Evidence evaluation for *Australian Drinking Water Guidelines* chemical factsheet – Manganese (Research Protocol Stage 1 – initial targeted review/adopt-adapt)

Organisation

National Health and Medical Research Council (NHMRC).

Team

NHMRC Environmental Health team with advice from the Water Quality Advisory Committee (the Committee).

Contact

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Date protocol completed

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Contents

Background

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 discolours water and can stain laundry and plumbing fixtures) 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.

Public health authorities in the Northern Territory requested that NHMRC 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. The European Food Safety Authority (EFSA) published a scientific opinion on the tolerable upper intake level for manganese in December 2023 (EFSA 2023).

Based on the changes in international advice, 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.

A preliminary search by NHMRC for international drinking water quality guidelines published in English in the past 5 years did not identify any other guidance/guidelines presenting health-based guideline value recommendations for manganese concentrations in drinking water. Given the currency of the reviews recently undertaken by WHO (2021), EFSA (2023) and Health Canada (2019), it was considered appropriate to undertake an initial targeted review of the identified guidelines in-house to determine if they are suitable to adopt/adapt for the Australian context. Further review can be undertaken as required if advised by the Committee and depending on available resources.

Objectives of the review

To consider recent guidance or guidelines published by WHO and Health Canada on the human health impacts of manganese intake via drinking water and by EFSA on tolerable upper intake levels for manganese, and to consider adopting or adapting this advice and associated health-based guideline values in Australia.

Information provided in these guidance/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).

Methods

This review will be 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 review of selected guidance/guidelines provided by WHO (2021, 2022) and Health Canada (2019) will be conducted (includes existing health-based guideline values and associated recommendations in guidelines for drinking water and/or appropriate guidance values that can be used to derive drinking water guideline values). The recently published EFSA Scientific opinion on the safe tolerable upper dietary intake level for manganese (EFSA 2023) will also be considered to support this review.

- The relevant data from selected guidance/guidelines will be 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 will be extracted and considered for updating the supporting information sections in the current factsheet.

The overall approach to reviewing different sections of the current factsheet is summarised in the table below:

Section of factsheet	Key steps
Health-related advice in chemical factsheet including: • Health-based guideline value • Aesthetic guideline value • Health considerations • Typical Australian exposure levels* • Derivation of guideline value	• Assess suitability of existing guidance/guidelines published by WHO (2021, 2022) and Health Canada (2019) including health-based guideline values or other relevant guidance values (if applicable) that can be adopted/adapted for drinking water using the Assessment Tool provided by NHMRC (see **Appendix A**). Assess recent EFSA scientific opinion (2023) to support review findings. • Summarise findings including the derivation of any potential options for guideline values and seek the advice of the Committee. • Report details of methods used to evaluate existing guidance/guidelines and derive any potential options for guideline values.
Supporting information in chemical factsheet including: • General description • Measurement (analytical methods) • Treatment options	• Review existing factsheet information and extract any relevant new information published by WHO (2021, 2022) and Health Canada (2019). Information from EFSA (2023) may also be considered if found relevant. • Summarise findings and seek the advice of the Committee.
* Australian exposure levels are not anticipated to be critically evaluated but the data are considered when evaluating risk of harm for the Australian setting and are often presented as a typical concentration range in a chemical factsheet. This information will be handled in a similar manner to the supporting information. This information is also not anticipated to be available in the selected guidance/guidelines but can be updated using other sources as required.	

The methods outlined below will govern the assessment and reporting of the evidence selected to inform the update to the manganese chemical factsheet.

Any changes to the Research Protocol, once finalised with input from the Committee, will be recorded and documented.

Health-related advice in factsheet

Research questions

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?	

Evidence review for health-related advice in factsheets

Criteria for considering existing guidelines/guidance

Guidelines considered for adopt/adapt approach	Selected guidance/guidelines on manganese published by WHO (2021, 2022), Health Canada (2019) and EFSA (2023) will be considered. The selected guidance/guidelines will be assessed against the applicable criteria outlined in the Assessment Tool in **Appendix A**.
Population	Humans, including the general population, as well as specific populations who may be at higher risk of adverse health outcomes such as:

	• Infants and children • People who are pregnant • Aboriginal and Torres Strait Islander peoples • People with pre-existing health conditions • People who ingest higher than average amounts of water (e.g. tropical locations, outdoor workers) ☒ Animals or cells as surrogates for human exposure (note that animal or *in vitro* studies should only be considered if there are insufficient human data to answer the research questions)
Exposure	The chemical/s of interest: • manganese Exposure parameters that will be considered for manganese include: • Exposure over a lifetime • Short-term exposure (e.g. over days or weeks during a water contamination event) including during critical time periods (e.g. pregnancy, *in utero*, childhood) • Exposure through drinking, cooking, washing, skin contact • Variants, specific chemicals within a group, etc. • Combination or reaction with other substances
Comparator(s)	In most cases, for the purposes of the Guidelines, the review will be used to determine whether an existing health-based guideline value(s) in the factsheet should be changed, so comparisons between the current value and higher/lower values would be of interest. Alternatively, comparisons between any higher and lower doses at different incremental levels would be of interest.
Outcome(s)	The human health outcomes of concern from exposure to manganese include: • Mortality • Severe human health outcomes, including incidence of life-threatening illness, disability or chronic disease with ongoing impact on quality of life. • Less severe or short-term human health outcomes, e.g. irritation. Consideration regarding these outcomes will be given to: • The level of manganese in drinking water considered to be acceptable to human health over a lifetime • If deemed relevant from the information reviewed, the level of manganese in drinking water considered to be acceptable to human health during a short-term exposure event

	• The level of manganese in drinking water considered to be acceptable in relation to aesthetic factors, for example taste, smell, colour, clarity, etc.
Guidelines considered for adopt/adapt approach	Recent guidance/guidelines from the following sources will be considered: ☒ World Health Organization (WHO) ☒ European Food Safety Authority (EFSA) ☐ United States Environmental Protection Agency (US EPA) ☐ US Agency for Toxic Substances and Disease Registry (ATSDR) ☐ Californian Office of Health and Hazard Assessment (OEHHA) ☐ Food Standards Australia New Zealand (FSANZ) ☐ Australian Pesticides and Veterinary Medicine Authority (APVMA) ☐ Other Australian agencies. ☒ Other international agency (Health Canada) ☒ Other relevant sources for updating information for the Australian context (e.g. typical Australian concentrations of manganese in drinking water, community preferences for aesthetics) (selected water agency reports, Australian Industrial Chemicals Introduction Scheme)
Limits:	We will include: ☒ Publicly available documents of the selected guidance/guidelines ☒ Publicly available evidence reviews or publications supporting the selected guidance/guidelines (near publication and consultation drafts will be accepted if available). ☒ Key publications as advised by the Committee to support the review as required, ☐ Other We will exclude: ☒ Guidance/guidelines in languages other than English ☒ Superseded guidelines unless requested (i.e. only the most current organisational guideline should be assessed in the first instance)

Data extraction and synthesis

Expertise	☒ Data extraction will be performed by the NHMRC Environmental Health Team. ☐ Data extraction will be performed by members of the Committee. ☐ Other
Data to be extracted from existing guidance/guidelines (if available)	☒ Guideline details (e.g. developing organisation, citation information, date of publication, date of evidence search used for underpinning review). ☒ Information on administrative/technical criteria as outlined in the Assessment Tool for each guidance document/guideline under consideration (see **Appendix A**). ☒ Health-based guideline values or equivalent guidance value for manganese (including any formulae or safety margins incorporated into the calculation of the values). ☒ Aesthetic guideline values for manganese (including any justifications provided). ☒ Outcomes/critical health effects used to inform the recommendation, including any thresholds for acceptable risk used. ☒ Information relevant to answering the research questions. ☒ Information relevant to decision making (e.g. community values and preferences, resources or cost, impacts on equity, acceptability and feasibility). [This will allow the Committee to identify areas where the existing recommendations may or may not be applicable to the Australian context and the Guidelines]. ☒ Information on the applicability of the guideline to the Australian context (e.g. setting and population, any issues with supporting evidence such as geographical or infrastructure differences, including to remote and tropical areas). [This will allow the Committee to assess whether there are barriers or the need for additional factors before the recommendations could be adopted in Australia, see https://www.nhmrc.gov.au/guidelinesforguidelines/plan/adopt-adapt-or-start-scratch.] ☒ Any considerations or health outcomes noted in the guidance/guideline that appear not to be addressed in the current version of the Guidelines, or vice versa ☐ Other

Data to be extracted from key studies underpinning the guidance/guidelines	☒ Relevant details on the review/study used to derive the selected guidance/guideline value [including key study design aspects and measured outcomes, uncertainty factors and any assumption values used] ☒ Population, setting, exposure, comparison and outcome characteristics (PECO) of the study ☒ Data relevant to answering the research questions. ☒ Other relevant information that should be considered by NHMRC and the Committee
Data extraction methods	☒ Single, no second reviewer ☐ Dual; second reviewer checks [all data or proportion] Note that internal review and Committee processes will include review of all extracted information.
Synthesis	☒ Results will be tabulated, grouping together information of relevance to each research question. ☒ Synthesis will be conducted to convert international values into Australian equivalent. The following tables will be presented: ☐ Table to compare guideline characteristics e.g. developing organisation, setting, context, PECO characteristics / study design features. ☒ Table of potential guideline options, health-based guidance/guidelines values (with calculated Australian equivalent for drinking water) for the specified chemical, with associated additional considerations and assumptions. ☒ Table summarising findings of Assessment Tool (**Appendix A**) against all included guidelines [e.g. heat map comparing performance of each guidance document against the assessment criteria to demonstrate areas of uncertainty] ☐ Table to compare PECO characteristics/key study design features ☐ Table of extracted numerical data for compilation of meta-analyses. Where multiple eligible numerical results are reported from a single study, all will be reported. ☐ Other
Overall confidence in results	☒ Determination of suitability of existing guidance/guidelines for adoption/adaption in the Australian context ☒ Overall confidence in body of evidence or key studies used for selected guidelines assessed by a content expert and a narrative summary provided (member/s of the Committee)

	☐ Overall confidence in body of evidence or key studies used for selected guidelines assessed by a content expert and a narrative summary provided (external reviewer or independent expert review)
Reporting	A summary of findings will be tabulated for consideration by the Committee. See Reporting section below.

Supporting information in factsheet

Research questions

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/guidelines 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?	

Evidence review for supporting information in factsheets

Criteria for considering existing guidance/guidelines

Relevant new information from the selected guidance/guidelines will be extracted and considered for updating the supporting information sections in the current factsheet (e.g. monitoring, treatment information).

Data extraction and synthesis

Expertise	☒ Data extraction will be performed by the NHMRC Environmental Health team. ☐ Data extraction will be performed by members of the Committee ☐ Other
Data to be extracted	☒ New data relevant to answering the research questions for supporting information in the factsheet ☐ Other [please specify]
Data extraction methods	☒ Single, no second reviewer ☐ Dual; second reviewer checks [all data or proportion] Note that internal review and Committee processes will include review of all extracted information.
Analysis	☐ Results will be tabulated, grouping together information of relevance to each research question. ☒ Synthesis will not be conducted. The following tables will be presented: ☒ Table of relevant extracted data to answer research questions. ☐ Other [please specify]

Reporting

An Evidence Evaluation Report will be prepared to capture the review process and summarise the findings to address the research questions.

Section	Description of content
Executive summary	Overarching statement about review and findings
Introduction and Background	Definitions (key terms, abbreviations), rationale for review and objectives.
Research questions	Questions underpinning the review for health-related advice and supporting information in factsheet.
Evidence Evaluation Methods	Methods for data extraction.
	Methods of assessing quality of existing guidance/guidelines (i.e. use of Assessment Tool). Completed copy of Assessment tool for each guidance/guideline document (**Appendix A**).
	Methods used to summarise or compare data from different sources.

	Methods used for any calculations and explanatory text for any assumptions if used.
Results	Summary of findings table outlining available information for each research question or section of factsheet.
Discussion	Strengths and limitations of the selected guidance/guidelines, a discussion of gaps in the evidence (if identified in the selected guidance/guidelines)
Conclusion	Summary of potential candidate guideline options for Australian guideline values (if any).
Declared interests	Statement of interests of project team. Documentation of relevant declared interest(s) of Committee members.
Acknowledgements	Documentation of any inputs from individuals not on the Team.
References	Included references.
Appendices	Additional technical details as required, e.g. completed Assessment Tool for each guidance/guideline document, research protocol.

Acknowledgements

NHMRC thanks the Committee for their advice on this protocol.

Further information about the Committee, including membership can be found at Water Quality Advisory Committee 2022 – 2025 | NHMRC

Declaration of interests

The NHMRC team undertaking the review of previously published guidance/guidelines on manganese in drinking water have no relevant interests to declare.

References

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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.

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Appendix A – Criteria for assessing existing guidance or guidelines.

Administrative and technical criteria for assessing existing guidance or guidelines.

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

	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?		
	Are the administrative processes documented and publicly available?		
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?		
	Are funding sources declared?		
	Was there public consultation on this work? If so, provide details.		
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?		
	Was the guidance/advice developed or updated recently? Provide details.		
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?		
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?		
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?		

Criteria		Y/N/?/NA	Notes
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?		
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?		
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?		
	Can grey literature such as government reports and policy documents be included?		
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?		
	Evidence search		
	Are databases and other sources of evidence specified?		
	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)?		
	Is it specified what date range the literature search covers? Is there a justification?		
	Are search terms and/or search strings specified?		
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?		
	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?		

Criteria		Y/N/?/NA	Notes
	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.		
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.		
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?		
	Are the parameter value assumptions documented and explained?		
	Are the mathematical workings/algorithms clearly documented and explained?		
	Does the organisation take into consideration non-health related matters to account for 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?		
	What processes are used when expert judgement is required and applied? Is the process documented and published?		
	Is dose response modelling (e.g. BMDL) routinely used?		
	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?		
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?		