supplementary survey data from public water systems supplied by surface water in five states reported concentration ranges similar to those of groundwater (US EPA, 2002). The United States Environmental Protection Agency is currently monitoring manganese at more locations than were studied for the National Inorganic and Radionuclide Survey in 1989. As of July 2020, 1.9% of systems detected manganese at levels higher than 300 µg/L, and 88.5% of these systems detected manganese at levels higher than 0.4 µg/L (US EPA, 2020).

In Germany, the manganese concentration in drinking-water supplied to more than 98% of all households was less than 20 µg/L in 1991 (Bundesgesundheitsamt, 1991). More recently in Germany, it was reported that less than 1% of approximately 52,000 drinking-water samples taken post-treatment from water works supplying more than 1000 m³ during 2017–2019 contained manganese at levels exceeding 50 µg/L (Federal Ministry of Health & Federal Environment Agency, 2021).

In the United Kingdom, four seasonal monitoring surveys were conducted on final drinking-water for up to 20 sites in England and Wales identified as being at potential risk of high manganese concentrations; 18 of these were public supplies, and two were private supplies. In general, low levels of total manganese, ranging from <0.1 to 11 µg/L, were reported (WRC, 2014). Among more than 44,000 drinking-water compliance samples taken in England and Wales in 2016, only 16 exceeded 50 µg/L; the maximum value reported was 706 µg/L, and the 95th percentile was 3.4 µg/L (PK Marsden, Drinking Water Inspectorate, personal communication, April 2017).

Low levels of manganese in source or treated water (current or historical) may accumulate in the distribution system and periodically lead to high levels of manganese at the tap due to physical disturbances or water quality changes (e.g. chemical release). In addition, other contaminants (such as heavy metals) that deposit with manganese oxides in the distribution system may also be released into the water and reach consumers’ taps (Friedman et al., 2010; Brandhuber et al., 2015).

Exposure to high levels (400–1700 µg/L) of manganese in drinking-water have been reported in some regions, including low- or middle-income countries such as Bangladesh, Burma, China
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and India (He, Liu & Zhang, 1994; Wasserman et al., 2006; Bacquart et al., 2012, 2015). Recent survey data from Costa Rica showed manganese levels up to 980 μg/L (Darner Mora Alvarado, Laboratorio National de Aguas, personal communication, June 2018).

2.1.1 Speciation of manganese in water

The concentration of manganese in groundwater and surface waters is influenced by the local chemical environment (e.g. organic carbon content, cation exchange capacity, pH, Eh – a measure of the redox state of a solution, and mineral and particulate content). These factors determine manganese speciation and, in turn, solubility (Stokes & NRCC, 1988; Kohl & Medlar, 2006). The most common oxidation states for manganese in natural water are Mn(II) and Mn(IV) (Stokes & NRCC, 1988; ATSDR, 2012; Rumsby et al., 2014)). The Mn(III), Mn(V) and Mn(VI) oxidation states are not stable in neutral (pH ≈7) solutions. In reducing environments and acidic media, and in the presence of nitrates, sulfates or chlorides, Mn(III) and Mn(IV) are reduced to Mn(II) (Stokes & NRCC, 1988; Kohl & Medlar, 2006; ATSDR, 2012). At alkaline pH (pH >8–9) and under oxidizing conditions (such as those found during water treatment where chlorine, chlorine dioxide, ozone or permanganate are used), Mn(II) is converted to Mn(IV), resulting in precipitation of manganese as Mn(IV) compounds, which are found as particulates in water (Kohl & Medlar, 2006). Mn(VII) can also be present within drinking-water treatment plants due its common use as a water treatment chemical.

A United Kingdom study (WRC, 2014) measured total and soluble manganese in 18 public supplies. The soluble manganese was reported as Mn(II), and the difference between the total and soluble was reported as Mn(IV). The Mn(II):Mn(IV) ratio varied from 8.3 to 0.04 but was typically about 1.4, indicating that slightly more Mn(II) than Mn(IV) was present in drinking-water. The survey also included analysis of two private borehole water supplies, in which high concentrations of manganese were detected, nearly all of which was in the Mn(II) form.

2.2 Food

Food is the most important source of manganese exposure for the general population. Since manganese is essential for photosynthesis and energy metabolism in plants, it is ubiquitous in vegetable-based foods, particularly whole grains, nuts and rice. Leafy vegetables, tea, seeds and legumes are also good sources (IOM, 2001; ATSDR, 2012; Freeland-Graves, Mousa & Kim, 2016). Co-exposure to dietary fibre, oxalic acids, tannins and phytic acids reduces manganese absorption (Gibson, 1994; Freeland-Graves, Mousa & Kim, 2016), whereas a low iron status (as reflected in low serum ferritin concentrations, which are possibly sex specific) can result in increased manganese absorption (Finley, 1999). For infants, both breast milk and breast milk substitutes may be sources of exposure, although constituents in both may affect bioavailability.

In the European Union, dietary manganese intakes in adolescents and adults were estimated to range between 2 and 6 mg/day, with most values being around 3 mg/day. Estimated manganese intake in children is lower: 1.5–3.5 mg/day (EFSA, 2013). The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment reviewed the results of the 2000 Total Diet Study, which measured exposure of the United Kingdom population to manganese. For adults, the mean and 97.5th percentile dietary intake rates of manganese were reported to be 5.2 mg/day and 9.2 mg/day, respectively. It was concluded that the estimated total dietary intake of manganese was unlikely to pose a risk to healthy adults (Committee on Toxicity, 2020). Dietary intakes in the Canadian population (all age groups) during the period 1993–
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2007 were between 3.1 and 4.3 mg/day (Health Canada, 2019). These levels are comparable to the estimated dietary intakes of 3.8 mg/day in the USA (ATSDR, 2012) and 4.2 mg/day in Sweden (VKM, 2018). People eating vegetarian diets and diets typical of more developed countries may have manganese intakes as high as 10.9 mg/day (IOM, 2001).

Based on the results of the United States Food and Drug Administration’s Total Diet Study (conducted from 1991 to 1997), among adults 19 years of age and older, the median and 95th percentile intakes of manganese from food were 2.1–2.3 mg/day and 5.2–6.3 mg/day, respectively, for men, and 1.6–1.8 mg/day and 4.3–4.6 mg/day, respectively, for women (IOM, 2001). Additionally, mean and 95th percentile manganese intakes from food among pregnant and lactating women were 2.1–2.6 mg/day and 5.8–5.9 mg/day, respectively (IOM, 2001).

Manganese concentrations reported in breast milk vary widely. A study of 70 human milk samples collected from breastfeeding women in Argentina (n = 21), Namibia (n = 6), Poland (n = 23) and the USA (n = 20) reported three- to four-fold differences in manganese concentrations in breast milk between the populations studied, with mean concentrations ranging between 1.6 and 11.6 µg/L (Klein et al., 2017). In this study, the average concentration of manganese from breast milk of US mothers was 2.71 µg/L (range 1.5–5.9 µg/L; n = 20) at approximately 7 months postpartum. In an earlier study of American mothers (Casey, Hambidge & Neville, 1985), the average concentration of manganese from breast milk was estimated at 3.7 µg/L (range 2.7–5.4 µg/L; n = 11) from days 6 to 31 postpartum, and the highest levels were measured at day 1 postpartum. Levels decreased to an average of 1.9 µg/L at 3 months postpartum (Casey, Hambidge & Neville, 1985; IOM, 2001).

In an analysis of seven studies of mothers residing in the European Union, the European Food Safety Authority (EFSA, 2013) reported mean manganese concentrations of 3–30 µg/L in breast milk. In an analysis conducted by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (Committee on Toxicity, 2020), the average exposure from breast milk for the 0–4-month age group was estimated to be 5.4 µg/kg/day, and 8.1 µg/kg/day for high-level exposure, in the United Kingdom, assuming a maximum concentration of manganese in breast milk of 40 µg/L. Based on preliminary data, Health Canada estimated a median manganese content of 2.2 ng/g (2.2 µg/L) in breast milk using data from the Total Diet Study (Health Canada, 2019).

Manganese concentrations reported in breast milk substitutes also vary widely and have been reported to be higher than in breast milk. In a study of manganese in infant breast milk substitutes and nutritional beverages for young children in the USA and France, the measured concentrations of manganese ranged from 230 to 830 µg/L in formulas labelled for infant use (Frisbie et al., 2019). Levels in soy-based human breast milk substitutes were particularly high. Mitchell et al. (2020) estimated mean daily manganese intakes in breast-fed infants and children in four age ranges (from 3 weeks to 18 months), based on estimated breast milk consumption rates among German breast-fed infants and published data on manganese concentrations in breast milk among populations in several countries in North America, Europe and Asia. The weighted mean of means for manganese concentrations in breast milk based on these data was 7.7 µg/L; the mean manganese intake from breast milk is estimated to be 1.2 µg/kg/day for a 3-week-old infant (maximum of 4.67 µg/kg/day) and 1.8 µg/kg/day for an 18-month old child (maximum of 6.97 µg/kg/day).

In the United Kingdom, average exposure to manganese for infants aged 0–6 months feeding exclusively on ready-to-feed formula was estimated to be 6.5–8.5 µg/kg/day and 10–
13 µg/kg/day in those who consumed high levels. Exposure to manganese where tap water with manganese concentrations of 1.4–15 µg/L was used to reconstitute formula was estimated at 9–14 µg/kg/day in average consumers and 14–21 µg/kg/day in high-level consumers (Committee on Toxicity, 2020). Average exposures based on concentrations detected in infant formulas in the USA and France (as reported by Frisbie et al., 2019, and assessed by Mitchell et al., 2020) would be higher. Once solid foods are introduced, the contribution of manganese intake from milk becomes less significant.

The World Health Organization (WHO)/Food and Agriculture Organization of the United Nations Codex Committee and the Expert Panel of the Life Science Research Office have set guidance levels of manganese for infant formula intended to be marketed as breast milk substitute to meet nutritional requirements. The minimum guidance level is 1 µg/100 kcal, and the upper level\(^2\) is 100 µg/100 kcal (67 µg/100 mL) (Raiten, Talbot & Waters, 1998; WHO & FAO, 2016).

### 2.3 Air

Levels of manganese compounds in air vary widely, depending on the proximity of point sources, such as ferroalloy production facilities, coke ovens and power plants. Average manganese levels in ambient air near industrial sources have been reported to range from 220 to 300 ng/m\(^3\), whereas ambient manganese levels in urban and rural areas without point sources have been reported to range from 10 to 70 ng/m\(^3\). Over the past 30 years, levels of manganese emitted from the metals industry have decreased substantially because of the installation of emission controls (ATSDR, 2012).

The United States Environmental Protection Agency (US EPA, 2007) estimated the geometric mean annual background concentration of manganese in particulate matter less than or equal to 10 µm in diameter (PM\(_{10}\)) in urban areas to be 6.68 ng/m\(^3\) (range 0.85–614 ng/m\(^3\)), based on 114 measurements in 20 urban locations across the USA. Existing data show little difference in manganese levels in ambient air between areas where MMT is used in petrol and areas where MMT is not used (Lynam et al., 1999).

Low manganese levels have been reported in atmospheric particulate matter in Canada, with a mean concentration of manganese in ambient air from 2009 to 2013 of 1.25 × 10\(^{-3}\) µg/m\(^3\) (ranging from below the limit of detection to 6.2 × 10\(^{-2}\) µg/m\(^3\)), as averaged over 24 hours by the National Air Pollution Surveillance Program (Galarneau et al., 2016). Levels of manganese (PM\(_{2.5}\) and PM\(_{10}\)) dropped between the late 1980s and early 2000s by 13–77% (Health Canada, 2010).

More recently, the United Kingdom reported average manganese concentrations in ambient air across rural and urban locations to be generally in the range 1–18 ng/m\(^3\), although levels up to 76 ng/m\(^3\) were also measured, associated with steel-making industries (DEFRA, 2019).

Loranger, Zayed & Forget (1994) found ambient air manganese concentrations to be significantly correlated with traffic density. Areas of intermediate and high traffic densities in

\(^2\) Upper guidance levels are for nutrients without sufficient information for a science-based risk assessment. These levels are derived on the basis of meeting nutritional requirements of infants and an established history of apparent safe use.
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Montreal had ambient air manganese concentrations above the natural background level of 40 ng/m³ (Loranger & Zayed, 1994; Loranger, Zayed & Forget, 1994).

2.4 Bioaccumulation

Manganese can bioaccumulate in lower organisms (e.g. phytoplankton, algae, molluscs, some fish) but not in higher organisms; biomagnification in food chains is not expected to be significant (ATSDR, 2012).

2.5 Biomarkers of exposure

Manganese levels in urine (see section 3.4) can be used as a biomarker of exposure. However, urinary manganese reflects short-term exposure of only a few hours (Andersen, Gearhart & Clewell, 1999; Signes Pastor et al., 2019). Other biomarkers of manganese exposure include blood concentration, with background levels ranging from 6.7 to 7.6 µg/ml (Roels et al., 1992; Mergler et al., 1994; Loranger & Zayed, 1995), hair concentration (Fergusson, Holzbecher & Ryan, 1983; Chutsch & Krause, 1987; Eastman et al., 2013), and toenail concentration (Signes Pastor et al., 2019).

Although manganese levels in blood do not reflect long-term exposure, the blood platelet level of monoamine oxidase is an early biochemical indicator of adverse oxidative effects of manganese (Benedetti & Dostert, 1989; Humfrey et al., 1990; Abdelouahab et al., 2010).

Hair has been used as a longer-term biomarker of exposure in epidemiological studies. Proper treatment is required to ensure that any potential external manganese contamination is removed (Eastman et al., 2013).

More recently, toenail samples have been reported to be reliable biomarkers of environmental manganese exposure, including exposure to manganese from drinking-water (Signes Pastor et al., 2019). In theory, the slow growth of nails could provide an indication of exposure over several months (Signes Pastor et al., 2019).

2.6 Estimated total exposure and relative contribution of drinking-water

Manganese is essential to proper physiological function in both humans and other animals. It is required as a component or cofactor for many cellular enzymes (e.g. manganese superoxide dismutase, pyruvate carboxylase) and can activate many others (e.g. kinases, decarboxylases, transferases, hydrolases) that are also activated by similar divalent cations (IPCS, 2002).

The highest exposure to manganese is usually from food and is estimated to range from 2 to 6 mg/day in adults, although higher values have been reported (see section 2.2). Manganese intake from drinking-water is normally substantially lower than intake from food. At the drinking-water concentrations described above (section 2.1), the intake of manganese from drinking-water could be one or more orders of magnitude less than intake from food, assuming a daily water intake of 2 L.

There is potential for increased exposure to manganese in bottle-fed infants compared with breastfed infants – from the concentrated or powdered formula itself as well as the tap water used to prepare the formula. As noted in sections 2.1 and 2.2, there is high variability in manganese levels in drinking-water and in breast milk substitutes. However, in 4–18-month-old children in the United Kingdom, the exposure to manganese from tap water (2–15 µg/L) was found to make a negligible contribution to total exposure (Committee on Toxicity, 2020).
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Further, once solid foods are introduced, the contribution from formula becomes less significant. The relative immaturity of the hepatobiliary excretion of manganese in infants can increase the internal dose or body burden in this age group (see sections 3.1 and 3.4).

Exposure to manganese from air is generally several orders of magnitude less than exposure from the diet, typically around 0.04 ng/day, on average (US EPA, 1990), although this can vary substantially depending on proximity to a manganese source.

Care should be taken when extrapolating estimated intakes from different sources to the relative uptake from each source, as factors such as bioavailability and manganese speciation play key roles in uptake and potential toxicity (Health Canada, 2019).

3 Toxicokinetics and metabolism in humans and animals

3.1 Absorption

Following ingestion, manganese is subject to homeostatic control through both regulation of its absorption from the gastrointestinal (GI) tract and its hepatobiliary excretion. Following inhalation exposure, manganese may bypass this homeostatic control and be transported to the brain via the olfactory system (Aschner, Erikson & Dorman, 2005; Roth, 2006). Therefore, absorption of manganese via inhalation differs significantly from absorption through ingestion of drinking-water. The metabolism of manganese, including its absorption, has been reviewed by Chen, Bornhorst & Aschner (2018).

Absorption of manganese from the GI tract is regulated by normal physiological processes. Absorption has been suggested to take place through both an active transport mechanism (Garcia-Aranda, Lifshitz & Wapnir, 1984) and passive diffusion (Bell, Keen & Lönnerdal, 1989). In humans, GI absorption of manganese appears to be influenced by sex, with higher levels of absorption reported in females than in males. This may be related to the lower iron status of women and their higher iron requirement (Finley, Johnson & Johnson, 1994).

A 7-week study in which seven adult male volunteers ingested high-fibre diets that naturally contained 12.0–17.7 mg of manganese per day (0.17–0.25 mg/kg body weight [bw] per day) found that an average of 7.6% ± 6.3% of the manganese was absorbed during weeks 5–7, with no measurable net retention of manganese (Schwartz, Apgar & Wein, 1986). Similarly, an average absorption of 8.4% ± 4.7% was observed in seven adults ingesting infant formula containing manganese (Sandström et al., 1986). Johnson, Lykken & Korynta (1991) studied the absorption of radiolabelled manganese from various plant foods in adult men and women, and reported absorption rates of 1.4–5.5%, which were significantly lower than the mean values of 7.8–10.2% from controls receiving Mn(II) chloride dissolved in water. A mean manganese absorption of 6.0–6.2% was observed from chard (Davidsson et al., 1991). Oral studies in animals generally yield similar absorption results (Pollack et al., 1965; Davis, Zech & Greger, 1993; Finley et al., 1997; Zheng, Kim & Zhao, 2000). EFSA noted that the absorption of manganese across the GI tract in adults is below 10% (EFSA, 2013).

Several factors can influence the degree to which manganese in foods is absorbed following ingestion. These include intake of dietary fibre, oxalic acids and phytic acids, which tend to decrease manganese absorption, in some cases substantially (Chen, Bornhorst & Aschner, 2018; Gibson, 1994; IOM, 2001; US EPA, 2002; Aschner, Erikson & Dorman, 2005; ATSDR, 2012). Iron and manganese are substrates of the same transport system for absorption (Davis,
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Malecki & Greger, 1992), and thus manganese absorption is closely linked to iron absorption; iron-deficient diets lead to increased absorption of both iron and manganese (Thomson, Olatunbosun & Valverg, 1971; Sandström et al., 1986; Finley, 1999), independent of manganese body stores (Mena et al., 1969; Chandra & Shukla, 1976; Shukla, Chandra & Seth, 1976; Finley & Davis, 1999; Arnich et al., 2004). The absorption of manganese is also related inversely to the level of calcium in the diet (Schroeder, Balassa & Tipton, 1966; McDermott & Kies, 1987; Lutz, Schroff & Scharrr, 1993). Certain constituents of tea, such as tannins, can result in reduced manganese absorption (Freeland-Graves & Llanes, 1994).

Some studies have reported no difference in tissue manganese concentrations or bioavailability following equivalent exposures to manganese from dietary and drinking-water sources (without consideration of fasted state) (Ruoff 1995; Foster et al., 2015). Conversely, other reports and risk assessments (Ruoff, 1995; US EPA, 2002; Bouchard et al., 2011; Health Canada, 2019) suggest that absorption and bioavailability of manganese are greater from drinking-water (in a fasted state) than from food. However, reliable quantitative data comparing the bioavailability and absorption of different chemical forms of manganese from drinking-water were not found.

Manganese absorption from the GI tract may be higher in infants than in adults (Keen, Bell & Lönnerdal, 1986; Davidsson et al., 1989; Johnson, Lykken & Korynta, 1991; Finley, Johnson & Johnson, 1994; IOM, 2001; Health Canada, 2010), with up to 40% absorption reported (Neal & Guilarte, 2013; Dörner et al., 1989). This may be attributable to a compensatory mechanism related to greater metabolic needs of infants compared with adults (Santamaria, 2008). The increased absorption may place neonates and infants at greater risk of exposure to high levels of manganese than older children and adults (Neal & Guilarte, 2013).

Studies in rats have demonstrated that young animals absorb significantly more manganese from the gut than do mature animals (Lönnerdal et al., 1987). Experimental animal studies have also shown that manganese crosses the blood–brain barrier at a rate four times higher in neonates than in adults (Mena, 1974).

Some constituents of both infant formula and breast milk may affect manganese bioavailability. Breast milk substitutes made from soy protein contain high levels of phytic acids and vegetable proteins, which probably decrease manganese bioavailability (Keen, Bell & Lönnerdal, 1986). If the formula is also iron fortified, manganese bioavailability may be reduced (as indicated above), since the use of the same transport system to cross the gut mucosa results in competition between non-haem iron and manganese (Davis, Malecki & Greger, 1992). However, studies on the inhibitory influences of iron have produced conflicting results (Freeland-Graves, 1994).

Soluble forms of manganese, such as manganese chloride, have been reported to be more readily absorbed than the complex-associated trivalent oxidation state of manganese found in breast milk (Roels et al., 1997). This complex can bind to lactoferrin; lactoferrin receptors in the brush border membranes of epithelial cells throughout the length of the small intestine subsequently regulate its uptake from the GI tract. In contrast, infant formula contains manganese in the divalent oxidation state. This divalent state does not bind to lactoferrin, and therefore lactoferrin receptors cannot regulate intestinal uptake (Erikson et al., 2007; Health Canada, 2019).

Absorption of manganese from breast milk (8.2% ± 2.9%) consumed by adults has been reported to be higher than from cow’s milk (2.4% ± 1.7%) or soy formula (0.7% ± 0.2%), as
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measured using extrinsic labelling and whole-body retention measurements (Davidsson et al., 1989). The difference in absorption may be due to manganese speciation differences, as well as levels of lactoferrin (Davidsson et al., 1989; US EPA, 1997; Health Canada, 2019).

3.2 Distribution

Following GI tract absorption, manganese is distributed via the systemic circulation to all tissues. The highest levels are usually found in the liver, kidney, pancreas and adrenal glands (Tipton & Cook, 1963; Sumino et al., 1975; Aschner & Aschner, 2005; ATSDR, 2012). Manganese accumulates preferentially in certain regions of the brain in infants and young animals (Zlotkin & Buchanan, 1986; Kontur & Fechter, 1988; Chan et al., 1992; Lai et al., 1999). Within blood, manganese may be present in plasma (bound to albumin), red blood cells (bound to haemoglobin) and white blood cells. The chemical form and solubility of manganese can influence its distribution (Health Canada, 2019).

In both rats and mice, exposure of fetuses, neonates and pups resulting from maternal exposure is reported to be possible, given that manganese crosses the placental barrier and may be found in milk (Health Canada, 2019).

3.3 Metabolism

Mn(II) is the predominant form of manganese in biological systems; however, in many enzymes, manganese is present as Mn(III) (Utter, 1976; Leach & Lilburn, 1978; Aschner, Erikson & Dorman, 2005). This suggests that, over time, Mn(II) in plasma is oxidized to Mn(III) (ATSDR, 2012), although the mechanisms involved in this conversion are not fully elucidated (Roth, 2006). The valence state of manganese is reported to influence manganese retention and toxicity (Yokel, Lasley & Dorman, 2006; Health Canada, 2019).

3.4 Elimination

The main route of elimination of manganese from the body is faecal elimination via hepatobiliary excretion (ATSDR, 2012). Only a small proportion (0.1–2%) is eliminated in the urine (Davis & Greger, 1992; Park et al., 2003). Small amounts of manganese are also excreted in sweat, hair, nails, and the milk of lactating mothers (Roels et al., 1992; Merian et al., 2004; Health Canada, 2010).

Possibly because of the incomplete development of the biliary excretion system in human infants, which is the primary route of manganese elimination (Cotzias et al., 1976; Lönnerdal, 1994), infants retain higher levels of manganese than adults during the early neonatal period, with up to 20% retention reported in formula-fed infants (Aschner & Aschner, 2005). Dörner et al. (1989) reported high retention of manganese in infants ingesting both human milk and cow’s milk formulas; absolute retention was highest in formula-fed infants. In addition, the manganese contents of erythrocytes in infants up to the age of 6 weeks are 7–9% higher than those in adults (Hatano et al., 1985). Collipp, Chen & Maitinsky (1983) reported manganese levels in hair that increased significantly from birth (0.19 µg/g) to 6 weeks of age (0.865 µg/g), and remained elevated at 4 months (0.685 µg/g) in infants given breast milk substitutes, whereas infants given breast milk exhibited no significant increase.

The reduced capacity of infants for biliary excretion compared with adults implies that neonates and young children will acquire a higher body burden of manganese from a given exposure. Along with the important neurodevelopmental processes occurring in neonates, this may render
them particularly susceptible to toxicity from exposure to manganese by exceeding the homeostatic concentration (Neal & Guilarte, 2013; Health Canada, 2019).

3.5 Physiologically based pharmacokinetic models

Physiologically based pharmacokinetic models have been developed for manganese in several species, including rats, monkeys and humans (reviewed by Health Canada, 2019). Models for monkeys and humans (Schroeter et al., 2011, 2012) allow estimation of manganese concentrations following exposure by multiple routes (ingestion, inhalation and injection) in numerous tissues (including, liver, lung, nasal cavity, bone, blood, olfactory bulb, cerebellum, globus pallidus and pituitary gland). The models also account for differences in manganese tissue-binding capacities, preferential fluxes of manganese in specific (brain) tissues and homeostatic control processes (i.e. reduced intestinal absorption and induced biliary secretion at elevated levels of exposure). The models could be useful for estimating manganese exposure levels that would cause an increase in tissue concentrations (Schroeter et al., 2011; Gentry et al., 2017). However, as the human model has not been validated against actual measurements in brain tissue, simulations for brain tissue using the model would need to be treated with caution (Health Canada, 2019).

A human model recently developed to predict brain manganese levels based on blood manganese levels from occupational epidemiological data showed consistency between model predictions and measurements (Ramoju et al., 2017). Further, Yoon et al. (2019) have updated a previously published model that includes drinking-water as an exposure source for manganese and predicts bioavailability of manganese from drinking-water in children. Based on model simulations, children did not appear to be at a greater risk from manganese in drinking-water than adults; however, more data and validation are needed.

4 Effects on humans

4.1 Essentiality

Manganese is an essential element for many living organisms, including humans. Some enzymes (e.g. manganese superoxide dismutase) structurally require manganese, and some (e.g. kinases, decarboxylases) are activated by manganese. These enzymes can play a role in several biological processes such as bone formation, free radical defence, neurotransmitter synthesis and ammonia clearance in the brain (Erikson & Aschner, 2019). Manganese plays a physiological role for a number of organ systems in the body, and is required for growth and development (including development of the nervous system and brain), especially in early life (Aschner & Aschner, 2005).

Adverse health effects can be caused by inadequate intake or overexposure. Manganese deficiency in humans appears to be rare because manganese is present in many common foods. A specific deficiency syndrome has not been clinically described in humans (IOM, 2001). In male subjects fed a conventional diet providing manganese at 2.59 mg/day for 3 weeks (baseline), followed by a purified diet containing manganese at 0.11 mg/day for 39 days, adverse effects were described. These included dermatitis and miliaria crystalline (prickly heat/heat rash) in five of the seven subjects at the end of the depletion period; the symptoms disappeared as repletion began (Friedman et al., 1987).

Requirements for manganese have not been established because of inadequate data (WHO, 1996; IOM, 2001; EFSA, 2013). Accordingly, some institutions have established adequate
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intake levels based primarily on studies of reported intakes, such as in the USA (IOM, 2001) and the European Union (EFSA, 2013). The Food and Nutrition Board of the Institute of Medicine (IOM, 2001) has set adequate intake levels for manganese at 2.3 mg/day for men and 1.8 mg/day for women. Adequate intake levels for manganese for other age groups were set at 0.003 mg/day for infants from birth to 6 months, 0.6 mg/day for infants from 7 months to 1 year, 1.2 mg/day for children aged 1–3 years, 1.5–1.9 mg/day for children aged 4–13 years and 1.6–2.3 mg/day for adolescents (IOM, 2001). EFSA (2013) also applied an adequate intake approach, proposing 3 mg/day for all adults, including pregnant and lactating women. An adequate intake of 0.02–0.5 mg/day was proposed for infants aged 7–11 months, reflecting the wide range of intakes in this age group that appear adequate. Adequate intake levels for manganese for other age groups were established at 0.5 mg/day in children aged 1–3 years and 3.0 mg/day for adolescents.

The Institute of Medicine (IOM, 2001) set a tolerable upper intake level for manganese of 11 mg/day for adults, based on a review of manganese intake (0.7–10.9 mg/day) for adults eating diets typical of developed countries, and vegetarian diets (Greger, 1999; IOM, 2001). This was supported by evidence reported by Davis & Greger (1992) that women given daily supplements of 15 mg of manganese (as an amino acid–chelated manganese supplement) for 90 days experienced no adverse effects other than a significant increase in lymphocyte manganese-dependent superoxide dismutase, a biomarker that increases in direct relation to manganese exposure (Greger, 1998, 1999).

The Expert Group on Vitamins and Minerals (EVM) conducted an evaluation of data to establish a safe upper limit for manganese in the diet (EVM, 2003). Although it was concluded that no safe upper limit could be derived for manganese, an acceptable total dietary intake of 12.2 mg/day for the general population and 8.7 mg/day for older adults was thought appropriate. The EVM considered two large cohort studies in its evaluation (Kondakis et al., 1989; Vieregge et al., 1995), both of which assessed neurotoxicity as an end-point following drinking-water exposure to manganese. Of these two studies, the EVM considered that reported by Vieregge et al. (1995) to be the most robust. This assessed manganese burden in a cross-sectional study of adults (mean age 57 years; range 41–86 years) in rural Germany with 10–40 years exposure to drinking-water supplied from well water. Two groups homogeneous with regard to age, sex, nutritional habits and drug intake were established, based on manganese levels in well water: Group A was exposed to levels >0.3 mg/L (range 0.3–2.16 mg/L) and Group B to levels <0.05 mg/L. Neurological assessment of parkinsonian symptoms (Columbia University Rating Scale) was carried out by clinicians blinded to the exposure status. The authors reported no significant difference in neurological outcomes between the two groups.

4.2 Acute exposure

No studies to assess potential adverse effects following acute exposure to manganese in humans were identified.

4.3 Short-term exposure

Accidental ingestion of low doses of potassium permanganate (containing manganese at about 1.8 mg/kg bw/day) for 4 weeks in a 66-year-old man was associated with muscle weakness and neurological disturbances, including impaired mental capacity (Holzgraefe et al., 1986; Bleich et al., 1999). However, the quantitative and qualitative details of exposure necessary to establish manganese as the direct cause are lacking. Consumption of hydrated manganese sulfate (three tablespoons daily, total duration unknown) was associated with lethargy,
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vomiting, abdominal pain, profuse diarrhoea, liver failure, acute renal injury, acute respiratory distress, myocardial dysfunction, shock with lactic acidosis and death within 72 hours in a 50-year-old man undertaking a protein-free diet and consuming several herbal teas during a liver-cleansing diet (Sánchez et al., 2012).

4.4 Long-term exposure

4.4.1 Systemic effects

Data are lacking on systemic toxic effects in humans following ingestion of manganese. This may be due to the homeostatic mechanisms that strictly control levels of manganese absorbed following oral exposure and protect the body from the toxic effects of excess manganese. A possible association between manganese exposure and infant mortality was reported by Hafeman et al. (2007). In Bangladesh, infants (<1 year of age) exposed to manganese in water at levels ≥0.4 mg/L experienced elevated mortality during the first year of life compared with unexposed infants (odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.2 to 2.6). The data were adjusted for water arsenic, indicators of social class and other variables without an appreciable impact on the results.

In a pilot study carried out in North Carolina, USA, Spangler & Spangler (2009) reported that, for every log increase in groundwater manganese concentration, there was an increase in the number of county-level infant deaths of 2.074 per 1000 live births, after adjustments were made for low birth weight, economic status, education and ethnicity.

The utility of these studies in the current assessment is limited because other confounding exposures, in addition to manganese exposure, could have been responsible for the deaths reported.

Organ-specific adverse effects are reported in the relevant sections below.

4.4.2 Neurologic effects

Evidence of adverse effects resulting from chronic exposure to high levels of manganese in humans is mainly derived from occupational inhalation exposures. The central nervous system (CNS) is the chief target of manganese toxicity. Neurotoxic effects resulting from exposure to manganese can be categorized as those affecting behavioural end-points (e.g. reflexes, motor activity, learning, memory, sensory ability), structural end-points (e.g. gliosis, neuroinflammation, neurostructural alterations) and neurochemical end-points (altered neurotransmitter systems) (Health Canada, 2019). The neurological impacts of inhaled manganese have been well documented in workplace studies of humans chronically exposed to elevated levels (Canavan, Cobb & Srinker, 1934; Cook, Fahn & Brait, 1974; Roels et al., 1999; ATSDR, 2012). The syndrome known as “manganism” is caused by inhalation exposure to very high levels of manganese dusts or fumes. It is characterized by weakness, anorexia, muscle pain, apathy, slow speech, a monotonous tone of voice, an emotionless “mask-like” facial expression and slow, clumsy movement of the limbs. These severe clinical effects that occur as the disease progresses are generally thought to be irreversible; however, reversibility of some early symptoms and clinical effects has been reported (ATSDR, 2012). Some motor functions may be affected following chronic exposure to levels of manganese of ≤1 mg/m³ (if the inhaled manganese is respirable). For example, overt clinical symptoms of manganism have been reported following chronic exposure to manganese at concentrations of 0.73 mg/m³ in
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respirable dust (Roels et al., 1992; Mergler et al., 1994). Also, subclinical neurological effects have been described in workers exposed to air manganese concentrations in the range 0.07–0.97 mg/m³. These effects include decreased performance in neurobehavioural tests; significantly poorer eye–hand coordination, hand steadiness and reaction time; poorer postural stability; and lower levels of cognitive flexibility (ATSDR, 2012).

By the oral exposure route, manganese is regarded as one of the least toxic essential elements. However, as a result of toxicokinetic differences between inhalation and oral intakes, there is some controversy about whether the neurological effects observed with inhalation exposure also occur following chronic oral exposure. Accidental ingestion of 125 mL of an 8% solution of potassium permanganate for 4 weeks was associated with impaired mental capacity and muscle weakness after several weeks. After 9 months, a Parkinson-like syndrome was noted (Holzgraefe et al., 1986).

A number of epidemiological studies have reported neurological effects in adult populations exposed to high environmental manganese concentrations (e.g. Kawanuma et al., 1941 – in drinking-water at a concentration possibly up to 28 mg/L; Florence & Staubner, 1989 – in soil; Kondakis et al., 1989 – in drinking-water up to 2.3 mg/L; Iwami et al., 1994 – in food and water, with higher concentrations in food). However, no neurological effects were found in another epidemiological study of the adult population exposed to manganese in drinking-water at a level of up to 2.2 mg/L (Vieregge et al., 1995). Due to limitations in the exposure assessment methods and related uncertainty in the oral exposure concentrations in the study populations, the epidemiological data are insufficient to evaluate the causal relationship between manganese exposure and neurological effects.

As noted in section 3.4, infants and children are potentially a sensitive group with regard to exposure to high levels of manganese. Case studies report potential neurological effects and/or behavioural problems in children following oral exposure to high levels of manganese (Woolf et al., 2002; Sahni et al., 2007).

A large number of epidemiological studies have been carried out to assess potential adverse neurological outcomes (e.g. behavioural disinhibition; lower scores in tests of executive function, reading and digit agility) in children and infants following environmental exposure to elevated levels of manganese in drinking-water and/or food (e.g. He, Liu & Zhang, 1994; Zhang, Liu & He, 1995; Wasserman et al., 2006, 2011; Wright et al., 2006; Bouchard et al., 2007, 2011; Kim et al., 2009; Claus Henn et al., 2010, 2012; Farias et al., 2010; Riojas-Rodríguez et al., 2010; Khan et al., 2011, 2012; Menezes-Filho et al., 2011; Oulhote et al., 2014; Yu et al., 2014; Haynes et al., 2015; and reviews of studies by Bjørklund, Chartand & Aaseth, 2017; Iyare, 2019; Kullar et al., 2019; Schullehner et al., 2020). Seven of these studies, which investigated the association between early-life manganese exposure (based on measured blood, hair or dentin manganese concentrations) and performance on tests of executive function, were reviewed by Leonhard et al. (2019), who reported that these associations were generally non-statistically significant but in the negative direction, although there were some positive (favourable) associations between dentin manganese and test performance. Although specific limitations are discussed below, some general limitations include the lack of establishment of causality due to cross-sectional design, potential limitations in exposure estimates from drinking-water and/or dietary intakes, and a need for enhanced validation of the biomarkers of exposure used. Therefore, none of these studies are sufficiently robust to be a key study on their own, because of limitations often related to the design of the epidemiological study or to the exposure assessment. However, together, they provide evidence to support
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neurotoxicity as the key end-point in humans. Given that many of the earlier (pre-2011) epidemiology studies were reviewed by ATSDR (2012), only a limited number of early studies and those published after 2012 are discussed below.

Canadian children aged 6–13 years exposed to well drinking-water with high (0.61 mg/L) or low (0.16 mg/L) manganese concentrations were estimated to have daily manganese exposures of 0.02 mg/kg bw/day and 0.007 mg/kg bw/day, respectively. Manganese levels in hair were significantly higher in those exposed to high concentrations of manganese in drinking-water. In this pilot study, a statistically significant relationship was established between increased levels of oppositional behaviours (breaking rules, getting annoyed or angered, and hyperactivity) and increased levels of manganese in drinking-water (Bouchard et al., 2007). No manganese-related differences were observed for tests related to cognitive problems (disorganization, slow learning, lack of concentration). In a follow-up study, the authors assessed intellectual function in Canadian children aged 6–13 years in relation to manganese intake from water and food (estimated as 0–0.03 mg/kg bw/day and 0.01–0.44 mg/kg bw/day, respectively). Findings demonstrated associations between increased estimated manganese intakes from water and intellectual impairment in children, as reflected in full scale and performance IQ scores. Higher concentrations of manganese measured in hair were also associated with a lower full scale IQ score, and manganese levels in hair increased with increased consumption of manganese from drinking-water, but not from food (Bouchard et al., 2011).

An analysis of the Canadian school-aged cohort by Oulhote et al. (2014) described associations of exposure to manganese, determined from measurements in water and hair, with adverse effects on memory, attention, motor function, and parent- and teacher-reported hyperactive behaviours. The authors concluded that exposure to manganese in water was associated with poorer neurobehavioural performance in children, even at low levels (a steeper decrease in memory and motor function was reported at drinking-water concentrations of >100 µg/L and >180 µg/L, respectively). There was no significant association between manganese exposure and hyperactivity.

A follow-up assessment of this cohort at age 10.5–18 years (n = 287) has recently been reported, using the same methodology (Dion et al., 2018). Manganese concentrations in tap water ranged from 0.2 to 90 µg/L (geometric mean 14.4 µg/L), with 40% of the cohort being exposed to levels >50 µg/L. Higher levels of manganese in tap water were associated with lower performance IQ scores in girls and higher performance IQ in boys. The authors proposed that this finding may indicate a sex-related difference in manganese toxicity. In addition, a significant decrease in performance IQ scores was reported for children who had been exposed to higher concentrations of manganese between the earlier study and the follow-up assessment. However, this only related to a small number of households. Thus, the finding should be interpreted carefully. The hair manganese exposure biomarker was not significantly associated with IQ score in this follow-up study.

These studies considered several covariates (e.g. lead and arsenic in the drinking-water, socioeconomic status and maternal factors) that may confound the association between manganese and cognitive abilities. These studies also have limitations that need careful consideration when interpreting findings, including the following.

• The cross-sectional design of the studies does not allow causality to be established (Bouchard et al., 2007, 2011; Oulhote et al., 2014).
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- The studies did not account for potential prenatal manganese exposure.
- Metabolic or genetic disorders that could alter manganese absorption and excretion were not considered.
- Selection bias cannot be discounted as few details were provided on the eligibility criteria of subjects and characteristics of those lost for follow-up.
- Although some important covariates were considered (e.g. lead, arsenic), there remains a possibility for unmeasured confounders.
- Potential confounding factors, including consumption of water from other sources and smoking in the household, were not evaluated in the Bouchard et al. (2007) pilot study but were evaluated in the Bouchard et al. (2011) and Dion et al. (2018) studies.

In an additional publication, Bouchard et al. (2018) assessed the IQ scores of 259 children aged 5.9–13.7 years from 189 households in New Brunswick, Canada, against additional indicators of manganese exposure from drinking-water: concentration in tap water; intake from the consumption of water divided by the child’s weight; and manganese concentration in children’s hair, toenail clippings and saliva. These biomarkers are considered by the authors to represent accumulation of manganese following long-term, low-level exposure (see also Ntihabose et al., 2018). Exposure levels from drinking-water were generally lower (geometric mean 5.96 µg/L; range <0.03–1046 µg/L) than those reported in the authors’ previous studies with a different cohort (Bouchard et al., 2011). Exposure levels were <5 µg/L in 48% of children and >400 µg/L in 4% of children. There was no clear evidence of an association between exposure to manganese and cognitive development in the cohort, although the authors suggested possible sex-specific associations between measured manganese concentrations and performance IQ scores. In boys, performance IQ scores were higher with higher manganese concentrations, whereas, in girls, higher manganese concentrations were associated with poorer performance IQ scores. It should be noted, however, that significance of this observation was not established for all parameters measured.

A pooled and sex-stratified analysis of cross-sectional study data from two Canadian populations suggests that boys are less sensitive to manganese exposure–related decrements in performance IQ than girls; benchmark concentration levels (BMCLs) of 75, 153 and 386 µg/L corresponded to decrements in performance IQ of 1%, 2% and 5%, respectively, in boys, whereas BMCLs of only 9, 21 and 74 µg/L corresponded to similar decrements in performance IQ in girls. Limitations described above preclude the use of this work for quantitative risk analysis, but the study’s findings nonetheless support neurotoxicity as a key end-point of concern following exposure to manganese in drinking-water (Kullar et al., 2019).

In a prospective cohort study, Rahman et al. (2017) evaluated the effects of exposure to manganese in drinking-water on cognitive and behavioural characteristics of schoolchildren in Bangladesh (n = 1265), from conception to 10 years of age. Exposure levels were in the range 0.001–6.6 mg/L (median 0.2 mg/L) during pregnancy and <0.001–8.7 mg/L (median 0.34 mg/L) at 10 years. As arsenic was also present in the drinking-water, the manganese statistical analysis was restricted to the children with low arsenic exposure. The authors reported that prenatal exposure to manganese (<3 mg/L) in drinking-water was positively
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associated with cognitive function in girls, whereas boys appeared to be unaffected. In boys, early life exposure to manganese in drinking-water was associated with a decreased risk of emotional problems (OR = 0.39; 95% CI = 0.19 to 0.82). In girls, there was an association between prenatal exposures and low prosocial scores (OR = 1.48; 95% CI = 1.06 to 1.88).

Henn et al. (2017) reported on a prospective birth cohort study that assessed associations between prenatal manganese exposure and placental transfer, and neurodevelopment in 2-year old children (n = 224) living near a former mining area in rural Oklahoma, USA. Increased concentrations of manganese in maternal blood at or near the time of delivery were associated with lower neurodevelopment scores at 2 years of age. When adjusted for potential confounders, including arsenic and lead, the interquartile range for maternal blood manganese level was associated with a reduction in mental and psychomotor indices of −3.0 (95% CI = −5.3 to −0.7) and −2.3 (95% CI = −4.1 to −0.4) points, respectively. Cord manganese concentration was not associated with the neurodevelopment scores. The authors highlighted several limitations of the study, including the potential influence of timing of sample collection on manganese levels (given that little is known about how levels of manganese in maternal blood vary during labour and delivery), the small sample size and potential sampling bias due to loss at follow-up.

The potential joint action of manganese and lead on full scale and verbal IQs was assessed in a study of Korean children (average age 9.6 years). Participants were separated into two groups, based on blood manganese levels of <14 μg/L (n = 131) and >14 μg/L (n = 130); blood lead levels showed no difference between the two exposure groups. A significant inverse association was found between blood manganese and blood lead (combined group) and full scale and verbal IQ scores when the group was considered as a whole. Blood lead levels were shown to be a significant predictive variable for full scale and verbal IQ scores in the high manganese group, but not in the low manganese group. The authors concluded that the results are consistent with a joint toxic action of lead and manganese on full scale and verbal IQ scores (Kim et al., 2009).

A longitudinal study of 448 children born in Mexico investigated the neurotoxic effects of early-life exposure to manganese. Blood samples from children at ages 12 and 24 months were measured, and mental and psychomotor development was scored at 6-month intervals between 12 and 36 months. The study reported a possible biphasic dose–response relationship for manganese exposure and neurodevelopment, which would be consistent with the fact that manganese is both an essential element and toxic (Claus Henn et al., 2010). The same authors published a second study that evaluated manganese–lead interactions in the cohort and suggested a possible synergism between lead and excessive manganese in the impairment of mental and psychomotor skill development (Claus Henn et al., 2012).

In a study of school-aged children in Bangladesh, Khan et al. (2011) reported an association between increasing manganese concentration in drinking-water and negative behaviour in the classroom. The authors adjusted for arsenic exposure, sex, body mass index, maternal education and arm circumference as confounders. A follow-up study addressed a potential association between combined exposure to manganese and arsenic in drinking-water and academic achievement in school-aged children (n = 840). Exposure to drinking-water containing manganese levels >400 μg/L was significantly associated with decreased mathematics test scores after adjustment for confounders (arsenic exposure, school grade, maternal education, paternal education, head circumference, and within-teacher correlations in rating the children) (Khan et al., 2012). These findings should be interpreted with caution.
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because the possibility of co-exposure to other neurotoxic substances such as lead could not be eliminated, and total manganese exposures were not well characterized.

A meta-analysis that included articles published between January 2000 and March 2012 assessed the potential for an association between manganese, arsenic and cadmium exposure and neurodevelopment and behavioural disorders in children (Rodríguez-Barranco et al., 2013). Of the 17 articles relating to manganese exposure, 14 reported a significant negative effect on neurodevelopment and behavioural disorders. Of these, four studies used measurements of manganese in hair as a biomarker of exposure (Wright et al., 2006; Riojas-Rodríguez et al., 2010; Bouchard et al., 2011; Menezes-Filho et al., 2011). Rodríguez-Barranco et al. (2013) suggested that a 50% increase in manganese levels in hair was associated with a decrease of 0.7 points in the IQ (performance and verbal) of children aged 6–13 years. However, the meta-analysis was limited by the low number of subjects (n = 556).

A longitudinal multicentre cohort study in China reported an association between high prenatal exposure to manganese (based on umbilical cord serum concentrations) and lower scores in Neonatal Behavioural Neurological Assessments in mother–newborn pairs (n = 933) (adjusted β = −1.1; 95% CI = −1.4 to 0.7; p < 0.01), after adjustment for confounders, including parents’ age, education, incomes, occupation and smoking status. Other variables evaluated included neonate gestational age, sex, birth weight, and lead and mercury exposures (Yu et al., 2014). Limitations to the assessment included lack of long-term follow-up and no consideration of socioeconomic impacts on prenatal development.

Haynes et al. (2015) described a significant association between high blood (>11.2 μg/L) and high hair (>747 ng/g) manganese concentrations and lower full scale IQ scores in US children aged 7–9 years (n = 404), compared with control groups (blood: 8.2–11.2 μg/L; hair: 207–747 ng/g). The authors reported an inverted U-shaped association between the biomarkers of blood and hair manganese and cognition: both low and high blood and hair manganese concentrations were associated with lower full scale IQ and subscale IQ scores. Significant negative associations were observed between full scale IQ and the highest and middle two quartiles of blood manganese (β = −3.51; 95% CI = −6.64 to −0.38) and hair manganese (β = −3.66; 95% CI = −6.9 to −0.43). Confounders including creatinine, blood lead, community, sex, and parents’ IQ and education were considered and adjusted for by the authors. However, a degree of bias may have been introduced to the analysis through exclusion of some participants as a result of missing data on one or more model covariates, as well as exclusion of participants with high manganese levels.

4.4.3 Reproductive and developmental effects

No studies to assess the potential reproductive toxicity of manganese following oral exposure in humans were identified.

A potential association between prenatal exposure to manganese and reduced birth weight was investigated in a number of studies (Zota et al., 2009; Yu, Cao & Yu, 2013; Chen et al., 2014; Eum et al., 2014; Guan et al., 2014). However, none of these studies established a statistical link. In addition, elevated maternal blood manganese was associated with depressed neurodevelopmental scores in children (Chung et al., 2015; Henn et al., 2017) and reduced intrinsic functional connectivity of emotional brain areas in children (de Water et al., 2017).
As discussed in section 4.4.2, there is some evidence of an adverse effect on neurodevelopment in infants and children exposed to elevated manganese levels, including through drinking-water (He, Liu & Zhang, 1994; Zhang, Liu & He, 1995; Wasserman et al., 2006, 2011; Bouchard et al., 2007, 2011; Kim et al., 2009; Claus Henn et al., 2010, 2012; Farias et al., 2010; Khan et al., 2011, 2012; Oulhote et al., 2014; Yu et al., 2014; Haynes et al., 2015; Henn et al., 2017; Rahman et al., 2017). Although, individually, these studies have limitations that prevent the establishment of causality, when evaluated collectively, the weight of evidence suggests an association between exposure to manganese and developmental neurotoxicity.

4.4.4 Immunological effects

No studies to assess potential adverse effects on the immune system following long-term exposure to manganese in humans were identified.

4.4.5 Genotoxicity and carcinogenicity

The genotoxic potential of manganese in humans has not been defined (IPCS, 1999; ATSDR, 2012). No monograph on manganese is available from the International Agency for Research on Cancer, and manganese is not listed in the United States National Toxicology Program’s 14th report on carcinogens (NTP, 2016).

5 Effects on animals and in vitro test systems

5.1 Essentiality

In animals experimentally maintained on manganese-deficient diets, effects include impaired growth, skeletal abnormalities, reproductive deficits, ataxia of the newborn, and defects in lipid and carbohydrate metabolism (Hurley & Keen, 1987).

5.2 Acute exposure

ATSDR (2012) noted that the acute lethality of manganese in animals appears to vary depending on the animal species and whether exposure is via gavage or dietary ingestion. The acute toxicity of manganese compounds is relatively low. The oral LD₅₀ of manganese chloride in adult rats is reported to range between 331 and 642 mg/kg bw. Manganese acetate has an oral LD₅₀ in rats of 1082 mg/kg bw, and manganese sulfate an oral LD₅₀ of 782 mg/kg bw.

Following a single exposure of rats to aqueous manganese chloride (50 mg/kg) by gavage, neurological effects were reported. These included a significant and reversible decrease in total activity, delayed acquisition of an avoidance reaction in response to unconditioned and conditioned stimuli, an increased latent period of conditioned reflex activity, and a temporary worsening of the learning process (Shukakidze, Lazriev & Mitagvariya, 2003).

5.3 Short-term exposure

5.3.1 Systemic effects

A 14-day exposure of rats to a manganese dose of 1300 mg/kg bw/day (as manganese sulfate) in feed resulted in no deaths. Hepatic changes appeared to vary depending on the chemical species and whether exposure was via gavage or dietary ingestion. Reductions in liver weight
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were reported in male rats but not in mice given manganese at 3900 mg/kg bw/day (as manganese sulfate) in feed for 14 days (NTP, 1993). Exposure of male rats to manganese at 271 mg/kg bw/day (as manganese chloride) in drinking-water for 2 or 4 weeks did not result in changes in liver weight, histology or function (Rivera-Mancía et al., 2009). However, in a 13-week study in which rats were fed manganese at up to 618 mg/kg bw/day (as manganese sulfate), liver weights were decreased in males (at ≥33 mg/kg bw/day) and females (at 618 mg/kg bw/day) (NTP, 1993). Similarly, male mice administered dietary manganese at concentrations of 1950 mg/kg bw/day (as manganese sulfate) for 13 weeks showed reduced relative and absolute liver weights, whereas similarly exposed female mice showed no hepatic effects (NTP, 1993).

Gastric irritation in the form of patchy necrosis of the stomach epithelium was observed in guinea-pigs administered manganese at 10 mg/kg bw/day via gavage for 30 days (Chandra & Imam, 1973); the method of administration might have contributed to the observed effects. Male mice fed high doses of manganese in food for 13 weeks showed mild hyperplasia and hyperkeratosis of the forestomach; no effects were seen in female mice, or male and female rats (NTP, 1993).

Decreased body weight gain was observed in rats and mice following oral exposure to manganese. In the 14-day NTP study, rats were administered dietary concentrations of 0–50 000 ppm Mn(II) sulfate monohydrate (equivalent to 25–370 mg/kg bw, according to the authors of the NTP report), and decreases in body weight gain of 57% in male rats and 20% in female rats were reported. Similar decreases of 50% were described by Ávila et al. (2008) in Wistar rats receiving manganese at 760 mg/kg bw/day (as manganese chloride) in drinking-water. No changes in eating habits in the lowest dose group were observed. Rats in the highest dose group showed decreased weight gain, which could in part be attributed to a decrease in feed consumption because the manganese presumably rendered it unpalatable. The authors noted signs of starvation in rats of this high-exposure group. No histopathological changes were reported in the exposed animals. The authors suggested that the decrease in weight gain might have been compounded by manganese interference in metabolism of calcium, phosphorus and iron.

5.3.2 Neurological effects

In infant monkeys exposed to manganese chloride in milk feed at a manganese level of 328 mg/kg bw/day for 4 months, there were no marked differences in gross motor maturation, growth, cerebrospinal fluid levels of dopamine or serotonin metabolites, or performance on tests of cognitive end-points in the exposed animals compared with controls. Decreased activity during sleep at 4 months of age and decreased play activity at 1–1.5 months of age were noted (Golub et al., 2005). The authors proposed that the behavioural effects were indicative of subtle neurobehavioural changes.

Neurobehavioural effects have also been observed in adult rats orally exposed to inorganic manganese for periods of 30 days to 22 weeks (Calabresi et al., 2001; Centonze et al., 2001; Shukakidze, Lazriev & Mitagvariya, 2003; Torrente, Colomina & Domingo, 2005; Vezér et al., 2005, 2007). The lowest daily dose of manganese reported to be associated with neurobehavioural effects in adult rats was 5.6 mg/kg bw/day (as manganese chloride in the diet for 30 days). The 5.6 mg/kg/day dose was identified as a lowest-observed-adverse-effect level (LOAEL), based on severely impaired cognitive performance in a maze test (Shukakidze, Lazriev & Mitagvariya, 2003). In adult mice exposed to 10 or 30 mg/kg bw/day (as manganese
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chloride) via gavage for 8 weeks, no changes in open-field activity were reported (Moreno et al., 2009a). Conversely, in mice exposed during postnatal days (PNDs) 20–34, subsequent exposure to manganese in adulthood at 10 or 30 mg/kg bw/day for 8 weeks was associated with a decrease in open-field novelty-seeking behaviour and total overall movement in the open field in males, but not in females (Moreno et al., 2009a).

Other studies have also reported subtle neurobehavioural effects in animals following oral exposure to manganese at 8–20 mg/kg bw/day during neonatal periods (Kristensson et al. 1986; Pappas et al., 1997; Brenneman et al., 1999; Dorman et al., 2000; Tran et al., 2002a, b; Garcia et al., 2006; Reichel et al., 2006; Moreno et al., 2009a; Kern, Stanwood & Smith, 2010; Kern & Smith, 2011; Beaudin, Nisam & Smith, 2013). In general, evidence from these studies supports subtle neurobehavioural effects following short-term neonatal exposures at manganese doses of ≥10–20 mg/kg bw/day. Kern, Stanwood & Smith (2010) reported a comprehensive evaluation of the neurodevelopmental effects of manganese exposure in Sprague–Dawley rats exposed via the oral route to manganese at 25 or 50 mg/kg bw/day from birth to PND 21, corresponding to the period of development of dopaminergic pathways in regions of the brain that are important in the regulation of executive function behaviours (involving attention, learning and memory). Behavioural tests (open arena, elevated plus maze and 8-arm radial maze) were performed, and levels of dopamine receptor and transporter proteins were measured in the brain. At the higher tested dose (50 mg/kg bw/day), altered locomotor activity and behavioural disinhibition in the open area test on PND 23, altered learning and increased number of errors in the radial maze on PND 23, and impaired learning/memory (delay/failure to reach the learning criterion and increased number of learning errors in the 8-arm radial test) over PNDs 33–46 were observed. In addition, at the lower dose (25 mg/kg bw/day), increased stereotypic behaviour on a greater number of session days during the 8-arm radial maze test (shift in goal-oriented behaviour, indicating impaired spatial memory) and a reduced level of D1-like receptors in the dorsal striatum were reported. Manganese exposure (up to 50 mg/kg bw/day) did not affect fear and anxiety (as measured by elevated plus maze performance). A LOAEL of 25 mg/kg bw/day can be identified from this study.

In a follow-up study, the authors reported that, without exposure beyond PND 21, the observed neurochemical effects lasting into adulthood, with altered dopamine receptor levels and astrogliosis (as measured by glial fibrillary acidic protein) being observed. Behavioural changes were not observed in animals exposed as adults; however, enhanced locomotor response to a D-amphetamine challenge was seen in adults exposed during the neonatal period (Kern & Smith, 2011).

Histopathological changes in the rat brain following short-term neonatal oral exposure to manganese are not consistently reported. Although several in vivo exposure studies reported an association between increased manganese exposure in rats and histopathological changes in the rat brain (Chandra & Shukla, 1978; Pappas et al., 1997; Bikashvili, Shukakidze & Kiknadze, 2001; Shukakidze et al., 2002; Lazrishvili et al., 2009; Moreno et al., 2009b; Wang et al., 2012; Krishna et al., 2014), other in vivo studies have reported no evidence of such a histopathological association, despite changes in brain biochemistry (Kristensson et al., 1986; Dorman et al., 2000).

Oral doses ranging from 1 to 150 mg/kg bw/day produced neurological effects in rats and mice, mainly involving alterations in neurotransmitter and enzyme levels in the brain. These changes were sometimes accompanied by clinical signs, such as incoordination and changes
in activity level (ATSDR, 2012). Deskin, Bursian & Edens (1980) reported an increase in monoamine oxidase activity in the hypothalamus in rats intubated with a daily dose of manganese at 20 mg/kg bw/day from birth to 24 days of age. In rats administered manganese at 150 mg/kg bw/day (as manganese chloride), a rigid and unsteady gait was observed after 2–3 weeks, which was no longer apparent after 7 weeks of exposure (Kristensson et al., 1986).

More recent studies have continued investigations of brain chemistry alterations in animals following acute to intermediate-duration oral exposure to manganese (Desole et al., 1997; Lipe et al., 1999; Ranasinghe et al., 2000; Calabresi et al., 2001; Liu et al., 2006; Morello et al., 2007; Ávila et al., 2008; Moreno et al., 2009a). Neuropathology was reported following manganese exposure, as evidenced by neuronal damage and/or increased oxidative stress (Spadoni et al., 2000; Liu et al., 2006; Ávila et al., 2008). Behavioural assessments in rats have found changes in measures related to fear, locomotor activity and cognitive performance (Calabresi et al., 2001; Shukakidze, Laziev & Mitagvariya, 2003; Torrente, Colomina & Domingo, 2005; Vezér et al., 2005, 2007). In some of these studies, electrophysiological changes in the brain were associated with behavioural changes (Calabresi et al., 2001; Vezér et al., 2005, 2007).

5.3.3 Immunological effects

Alterations in white blood cell counts were reported in rats and mice following oral exposure to manganese in a 13-week study (NTP, 1993). Male rats were administered manganese at 33–520 mg/kg bw/day and female rats 40–618 mg/kg bw/day. Increased neutrophil counts were seen in the males at levels of manganese ≥33 mg/kg bw/day. There was a decrease in lymphocyte count in males at ≥130 mg/kg bw/day, and in total leukocytes in females at ≥155 mg/kg bw/day (NTP, 1993). Komura & Sakamoto (1991) reported decreased white blood cell counts in mice following exposure to manganese at 284 mg/kg bw/day (as manganese acetate, manganese chloride or manganese dioxide) for 100 days. It is not known if any of these changes are associated with significant impairment of immune system function.

5.4 Long-term exposure

5.4.1 Systemic effects

Limited animal data are available on the effects on systemic target tissues of exposure to manganese by ingestion.

Chronic ingestion of manganese at 1–2 mg/kg bw/day produced changes in appetite and a reduction in haemoglobin synthesis in rabbits, pigs and cattle (Hurley & Keen, 1987). Two-year oral exposures to extremely high doses (1800–2250 mg/kg bw/day as Mn(II) sulfate) in male and female mice resulted in hyperplasia, erosion and inflammation of the forestomach. The authors concluded that this was due to direct contact irritation of the GI epithelium and was of minor consequence; no effects were seen in rats (NTP, 1993). When rats were fed manganese at up to 232 mg/kg bw/day (as manganese sulfate) and mice up to 731 mg/kg bw/day (as manganese sulfate) for 2 years, no significant hepatic histological changes were observed in either species (NTP, 1993).

In a 2-year study, male rats exposed to manganese at 200 mg/kg bw/day (as manganese sulfate in food) showed a significant fall in body weight (10% lower than controls); however, in
females, body weights were unaffected. This was unrelated to food intakes, which were similar for males and females in all groups (NTP, 1993).

5.4.2 Neurological effects

Neurotoxicity is a known effect of long-term exposure to inhaled manganese in humans and animals. However, the potential for neurotoxicity in animals resulting from chronic oral exposure is less well characterized.

A limited number of animal studies have observed manganism-type effects in animals similar to those seen in humans. Muscular weakness and lower limb rigidity were observed in four male rhesus monkeys given oral doses of manganese at 6.9 mg/kg bw/day (as manganese chloride) for 18 months. Degenerated neurons in the substantia nigra were observed at autopsy (Gupta, Murthy & Chandra, 1980). A staggered gait and histochemical changes were also reported in two third-generation mice (total number not stated) treated with manganese at 10.6 mg/kg bw/day (as manganese chloride) in drinking-water (Ishizuka, Nishida & Kawada, 1991). Fine sensorimotor function, learning and attention tasks were affected in adult male Long Evans rats orally exposed to manganese at ≥25 mg/kg bw/day during PNDs 1–21 or throughout life (beginning at PND 1) (Beaudin, Nisam & Smith, 2013; Beaudin et al., 2017). The presence and severity of effects were dependent on the dose and duration of exposure. Many studies report altered behaviours following developmental manganese exposure, including hyperactivity, altered social interactions, transient ataxia, altered acoustic startle, impaired learning and increased stereotypic behaviours (Kristensson et al. 1986; Dorman et al., 2000; Tran et al., 2002a, b; Golub et al., 2005; Moreno et al. 2009b; Kern, Stanwood & Smith, 2010; Kern & Smith, 2011).

Many of the animal studies address changes in brain chemical end-points following exposure to manganese, particularly during the early postnatal and juvenile periods. Alterations in the dopaminergic, noradrenergic, serotonergic or gabaergic systems; increased monoamine oxidase; and decreased iron levels have been reported (Chandra & Shukla, 1978; Deskin, Bursian & Edens, 1981; Kristensson et al., 1986; Dorman et al., 2000; Tran et al., 2002a, b; Reichel et al., 2006; Anderson, Cooney & Erikson, 2007; Anderson et al., 2009; Moreno et al., 2009a; Kern, Stanwood & Smith, 2010; Kern & Smith, 2011). Transient effects on biogenic amine levels, and activities of dopamine β-hydroxylase and monoamine oxidase in rat brain were noted with long-term exposures to manganese at oral exposure levels ranging from around 1 to >2000 mg/kg bw/day (as manganese chloride, manganese acetate, or Mn(II, III) oxide) (Lai, Leung & Lim, 1984; Eriksson, Lenngren & Heilbronn, 1987; Subhash & Padmashree, 1990; Desole et al., 1997; Ranasinghe et al., 2000; Calabresi et al., 2001). An increase in physical activity level and a transient increase in dopaminergic function were observed in rats given manganese at 40 mg/kg bw/day for 65 weeks (Nachtmann, Tubben & Commissaris, 1986).

5.4.3 Reproductive and developmental effects

The results of several studies in rats and mice indicate that ingestion of manganese can delay reproductive maturation in male animals (ATSDR, 2012). Testosterone levels were reduced in male rats given an oral manganese dose of 13 mg/kg bw/day for 100–224 days (Laskey et al., 1982), and delayed growth of the testes was observed in young rats ingesting manganese at 140 mg/kg bw/day for 90 days (Gray & Laskey, 1980). These effects do not appear to have been severe enough to affect male reproductive function (ATSDR, 2012). Sperm abnormalities
were reported in several studies in mice following oral exposure to manganese (Joardar & Sharma, 1990; Elbetieha et al., 2001; Ponnapakkam, Sam & Izard, 2003; Ponnapakkam et al., 2003). Male reproductive performance was lowered at manganese levels as low as 23 mg/kg bw/day in mice exposed over a 21-day period (Joardar & Sharma, 1990).

The results of most studies indicate that oral exposure to manganese does not result in reproductive toxicity in female rodents (e.g. rats, mice) or rabbits (ATSDR, 2012), although increased post-implantation loss was observed in female rats in at least one study (Szakmáry et al., 1995).

Results from several developmental studies in rodents and rabbits are equivocal. Data from the majority of these studies indicate that manganese exposure during part or all of gestation results in increased manganese levels in the pups (Järvinen & Ahlström, 1975; Kontur & Fechter, 1988) but generally caused either no measurable effect (Grant, Blazak & Brown, 1997), transient effects such as weight decreases and hyperactivity (Pappas et al., 1997), or self-correcting effects on skeletal and organ development (Szakmáry et al., 1995).

Studies involving oral exposures to manganese in drinking-water or by gavage in neonatal pups reported changes in brain neurochemistry (ATSDR, 2012). The data from one recent study indicate that rodent pups administered manganese at 22 mg/kg bw/day in drinking-water from birth to weaning (21 days) had changes in brain neurochemistry and evoked sensory response (Dorman et al., 2000).

Although results are varied and inconsistent, taken together, the weight of evidence suggests that excess manganese exposure during development can lead to alterations in brain chemistry and behavioural development (ATSDR, 2012).

Several animal studies of the effects of manganese on reproductive development report developmental effects (Gray & Laskey 1980; Laskey et al., 1982, 1985). In pre-weanling mice exposed to manganese at 1050 mg/kg bw/day (as Mn(II, III) oxide) from PND 15 (to a maximum of 90 days), decreased growth of reproductive organs (preputial gland, seminal vesicle and testes) was reported. Laskey et al. (1982) showed a significant decrease in the number of pregnancies in rats following dietary manganese exposure at feed concentrations ranging from 0 to 3500 ppm during gestation, continuing during nursing and after weaning. No other adverse effects were noted. In a further study, Laskey et al. (1985) showed decreased serum testosterone levels in pre-weanling rats administered manganese at levels between 0 and 214 μg/kg bw/day (as Mn(II, III) oxide) from birth to 21 days of age.

5.4.4 Immunological effects

Alterations in white blood cell counts were reported in rats and mice following oral exposure to manganese. Rats fed manganese at up to 232 mg/kg bw/day (as manganese sulfate) and mice fed up to 731 mg/kg bw/day (as manganese sulfate) for 2 years showed no gross or histopathological changes, or organ weight changes in the lymph nodes, pancreas, thymus or spleen (NTP, 1993).
5.4.5 Genotoxicity and carcinogenicity

5.4.5.1 Genotoxicity

Results of genotoxicity testing are equivocal and do not allow for a clear understanding of the genotoxic potential of manganese. In vitro studies, including tests for mutagenicity, chromosomal aberrations, sister chromatid exchanges and cell transformations, have reported mutagenic or clastogenic potential associated with manganese; however, results vary depending on the form of manganese and test system used. Results of in vivo studies in mammals are inconsistent and do not allow for an overall conclusion about the genotoxic potential of manganese. This information has been summarized in detail in a number of published reviews (European Commission, 2000; Health Canada, 2010, 2019; Assem, Holmes & Levy, 2011).

In vitro bacterial gene mutation tests have yielded both positive and negative results, whereas in vitro tests with fungi and mammalian cells have been predominantly positive. Manganese chloride produced an increased frequency of mutations in Salmonella Typhimurium strain TA1537, but negative results in other strains, whereas manganese sulfate was reported to produce both positive and negative results in separate studies in Salmonella strain TA97, but negative results in other strains (ATSDR, 2012). Several positive results were obtained with various manganese compounds (including manganese sulfate and manganese chloride) in Photobacterium fischeri and Escherichia coli, as well as in Saccharomyces cerevisiae, mouse lymphoma cells and hamster embryo cells (NTP, 1993; ATSDR, 2012). It has been suggested that the absence of mutagenicity of manganese in some of the Ames assays could be due to lack of bioavailability of the metal ion, which may result from chelation of the metal ions by components of the culture media, or from competition for active transport sites (NTP, 1993).

Oberly, Piper & McDonald (1982) reported positive results for manganese chloride in the mouse lymphoma assay, without metabolic activation, at doses of 80, 60 and 40 µg/mL. Manganese chloride was also positive in the Comet assay (single cell gel assay) with cultured human lymphocytes (De Méo et al., 1991). Induction of cell transformations in Syrian hamster embryo cells has also been shown at a manganese chloride concentration of 0.13 mM (16.4 µg/mL) (Casto, Meyers & DiPaolo, 1979).

NTP (1993) reported that manganese sulfate (12 500 ppm, or 12 500 µg/mL assuming the density of the culture media is 1 g/mL) induced sister chromatid exchanges without metabolic activation in mouse fibroblasts (Andersen, 1983), Chinese hamster ovary (CHO) cells (Galloway et al., 1987) and human lymphocytes (Andersen, 1983). With metabolic activation, manganese sulfate was also positive for sister chromatid exchanges in CHO cells (NTP, 1993). Potassium permanganate did not induce chromosomal aberrations in Syrian hamster embryo cells when tested without metabolic activation (Tsuda & Kato, 1977).

In vivo tests in Drosophila melanogaster did not report an association between exposure to manganese sulfate or manganese chloride and induction of sex-linked recessive lethal mutations or somatic mutations, respectively (Rasmuson, 1985; Valencia et al., 1985; NTP, 1993). No heritable translocations in mice were detected following administration of manganese sulfate in the diet for 7 weeks, and no dominant lethal mutations in rats were found following administration of manganese sulfate by gavage once a day for 1–5 days (Newell, Jorgenson & Simmon, 1974, as cited in NTP, 1993).
Administration of manganese sulfate and potassium permanganate increased the frequency of sperm head abnormalities, chromosomal aberrations and micronuclei in rat bone marrow (ATSDR, 2012). In Swiss albino mice exposed to manganese sulfate by the oral route at manganese doses of 33–132 mg/kg bw/day for 3 weeks, there was also an increase in the frequency of sperm head abnormalities, chromosomal aberrations and micronuclei in bone marrow cells (Joardar & Sharma, 1990). Similar findings were reported for oral exposure to potassium permanganate at manganese doses of 22.6, 45.2 and 132.1 mg/kg bw/day for 3 weeks, with an increase in the frequency of sperm head abnormalities and chromosomal aberrations in bone marrow cells (Joardar & Sharma, 1990). Significant chromosomal damage did not occur in bone marrow or in spermatogonial cells of male rats orally exposed to manganese at 0.014 mg/kg bw/day (as manganese chloride) for 180 days (Dikshith & Chandra, 1978).

5.4.5.2 Carcinogenicity

Clear evidence for the carcinogenicity of manganese from an oral route of exposure has not been established. A 2-year oral study of manganese sulfate in rats and mice produced equivocal evidence of carcinogenicity (NTP, 1993). In rats fed manganese sulfate (manganese at 30–331 mg/kg bw/day in males and 26–270 mg/kg bw/day in females), no treatment-related increases in tumour incidence were reported. In mice fed manganese sulfate (manganese at 63–722 mg/kg bw/day in males and 77–905 mg/kg bw/day in females), the incidence of follicular cell adenoma of the thyroid was increased slightly in high-dose animals compared with controls. These increases were not statistically significant, and the tumours were observed at the end of the study only. As well, follicular cell adenoma of the thyroid appears with low frequency in historical control male mice of this strain. Thus, the significance of these results and their relevance to normal human exposure to manganese are questionable.

5.6 Mode of action

Although there is clear evidence that the primary target of manganese toxicity is the CNS – where it impairs cellular transport systems, enzyme activities and receptor functions – the principal mode of action of manganese neurotoxicity has not been clearly established (Aschner & Aschner, 1991; Aschner et al., 2007). Occupational studies reporting severe neurotoxic effects have focused research into potential modes of action on areas of the brain concerned with movement, principally the organs of the basal ganglia, the globus pallidus, the putamen and caudate nucleus, the substantia nigra and the dopaminergic system (WRC, 2014). Many studies investigating effects of manganese on these areas of the brain have been published, but interpretation is difficult because of differences in the experimental methodologies used.

Manganese is selectively taken up by the globus pallidus and the substantia nigra, accumulating in neurons, astrocytes and oligodendrocytes. This is mediated by transferrin receptors. Once inside the cell, manganese is transported through a calcium one-way transporter into mitochondria, where it accumulates. It is hypothesized that accumulation of manganese results in several interrelated processes, ultimately leading to neurotoxicity. These processes include free radical formation (Desole et al., 1994, 1995; Hussain et al., 1997; Taylor et al., 2006), neurotransmitter impairment (Chandra, Srivastava & Shukla, 1979; Deskin, Bursian & Edens, 1980; Chandra & Shukla, 1981; Lai et al., 1982; Lai, Leung & Lim, 1984; Subhash & Padmashree, 1991; Komura & Sakamoto, 1994; Ranasinghe et al., 2000; Calabresi et al., 2001; Montes et al., 2001; Tran et al., 2002a, b; Fitsanakis et al., 2006; McDougall et al., 2008; Peneder et al., 2011) and mitochondrial dysfunction (Gavin, Gunter & Gunter, 1992; Zheng, Ren &
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Graziano, 1998). The generation of free radicals can disrupt the processes of oxidative phosphorylation and ATP synthesis, and lead to cellular dysfunction, apoptosis/necrosis and cell death.

Elevated intracellular manganese levels are linked with the pharmacologic disruption of iron regulation, a process that appears to play a role in neurotoxicity (Kwik-Uribe et al., 2003; Kwik-Uribe & Smith, 2006; Reaney, Bench & Smith, 2006; Crooks et al., 2007). A further consequence of elevated intracellular manganese levels is disruption of the regulation and interaction of neurotransmitters, including dopamine, glutamate and gamma-aminobutyric acid (GABA) in the basal ganglia (Chandra, Srivastava & Shukla, 1979; Deskin, Bursian & Edens, 1980; Chandra & Shukla, 1981; Lai et al., 1982; Lai, Leung & Lim, 1984; Subhash & Padmashree, 1991; Komura & Sakamoto, 1994; Ranasinghe et al., 2000; Calabresi et al., 2001; Montes et al., 2001; Tran et al., 2002a, b; Fitsanakis et al., 2006; McDougall et al., 2008; Burton & Guilarte, 2009; Peneder et al., 2011).

Dopamine plays a role in regulating cognition, behaviour, locomotor activity and neuroendocrine secretion (Fitsanakis et al., 2006; Farina et al., 2013; Guilarte, 2013). In addition, executive function behaviours (e.g. memory, learning, attention) are regulated by dopaminergic pathways (Kern, Stanwood & Smith, 2010). Neurological deficits in animal studies were reported to be accompanied by altered dopamine transporter and dopamine receptor levels, in addition to altered response to dopamine antagonists. Given that dopamine transporter levels are known to increase throughout development, it is possible that cognitive and neurobehavioural effects reported in children following manganese exposure are related to its effects on the dopaminergic system during development (Neal & Guilarte, 2013).

Glutamate is the most prevalent excitatory neurotransmitter in the brain and appears to play a role in various CNS functions, including cognition, learning and memory, as well as in CNS development (Fitsanakis et al., 2006). Mechanistic studies demonstrate that elevated levels of manganese in astrocytes can impair the glycine/glutamate–GABA cycle, which is essential for optimal CNS function because it produces excitatory (glutamate) and inhibitory (GABA) neurotransmitters (Erikson & Aschner, 2003; Aschner et al., 2009; Sidoryk-Wegrzynowicz et al., 2009; Farina et al., 2013; Karki, Lee & Aschner, 2013; Sidoryk-Wegrzynowicz & Aschner, 2013a, b).

6 Overall database and quality of evidence

6.1 Summary of health effects

Manganese is an essential element, and trace levels are necessary for human health. The acute toxicity of manganese compounds may vary depending on route of administration; however, in general, inorganic manganese compounds have low acute oral toxicity.

Manganese is able to cross the blood–brain barrier through capillary endothelial cells (ATSDR, 2012), and the weight of evidence from animal and human studies suggests that the CNS is the primary concern for manganese toxicity in mammals, with effects reported at low doses. Exposure to high levels of manganese is associated primarily with neurological and cognitive effects, including reduced intellectual function, hyperactive behaviours and neurodevelopmental effects. A number of epidemiological studies have reported neurological effects in adult populations exposed to high levels in drinking-water, as well as in children following ingestion of manganese-contaminated water (He, Liu & Zhang, 1994; Zhang, Liu &
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He, 1995; Wasserman et al., 2006, 2011; Kim et al., 2009; Claus Henn et al., 2010, 2011; Farias et al., 2010; Bouchard et al., 2011; Khan et al., 2011, 2012; Oulhote et al., 2014; Yu et al., 2014; Haynes et al., 2015; Henn et al., 2017; Rahman et al., 2017; Iyare, 2019). Another study (described in section 4.4.2) did not find any association (Vieregge et al., 1995).

However, the quality of the epidemiological studies is variable, particularly with respect to the reliability of the exposure estimates. No single study shows a clear causal relationship between manganese dose and neurotoxicity. Although limitations in these studies prevent their use in quantitative risk assessment, collectively they provide qualitative support that the critical effect in animal studies – neurotoxicity – is also relevant in humans.

Animal studies identified neurotoxicity as an end-point of concern following oral exposure to manganese. Some of these studies assessed neurodevelopmental end-points in early life that were supported by corresponding neurochemical findings (Kern, Stanwood & Smith, 2010; Kern & Smith, 2011; Beaudin, Nisam & Smith, 2013).

Infants and children are considered to have a greater sensitivity to manganese toxicity than adults. Infants are particularly vulnerable because of greater GI absorption and immaturity of their homeostatic control of bile excretion, meaning that they excrete less manganese (Valcke et al., 2018).

Existing studies and reports do not provide adequate evidence to assess potential carcinogenicity from oral exposure to manganese in humans. Equivocal evidence of the carcinogenicity of manganese sulfate in a 2-year oral toxicity study in rats and mice was reported (NTP, 1993). Further, no manganese compounds have been reviewed by the International Agency for Research on Cancer with respect to their carcinogenic potential or are included in the National Toxicology Program’s report on substances that are known, or may be reasonably anticipated, to cause cancer in humans (NTP, 2016).

6.2 Adequacy of the database

Cross-sectional and prospective cohort epidemiology studies have investigated the potential adverse neurological effects in humans following chronic exposure to manganese though drinking-water. However, the ability to quantify the findings is limited by numerous uncertainties, particularly with regard to assessing manganese exposure levels. Longitudinal epidemiology studies with robust exposure measurements and valid established or novel biomarkers of effect would inform and refine the dose–response relationship for the spectrum of end-points observed.

Other data gaps in humans include the limited information on reproductive or immunological effects following oral exposures, effects of chronic exposure, and information on the mode of action associated with neurological effects.

Laboratory animal studies report subtle neurobehavioural effects following manganese exposure during the neonatal period (Kristensson et al., 1986; Pappas et al., 1997; Brenneman et al., 1999; Dorman et al., 2000; Tran et al., 2002a, b; Reichel et al., 2006; Moreno et al., 2009a; Kern, Stanwood & Smith, 2010; Kern & Smith, 2011; Beaudin, Nisam & Smith, 2013; Beaudin et al., 2017). Although a number of LOAELs have been identified in rodents, the suitability of rodent models to assess potential neurotoxicity in humans has been debated, because of differences in the neurological effects seen in humans and rodents. The human
tremor and gait disorders that are preceded by psychological symptoms, including irritability and emotional lability, are not seen in rodents. Although there may be differences in species’ nutritional requirements for dietary manganese (US EPA, 2004), only an adequate intake level and tolerable upper intake level for manganese in humans have been reported to date (IOM, 2001), and a level representing essentiality has not been established. Effects seen in children following exposure to manganese involve the dopaminergic system, and mechanistic data indicate that there are commonalities between rodents and non-human primates with respect to the involvement of this system in manganese-induced neurotoxicity (Neal & Guilarte, 2013).

Results from the most robust animal dose–response studies that assessed and quantified neurological effects are consistent with the epidemiological studies. They identified a neurodevelopmental LOAEL for manganese of 25 mg/kg bw/day in rats following oral exposure in early life (Kern, Stanwood & Smith, 2010; Kern & Smith, 2011; Beaudin, Nisam & Smith, 2013; Beaudin et al., 2017). These studies characterized executive function parameters that reflect effects reported in epidemiological studies, such as behavioural hyperactivity (as measured using the open arena assessment) and learning deficits (measured using the 8-arm radial maze) following early-life exposures. They demonstrated that the behavioural and sensorimotor effects observed are accompanied by corresponding neurostructural and neurochemical changes. Long-term follow-up demonstrated the ability of manganese exposure in early life to result in effects that persist into adulthood, after levels in the brain have returned to normal (Beaudin, Nisam & Smith, 2013).

### 7 Practical considerations

#### 7.1 Monitoring

As part of the hazard assessment phase of water safety planning, water sources should be assessed to determine if manganese is present. In general, manganese concentrations are stable between seasons in groundwater but may vary between wells in close proximity to each other. Manganese concentrations in lakes and reservoirs where there is sufficient depth for the development of thermoclines and layers of low oxygen can vary substantially seasonally, and more frequent and targeted monitoring may be needed. (Health Canada, 2019). Management of these source waters is important, where possible; otherwise water should be treated to remove manganese.

Where manganese is present at concentrations close to the guideline value (GV) or the water is treated to remove manganese, routine monitoring should be conducted post-treatment. In many small rural supplies, if resources are limited, monitoring may be minimal. Whenever possible, sampling should be designed to determine whether manganese is at concentrations in excess of the GV. If manganese deposits or precipitation of insoluble manganese result in lack of acceptability of drinking-water because of its organoleptic properties, this indicates that treatment for manganese removal is not optimized or that the distribution system is not appropriately managed.

#### 7.2 Analytical methods and achievability

Total manganese (dissolved and particulate fractions) should be monitored. Quantifying the individual fractions is also important for determining the appropriate manganese treatment method and for monitoring treatment performance. In general, membrane filters with pore diameters between 0.22 µm and 0.45 µm are recommended for fractionating dissolved and particulate manganese (Carlson, Knocke & Gertig, 1997; Kohl & Medlar, 2006; Brandhuber
et al., 2013). Guidance is available on filtration and preservation procedures for measuring dissolved or particulate metal concentrations (APHA, AWWA & WEF, 2012). Water systems that are experiencing difficulties controlling manganese in treated water, and that are directly oxidizing manganese using potassium permanganate, chlorine dioxide or ozone, may also consider quantifying the colloidal fraction of selected samples within the treatment plant.

Sensitive methods are available for measuring manganese in biological and environmental samples. Colorimetric methods are suited to monitoring source waters and water within treatment plants to assess treatment effectiveness; they have detection limits of 10–70 µg/L (ISO, 1986; Brandhuber et al., 2013). The United States Environmental Protection Agency has four recommended analytical methods for analysing total manganese in drinking-water: Method 200.5 revision 4.2, Method 200.7. revision 4.4, Method 200.8 revision 5.4 and Method 200.9 revision 2.2 (US EPA, 2014). These use inductively coupled plasma atomic emission spectrometry (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS) and graphite furnace atomic absorption (GFAA) spectrometry, and have detection limits of 0.005–50 µg/L (ATSDR, 2012). In addition, one standardized analytical method is available (SM3125), which uses ICP-MS and has a detection limit of 0.002 µg/L (APHA, AWWA & WEF, 1992, 1995, 1998, 2005, 2012). Atomic absorption spectroscopy is also used for determining manganese concentrations in biological samples (e.g. urine, faeces, hair) at a detection limit as low as 1 µg/L for urine and 0.2 µg/g for hair (ATSDR, 2012). None of the methods described above distinguish between the different oxidation states of manganese (ATSDR, 2012).

### 7.3 Source control

Manganese contamination of drinking-water sources is generally due to natural occurrence in the underlying rocks and soil; as a result, source control may be limited. Options for controlling levels in groundwater include drilling a new well or blending water from different wells, where possible. For lake and reservoir sources, management of the sources to prevent release of manganese from sediment, particularly when there is a thermocline and the lower water levels become anoxic, is important. Aeration and variable depth intakes are control options for lowering manganese levels in water entering the treatment plant. Hypolimnetic aeration and oxygenation can be used to add dissolved oxygen to reservoirs to minimize manganese release from sediments while maintaining stratification (Gantzer, Bryant & Little, 2009; Bryant et al., 2011; Munger et al., 2016). Variable depth intake is an option for treatment plants that have deep reservoirs and a multilevel intake system. These systems can select the level in the reservoir from which water is drawn into a plant, based on the water quality at different depths (Brandhuber et al., 2013).

### 7.4 Treatment methods and performance

Manganese concentrations in drinking-water are easily lowered to less than 0.05 mg/L using common treatment methods, including oxidation/filtration, adsorption/oxidation, softening/ion exchange, and biological filtration. In well-operated and optimized systems, manganese concentrations can be reduced to less than 0.02 mg/L (Kohl & Medlar, 2006; Tobaison et al., 2008, 2016; Knocke et al., 2010; Brandhuber et al., 2013). Selection of the appropriate treatment system for manganese removal depends on the form of manganese (dissolved or particulate) present in the source water. Dissolved Mn(II) is most often the predominant form present in anoxic and acidic groundwater or lakes. However, depending on the pH and the dissolved oxygen content of the water, a combination of dissolved and particulate manganese can be present. In general, treatment methods used for manganese rely on a combination of
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processes (e.g. oxidation, adsorption, filtration) to remove both the dissolved and particulate forms (Health Canada, 2019).

A commonly used technology for decreasing manganese concentrations in drinking-water is based on directly oxidizing dissolved Mn(II) to form MnO\(_2\)(s) particulates, which are then physically removed – for example, by clarification and granular media filtration or low-pressure membrane filtration. The chemical oxidants typically used include permanganate (MnO\(_4\)\(^{-}\)), chlorine dioxide (ClO\(_2\)) and ozone. Under high pH conditions, chlorine and oxygen may also be effective (Knocke, Hoehn & Sinsabaugh, 1987; Knocke et al., 1990). Effective oxidation of manganese depends on several factors, including pH and Eh, temperature, reaction time, alkalinity, and the total oxidant demand in the water (e.g. presence of iron, sulfide, nitrate, ammonia and organic compounds) (Casale, LeChevallier & Pontius, 2002; Brandhuber et al., 2013). The use of oxidation for the removal of manganese may form disinfection by-products, which should be considered when selecting and optimizing treatment processes. In addition, treatment plants using ozone should be aware that, depending on the water quality, ozone can oxidize Mn(II) into soluble MnO\(_4\)\(^{-}\), and effective removal will not occur (Gregory & Carlson, 2001; Reisz et al., 2008). The effectiveness of physical removal processes depends on manganese entering the filter being in the particulate form (Tobiason et al., 2008). These processes typically remove 80–99% of manganese and, depending on the oxidant, can easily achieve treated water concentrations below 0.04 mg/L (Health Canada, 2019).

Another treatment technique for manganese removal is the use of MnO\(_2\)(s)-coated filter media that adsorb dissolved Mn(II) and catalyse oxidation at the surface in the presence of free chlorine. These coatings develop on anthracite coal or silica sand filter media as a result of the presence of dissolved Mn(II) and free chlorine across the filter bed (Knocke, Hamon & Thompson, 1988; Knocke, Occiano & Hungate, 1990; Tobiason et al., 2008; Islam et al., 2010; Knocke et al., 2010; Bazilio et al., 2016). The adsorbed Mn(II) is subsequently oxidized by the presence of free chlorine across the filter to create new MnO\(_2\)(s) adsorption sites (i.e. continuously regenerated). Only partial removal of the MnO\(_2\)(s) coating occurs during backwashing, resulting in a net increase in MnO\(_2\)(s) adsorption sites over the time of operation (Hargette & Knocke, 2001). In many treatment plants, the MnO\(_2\)(s)-coated media process initiates and sustains itself without operators being aware that it is occurring (Kohl & Medlar, 2006; Brandhuber et al., 2013). This process can routinely achieve very low treated water manganese concentrations (<0.015 mg/L), even when pre-filter manganese concentrations are as high as 0.5 mg/L. The location of this process within a treatment plant can vary. For surface water treatment plants that chlorinate before filtration, it is often part of the existing particle removal filtration process. When pre-filter chlorination is not practised, an adsorptive contactor unit can be placed following filtration (Knocke et al., 2010; Brandhuber et al., 2013; Tobiason et al., 2016).

Traditional manganese greensand is another adsorption/oxidation process using a granular filter media processed from glauconite sand. Glauconite is synthetically coated with a thin layer of manganese base material (manganous ions), which is then converted to a MnO\(_x\)(s) coating by conditioning the greensand in a KMnO\(_4\) or chlorine solution (Knocke, Occiano & Hungate, 1990; Sommerfield, 1999). This medium has a large adsorptive capacity for removing dissolved Mn(II) (1.5 kg/m\(^3\)). Greensand is typically smaller (effective size 0.30–0.35 mm) than silica sand, so it is good at capturing small particles. Since the head loss generated is higher than an equivalent bed depth of silica sand, most applications of greensand use pressure filtration (Brandhuber et al., 2013). Kohl & Medlar (2006) reported that groundwater treatment
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plants using manganese greensand filtration achieved manganese removals of 86–100%: from average influent concentrations of 0.35–0.52 mg/L to average treated water concentrations of below 0.020 mg/L. Greensand filters are best applied in groundwater systems with iron and manganese concentrations <5 mg/L (Kohl & Medlar, 2006).

Biofiltration can successfully remove manganese from groundwater (Mouchet, 1992; Li et al., 2005; Burger et al., 2008; Kohl & Dixon, 2012) and to a lesser extent from surface water (Kohl & Dixon, 2012; Granger, Stoddart & Gagnon, 2014; Hoyland et al., 2014). Removal of manganese using biofiltration relies on the ability of naturally occurring manganese-oxidizing bacteria present in biofilms on filter media to adsorb and oxidize dissolved Mn(II) and form particulate Mn(IV), which can then be removed by backwashing. Kohl & Dixon (2012) reported data from eight treatment plants in Canada, Europe and China that used downflow mono-medium sand biofilters. These treatment plants were capable of >93% removal of manganese to achieve treated water concentrations below the method detection limit of 0.03 mg/L. An important consideration for utilities considering a transition from MnOx(s)-coated media filtration to biofiltration is the potential for release of previously accumulated manganese on the filter media once the free chlorine residual across the filters is terminated (Gabelich et al., 2006; Kohl & Dixon, 2012).

Treatment plants that use lime or soda ash softening can also remove manganese by raising the pH of the water (e.g. >9.5–10) above the solubility of various manganese hydroxide and carbonate solid phases. The elevated pH in lime or lime–soda ash softening will also greatly increase the rate at which dissolved Mn(II) is oxidized in the presence of dissolved oxygen. Where dissolved oxygen is present, oxidized MnOx(s) solids will be formed. Raising the pH of the source water to remove dissolved Mn(II) is not a cost-effective treatment approach by itself; rather, this treatment method is typically used only if softening of the source water is also required. A lime softening treatment plant reported a reduction in the average manganese concentration from 0.520 mg/L in the source water to an average of 0.001 mg/L in the treated water (Kohl & Medlar, 2006). Dissolved Mn(II) can also be removed through cation exchange in zeolite softening processes. As with other cation exchange processes, backwashing the zeolite, typically with a brine solution, removes the manganese (as well as iron, calcium and magnesium) accumulated on the resin.

In addition to manganese in source water, chemical addition and treatment plant processes can contribute to the total amount of manganese that must be managed in drinking-water systems. The three main sources of manganese from treatment plant operations are (Tobiason et al., 2008):

• the presence of manganese impurities in coagulants (principally ferric-based coagulants);
• resolubilization of Mn(II) from the reduction of MnOx(s) solids stored in sedimentation basins as a result of anoxic conditions in the basin; and
• the presence of dissolved manganese in recycle streams from solid-processing operations.

Where a community water supply is not available, manganese removal on a small scale or at the household level is an option. Ion exchange (i.e. water softener) and greensand filtration can be used at the point of entry to a home to reduce the likelihood of discoloured water, and staining of laundry and fixtures. However, deficient operation or maintenance of greensand filters and softeners has been associated with increased manganese concentrations in homes treating well water (Barbeau, Carriere & Bouchard, 2011). To remove manganese for drinking-
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water at a specific tap in a home, point-of-use units based on reverse osmosis are the most effective and reliable treatment technology. Point-of-use units using cation exchange media, such as pour-through filters, are also moderately effective in reducing manganese concentrations (Health Canada, 2019).

7.5 Distribution system

Low levels of manganese in source or treated water (current or historical) can accumulate in the distribution system and periodically release manganese to result in high levels at the tap. Notably, Brandhuber et al. (2015) estimated manganese stored on distribution system pipes based on data collected in Friedman et al. (2010). The mass of deposited manganese ranged from 0.1 mg/ft² to 10 000 mg/ft², with an estimated median of 210 mg/ft², equivalent to approximately 3.8 lbs manganese/mile (based on a 6-inch-diameter pipe) or 7.7 lbs manganese/mile (based on a 12-inch-diameter pipe). Brandhuber et al. (2015) noted that only 1.5% of the deposit would need to be released to exceed a concentration of 1 mg/L in water.

Releases of manganese can occur periodically due to physical or hydraulic disturbances to the system (e.g. mains breaks or hydrant flushing) or changes in water chemistry (e.g. changes in pH, temperature, chlorine residual, and source water type/blending). Physical and hydraulic disturbances most often release particulate manganese and can cause discoloured water and consumer complaints. Chemical releases can go unnoticed if manganese occurs predominantly in the dissolved form. Both types of releases can result in manganese exposure from drinking-water at the tap. Other contaminants (e.g. arsenic, barium, chromium, lead, uranium) that deposit with manganese oxides in the distribution system may also be released into the water and reach consumers’ taps (Schock, 2005; Friedman et al., 2016).

Another detrimental influence of manganese in distribution systems is its impact on the stability of lead scales in lead pipes, lead service lines, lead solders and lead-containing fixtures, which can increase the risk of lead release (Del Toral, Porter & Schock, 2013; Schock et al., 2014). The presence of manganese in distribution systems can also interfere with the effectiveness of corrosion control chemicals (Wasserstrom et al., 2017; Trueman et al., 2019).

It is therefore appropriate to implement a range of controls within the distribution system to minimize the likelihood of manganese release events. These typically involve maintaining stable water chemistry and minimizing several factors: the manganese levels entering the distribution system, the amount of manganese oxide deposits in the distribution system (through best practices for water mains cleaning), and physical or hydraulic disturbances (US EPA, 2006; Friedman et al., 2010; Ginige, Wylie & Plumb, 2011; Brandhuber et al., 2015; Health Canada, 2019).

8 Conclusions

Manganese is an essential nutrient that acts as a component of several enzymes and participates in a number of important physiological processes. Although manganese is essential, deficiencies are unlikely because levels in the diet are generally ample to provide adequate amounts for human health. However, elevated levels of manganese in drinking-water have been associated with toxicity. Recognizing data gaps and uncertainty, a number of authoritative bodies have established health-based values for manganese, including lifetime drinking-water levels and dietary upper levels. Differences and limitations in terms of the data considered at
the time of assessment and their interpretation result in a wide range of proposed values (Health Canada, 2019).

8.1 Derivation of the provisional guideline value

The reassessment of the risk posed by manganese identified emerging evidence supporting the oral route as a potentially important route of exposure for manganese toxicity. For drinking-water, a health-based GV is therefore warranted. In 2004, WHO derived a health-based value based on average daily intakes reported in dietary studies in healthy adult women (Greger, 1999; IOM, 2001; WHO, 2004). However, the current reassessment also considers more recent epidemiological data that indicate potential for adverse effects in populations exposed to lower concentrations of manganese in drinking-water.

Despite the data from more recent epidemiological studies (Bouchard et al., 2011, 2018; Khan et al., 2011, 2012; Rodríguez-Barranco et al., 2013; Oulhote et al., 2014; Yu et al., 2014; Haynes et al., 2015; Henn et al., 2017; Rahman et al., 2017; Dion et al., 2018; Ntihabose et al., 2018), uncertainties regarding manganese dose–response properties in the susceptible population remain. Further, there are questions about the bioavailability of the different chemical forms of manganese in drinking-water, including in comparison with food. The limitations in the human epidemiological oral studies, such as lack of an accurate assessment of manganese exposure levels, absence of determination of temporality of effects, and potential confounding factors, preclude their use in GV derivation. Further, no studies are available that specifically address the potential for increased susceptibility to manganese of infants (0–4 months of age), especially bottle-fed infants. Although these studies cannot be used in a quantitative manner to establish a health-based value, they qualitatively support the use of the identified critical end-point of developmental neurotoxicity in animal studies.

The most robust animal toxicity data are from studies conducted in rats. These include exposure during the neonatal period, a life stage with increased susceptibility. From multiple well-conducted studies in rats, a LOAEL for manganese of 25 mg/kg bw/day can be identified based on adverse neurological indices, such as behavioural and sensorimotor effects, and corresponding neurostructural and neurochemical changes in exposed offspring, some of which persisted into adulthood after levels of manganese in the brain had returned to normal (Kern, Stanwood & Smith, 2010; Kern & Smith, 2011; Beaudin, Nisam & Smith, 2013; Beaudin et al., 2017). As noted by Health Canada (2019), several other studies reported neurotoxicity resulting from oral exposure to manganese in rats, mice or monkeys at lower doses (Chandra & Shukla, 1978; Chandra, Shukla & Saxena, 1979; Chandra, Srivastava & Shukla, 1979; Deskin, Bursian & Edens, 1980; Gupta, Murthy & Chandra, 1980; Öner & Sentürk, 1995; Sentürk & Öner, 1996; Shukakidze et al., 2002; Tran et al., 2002b; Shukakidze, Lazriev & Mitagvariya, 2003; Golub et al., 2005; Vezér et al., 2005, 2007; Lazrishvili et al., 2009; Moreno et al., 2009a, b). However, study limitations, such as the lack of a clear account of animal dosing and lack of information concerning long-term effects, confound the interpretation of these studies. Nonetheless, these studies support neurotoxicity as a key end-point of concern for risk assessment.

To calculate the tolerable daily intake (TDI) based on exposure through drinking-water, the 25 mg/kg/day LOAEL is divided by an uncertainty factor (UF) of 1000, comprising:

- 10 for interspecies uncertainty due to the noted interspecies differences between rodents and humans;
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- 10 for intraspecies differences due to uncertainties in the level of variation within the human population; and
- 10 for database uncertainties, including the use of a LOAEL rather than a NOAEL.

\[
\text{TDI} = \frac{25 \text{mg/kg bw/day}}{1000} = 0.025 \text{mg total manganese/kg bw/day}
\]

Numerous factors might influence the extent of toxicity specific to drinking-water exposure, such as differing chemical forms and valence states in drinking-water, and the higher absorption and increased retention of manganese in infants compared with adults (Health Canada, 2019). Milk or soy-based formula comprises the total diet in non-breast-fed infants for the first few months of life. As noted in section 2.6, there is potential for increased exposure to manganese in this group compared with breast-fed infants because of manganese in both the tap water used to prepare formula and the concentrated or powdered formula itself. The source allocation from drinking-water is assumed to be half of the total potential exposure, with the balance from the formula. Accordingly, an allocation factor of 50% for drinking-water is applied for this assessment. As noted in sections 2.1 and 2.3, there is high variability in manganese concentrations in both drinking-water and formula. Contributions from other sources are not expected to be significant for this age group.

Using the above TDI, allowing for a 50% allocation and a 5 kg body weight for a bottle-fed infant consuming 0.75 L water per day, yields a **health-based GV for manganese of 0.08 mg/L for bottle-fed infants**. This is the subpopulation most susceptible to manganese exposure; therefore, this health-based GV is applicable for the general population as a whole.

Health-based guideline value = \[
\frac{0.025 \text{mg/kg bw/day} \times 5 \text{ kg} \times 0.5}{0.75 \text{ L/day}}
\]

= 0.08 mg/L

This GV is provisional (pGV) because of the high level of uncertainty (as reflected in the composite UF of 1000). It is important to note that levels below this health-based value may result in significant organoleptic acceptability problems – for example, at concentrations as low as 0.02 mg/L. Manganese can deposit on the surface of pipes, causing discolouration of the water and affecting consumer acceptability when it is disturbed.

### 8.2 Considerations in applying the guideline value

The pGV is for total manganese. The presence of particulate manganese in drinking-water systems can also cause acceptability problems; therefore, aesthetic as well as health aspects should be considered when setting regulations and standards for drinking-water quality.

Manganese levels in drinking-water can be an issue in both high- and low-income countries, and should be considered in establishing national standards and local guidance. Resource-limited suppliers, in particular, may have difficulty in achieving the pGV; in such cases, incremental improvements towards meeting the pGV are encouraged. This is a particular problem for groundwater, for which treatment may be minimal and prohibitively expensive. In such instances, benefits from a reliable, microbiologically safe groundwater source should be assessed against the risks posed by an alternative source that may be subject to faecal
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contamination. Issues of acceptability of the drinking-water should also be taken into account, since reduced acceptability may lead consumers to turn to more aesthetically acceptable but less microbiologically safe water supplies. However, what is acceptable varies, and it is vital that a sufficient supply of microbiologically safe water that is acceptable is always available, even if some guidelines or standards for chemicals such as manganese cannot be immediately met.

It should be remembered that the GV is provisional, having been derived with an uncertainty factor of 1000 applied; the previous health-based value was 400 µg/L. As well, the end-point for the pGV, which is cognitive effects, is affected by many other factors. Understanding that the pGV was derived considering the most susceptible subpopulation (bottle-fed infants), risks to infants arising from exceedance of the pGV may be mitigated by following WHO’s recommendation for exclusive breastfeeding (WHO, 2014). If this is not possible or supplementary feeding is required, an alternative safe drinking-water source (e.g. bottled water that is certified by the responsible authorities), if available, may be used to prepare infant formula.
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