Australian Government
National Health and Medical Research Council

Evidence Evaluation Report – Manganese in drinking water

April 2024

Executive Summary

Three recent guidance/guideline documents assessing the toxicity of manganese from the World Health Organization (WHO 2021; 2022), Health Canada (2019) and the European Food Safety Authority (EFSA 2023) were reviewed. All identified the same critical health endpoint of neurotoxicity and in particular developmental neurotoxicity in infants or children.

WHO (2021, 2022) and Health Canada (2019) derived drinking water guideline values for manganese of **0.08 mg/L** and **0.12 mg/L** respectively using different infant weight assumptions (5 kg and 7kg respectively). These guideline values were based on the same point of departure identified in three or four neonatal rat toxicology studies assessing 0, 25 or 50 mg Mn/kg bw/day that identified a lowest observed adverse effect level (LOAEL) of 25 mg/kg bw/day.

Potential adoption of the 25 mg/kg bw/day LOAEL which was relied upon by WHO and Health Canada in Australia would result in a health-based guideline value for manganese of **0.1 mg/L**. This is lower than the current Australian health-based guideline value of **0.5 mg/L**.

Some international jurisdictions have aesthetic guideline values that are lower than the current Australian aesthetic guideline value of **0.1 mg/L**. The current manganese fact sheet in the Australian Drinking Water Guidelines mentions that even at concentrations of 0.02 mg/L, manganese can form a coating on pipes, and suggests a discretionary target of 0.01 mg/L at the water treatment plant.

Manganese concentrations in distributed drinking water across Australia is usually well below 0.1 mg/L. However, in certain regions in Australia (e.g. regional Northern Territory), manganese concentrations in distributed drinking water may be high and exceedances of the current aesthetic and health-based guideline values have occurred (refer to Table 2, Section 5.2). Meeting a lower aesthetic and health-based guideline value in these regions may require additional water treatment measures to ensure that water is safe and acceptable to consume. In addition, a health-based guideline value of 0.1 mg/L is readily measurable with current commercial analytical techniques.

Contents

Acronyms and abbreviations

bw	body weight
DWD	EU Drinking Water Directive (DWD)
EFSA	European Food Safety Authority
L	litre
LOAEL	Lowest observed adverse effect level
mg	milligram
TDI	Tolerable daily intake
US EPA	United States Environmental Protection Agency
The Guidelines	Australian Drinking Water Guidelines

1. Background

Public health authorities in the Northern Territory requested NHMRC to review the health-based guideline value for manganese in drinking water following reported exceedances of manganese in the drinking water of remote communities in the Northern Territory. It was also noted that recent reviews by the World Health Organization (WHO, 2021) and Health Canada (2019) have identified new evidence that have resulted in changes to advice from those organisations and may support lowering the health-based drinking water guideline value for manganese in Australia. In addition, the European Food Safety Authority (EFSA) also published their scientific opinion on the safe tolerable upper intake level of dietary manganese in December 2023 (EFSA 2023).

Based on the changes in advice by WHO and Health Canada, the Water Quality Advisory Committee (the Committee) and the Environmental Health Standing Committee (enHealth) Water Quality Expert Reference Panel supported a review of the Australian health-based guideline value for manganese in 2023. An initial targeted review of these recent guidelines and scientific opinion was undertaken at NHMRC to determine if they were suitable to adopt/adapt in Australia and is presented here. Further review can be undertaken as required if advised by the Committee and depending on available resources.

The Australian Drinking Water Guidelines (the Guidelines) chemical factsheet on manganese was last endorsed by NHMRC Council in 2011. The Guidelines currently provide an aesthetic guideline value for manganese in drinking water of 0.1 mg/L (as manganese precipitates discolour water, can stain laundry, form deposits in plumbing and alter palatability) and a health-based guideline value of 0.5 mg/L. The current health-based guideline value is based on a total dietary intake of manganese of 10 mg/day as recommended by the World Health Organization (WHO) in 1973.

2. Objectives of the review

To consider recent drinking water guidelines published by WHO and Health Canada on the human health impacts of manganese intake via drinking water and to consider adopting or adapting this advice and associated health-based guideline values in Australia. Recent work by EFSA to determine the tolerable upper dietary intake level for manganese was also considered in this review.

Information provided in these guideline documents will also be considered to update supporting information provided in the current manganese factsheet (e.g. analytical/detection, monitoring and water treatment guidance).

3. Research questions

This evidence evaluation was undertaken according to a research protocol developed by the NHMRC and reviewed and approved by the Committee. The research questions below are derived from the approved protocol (NHMRC 2024).

3.1 Health-related advice in factsheet

Health-related advice	Research questions to guide extraction of information for consideration by the Committee
Health-based guideline value	What level of manganese in drinking water does the selected guidance/guideline identify as causing adverse health effects? What is the critical human health endpoint that determines this value? What are the justifications for choosing this endpoint? Are the selected health-based guidance/guideline values relevant to the Australian context? How were they derived and are there any uncertainties with the key studies or the approaches used? Are they suitable to adopt/adapt (for example, do any additional uncertainty factors need to be applied for consistency with the Australian context)?
Aesthetic guideline value	Is the current aesthetic guideline value still suitable for the Australian context?
Health considerations	What are the key adverse health hazards from exposure to manganese in Australian drinking water? Does the selected guidance/guideline consider all relevant exposure pathways?
Typical Australian water levels or exposure profile	Does the selected guidance/guideline identify any typical levels of manganese in drinking water? If so, how do these levels compare to the Australian context? What other factors should be considered (e.g. differences between groundwater versus surface water sources, variations around the country or under certain conditions such as drought, other sources of potential exposure such as leaching from in-premise plumbing?) What are typical concentrations of manganese in rural, remote and urban drinking water sources in Australia? (can seek information from Australian authorities or water utilities if required).
Other research questions?	

3.2 Supporting information in factsheet

Supporting information	Research questions to guide extraction of information for consideration by the Committee
General description	Is the information in the factsheet current? Does the selected guidance/guidelines identify any new information about: • what the chemical is used for and how people might be exposed? • how the specified chemical ends up in drinking water and what form it is in?
Measurement	Is the information in the factsheet current? Does the selected guidance/guideline identify any new information about: • the current analytical methods used to measure/detect the concentration of the specified chemical in water? • the indicators of the risks and how this exposure can be measured? • the limits of quantification or limit of reporting for this chemical in drinking water?
Treatment options	Is the information in the factsheet current? Does the selected guidance/guideline identify any new information about the available options for removing the specified chemical from drinking water?
Are there any new/additional sections that should be added to the factsheet? Should anything be removed?	
Other research questions?	

4. Evidence Evaluation Method

This evidence review was conducted using different approaches depending on the factsheet sections to be updated. For the health-based guideline value and health-related advice in the factsheet:

- A preliminary search by NHMRC for international drinking water quality guidelines published in English in the past 5 years (January 2019-December 2023) did not identify any other guidelines presenting health-based guideline value recommendations for manganese concentrations in drinking water other than WHO (2021, 2022) and Health Canada (2019) publications.
- A targeted review of the selected guidelines (WHO 2021, 2022 and Health Canada 2019) was undertaken in December 2023–January 2024 to assess, amongst other topics, existing health-based guideline values, associated recommendations for drinking water and/or appropriate guidance values that can be used to derive drinking water guideline values. The recent scientific opinion by EFSA (2023) on the tolerable upper dietary intake level for manganese was also considered relevant to this review.
- The relevant data from selected guidance/guidelines was compiled and summarised to answer each research question.

For supporting information in the factsheet (e.g. monitoring, treatment information), relevant new information from the selected guidance/guidelines was extracted to be considered for updating the supporting information sections in the current factsheet.

4.1 Method for data extraction

Guidance/guidelines reviewed:

- EFSA (2023). EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens). Scientific opinion on the tolerable upper intake level for manganese. EFSA Journal, 21(11), e8413. https://doi.org/10.2903/j.efsa.2023.8413. First published: 08 December 2023.
- Health Canada (2019). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Manganese. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-manganese.html. Published 10 May 2019.
- WHO (2021). Manganese in drinking-water. Background document for development of WHO Guidelines for drinking-water quality. World Health Organization, Geneva. https://www.who.int/publications/i/item/WHO-HEP-ECH-WSH-2021.5 (Background technical document). Published 22 December 2021.
- WHO (2022). Guidelines for drinking-water quality: fourth edition incorporating the first and second addenda. Geneva: World Health Organization; 2022. https://www.who.int/publications/i/item/9789240045064 (Guidelines). Published 21 March 2022.

4.2 Method for appraising existing guidance/guidelines

The guidance/guidelines selected for possible adoption/adaption in Australia were evaluated using the Assessment Tool outlined in Appendix A of the Research Protocol. This tool evaluates each document against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. Guidance/guidelines that fail to meet a reasonable proportion of key criteria may be considered unsuitable to adopt/adapt for the Australian context.

4.3 Calculation of candidate health-based guideline values for drinking water

Where health-based guideline/guidance values from the selected jurisdictions were considered reasonable for potential adaption into the Australian Drinking Water Guidelines, calculations of prospective health-based guideline values for drinking water were undertaken using the methodology and assumptions outlined in the Guidelines (NHMRC and NRMMC 2011).

Derivation of a guideline value followed the equation in Section 6.3.3. of the Guidelines as outlined below:

$$\text{Guideline value} = \frac{\text{animal dose} \times \text{human weight} \times \text{proportion of intake from water}}{\text{volume of water consumed} \times \text{safety factor}}$$

Default assumptions typically used in the Guidelines include:

- 70 kg body weight for an adult or 13 kg body weight for a 2-year-old child,
- 10% (0.1) for the proportion of intake from drinking water for adults (unless more specific information is available), and
- 2 L/day of water consumption by an adult (or 1 L/day by a 2-year-old child).

Where default values were not specified in the Guidelines but are relevant for guideline derivation (for example, relevant body weight and water consumption for infants), assumed values have been sourced from available Australian data (for example, the Australian Exposure Factor Guide (enHealth 2012))[1].

[1] The chemical fact sheet on nitrate and nitrite in the Guidelines includes a guideline derivation calculation for infants, assuming a body weight of 5 kg and drinking water consumption of 0.75L. However the source of these assumptions are not specified in the fact sheet.

5. Results

5.1 Health-based aspects in factsheet

Table 1. Summary of findings from data extraction for health-based research questions

#	Research question	Ref.	Response to Research Question
1	What level of manganese in drinking water does the selected guidance/guideline identify as causing adverse health effects?	WHO 2021, 2022	WHO has derived a provisional drinking water guideline value for manganese of **0.08 mg/L** based on studies in rats orally exposed to manganese that report neurotoxic effects consistent with those observed in epidemiological studies.
		Health Canada 2019	Health Canada has derived a drinking water guideline value for manganese of **0.12 mg/L** based on animal studies that observed neurodevelopmental effects following oral exposure.
		EFSA 2023	Not applicable. EFSA has not set a health-based guideline value for drinking water based on adverse health effects. A safe level of intake (overall manganese intake from all dietary sources, including water, fortified foods and supplements) was established by EFSA for different population groups: 2 mg/day for infants (4 -12 months); 4 mg/day for 1-2 yr olds; 5 mg/day for 3-6 yr olds; 6 mg/day for 7-13 yr olds; 7 mg/day for 14-17 yr olds; 8 mg/day for adults (≥18 yrs including pregnant and lactating women). No upper limit (maximum level of total chronic daily intake of a nutrient from all sources which is not expected to pose a risk of adverse health effects to humans) for manganese intake was established for any population group.
2	What is the critical human health endpoint that	WHO 2021, 2022	WHO identified the central nervous system as the primary concern of manganese toxicity in mammals, including humans. A LOAEL (Lowest observed adverse effect level) for manganese of 25 mg/kg bw/day was identified from several rat studies 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 the

#	Research question	Ref.	Response to Research Question
	determines this value?		levels of manganese in the brain returned to normal (Kern et al. 2010, Kern and Smith 2011, Beaudin et al. 2013, and Beaudin et al. 2017, as cited in WHO 2021).
		Health Canada 2019	Health Canada identified the central nervous system as appearing to be the primary target of manganese toxicity in both humans and animals, followed by reproductive toxicity. Health Canada stated that several epidemiological studies suggest an association between exposure to manganese in drinking water and neurological effects in children (e.g. intellectual impairment and poorer neurobehavioural function, including memory, attention, motor function and hyperactivity). Manganese has also been shown to be readily taken up into the central nervous system following oral exposure. Three animal studies (Kern et al. 2010, Kern and Smith 2011, Beaudin et al. 2013, as cited in Health Canada 2019) were selected by Health Canada for derivation of a guideline value as the studies collectively identified a LOAEL of 25 mg Mn/kg bw/day for various neurological endpoints in rats.
		EFSA 2023	Not applicable. EFSA did not set a guidance value based on a critical health effect. EFSA identified the most important target of manganese toxicity as the central nervous system, indicating that available human and animal studies support neurotoxicity as a critical effect of excess dietary intake of manganese. EFSA determined that data from available studies (human or animal) was inadequate to characterise a dose-response relationship and identify a reference point for manganese-induced neurotoxicity.
3	What are the justifications for choosing this endpoint?	WHO 2021, 2022	WHO stated that in addition to the key studies used to derive a drinking water guideline value, several other studies reported neurotoxicity resulting from oral exposure to manganese in rats, mice or monkeys at lower doses. WHO identified study limitations, such as the lack of a clear account of animal dosing and lack of information concerning long term effects as confounding the interpretation of these studies. However, these studies supported neurotoxicity as the endpoint of concern for guideline derivation. Additionally, several epidemiological studies were described to have also reported neurological effects (including reduced cognitive ability) in adult populations and children after exposure to manganese in drinking water. Study limitations (such as uncertain manganese exposure levels, unclear temporality of effects and other confounding factors) were stated to preclude use in guideline derivation. However, collectively the studies were described to provide qualitative support that the neurological effects reported in animal studies are relevant in humans. WHO also reported that infants and children are considered to have a greater sensitivity to manganese toxicity than

#	Research question	Ref.	Response to Research Question
			adults, due to greater gastrointestinal absorption and immaturity of their homeostatic control of bile excretion (i.e. they excrete less manganese). WHO stated that existing studies and reports do not provide adequate evidence to assess potential carcinogenicity from oral exposure to manganese in humans, and that no manganese compounds have been reviewed by IARC with respect to carcinogenicity potential.
		Health Canada 2019	Health Canada reported that a number of LOAELs have been identified in animal studies following oral exposure to manganese but many studies only examine the effects following a short duration without long-term follow up. Additionally, it was reported that the human relevance of some of the end points studied has been questioned in the published literature. In addition, although assessment of the available epidemiological data identified several study limitations that preclude their use in establishing a maximum acceptable concentration (such as potential confounding factors, inadequate exposure estimates, risk of bias, absence of a determination of the temporality of effects, and absence of a clear point of departure for dose-response analysis), Health Canada maintained that the findings can be used qualitatively to support the choice of the key endpoint in animal studies. Collectively, three animal studies (Kern et al. 2010, Kern and Smith 2011, Beaudin et al. 2013, as cited in Health Canada 2019) were identified by Health Canada for derivation of a guideline value due to their thoroughness in assessing neurodevelopmental endpoints (observed neurobehavioural effects are supported with corresponding neurochemical findings) in early life that are consistent with the findings reported in epidemiological studies. Additionally, it was reported that these studies consider observed effects measured over a long term and Kern and Smith (2011) and Beaudin et al. (2013) demonstrate the ability of manganese exposure in early life to result in effects that persist into adulthood, after levels of manganese in the brain returned to normal. Health Canada reported that there is evidence that exposure to manganese in early life, during a critical period of development of the dopaminergic system, may result in lasting effects in adults. Mechanistic data also appears to suggest common elements between rodents and non-human primates regarding the involvement of the dopaminergic system in manganese-induced neurotoxicity. Health Canada states that the OECD (OECD 2007, as cited by Health Canada) recommends the rat as the species of choice for extrapolation of developmental neurotoxicity to humans. Health Canada indicated that existing studies are inadequate to determine carcinogenicity and that manganese has not been classified by IARC.

#	Research question	Ref.	Response to Research Question
		EFSA 2023	EFSA reported that several recently available observational studies investigate the association between manganese concentration in drinking water and neurological outcomes, especially in infants and children. EFSA mentions that limited conclusions can be drawn from these studies due to insufficient characterisation of manganese dietary exposure, concerns regarding incomplete adjustment for confounding factors, and/or uncertainties regarding the temporality of the relationship. Similarly, EFSA considered that the available studies of manganese toxicity in animals were mostly mechanistic and not designed to identify a reference point. Additionally, methodological limitations were reported to affect confidence in the robustness of the available data. EFSA reported that despite the limitations, the body of evidence indicates that oral exposure to manganese can affect neurological functions in animals (both motor and learning abilities). It was noted in EFSA (2023) that manganese may increase in the brain at a higher rate in the neonatal phase or juvenile phase compared to adulthood, but that there was limited data to assess rodent susceptibility during the developmental period compared to adulthood. Overall, EFSA reported that the available human and animal studies were considered sufficient to support neurotoxicity as a critical effect of excess dietary manganese intake. However, data were not considered sufficient or suitable to characterise a dose-response relationship and identify a reference point for manganese-induced toxicity.
4	Are the selected health-based guidance/guideline values relevant to the Australian context?	WHO 2021, 2022	Yes. The provisional drinking water guideline value of 0.08 mg/L is considered by WHO to be protective against neurological effects in the most sensitive subpopulation (bottle-fed infants) and consequently the general population.
		Health Canada 2019	Yes. Although the health-based guideline value for drinking water (0.12 mg/L) was established for the most sensitive subpopulation (i.e. bottle-fed infants), it is also considered by Health Canada to be protective for chronic exposure in children and adults.
		EFSA 2023	Yes. In the absence of Australian-specific dietary intake values for manganese, the safe levels of intake established by EFSA could be applicable to the Australian context as they are based on estimated background dietary intakes of manganese observed among high consumers across European countries. However, the level of intake may differ to that of the Australian population due to various factors, including variations in diet and the level of naturally occurring manganese in the environment.

#	Research question	Ref.	Response to Research Question
5	How were they derived and are there any uncertainties with the key studies or the approaches used?	WHO 2021, 2022	A tolerable daily intake (TDI) of 0.025 mg/kg bw/day was derived by applying an uncertainty factor of 1,000 to a LOAEL of 25 mg/kg bw/day. The uncertainty factor considers interspecies variation (x10), intraspecies variation (x10) and database uncertainties (x10, including use of a LOAEL instead of a NOAEL). The provisional guideline value was derived using: • the calculated TDI of 0.025 mg/kg bw • 50% allocation of the TDI to water • 5 kg body weight for a bottle-fed infant • 0.75 L water consumption per day for a bottle-fed infant. Identified data gaps reported by WHO include limited information on reproductive and immunological effects following oral exposure, effects of chronic exposure, and information on mode-of-action associated with neurological effects. WHO states that LOAELs have been identified in rodents, however the suitability of rodent models to assess potential neurotoxicity in humans has been debated due to differences in the neurological effects seen in humans and rodents. Additionally, it was stated that the human tremor and gait effects that are preceded by psychological symptoms (including irritability and emotional liability) are not observed in rodents. WHO reports that only an adequate intake level and tolerable upper intake level for manganese in humans has been reported to date and a level representing essentiality has not been established.
		Health Canada 2019	A tolerable daily intake (TDI) of 0.025 mg/kg bw/day was calculated by applying an uncertainty factor of 1,000 to a LOAEL of 25 mg/kg bw/day (from the Kern and Smith (2010), Kern et al. (2011) and Beaudin et al. (2013) studies, based on neurological effects occurring from postnatal exposure to manganese in rats). The uncertainty factor of 1,000 was selected to account for interspecies variation (x10), intraspecies variation (x10), and the use of a LOAEL rather than a NOAEL (x10). The health-based value (HBV) for total manganese in drinking water was calculated using:

#	Research question	Ref.	Response to Research Question
			• 0.025 mg/kg bw per day as the TDI (as derived above) • 7 kg is the average body weight of an infant (0-6 months) • 0.5 is the allocation estimated for drinking water. Health Canada noted that as infant formula represents the total diet in bottle-fed infants in the first few months of life, the main source of manganese exposure is both the water used to prepare the formula, as well as the formula itself. Due to the high variability of manganese in drinking water and infant formula, the source allocation from drinking water was assumed to be half of the total potential exposure, with the balance coming from the infant formula itself. Other source contributions were not expected to be significant for this age group. • 0.75 L per day is the estimated daily volume of tap water consumed by a bottle-fed infant (0–6 months). Health Canada reports that the key studies used for derivation of a guideline value did not reflect the lowest reported LOAEL for neurological effects following oral exposure to manganese, and that benchmark dose analysis was not possible as only two doses were tested. It was also reported that other studies demonstrated neurotoxicity from oral exposure to manganese in rats, mice and non-human primates (levels ranged between 0.106 – 6.5 mg/kg bw per day) and support the choice of neurotoxicity as the key endpoint for guideline derivation. Health Canada notes that these studies were not considered strong candidates for derivation of a guideline value on their own due to study limitations (such as lack of a clear account of animal dosing, lack of information regarding long-term effects, and confounding factors that impacted the interpretation of the results). Health Canada identified other factors as potentially influencing the extent of toxicity specific to drinking water in infants, including the increased bioavailability of manganese when ingested in a fasted state, the differing chemical form and valence states in water, and the higher absorption and increased retention of manganese in infants compared with adults.
		EFSA 2023	EFSA reported that in the absence of adequate data to characterise a dose-response relationship and identify a point of departure for manganese-induced neurotoxicity, an upper level for manganese intake was not established for any population group. EFSA considered that there is no indication in the general population that manganese intake is associated with adverse effects at the levels of background dietary intake (natural dietary sources only). As such, the estimated

#	Research question	Ref.	Response to Research Question
			background dietary intakes of manganese observed among high consumers (95th percentile) in representative groups of the population were considered indicative of the highest level of intake where there is reasonable confidence on the absence of adverse effects. EFSA derived the 95th percentile estimates of background intakes of manganese from the average value of the four highest 95th percentile estimates across European countries for the respective population groups and used those estimates to establish safe levels of intake. EFSA stated that, as data are insufficient to determine when manganese homeostatic processes become fully mature during infancy, a more conservative approach was taken for infants and the average value of all available 95th percentile estimates across European countries was used for this age group. EFSA also stated that the safe levels of intake for manganese are based on a conservative approach and deemed appropriate until adequate data becomes available to specify the manganese upper level. EFSA explained that data to identify critical intakes associated with increased risks of neurotoxicity are lacking both in animals and humans. It was reported that, in humans, most evidence indicated associations between manganese concentrations in drinking water and neurological adverse effects, however, studies investigating the association between total manganese dietary exposure and neurological effects are scarce. EFSA concluded that due to methodological limitations, robust conclusions could not be drawn. Additionally, it was reported that most animal studies were not designed to investigate the dose-response relationship between dietary exposure to manganese and neurological effects and therefore were not suitable for use in determining a manganese upper level in humans. EFSA stated that the application of safe levels of intake is limited because the proportion of people at risk of adverse effects in a population cannot be estimated, as the intake level at which the risk of adverse effects starts to increase is not defined.
6	Are they suitable to adopt/adapt (for example, do any additional uncertainty factors need	WHO 2021, 2022	The WHO guideline value is suitable to adopt/adapt based on an assessment of administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes (see Appendix A). The WHO derivation of the health-based value uses assumption values that differ to the default values used to derive the current Australian drinking water health-based guideline value.
		Health Canada 2019	The Health Canada guideline value is suitable to adopt/adapt based on an assessment of administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes (see Appendix A).

#	Research question	Ref.	Response to Research Question
	to be applied for consistency with the Australian context)?		The Health Canada derivation of the health-based value uses assumption values that differ to the default values used to calculate the current Australian drinking water health-based guideline value.
		EFSA 2023	The EFSA guidance is suitable to adopt/adapt based on an assessment of administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes (see Appendix A). The safe levels of intake established by EFSA for manganese are more limited in applicability than a tolerable upper intake level that describes the maximum daily intake of a nutrient which is not expected to pose a risk of adverse health effects in humans (equivalent to a Tolerable Daily Intake). A tolerable upper intake level could be used in the derivation of a drinking water guideline value, however as safe levels of intake are not based on an identified threshold for adverse health effects, they cannot be used to characterise the proportion of the population at risk of adverse effects. As stated by EFSA, intake levels above the safe levels of intake do not necessarily mean that there is a risk of adverse effects.
7	What are the key adverse health hazards from exposure to manganese in Australian drinking water?	WHO 2021, 2022	WHO does not specifically consider exposure to manganese in the Australian drinking water context. WHO considered manganese an essential element and that trace levels are necessary for human health. WHO notes that: • the acute toxicity of manganese compounds may vary depending on route of administration but, generally, inorganic manganese compounds have low acute oral toxicity • the extent of toxicity from exposure to manganese can be influenced by the chemical form and valence state of the manganese in drinking water • levels of manganese were found to increase in several tissues following oral exposure, including some areas of the brain in infants and adults • absorption of manganese in the gastrointestinal tract is influenced by several factors, including dietary factors. WHO 2021 states that some studies and reports have suggested that absorption and bioavailability of manganese are greater from drinking water than from food, although other studies have reported no differences and that absorption from drinking water may be influenced by fasting conditions and the chemical form of manganese

#	Research question	Ref.	Response to Research Question
			• exposure to manganese is associated primarily with neurological and cognitive effects, including reduced intellectual function, hyperactive behaviours and neurodevelopmental effects. WHO indicated that a number of epidemiological studies have reported neurological effects in adult populations exposed to high levels in drinking water and in children following ingestion of manganese-contaminated water. Additionally, animal studies report subtle neurobehavioural effects after neonatal exposure to manganese.
		Health Canada 2019	Health Canada does not specifically consider exposure to manganese in the Australian drinking water context. Health Canada reports that manganese is considered an essential element with deficiency unlikely (in Canada) as adequate amounts are obtained from food. Health Canada noted that: • the chemical form (speciation) and valence state of manganese affects absorption • in both humans and animals, low iron status has been shown to increase manganese absorption • gastrointestinal absorption is also influenced by individual factors such as sex and age. It was stated that increased absorption and retention of manganese have been observed in neonates and infants in both humans and rodents (due to a reduced capacity for biliary excretion) resulting in a higher body burden of manganese compared with adults • some epidemiology studies (i.e. case reports, cross-sectional and cohort studies) have suggested an association between exposure to manganese in drinking water at elevated levels and neuropsychological issues in infants and children, such as changes in behaviour, lower IQ, speech and memory difficulties, lack of coordination and movement control. However, it was stated that most studies did not allow determination of temporality (i.e. effect coming after the cause) of the association, the risk for spurious associations was estimated to be high, and exposure measurements were generally poor and relied on a single measurement of a single sample • results of studies on experimental animals indicate uptake into the central nervous system but also a range of other tissues, including the lungs, kidneys and testes. It was reported that toxicological information from these studies is usually based on oral exposure to soluble manganese salts. However, it was also reported that animal studies using manganese salts often do not clearly indicate whether the reported dose is

#	Research question	Ref.	Response to Research Question
			reflective of manganese or a manganese complex (generally, reported dosing in the majority of studies was found to refer to ionic manganese) • short-term and chronic neurotoxic effects in animals resulting from exposure to manganese can be categorised as affecting behavioural endpoints (including information related to altered reflex, motor activity, learning, memory, or sensory alterations), structural endpoints (including gliosis and neuroinflammation, in addition to neurostructural alterations), and neurochemical endpoints (altered neurotransmitter systems). Health Canada indicates that neurobehavioural effects were reported in rats and mice (pups or neonates) following exposure during gestation, lactation and/or after weaning through direct exposure. Additionally, oral and/or inhalation exposure to manganese was shown in a number of studies to cause additional developmental effects (such as altered growth and/or survival) • manganese was found to adversely affect both male and female reproductive systems after short- and long-term exposures in animals • chronic exposure to air-borne manganese has been repeatedly associated with adverse neurological effects. However, Health Canada advised that it is not clear whether the effects associated with inhalational exposure can be extrapolated to the oral exposure route due to toxicokinetic differences observed across exposure routes and oxidation states.
		EFSA 2023	EFSA does not specifically consider the Australian drinking water context in their review. EFSA states that individuals with impaired hepatic function or with iron deficiency have been suggested to be possibly at higher risk of manganese toxicity. Additionally, evidence from some case reports indicates that some individuals may be vulnerable to manganese toxicity due to specific genetic mutations of manganese transporters impairing manganese excretion. However, EFSA considers that current data are insufficient to characterise subgroups of the population who may potentially be at higher risk of manganese toxicity. EFSA noted that $MnCl_2$ was used in all the animal studies included in the assessment, and that most of the evidence from human data relates to manganese forms as present in drinking water. EFSA reported that some data indicate that manganese intestinal absorption may be affected by the oxidation state and solubility of manganese forms and the presence of some food compounds (e.g. iron phytates), however data on the influence of these factors on manganese toxicity are limited. EFSA also noted that:

#	Research question	Ref.	Response to Research Question
			• absorption of dietary manganese is low (<10%) • available data are insufficient to characterise levels of dietary intake at which manganese excretion mechanisms may be overwhelmed, leading to excess manganese body burden • manganese homeostasis is primarily achieved by biliary excretion • there is a scarcity of data regarding the maturation process of manganese homeostatic mechanisms in human infants and that available data is inadequate to determine whether infants have a similar capacity as older age groups to regulate manganese body burden.

5.2 Exposure-related aspects in factsheet

Table 2. Summary of findings from data extraction for exposure-related research questions

#	Research question	Ref.	Response to Research Question
8	Does the selected guidance/guideline consider all relevant exposure pathways?	WHO 2021, 2022	Not clear. The highest exposure to manganese in the general population is usually from food and has been considered in the allocation of the TDI to drinking water. Exposure to manganese in air is generally several orders of magnitude less than exposure from the diet.
		Health Canada 2019	Yes. Exposure through inhalation from drinking water is likely negligible due to the low volatility of manganese. Dermal exposure via showering or bathing is also unlikely to be significant based on the few reports on the dermal toxicity of manganese.
		EFSA 2023	No, EFSA is concerned with the tolerable upper intake level for manganese and as such, is focused on oral intake, primarily dietary exposure from foods, beverages and supplements. EFSA reported that chronic exposure to high manganese concentrations by inhalation, particularly in occupational settings, is well documented to be associated with neurotoxic effects, noting however that the relevant doses cannot be readily extrapolated to the oral exposure route due to toxicokinetic differences between the different exposure routes.

#	Research question	Ref.	Response to Research Question
9	Does the selected guidance/guideline identify any typical levels of manganese in drinking water? If so, how do these levels compare to the Australian context?	WHO 2021, 2022	The WHO guidelines summarise manganese concentrations and speciation in drinking water and natural water bodies in other countries (USA, Germany, UK, Bangladesh, Burma, China). When reducing conditions are present in groundwater, higher concentrations of dissolved manganese are favoured; up to 1,300 µg/L in neutral groundwater and 9,600 µg/L in acidic groundwater have been reported (ATSDR, 2012). Maximum average annual concentrations were reported to be 3000 µg/L for groundwater and 500 µg/L for surface water entering 179 treatment plants located across North America. However, the median values for groundwater and surface waters were similar and below 100 µg/L. The range of average manganese values for surface water is tighter than for ground water, indicating that the natural processes of oxidation and settling help to moderate manganese concentrations (Kohl & Medlar, 2006). As of January 2022, US EPA monitoring reported manganese at levels higher than 300 µg/L in 2.1% of drinking water distribution systems (US EPA, 2022). 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 m^3/day during 2017–2019 contained manganese at levels exceeding 50 µg/L (Federal Ministry of Health & Federal Environment Agency, 2019). 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. Exposure to high levels (400–1700 µg/L) of manganese in drinking water has been reported in some regions, including low- or middle-income countries such as Bangladesh, Burma, China and India.
		Health Canada 2019	Health Canada reports that typical levels of manganese in Canadian fresh water supplies are 1–200 µg/L, as either dissolved Mn(II) or as particulate manganese oxides, hydroxides and carbonates (Mn(IV)). Higher levels can occur in groundwaters or surface waters that are acidic, have a low Eh (redox potential) or are affected by industrial discharges. This is reflected in Canadian data, which indicates that most drinking water (from different sources including wells) contains less than 100 µg/L of Mn, with a few cases where water manganese levels may reach thousands of micrograms per litre.
		EFSA 2023	Not applicable.

#	Research question	Ref.	Response to Research Question
10	What are typical concentrations of manganese in rural, remote and urban drinking water sources in Australia?	WHO 2021, 2022 Health Canada 2019 EFSA 2023	The international guidance documents reviewed did not discuss typical levels in Australian water supplies.
		Australian water utility annual reports	A summary of Australian distributed drinking water supply monitoring data for manganese from a selection of water utility reports is provided below: • Mean concentration **<0.002 – 0.026 mg/L** and maximum concentration of **0.055 mg/L** was recorded across urban and regional Western Australia during 2022–2023 (Water Corp. 2023). • Average manganese concentrations of **<0.005–0.03 mg/L** in town centres and **<0.005–0.3 mg/L** in 72 regional First Nations communities of the Northern Territory during 2021–2022. Exceedances were noted in Pine Creek urban centre (**0.7 mg/L)** and regional towns Nauiyu (**0.8 mg/L)** and Nganmarriyanga (**0.3 mg/L)** that rely on bore water (Power & Water Corp. 2023). • Average concentrations of **<0.001–0.006 mg/L** were measured in the bulk water supplied to councils and water retail distributors in South-East Queensland by Seqwater from February 2023–January 2024 (Seqwater 2024). • Mean concentration in Adelaide's metropolitan distribution system (customer tap water quality) measured **0.0015 mg/L** and a maximum of **0.0075 mg/L** during 2022–2023. All regional drinking water distributions systems including those supplying First Nations communities (regional customer tap water quality) recorded mean concentrations in the range **<0.0001–0.0208 mg/L** during 2022–2023 (South Australian Water Corp. 2023).

#	Research question	Ref.	Response to Research Question
			• Manganese concentrations measured in drinking water derived from the six major storage reservoirs following primary treatment processes were in the range **0.0001–0.0138 mg/L** during 2022 (Melbourne Water 2023). • Average concentration measured at participating customers' taps was **0.004 mg/L** (range **<0.001–0.183 mg/L**) in Canberra during 2022–2023 (Icon Water 2023).

5.3 Aesthetic considerations

Table 3. Summary of findings from data extraction for aesthetic considerations

#	Research question	Ref.	Response to Research Question
11	Is the current aesthetic guideline value still suitable for the Australian context?	WHO 2021, 2022	No aesthetic guideline value was established; however, WHO states that insoluble manganese can cause aesthetic effects at 0.02 mg/L. This level is lower than the current Australian aesthetic guideline value of 0.1 mg/L.
		Health Canada 2019	The aesthetic objective reported by Health Canada for total manganese in drinking water is 0.02 mg/L (20 µg/L) to reduce consumer complaints regarding discoloured water and staining of laundry. This is lower than the current Australian aesthetic guideline value of 0.1 mg/L.
		EFSA 2023	Not applicable.
		US EPA website, current in Feb 2024	The current USA EPA aesthetic guideline value for manganese in drinking water is 0.05 mg/L. This aesthetic guideline is described in Secondary Drinking Water Regulations which are non-enforceable federal guidelines regarding cosmetic effects (such as tooth or skin discoloration) or aesthetic effects (such as taste, odour, or colour) of drinking water.
		European Union website,	The EU Drinking Water Directive (DWD) came into effect in January 2021 and Member States were required to comply with its provisions by 12 January 2023. The DWD lists manganese concentrations of 0.05 mg/L (50 µg/L) as a parametric indicator value for water discolouration and consumer acceptability (i.e. an aesthetic value). The

#	Research question	Ref.	Response to Research Question
		current in Feb 2024	DWD provides a general framework and sets concrete minimum quality standards in the form of maximum parametric values. The background technical report (WHO 2017) notes that at levels exceeding 0.1 mg/L (100 µg/L), manganese in water supplies causes an undesirable taste in beverages and stains sanitary ware and laundry.

5.4 Supporting information in factsheet

Table 4. Summary of findings from data extraction for supporting information

#	Research question	Ref.	Response to Research Question
1	Does the selected guidance/guidelines identify any new information about: • what manganese is used for and how people might be exposed? • how manganese ends up in drinking water and what form it is in?	WHO 2021, 2022	WHO reports that: • Manganese occurs naturally in the environment and also from human activity. Higher levels can occur as a result of industrial discharges, under acidic or reducing conditions that are found in groundwater and in some lakes and reservoirs. • Food is the main source of dietary exposure to manganese and is estimated to range from 2 to 6 mg/day in adults. Manganese is ubiquitous in vegetable-based foods, particularly whole grains, nuts and rice, leafy vegetables, tea, seeds and legumes. • Bottle-fed infants may be at risk of high exposure from powdered formula which can be fortified with manganese, as well as the tap water used to prepare the formula. In addition, the relative immaturity of the hepatobiliary excretion of manganese in infants can increase the internal dose or body burden in this age group. • 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.

#	Research question	Ref.	Response to Research Question
			• 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). • 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. WHO also notes that the addition of chemicals during water treatment can contribute to the total manganese that must be managed in drinking water systems. 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). The main sources of manganese from treatment plant operations are: • the presence of manganese impurities in coagulants (principally ferric-based coagulants); • resolubilisation of Mn(II) from the reduction of manganese oxides stored in sedimentation basins as a result of anoxic conditions in the basin • the presence of dissolved manganese in recycle streams from solid-processing operations. Information in the updated WHO manganese factsheet (WHO 2022) includes: • Manganese can exist in 11 oxidation states, often as chloride, oxides and sulfates. The most common oxidation states for manganese in natural water are manganese(II) and manganese(IV). • Manganese compounds are additionally used in some locations for potable water treatment and can also be an impurity in coagulants used during water treatment. • Manganese occurs naturally in many surface water and groundwater sources, anthropogenic activities can also contribute to high levels. • Manganese occurs naturally in many food sources, and the greatest dietary exposure to manganese is usually from food.

#	Research question	Ref.	Response to Research Question
			Levels in fresh waters vary widely. They are typically in the range 1–200 µg/L. Higher levels are usually associated with groundwater, lakes and reservoirs under acidic or reducing conditions, or in aerobic waters with industrial pollution. Very high concentrations (up to 10 mg/L) have been reported in acidic groundwater. In treated drinking water, concentrations are typically less than 50 µg/L.
1		Health Canada 2019	Health Canada reports that: • Manganese occurs naturally and is widely distributed in the environment. It is present in air, food, consumer products, soil and drinking water; however, the main source of exposure is through diet with grains, nuts and vegetables contributing to most of the intake. Manganese is more readily absorbed from drinking water than when it is ingested with food. Intake of manganese from drinking water is not expected through either skin contact or inhalation. • Surface water and groundwater sources of manganese can be natural (from dissolution of manganese oxides, carbonates and silicates in soil and rock) and anthropogenic (from industrial discharges, mining activities and landfill leaching). Generally, manganese is more prevalent and found at higher concentrations in groundwater supplies. The physicochemical properties of the local environment influence the speciation and solubility of manganese in water, with pH and redox conditions most influential. In surface water, manganese occurs in particulate, colloidal, and dissolved forms, whereas manganese in groundwater is most often present in the dissolved Mn(II) form, as a result of low dissolved oxygen levels that result in the reduction of Mn(IV) into dissolved Mn(II). • Manganese is used in various industries (fertilizers, fungicides, cosmetics and paints) and may be added to water as an oxidising agent (permanganate) to remove iron, manganese and other reduced species or as an impurity in coagulants used to treat drinking water. • It is recommended that utilities establish a treated water goal of 0.015 mg/L or less for the design and operation of manganese treatment plants. Low levels of manganese in source or treated water (current or historic) may accumulate in the distribution system and periodically lead to high levels of manganese at the tap. In addition, 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. It is recommended that utilities develop a distribution system management plan to minimize the likelihood of manganese release events in the distribution system.

#	Research question	Ref.	Response to Research Question
1		EFSA 2023	EFSA reports that manganese can exist in a number of oxidation states, ranging from −3 to +7, with Mn^{2+} and Mn^{3+} being the predominant forms in biological systems. Manganese is found in nature in both inorganic and organic species. The inorganic forms include manganese dioxide (MnO_2), which is the most common naturally-occurring form, manganese dichloride ($MnCl_2$), manganese sulfate ($MnSO_4$), manganese phosphate ($MnPO_4$), manganese tetroxide (Mn_3O_4) and manganese carbonate ($MnCO_3$). Most manganese salts are readily soluble in water, with only phosphate and carbonate salts having lower solubilities. The manganese oxides are poorly soluble in water. In natural water, manganese is mostly present as soluble Mn^{2+} species. Depending on the pH and dissolved oxygen content in water, Mn^{2+} compounds may undergo oxidation, e.g. as a consequence of chlorination and ozonation (during water treatment) forming insoluble/particulate compounds such as manganese oxides, which can influence the organoleptic properties of water (Health Canada, 2019; WHO, 2021). In the EU, several manganese salts are authorised for addition to foods or use in food supplements. EFSA noted that the main food groups contributing to background manganese intake were grains and grain-based products (mainly bread and similar products and breakfast cereals), tea beverages and fruits (with highest contribution from banana) in all age groups, except for infants and toddlers, where, instead of the tea beverages, foods for the young populations (mostly cereal based products) were important contributors.
2	Does the selected guidance/guideline identify any new information about: • the current analytical methods used to measure/detect the concentration of manganese in water? • the indicators of the risks and how	WHO 2021, 2022	WHO reports that: • The US EPA has four recommended analytical methods for analysing total manganese in drinking water. These use inductively coupled plasma-atomic emission spectroscopy (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS) and graphite furnace atomic absorption (GFAA) spectroscopy; detection limits are 0.005– 50 µg/L. • A standardised analytical method, SM3125, uses ICP-MS and has a detection limit of 0.002 µg/L. • 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. • Limit of detection of 10–70 µg/L by colorimetric methods reported. • None of these methods distinguish between the different oxidation states of manganese.

#	Research question	Ref.	Response to Research Question
	this exposure can be measured? • the limits of quantification or limit of reporting for manganese in drinking water?		
2		Health Canada 2019	Health Canada notes that the US EPA currently has four recommended analytical methods for the analysis of total manganese in drinking water. The US EPA also recommends several methods developed by a voluntary consensus standard organization (US EPA 2014). The manganese concentration in drinking water can be determined using inductively coupled plasma-atomic emission spectroscopy, graphite furnace atomic absorption spectroscopy, inductively coupled plasma-mass spectrometry, air-acetylene atomic absorption spectroscopy, electrothermal atomic absorption spectroscopy. Some of these methods are not listed in the current Australian manganese factsheet. The limits of quantification of each method are also described. Total manganese is defined as the sum concentration of both the dissolved and particulate (suspended) fractions of a water sample and is analysed using methods to determine total recoverable manganese.
2		EFSA 2023	Not examined.
3	Does the selected guidance/guidelines identify any new information about the available options for removing manganese from drinking water?	WHO 2021, 2022	Manganese concentrations in drinking water can be easily lowered to less than 0.05 mg/L using several treatment methods, 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) in the source water (WHO 2021). WHO (2022) states that treatment methods to remove manganese will rely on a combination of processes (e.g. oxidation, adsorption, filtration) to remove both the dissolved and particulate forms. Reverse osmosis is the most effective and reliable treatment technology at the point of use; ion exchange media are also moderately effective and, when combined with greensand filtration, careful operation and maintenance, can also be used at the point of entry.

#	Research question	Ref.	Response to Research Question
			WHO (2022) also notes that control measures to minimize manganese release events in distribution systems include maintaining stable water chemistry and minimizing 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.
3		Health Canada 2019	Manganese may be added to water as an oxidising agent (permanganate) to remove iron, manganese and other reduced species or as an impurity in coagulants used to treat drinking water. Health Canada (2019) discusses a number of water treatment technology options and distribution system considerations in considerable detail.
3		EFSA 2023	Not examined.
4	Are there any new sections that should be added to the factsheet? Should anything be removed?		Not identified.

6. Discussion

A targeted review of recent guidance/guidelines assessing the safe level of manganese intake via drinking water or diet was undertaken with a view to adopting or adapting the advice of selected international agencies for the Australian context.

6.1 Suitability of existing guidance/guidelines for adoption/adaption

The guidance/guidelines selected for possible adoption/adaption in Australia were evaluated using the Assessment Tool outlined in Appendix A of the Research Protocol. This tool evaluates each document against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. Completed assessments for the selected guidance/guidelines are provided in Appendix A.

All three jurisdictions meet a high proportion of criteria which confers higher confidence in the evaluations underpinning the derivation of the guidance values from these agencies. All three guidelines were found to be suitable for adoption/adaption. EFSA (2023) met a higher proportion of criteria due to the use of systematic review methods when searching and evaluating the evidence.

6.2 Candidate health-based guideline values for manganese in drinking water

Candidate health-based guidance/guideline values for manganese for possible adoption/ adaption in Australia were evaluated against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. All three guidance/guideline documents were found suitable to adopt or adapt based on administrative and technical criteria for best practice guideline development. The analysis indicated slight differences in suitability of the candidate guidance/guideline values for adoption/adaption based on an assessment of administrative and technical characteristics of the identified guidance documents. Further analysis of the toxicological basis and methods used for deriving the different guidance values was also undertaken.

The following summary comments are made with respect to the toxicological basis and methods for the health-based guidance values for manganese cited or derived by the jurisdictions:

- Both drinking water guidelines (WHO 2022, Health Canada 2019) and the scientific opinion of EFSA (2023) on total dietary intake identify neurotoxicity as a critical human health effect.
- The drinking water guideline value for manganese published by WHO was derived from the LOAEL determined from four neonatal rat studies (representative of the most sensitive group) assessing the effects of 0, 25 or 50 mg Mn/kg bw/day (Kern and Smith (2010), Kern et al. (2011), Beaudin et al. (2013), Beaudin et al. (2017)). The drinking water guideline value for manganese published by Health Canada (2019) did not assess the newer study by Beaudin et al. (2017).
- All three agency assessments determined that epidemiology studies were insufficient to characterise a dose–response relationship to identify a reference point for manganese-induced neurotoxicity in humans.

- Infants and children are considered to have a greater sensitivity to manganese toxicity than adults. Infants are particularly vulnerable because of greater gastrointestinal absorption and immaturity of their homeostatic control of bile excretion, meaning that they excrete less manganese.
- WHO and Health Canada considered that bottle-fed infants were the most sensitive subpopulation at risk of developmental neurotoxicity. Health Canada (2019) noted that as infant formula represents the total diet in bottle-fed infants in the first few months of life, the main source of manganese exposure is due to both the water used to prepare the formula, as well as the fortified formula itself. As a result, both Health Canada (2019) and WHO (2022) estimated an intake allocation of 50% for manganese in drinking water for bottle-fed infants.
- The WHO (2022) drinking water guideline value for manganese is a provisional guideline value of 0.08 mg/L, due to the high level of uncertainty, as reflected in the composite uncertainty factor of 1,000. WHO consider this value to be protective of neurological effects in the most sensitive subpopulation (bottle-fed infants) and consequently the general population. The WHO guidance also notes that risks to infants arising from exceedance of the provisional guideline value may be mitigated by following WHO's recommendation for exclusive breastfeeding or, if not possible and supplementary feeding is required, an alternative safe drinking water source (e.g. bottled water that is certified by the responsible authorities) may be used to prepare infant formula (WHO 2022).
- Health Canada (2019) established a health-based guideline value for manganese in drinking water of 0.12 mg/L to protect the most sensitive subpopulation (i.e. bottle-fed infants) which is also protective for chronic exposure in children and adults.
- While EFSA (2023) reported that the available human and animal studies were considered sufficient to support neurotoxicity as a critical effect of excess dietary manganese intake, the data were not considered sufficient or suitable to characterise a dose-response relationship and identify a reference point for manganese-induced toxicity. This determination was based on methodological limitations identified through a critical appraisal of the evidence base. Safe levels of intakes for different age cohorts were determined based on estimated background dietary intakes of manganese amongst high consumers across European countries.
- WHO (2021) and Health Canada (2019) also considered the methodological limitations of the evidence base and have incorporated a high uncertainty factor (1,000) to provide a level of conservatism to the best available evidence so that their derived guideline values remain protective of human health.
- Potential adaption of the health-based guideline values for manganese in drinking water developed by WHO (2022) and Health Canada (2019) would result in a health-based guideline value of 0.1 mg/L (see Section 6.3).

Table 5. Summary of candidate health-based guidance/guideline values for manganese

Parameter	NHMRC and NRMMC (2011)	WHO (2022)	Health Canada (2019)	EFSA (2023)
Critical studies	N/A	Critical studies in rats: Kern and Smith (2010), Kern et al. (2011), Beaudin et al. (2013), Beaudin et al. (2017).	Critical studies in rats: Kern and Smith (2010), Kern et al. (2011), Beaudin et al. (2013)	N/A
Critical health effect	N/A	Developmental neurotoxicity	Developmental neurotoxicity	Neurotoxicity
Doses tested in critical studies	N/A	0, 25 and 50 mg Mn/kg bw/day	0, 25 and 50 mg Mn/kg bw/day	N/A
Point of departure	10 mg/day (WHO 1973)	LOAEL: 25 mg/kg bw/d	LOAEL: 25 mg/kg bw/d	N/A
Uncertainty factor	1,000 (10 UF_A, 10 UF_H, 10 UF_{LOAEL})	1,000 (10 UF_A, 10 UF_H, 10 UF_{LOAEL})	1,000 (10 UF_A, 10 UF_H, 10 UF_{LOAEL})	N/A
Average body weight	N/A	5 kg	7 kg	N/A
Average intake of water	2 L/day for an adult	0.75 L/day	0.75 L/day	N/A
Allocation for drinking water	0.1	0.5	0.5	N/A
Health-based guidance or guideline values (mg/day or mg/L)	0.5 mg/L	0.08 mg/L (provisional)	0.12 mg/L	Safe daily intake values for different age cohorts including: 2 mg/day (infants 4 -12 months) 8 mg/day (adults ≥ 18 yrs including pregnant and lactating women)

LOAEL = Lowest Observed Adverse Effect Level; UF_A = Uncertainty factor for extrapolation from animals to humans; UF_H = Uncertainty factor for human variability; UF_{LOAEL} = Uncertainty factor to account for the limited database and the use of a LOAEL instead of a NOAEL.

6.3 Calculation of potential health-based guideline value for manganese in Australian drinking water

Candidate health-based guideline value (mg/L) =

$$\frac{\text{animal dose (mg/kg bw/day) x body weight (kg) x proportion of intake from water}}{\text{volume of water consumed (L/day) x safety factor}}$$

= 25 mg/kg bw/day x 7 kg x 0.5 / (0.85 L/day x 1,000)

= 0.1 mg/L (rounded)

where:

- 25 mg/kg bw/day is the LOAEL identified in WHO (2021, 2022) and Health Canada (2019).
- 7 kg is the average body weight for an infant 0–<1 years (suggested average for screening risk assessments for 0–1-year-old age group, enHealth 2012).
- 0.85 L/day is the average amount of water consumed by an infant (suggested average for screening risk assessments for infants less than 6 months of age, based on the estimated daily volume of breast milk, enHealth 2012).
- 0.5 is the proportion allocation from drinking water for bottle-fed infants (assuming that infant formula represents the total diet for bottle-fed infants and that 50% of manganese intake may be due to the water used to prepare the formula with the remaining intake due to the infant formula itself.
- 1,000 is the uncertainty factor applied for interspecies variation (×10), intraspecies variation (×10), and the use of a LOAEL rather than a NOAEL (×10).

6.4 Candidate aesthetic guideline values for manganese in drinking water

The current Guidelines state that based on aesthetic considerations, the concentration of manganese in drinking water should not exceed 0.1 mg/L, measured at the customer's tap. This value is based on the level at which manganese precipitates can discolour water, stain laundry, form deposits in plumbing and alter palatability. The Guidelines suggest a discretionary target of 0.01 mg/L of manganese at the water treatment plant.

The following summary comments are made with respect to the justifications for lower aesthetic values set by other jurisdictions considered in this review and others considered relevant following Committee feedback:

- Health Canada (2019) have set an aesthetic objective of 0.02 mg/L (20 µg/L) intended to minimise the occurrence of discoloured water complaints based on the presence of manganese oxides and to improve consumer confidence in drinking water quality.
- The EU Drinking Water Directive (DWD) came into effect in January 2021 and Member States were required to transpose the Directive into national law and comply with its provisions by 12 January 2023. The DWD lists manganese concentrations of 0.05 mg/L

(50 µg/L) as a parametric indicator value for water discolouration and consumer acceptability (i.e. an aesthetic value). The DWD provides a general framework and sets concrete minimum quality standards in the form of maximum parametric values. The background technical report (WHO 2017) notes that at levels exceeding 0.1 mg/L (100 µg/L), manganese in water causes an undesirable taste in beverages and stains sanitary ware and laundry.

- The current USA EPA aesthetic guideline value for manganese in drinking water is 0.05 mg/L (50 µg/L). This aesthetic guideline is described in Secondary Drinking Water Regulations which are non-enforceable federal guidelines regarding cosmetic effects (such as tooth or skin discoloration) or aesthetic effects (such as taste, odour, or colour) of drinking water.
- WHO (2022) have not set an aesthetic guideline value but recommend that aesthetic as well as health aspects should be considered when setting regulations and standards for drinking water quality. The WHO recognises that insoluble manganese can cause aesthetic effects at 0.02 mg/L (20 µg/L).

7. Conclusions

Guidance/guidelines from three different jurisdictions were found to be suitable to adopt/adapt based on an assessment of the administrative and technical criteria described in Appendix A of the Research Protocol. There was general agreement across the available guidance/guideline documents from WHO (2021,2022), Health Canada (2019) and EFSA (2023) on the same critical health endpoint of neurotoxicity and in particular developmental neurotoxicity. WHO (2021, 2022) and Health Canada (2019) also derived similar drinking water guideline values using the same point of departure from key animal studies (i.e. a LOAEL of 25 mg/kg bw/day). In contrast, EFSA (2023) considered that there was insufficient evidence to derive a tolerable upper limit of intake based on adverse health effects in epidemiology and animal studies.

Potential adoption of the guidance value used by WHO and Health Canada of 25 mg/kg bw/day would result in a **new health-based guideline value for manganese of 0.1 mg/**L in drinking water. This is lower than the current Australian health-based guideline value of 0.5 mg/L.

In addition, some international jurisdictions have aesthetic guideline values that are lower than the current Australian aesthetic guideline value of 0.1 mg/L. The current Guidelines also recommend a discretionary target of 0.01 mg/L of manganese at the water treatment plant.

Most regions in Australia have manganese concentrations in distributed drinking water well below a health-based guideline value of 0.1 mg/L. There are, however, regions in Australia (e.g. regional areas in the NT) where concentrations of manganese in distributed drinking water can be high and exceedances of the current aesthetic and health-based guideline values have been observed (Water and Power Corporation 2023). Meeting a lower aesthetic or health-based guideline value in these regions will require additional treatment to ensure that water is safe and acceptable to consume. A health-based guideline value of 0.1 mg/L is readily measurable with current commercial analytical techniques.

8. Declared interests

The NHMRC team who undertook the targeted review of existing guidance/guidelines on manganese in drinking water have no conflicts of interest to declare.

Members of the Water Quality Advisory Committee did not declare any new interests relevant to this review:

9. Acknowledgements

NHMRC wishes to acknowledge the Water Quality Advisory Committee for feedback received on the draft evidence evaluation report.

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Report finalised April 2024

Appendix A: Assessment of existing guidance/guidelines

Administrative and technical criteria for assessing existing guidance or guidelines – WHO guidelines.

Criteria have been colour-coded to assess minimum requirements as follows: 'Must have', 'Should have' or 'May have'

Guideline reviewed:

Current WHO drinking-water quality guideline, chemical factsheet and associated supporting technical review of manganese in drinking water.

- WHO (2022) Guidelines for drinking-water quality: fourth edition incorporating the first and second addenda. Geneva: World Health Organization; 2022. (Guidelines)
- WHO (2021) Manganese in drinking-water. Background document for development of WHO Guidelines for drinking-water quality. Geneva, World Health Organization (WHO/HEP/ECH/WSH/2021.5). (Background document)

Criteria		Y/N/?/NA	Notes
	Overall guidance/advice development process		
	Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	Processes for guideline development are documented in WHO (2009) and WHO (2014).
	Are the administrative processes documented and publicly available?	Y	The rolling revision process to develop and revise the WHO *Guidelines for Drinking-water Quality* (GDWQ) is detailed in WHO (2009). It includes: • the process for revision and approval • functions of the Drinking-Water Quality Committee (DWQC), its working groups and coordinators • derivation of guidelines for chemical safety, guideline values and fact sheets.
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Overseen by the DWQC. All members of the DWQC and its working groups were invited to serve as individual scientists and not as representatives of any government or other organization (WHO 2009). The management of interests, including conflicts of interest, are detailed in WHO (2009).

Criteria		Y/N/?/NA	Notes
	Are funding sources declared?	Y	Financial contributions to the GDWQ are detailed in the Acknowledgements section of the WHO Guidelines (2022). Funding sources for the manganese background document are not declared.
	Was there public consultation on this work? If so, provide details.	Y	The draft background document on manganese was released for public comment. Changes to guideline values or new guideline values developed during the rolling revision process are released for public consultation. A truncated chemical review document (including the guideline value and identification of the critical study) is made available for public comment for 3–6 months in parallel with expert peer review of the draft background technical document (WHO 2009). The final draft background document is then made available for public comment for an additional 6 weeks to 3 months.
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	The draft background document on manganese was provided to several scientific institutions and selected experts for peer review and the revised draft was submitted for final evaluation at expert consultations *(*WHO 2021). Additionally, all 6 WHO regional offices participated in the process of the latest revision to the GDWQ, in consultation with Member States (WHO 2022). The peer review outcomes are not made available publicly, however are retained by the WHO Secretariat (WHO 2009).
	Was the guidance/advice developed or updated recently? Provide details.	Y	The background document evaluating the risks to human health from exposure to manganese in drinking water was published in 2021 (WHO 2021). The recommendations from the review were incorporated into the current edition of the GDWQ (WHO 2022).
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Details regarding evidence review scope and parameters are not reported in the manganese background document (WHO 2021); however, some details about the scope, definitions and application of the guidelines are provided in WHO (2009).

Criteria		Y/N/?/NA	Notes
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	Y	Not specified in the manganese background document (WHO 2021). There is a preference for data in the public domain that is published in peer-reviewed literature. For derivation of chemical guideline values, they should meet well-defined content and data presentation criteria and informed by well-conducted studies (WHO 2009).
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	The background document (WHO 2021) did not provide details on the review methodology used.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	N/A	Use of unpublished proprietary data is usually limited to the evaluation of pesticides, and only when the data have undergone evaluation and peer-review by a WHO body or by a similar recognized, international organisation (WHO 2009). All references cited appear to be available to the public.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N/A	The background document (WHO 2021) did not provide details on the review methodology used.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Preparation of the background document included consideration of information available in previous risk assessments carried out by the International Programme on Chemical Safety (Environmental Health 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. WHO (2022) considers that these international organisations apply high levels of rigour in their risk assessment processes and scientific literature reviews which are subsequently peer reviewed by panels of international experts prior to approval and publication. The risk assessments are relied upon except where new information justifies a reassessment, but the quality of new data is critically evaluated before it is used in any risk assessment.

Criteria		Y/N/?/NA	Notes
	Can grey literature such as government reports and policy documents be included?	Y	Grey literature is considered in the background document for manganese in drinking water (WHO 2021). WHO (2022) states that where international reviews are not available, other sources of data are used in the derivation of guideline values, including published reports from peer-reviewed open literature, national reviews recognized to be of high quality, information submitted by governments and other interested parties and, to a limited extent, unpublished proprietary data (primarily for the evaluation of pesticides).
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	The relevant toxicological data and reasons for selecting the most sensitive endpoint for guideline derivation is detailed in the background document (WHO 2021).
	Evidence search		
	Are databases and other sources of evidence specified?	N	Not reported.
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	N/A	The background document (WHO 2021) did not provide details on the review methodology used. The references cited in the background report are peer-reviewed published scientific studies or risk assessments undertaken by international agencies.
	Is it specified what date range the literature search covers? Is there a justification?	N	Not specifically reported, although it is reasonable to assume that the review considered evidence published since the last reassessment of the guideline value for manganese which was published in the GDWQ in 2017.
	Are search terms and/or search strings specified?	N	The background document (WHO 2021) did not provide details on the review methodology used.
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	N	The background document (WHO 2021) did not provide details on the review methodology used.

Criteria		Y/N/?/NA	Notes
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	The background document did not detail any systematic review methodology, such as assessing risk of bias. It is unclear if a risk of bias assessment was completed for individual studies, however some analysis of study quality was included where relevant.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	This peer-reviewed scientific report was not based on systematic review methodology.
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	Y	WHO (2021) details the relevant evidence and discusses the results from an overall weight of evidence viewpoint to develop recommendations (guidelines) and derive a provisional guideline value.
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	Y	WHO (2021) provides justification for the uncertainty factors chosen to derive the provisional guideline value for manganese.
	Are the parameter value assumptions documented and explained?	Y	Assumptions used in the derivation of the provisional guideline value reported in background document (WHO 2021).
	Are the mathematical workings/algorithms clearly documented and explained?	Y	Derivation of the provisional guideline value clearly outlined in background document (WHO 2021).
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	Y	The background document (WHO 2021) discusses several other considerations for the management of manganese in drinking water, including feasibility of treatment processes.

Criteria		Y/N/?/NA	Notes
	Is there documentation directing use of mechanistic, mode-of-action, or key events in adverse outcome pathways in deriving health-based guideline values?	N	WHO (2021) considered mode of action in the assessment of manganese toxicity; however, it was noted that the principal mode-of-action for manganese neurotoxicity (the critical health endpoint) had not been clearly established. WHO policy on how mode-of action is considered is provided in WHO (2009).
	What processes are used when expert judgement is required and applied? Is the process documented and published?	Y	Peer review, public consultation, expert review by the Drinking-Water Quality Committee (DWQC) and consultation with international water experts at meetings held from 2017-2021 all informed the updated recommendations (WHO 2009, 2021). No details on consultation processes are reported in WHO (2021).
	Is dose response modelling (e.g. BMDL) routinely used?	N/A	WHO derived the manganese provisional guideline value using a LOAEL identified from several animal studies. The WHO policy on BMDL is outlined in WHO (2009).
	What is the organisation's policy for dealing with substances for which a non-threshold mode-of-action may be applicable in humans? Has the policy been articulated and recorded?	N/A	Relevant chemical (manganese) exhibits a threshold dose response. The WHO policy on non-threshold substances is outlined in WHO (2009).
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	N/A	WHO (2021) states that there is insufficient evidence to assess potential carcinogenicity from oral exposure to manganese in humans. The level of cancer risk used by WHO is reported in WHO (2009).

The criteria are assigned to one of the following categories:

- '**Must have**': These are elements regarded as essential to meet the 'minimum threshold' for good practice, thereby placing that organisation's work into a candidate pool to consider when updating the ADWGs.
- '**Should have**': Elements considered part of international best practice which contribute to robustness of the process and facilitate third party participation. They are, however, not essential for considering adaption of organisation's deliberations for use in Australia as these elements for a particular HBGV can be undertaken in Australia if required.
- '**May have**': Elements that contribute to transparency but are not vital for delivering a robust 'fit for purpose' outcome as they do not directly impinge on the veracity of the actual guideline value, or third-party ability to independently review the HBGV or DWG, should that be necessary.

References:

WHO (2009). *WHO Guidelines for Drinking-water Quality. Policies and Procedures used in updating the WHO Guidelines for Drinking-water Quality*. World Health Organization, Geneva 2009. WHO/HSE/WSH/09.05.

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WHO (2021) Manganese in drinking-water. Background document for development of WHO Guidelines for drinking-water quality. Geneva, World Health Organization (WHO/HEP/ECH/WSH/2021.5). (Background document)

WHO (2022). Guidelines for drinking-water quality: fourth edition incorporating the first and second addenda. Geneva: World Health Organization; 2022. https://www.who.int/publications/i/item/9789240045064 (Guidelines)

Date of assessment: 24/11/2023, updated 21 February 2024. Undertaken by the Environmental Health Team, NHMRC.

Administrative and technical criteria for assessing existing guidance or guidelines – Health Canada guidelines

Criteria have been colour-coded to assess minimum requirements as follows: 'Must have', 'Should have' or 'May have'

Guideline reviewed:

- Health Canada (2019). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Manganese. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. (the Guideline)

Criteria		Y/N/ ?/NA	Notes
	Overall guidance/advice development process		
	Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	Similar to Australian processes, Health Canada's Water Quality and Health Bureau prepares a guideline document which outlines the latest research on the health effects associated with the contaminant, Canadian exposure to the contaminant, and treatment and analytical considerations. The technical document and a proposed guideline value are peer-reviewed by external experts, reviewed by the Federal-Provincial-Territorial Committee on Drinking Water (CDW) and undergo a public consultation.
	Are the administrative processes documented and publicly available?	Y	Details on the administrative processes used by Health Canada are provided in multiple publications. Refer to reference list below.
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	The Federal-Provincial-Territorial Committee on Drinking Water (CDW). Health Canada provides scientific and technical expertise to the Committee and coordinates its activities. The CDW reports to the Federal-Provincial-Territorial Committee on Health and the Environment (CHE) which is also responsible for final approval of the Guideline. Management of conflicts of interest is not described or reported online.
	Are funding sources declared?	N	Funding is not described but is likely to be supported by the Federal, Provincial and Territorial agencies/partners involved in Guideline development and described above.

Criteria		Y/N/ ?/NA	Notes
	Was there public consultation on this work? If so, provide details.	Y	Public consultation was undertaken online from June 3 to August 5, 2016.
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	The technical document and a proposed guideline value are peer-reviewed by external experts and reviewed by the Federal-Provincial-Territorial Committee on Drinking Water (CDW). The peer reviewed Guideline was published online on 10 May 2019, specific details of the peer review process are not published but may be available from Health Canada upon request.
	Was the guidance/advice developed or updated recently? Provide details.	Y	The peer reviewed Guideline was published online on 10 May 2019.
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	The scope and parameters of the evidence review underpinning the Guidelines are not reported.
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	?	Preferences for data sources were not reported.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	No information on the methods used to evaluate the evidence were reported.

Criteria		Y/N/ ?/NA	Notes
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	The Guidelines incorporate proprietary information about the concentrations of manganese found in Canadian waters and reported by the responsible government agency in different provinces and territories and a single confidential study undertaken for Health Canada by NSF International on drinking water treatment system testing. These references are cited as personal communications from relevant agencies in the technical document.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	No inclusion/exclusion parameters were reported.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	The health-based and aesthetic guideline values from international guidelines were considered and cited in the Guidelines but processes used to critically assess these values are not described.
	Can grey literature such as government reports and policy documents be included?	Y	Grey literature such as international and Canadian agency reports examining manganese levels in source waters are cited in the technical document.
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	The Guidelines discuss the relevant toxicological data (animal and human) and reasons for selecting the most sensitive endpoint for guideline derivation.
	Evidence search		
	Are databases and other sources of evidence specified?	N	No information on the databases searched was provided.

Criteria		Y/N/ ?/NA	Notes
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	N/A	No information on the databases searched was provided. The references cited in the Guidelines include peer-reviewed published scientific studies, risk assessments undertaken by international agencies and government reports.
	Is it specified what date range the literature search covers? Is there a justification?	N	A date range for the evidence review is not reported.
	Are search terms and/or search strings specified?	N	No details provided.
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	N	No details reported.
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	Risk of bias assessment of individual studies was not reported.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	Details on the evidence review methods were not reported.
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	Y	The Guideline details the relevant evidence and discusses the certainty of the results from an overall weight of evidence viewpoint to develop recommendations.
	Derivation of health-based guideline values		

Criteria		Y/N/ ?/NA	Notes
	Is there justification for the choice of uncertainty and safety factors?	Y	The Guidelines state why each uncertainty factor is used in the guideline derivation.
	Are the parameter value assumptions documented and explained?	Y	Assumptions for the derivation of the guideline value are reported.
	Are the mathematical workings/algorithms clearly documented and explained?	Y	Details of the derivation of the guideline value are reported.
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	Y	The Guidelines discuss several other considerations for the management of manganese in drinking water, including feasibility of treatment processes, distribution system management plans and water management at a residence e.g. if household water is accessed from a well.
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	Scientific evidence for the mode-of-action of manganese is considered in the Guidelines.
	What processes are used when expert judgement is required and applied? Is the process documented and published?	Y	As per processes reported by Health Canada, the technical document and the proposed guideline value were peer-reviewed by external experts, reviewed by the Federal-Provincial-Territorial Committee on Drinking Water (CDW) and underwent public consultation. In addition, experts are called to give presentations on the proposed guideline when the CDW meets.
	Is dose response modelling (e.g. BMDL) routinely used?	N/A	Benchmark dose analysis was not possible for this risk assessment because only two doses were tested in the three animal studies that underpin the risk assessment.
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	N/A	The relevant chemical (manganese) was found to exhibit a threshold dose response. Approaches for dealing with non-threshold chemicals are described in the relevant guidelines.

Criteria		Y/N/ ?/NA	Notes
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	N/A	The Guidelines selected a non-cancer endpoint for the risk assessment and derivation of a guideline value as the review found that existing studies were inadequate to determine whether manganese could be carcinogenic.

References:

- Health Canada (2019). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Manganese. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-manganese.html
- Health Canada (2022). Guidelines for Canadian Drinking Water Quality. Summary Tables. Published September 2022, accessed 30/11/2023. (The *Guidelines for Canadian Drinking Water Quality* comprise a series of guidelines for different chemical and microbiological parameters that are updated regularly by Health Canada in these summary tables. The tables summarise the values and key information from each of the underpinning guidelines). https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html
- Health Canada (2023). Water Quality - Reports and Publications Accessed 30/11/2023 https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality.html
- Health Canada (2023). Federal-Provincial-Territorial Committee on Drinking Water (CDW). Accessed 30/11/2023. https://www.canada.ca/en/health-canada/services/environmental-workplace-health/water-quality/drinking-water/federal-provincial-territorial-committee-drinking-water-health-canada.html
- Health Canada (2023). Canadian Drinking Water Guideline – summary webpage. Accessed 30/11/2023. https://www.canada.ca/en/health-canada/services/environmental-workplace-health/water-quality/drinking-water/canadian-drinking-water-guidelines.html
- Health Canada (2023). Environment and workplace health consultations. Accessed 30/11/2023. https://www.canada.ca/en/health-canada/services/environmental-workplace-health/consultations.html
- Health Canada (2023). Prioritization process for the development of guidelines for Canadian Drinking Water Quality. Accessed 30/11/2023. https://www.canada.ca/en/health-canada/services/environmental-workplace-health/water-quality/drinking-water/prioritization-process-development-guidelines.html

Administrative and technical criteria for assessing existing guidance or guidelines – EFSA guidelines

Criteria have been colour-coded to assess minimum requirements as follows: 'Must have', 'Should have' or 'May have'

Guideline reviewed:

- EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.-I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Bornhorst, J., Cubadda, F., Dopter, A., FitzGerald, R., de Sesmaisons Lecarré, A., das Neves Ferreira, P. Fabiani, L., Horvath, Z., Matijević, L., Naska, A. (2023). Scientific opinion on the tolerable upper intake level for manganese. EFSA Journal, 21(11), e8413. https://doi.org/10.2903/j.efsa.2023.8413 First published: 08 December 2023
- Halldorsson, T.I., Birgisdottir, B.E., Dudele, A., Christensen, J.J., Thorisdottir, B. 2023. Preparatory work for the update of the tolerable upper intake levels for manganese. EFSA supporting publication 2023:EN-8193. 137 pp. published online 31 August 2023. doi:10.2903/sp.efsa.2023.EN-8193, https://www.efsa.europa.eu/en/supporting/pub/en-8193 (External Scientific Report by Halldorsson et al. University of Iceland and University of Oslo).

Criteria		Y/N/?/NA	Notes
	Overall guidance/advice development process		
	Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	Several of the key steps used to develop guidance by the European Food Safety Authority (EFSA) are compatible with Australian processes, including: • contracting independent evidence reviews through a competitive tender process • undertaking comprehensive risk assessments supported by systematic reviews • using a research protocol to inform the review process • undertaking public consultation.
	Are the administrative processes documented and publicly available?	Y	Details on EFSA's administrative processes are available at https://www.efsa.europa.eu/en/science/methodology
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	The EFSA Panel on Nutrition, Novel Foods and Food Allergens (the Panel), one of 11 expert scientific committees, is responsible for updating the Tolerable Upper Intake Level (UL) for manganese for the European Commission. The Panel was supported by the EFSA Nutrition Unit and by the Working Group on Upper Levels. EFSA sets up a Working Group of experts to carry out the risk assessment, which generally consists of members of the Panel plus additional scientists from specialist

Criteria		Y/N/?/NA	Notes
			fields (https://www.efsa.europa.eu/en/howwework/workingpractices). Additional experts on manganese that supported the review are named in the Scientific Report (EFSA 2023). The working group develops a draft and submits it to the Panel for discussion. Following public consultations on draft outputs comments are considered and outcomes reflected in the revised document. The expertise of the Panel and its members is described online: https://www.efsa.europa.eu/en/science/scientific-committee-and-panels/nda Declarations of conflicts of interest by Panel members are also reported online https://open.efsa.europa.eu/scientific-panel/8
	Are funding sources declared?	Y	The independent scientific review was undertaken with funding from the European Food Safety Authority following a tender process (Halldorsson et al. 2023).
	Was there public consultation on this work? If so, provide details.	Y	The draft Scientific Opinion was released for public consultation from 29 August 2023 to 10 October 2023. The outcome of the public consultation is described in a technical report (EFSA 2023).
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	Preparatory work to address sQ1 to sQ4 has been provided by a contractor and, subsequently, a technical report was published (Halldorsson et al., 2023). The technical report served as the primary source of information for this assessment, however, the Panel conducted an independent evaluation of the evidence and adapted the outcome of the contractor's work, where considered appropriate. The technical report describes the collection and appraisal of scientific evidence for manganese as described in the research protocol and was undertaken by an independent contractor. The publication of the technical report does not represent the position/endorsement of EFSA but rather to maintain transparency in their processes.
	Was the guidance/advice developed or updated recently? Provide details.	Y	The Panel of external scientific experts from across Europe published their scientific opinion on the safe levels of manganese uptake on 8 December 2023 (EFSA 2023).
	Evidence review parameters		

Criteria		Y/N/?/NA	Notes
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	Y	Article 6 of Regulation (European Commission, EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods and Article 5 of Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements provide that maximum amounts of vitamins and minerals added to foods and to food supplements respectively, shall be set. These provisions lay down the criteria to be taken into account when establishing these maximum amounts that include the upper safe levels (ULs) of vitamins and minerals established by scientific risk assessment based on "generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different groups of consumers". Further details about the scope and interpretation of the European Commission's directive are described in EFSA (2023). Details about the scope, definition and evidence review parameters provided by EFSA are summarised in the *High Level protocol for the Scientific Opinion on the revision of the Tolerable Upper Intake Level (UL) for manganese* and is attached as Annex A in the online supporting information for the published technical report (Halldorsson et al. 2023) and as Annex A of the published Scientific Opinion (EFSA 2023).
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards? (*e.g. GLP, OECD test guidelines*)	Y	EFSA (2009) guidance provides advice on the quality of data and data sources and also the considerations for the inclusion and exclusion of data.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	Y	Two systematic reviews were conducted to assess the relationship between 'high' manganese oral exposure and neurological effects in i) humans (all life-stages) and ii) animals (mammals) and all methods are documented clearly (Halldorsson et al. 2023; EFSA 2023). In addition, narrative reviews were conducted on some research questions. The methods used are documented in Halldorsson et al. (2023). EFSA's Scientific Opinion outlines the processes involved in evidence retrieval, study selection and data extraction (EFSA 2023).

Criteria		Y/N/?/NA	Notes
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	Food intake data from the EFSA Comprehensive European Food Consumption Database and data on manganese content in foods from the EFSA food composition database as available in 2022 were used. Unpublished data taken under consideration were cited where relevant.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	Y	Details for inclusion and exclusion criteria for human and animal studies are described in Halldorsson et al. (2023), with justification for exclusion of studies provided. EFSA's Scientific Opinion outlines the processes involved in evidence retrieval, study selection and data extraction (EFSA 2023).
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Relevant risk assessments performed by other EU or international bodies can be used, provided a comprehensive description of all data, processes and methods is available. The relevance of the assessment in light of more recent data is also considered (EFSA 2009). The Panel considered risk assessments by international agencies (EFSA 2023).
	Can grey literature such as government reports and policy documents be included?	N/A	Grey literature and unpublished studies were not searched nor reviewed in the independent scientific review for the Tolerable Upper Intake Level (UL) for manganese (Halldorsson et al. 2023). Grey literature (e.g. government reports and policy documents) may be taken into account by the Panel in developing their Scientific Opinion for manganese uptake however there are no references to these in the published scientific opinion (EFSA 2023).
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	In consultation with a panel of qualified experts on manganese and after discussion by the Upper Levels Working Group, neurotoxicity was identified as priority adverse health effect for the risk assessment, i.e. the one that is expected to play a critical role for establishing an upper level. Following the data review the Panel retained neurotoxicity as the critical effect of excess manganese dietary intake. Overall, the Panel considered that available human and animal studies support neurotoxicity as a critical effect of excess dietary intake of

Criteria		Y/N/?/NA	Notes
			manganese. However, data were not sufficient and suitable to characterise a dose–response relationship and identify a reference point for manganese-induced neurotoxicity. The Panel relied on data of manganese intake across EU subpopulations and data on the manganese content of foods to determine safe levels of manganese intake.
	Evidence search		
	Are databases and other sources of evidence specified?	Y	Systematic searches of the literature were undertaken in MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials (EFSA 2023). The evidence sources for the narrative reviews undertaken were based on grey literature such as several agency reports, together with non-systematic literature review searches by authors in SCOPUS and PubMed performed in October-November 2022 (Halldorsson et al. 2023)
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	Y	Multiple scientific databases were searched (EFSA 2023).
	Is it specified what date range the literature search covers? Is there a justification?	Y	The Scientific Opinion notes that no limitation on publication date was applied for the systematic reviews (EFSA 2023). Specific date ranges searched were summarised in the technical report of the literature searches (Halldorsson et al. 2023).
	Are search terms and/or search strings specified?	Y	Search strategies are documented in Halldorsson et al. (2023).
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	Y	Other exclusion criteria were reported, e.g. only papers written in English were reviewed (EFSA 2023).
	Critical appraisal methods and tools		

Criteria		Y/N/?/NA	Notes
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	Y	EFSA (2023) assessed the internal validity of eligible studies using OHAT risk of bias tools (OHAT/NTP, 2015) by two independent reviewers. The outcome of the appraisals were reported in EFSA (2023). The critical appraisal tools for either human or animal studies was provided in Halldorsson et al. (2023).
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	Y	The methods used for evidence synthesis were reported in EFSA (2023). However, the evidence from both human and animal studies was not considered suitable for meta-analysis in the independent scientific report (Halldorsson et al. 2023).
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	Y	EFSA (2023) reported that the certainty in the body of evidence was assessed based on the quality of the human and animal studies, taking into account the risk of bias assessments and other uncertainties identified using the framework for assessing certainty outlined in OHAT/NTP (2019).
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	N/A	EFSA are not responsible for deriving health-based guideline values for drinking water in the European Union. EFSA does however provide guidance on the use of uncertainty factors (EFSA 2018). Uncertainty factors and safety factors were not required for this assessment as animal and human studies of manganese intake were not used to derive health-based guidelines, rather safe levels of intake were determined from estimates of background dietary intakes amongst high consumers (95th percentile) in different age groups.
	Are the parameter value assumptions documented and explained?	N/A	As above
	Are the mathematical workings/algorithms clearly documented and explained?	N/A	As above
	Does the organisation take into consideration non-health related matters to account for	N/A	As above

Criteria		Y/N/?/NA	Notes
	feasibility of implementing the guideline values (e.g. measurement attainability)?		
	Is there documentation directing use of mechanistic, mode-of-action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	The Panel determined that the molecular and cellular mechanisms underlying detrimental effects of manganese on the nervous system remain poorly understood, although several mechanisms have been proposed and studied (EFSA 2023).
	What processes are used when expert judgement is required and applied? Is the process documented and published?	Y	As noted above, the Panel and its expert working group are responsible for the recommendation of a Tolerable Upper Level of manganese but not a health-based guideline value for drinking water for the EU. The systematic and narrative reviews provided in the independent scientific report were provided to support the working group to develop a scientific opinion for the purposes of setting a Tolerable Upper Level of manganese. EFSA provides detailed guidance on the processes for expert judgement on their website (https://www.efsa.europa.eu/en/methodology/evidence) and in EFSA (2015) Scientific report on Principles and process for dealing with data and evidence in scientific assessments.
	Is dose response modelling (e.g. BMDL) routinely used?	Y	The proposed methods to characterise dose-responses for different health outcomes and proposes data modelling are detailed in the research protocol (EFSA 2023). However, the scientific opinion of the Panel assessed the available evidence in human and animal studies as insufficient to determine a dose-response for manganese neurotoxicity.
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	N/A	EFSA (2023) determined that manganese exhibits a threshold dose response and is also an essential element in human diets.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	N/A	The evidence for carcinogenicity was not reviewed in this technical report.

References:

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