Australian Government
National Health and Medical Research Council

NHMRC

Evidence evaluation for *Australian Drinking Water Guidelines* chemical factsheet – Silicon (Research Protocol – full review)

Organisation

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IMPORTANT: This Research Protocol template is designed for reviews commissioned by NHMRC to inform the update or development of the *Australian Drinking Water Guidelines* (the Guidelines) chemical factsheets and/or related advice in the Guidelines. The Research Protocol should be finalised in collaboration with the NHMRC Water Quality Advisory Committee before commencing work to conduct the search or make eligibility decisions.

A separate Research Protocol should be developed for each chemical (or closely related group of chemicals) for which an evidence review is to be conducted, as the current state of knowledge, health outcomes of interest and sources of evidence will vary.

This template was developed to maximise quality and efficiency in the review process, and has been adapted from an existing template developed for rapid reviews by Cochrane.[1] All sections should be completed. Rationales should be provided throughout for all methodological decisions in the final Technical Report, including any decisions to vary the recommended approaches noted in this template.

For further information about this template or the Guidelines, contact water@nhmrc.gov.au.

Contents

Background

There is currently no Australian drinking water guideline or existing fact sheet for silicon. Nevertheless, silicon has been identified as being used to replace lead-based alloys in plumbing. Therefore, a fact sheet will likely need to be developed for silicon.

Silicon currently has a wide range of applications including as a major constituent of ceramics and bricks, in various electronic products, in Portland cement, in manufacturing several industrial and consumer products (e.g. waterproofing systems, moulding agents), as a component of ferrosilicon (used widely in the steel industry), and as a component and delivery system of pharmaceuticals.

Elemental silicon is commonly regarded as a virtually safe element via the oral route of exposure [2]. For example, in a 2-year mouse and rat oral study with silica gel (amorphous silica) with doses up to 10,000 mg/kg and 2,500 mg/kg, respectively, no significant treatment-related effects were seen at any dose [2].

Objectives of the review

To identify relevant information on the impact of exposure to silicon in drinking water on human health outcomes. The process will involve searching for information in relevant guidelines, recent literature and other relevant evidence, and combining evidence appropriately to derive options for up-to-date health-based guideline values for silicon in Australian drinking water supplies.

An evidence scan to inform development of supporting information (e.g. analytical/detection, monitoring and treatment guidance) provided in the factsheet will also be undertaken.

Methods

This review will be conducted using different approaches depending on the factsheet sections being updated or developed.

For the health-based guideline value and health-related advice in the factsheet:

- A review of existing advice (guidelines/guidance) will be conducted (includes any 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).
- At the same time, a review of relevant primary studies or other sources of evidence will be conducted.
- The relevant data from existing guidelines/guidance, primary studies and other relevant sources will be compiled and summarised to answer each research question.

For supporting information in the factsheet (e.g. monitoring, treatment information) an evidence scan will be conducted to collate information that would be useful to include in a factsheet. This information will be used to inform the development of the supporting information sections in the factsheet.

The overall approach to reviewing evidence for different sections of a new factsheet is summarised in the table below:

Section of factsheet	Key steps
Health-related advice in chemical factsheet including: • Health-based guideline value • Health considerations • Typical Australian exposure levels(1) • Risk summary • Derivation of guideline value	• Search for relevant health-related evidence (e.g. guidance, guidelines and primary studies) that can be used to inform development of a new factsheet • Screen and assess quality of existing guidance for health-based guideline values or other relevant guidance values (if applicable) that can be adopted/adapted for drinking water using an Assessment Tool provided by NHMRC (see **Appendix C**) • Screen and assess quality of primary studies and other relevant evidence relating to health-based guideline values for drinking water using an appropriate risk of bias tool (see **Appendix D**) • Present summary of findings from combined information (including the derivation of any potential options for guideline values for consideration) • Report details of methods used to search and evaluate the evidence and derive any potential options for guideline values.
Supporting information in chemical factsheet including: • General description • Measurement (analytical methods) • Treatment options • Risk management options	• Scan and collate evidence that could be used to inform development of a new factsheet • Present summary of findings • Report details of literature search.
(1) Australian exposure levels are not anticipated to be critically evaluated but the data are considered when evaluating risk of harm and are often presented as a concentration range in a chemical factsheet. This information will be handled in a similar manner to the supporting information.	

The methods outlined below will govern the searching, selecting, assessment and reporting of the evidence used to inform the development of the chemical factsheet.

Any changes to the Research Protocol once finalised on the advice of the Water Quality Advisory Committee will be recorded and documented in the Technical Report.

Health-related advice in factsheet

Research questions

Health-related advice	Research questions to consider
Health-based guideline value	What level of silicon in drinking water causes adverse health effects? What is the endpoint that determines this value? If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context? Is there a knowledge gap from the time at which existing guideline values were developed? Does any recent literature change the proposed guideline value? (e.g. demonstrating a new critical endpoint or changed level of effect that should be considered?)
Health considerations	What are the key adverse health hazards from exposure to silicon in Australian drinking water? Are there studies quantifying the health burden (reduce or increase) due to silicon? What is the critical human health endpoint for silicon? What are the justifications for choosing this endpoint?
Typical Australian water levels or exposure profile	What are the typical levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought? Are there any data for silicon levels leaching into water from in-premise plumbing?
Risk summary	What are the risks to human health from exposure to silicon in Australian drinking water? Is there evidence of any emerging risks that require review or further research?

Evidence review for health-related advice in factsheets

Criteria for considering evidence

Study designs	☒ Existing guidelines and guidance from national and international agencies ☒ Existing systematic reviews or literature reviews ☒ Human epidemiological studies ☒ Animal studies[1] ☐ In vitro studies ☐ Other relevant studies or data [please specify]
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 (see footnote 1)
Exposure	Exposure parameters that will be considered for silicon include: • Exposure over a lifetime • Short-term exposure (e.g. over days or weeks during a water contamination event) • Exposure through drinking, cooking, washing, skin contact • Variants, specific chemicals within a group, etc. • Combination or reaction with other substances
Comparator(s)	As there is no existing health-based guideline, the comparator will likely be between higher and lower (or zero) doses or intakes of silicon (if the information allows).

[1] Animal studies may only be consulted if there are insufficient human data.

Outcome(s)	The human health and aesthetic outcomes of concern from exposure to silicon 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. • Aesthetic outcomes, including taste, smell, colour, clarity, etc. Consideration regarding these outcomes will be given to: • The level of silicon in drinking water considered to be safe or acceptable to human health over a lifetime • The level of silicon in drinking water considered to be safe or acceptable to human health during a short-term event (if information allows) • The level of silicon in drinking water considered to be acceptable in relation to aesthetic factors, including taste, smell, colour, clarity, etc.

Search and screening methods

Expertise	The searches will be: ☒ verified by a content expert [TH] ☐ [conducted/informed/verified] by an information specialist [initials] ☐ independently peer reviewed.
Sources of existing guidance or guidelines	The following sources will be screened for existing guidance or guidelines: ☒ World Health Organization (WHO) (including the Joint FAO/WHO Expert Committee on Food Additives [JECFA]) ☒ 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 Safety Australia New Zealand (FSANZ)

	☒ Australian Pesticides and Veterinary Medicine Authority (APVMA)
Electronic databases (to search for primary studies published in journal articles and reviews) (select at least two)	☒ MEDLINE/PubMed/TOXLINE ☐ EMBASE ☐ Scopus ☒ SciFinder ☐ Web of Science ☐ Trials registers [please specify] ☐ Other relevant databases [please specify]
Other sources of evidence	☒ References identified in existing reviews and/or key articles (backward searching) ☒ Articles citing existing reviews and/or key articles (forward searching) ☒ Systematic review references ☒ Data from government/ intergovernmental agencies [see agencies to be searched for existing guidance/guidelines] ☒ Data from industry [e.g. published peer-reviewed articles written by industry, industry reports for exposure information which may or may not have been peer-reviewed] ☐ Contact experts for references ☒ Other [commercial laboratories may be contacted for limits of reporting information]
Limits:	We will include: ☒ Publicly available documents of guidelines or evidence supporting guidelines (near publication drafts will be accepted if available). ☒ Peer reviewed published or in press studies ☒ Unpublished but publicly available studies (e.g. government reports) ☒ Ongoing studies (e.g. published water quality datasets). ☐ Abstracts and conferences proceedings ☐ Guidance/guideline/studies in languages other than English [please specify] ☐ Other [please specify]

Dates:	As there is no existing fact sheet for silicon, the search will not have a minimum cutoff date and will be conducted to present day (date to be noted).
Key search terms to be used:	(Silicon) AND (toxicity) AND (oral) (Silicon) AND (health) AND (oral) (Silion) AND (drinking water) (Silicon) AND (plumbing) AND [leach(ing)] (search terms to be refined as project progresses)
Search strategy:	☐ The complete search strategy for [at least one database] is provided in [Appendix X – please attach]. ☒ Complete search strategies for all electronic sources will be documented in sufficient detail to enable reasonable replication and will be provided in the final report. ☐ If available, the search strategies used to underpin an eligible guideline will be replicated.
Screening search results:	☒ Screening of titles will be performed by researcher [MCRC] and verified by content expert [TH] based on inclusion/exclusion criteria and other limits/parameters outlined in this Research Protocol in Excel ☐ Other [please specify]
Screening content of existing guidelines and guidance:	☒ Single reviewer screens all records ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records
Abstracts of primary studies:	☒ Single reviewer screens all records. ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records
Full text of primary studies:	☒ Single reviewer screens all records ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records

Screening other relevant data:	☒ Single reviewer screens all records ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records
Discrepancy resolution:	☐ Consensus and/or third reviewer ☒ Other [note second reviewer, GDN, will independently check consistency in application of risk of bias tool for a couple of studies]
Excluded guidance/ guidelines and primary studies:	☐ Retracted studies will be excluded using [specify method - Endnote 20 will automatically check citations against Retraction Watch database, otherwise citation lists may need to be compared to the database using Zotero]. ☐ All decisions taken during screening will be documented and outlined in the final report with a list of excluded studies and justification of exclusion (summary justification for title/abstract exclusions, full citations and justifications for full-text exclusions). [OR] ☒ Studies that are found to be relevant at title/abstract but not included in the final list of studies evaluated are to be listed with a brief justification of why they were excluded.

Data collection and analysis

Expertise	☒ Data extraction will be performed by content expert [TH] or will be performed by researcher [MCRC] under supervision of content expert [TH]. ☐ Data extraction will be performed by [initials] based on framework developed and demonstrated by [specify content expert/methodologist etc and initials]. ☐ Other [please specify]
Data to be extracted from existing guidance/ guidelines	☒ 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 C**). where relevant. ☒ Health-based guideline values or equivalent guidance value for silicon (including any formulae or safety margins incorporated into the calculation of the values).

	☒ Outcomes/critical health effects used to inform the recommendation, including any thresholds for acceptable risk used. ☒ An assessment of the certainty of the evidence on which each recommendation is based (either drawn from the guideline or assessed by the providers). [If applicable this will be undertaken consistent with the GRADE approach considering: risk of bias, imprecision, inconsistency, indirectness, publication bias, size of effect, dose response effect and direction of residual confounding. This will allow WQAC to assess the extent to which new evidence would be likely to modify the existing recommendations, see https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence.] ☒ Information relevant to decision making (e.g. community values and preferences, resources or cost, impacts on equity, acceptability and feasibility). [This will allow WQAC to identify areas where the existing recommendations may or may not be applicable to the Australian context and the ADWG[3]]. ☒ 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 WQAC to assess whether there are barriers or adaptations required 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 guideline that appear not to be addressed in the current version of the ADWG [please specify] ☐ Other [please specify]
Data to be extracted from primary studies or other relevant evidence	☒ Details on the review/study [including citation information, publication status, type of study, sample size, and summary of methods] ☒ Population, setting, exposure, comparison and outcome characteristics (PECO) of the study ☒ Data relevant to answering the research questions, along with definitions of outcomes measured, measurement instruments/tools used, and the main conclusions of the study. Where multiple numerical results are presented, all will be extracted. ☐ Other relevant information that should be considered by NHMRC and the Committee [please specify]
Data extraction methods	☒ Single, no second reviewer ☐ Dual; second reviewer checks all data ☐ Dual; second reviewer checks [add proportion]

	☐ Dual; independent screen and cross check [add proportion]
Analysis	☒ Results will be tabulated across studies, grouping together studies of relevance to each research question, and by study design. ☒ Synthesis will be conducted [specify e.g., presenting combined raw data for same health outcome, converting 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 health-based guideline/guidance values (with calculated Australian equivalent for drinking water) for silicon and associated additional considerations and assumptions. ☒ Table summarising findings of Assessment Tool (**Appendix C**) against all included guidelines if applicable ☐ Table to compare PECO characteristics/ study design features ☐ Table of potential guideline options, comparisons and assumptions ☐ 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 [Comparisons of individual study results will likely be presented for: • Overall certainty of evidence for different health endpoints. • Threshold doses of silicon (if possible) associated with no adverse effects and critical adverse health effect. This may be presented (in the form of a heat map, for example) along with study bias/quality.]
Risk of Bias for included primary studies	☐ Included primary studies will be assessed for Risk of Bias and a narrative summary provided ☒ Studies will be assessed with a Risk of Bias tool [e.g., OHAT/modified OHAT[2] (**Appendix D**)], and information provided about the outcomes as a rating

[2] See Appendix D

Overall confidence in results for recent studies	☐ Overall confidence in body of evidence assessed by a content expert and a narrative summary provided ☒ Overall confidence in body of evidence assessed with regard to Risk of Bias, indirectness/applicability, imprecision, inconsistency between studies and publication bias and any additional factors, with information provided about the outcomes as a rating (e,g. GRADE or OHAT), where possible.
Reporting	Following assessment of the existing guidance/ guidelines and recent evidence, a summary of findings will be provided to the Water Quality Advisory Committee to consider. See Reporting section below.

Supporting information in factsheet

Research questions

Supporting information	Research questions to consider
General description	What is silicon used for and how might people be exposed?
Measurement	How is the concentration of silicon measured in drinking water? What are the indicators of the risks? How can we measure this exposure? What analytical methods are currently used to measure silicon in drinking water? What are the limits of quantification or limit of reporting for silicon in drinking water?
Treatment options	How is drinking water treated to minimise silicon concentrations?
Risk management options	What are the current practices to minimise or manage the risks identified?
Are there any additional sections that should be added?	

Evidence scan for supporting information

Relevant information will be collected through an evidence scan and collated for possible inclusion in a new factsheet.

Criteria for considering evidence

All study types that are relevant to answering the research questions will be considered.

Search and screening methods

Expertise	The searches will be: ☒ conducted by a researcher (MCRC) and verified by a content expert [TH] ☐ [conducted/informed/verified] by an information specialist [initials] ☐ independently peer reviewed.
Electronic databases	☒ MEDLINE/PubMed/TOXLINE ☐ EMBASE ☒ Scopus ☐ SciFinder ☐ Web of Science ☐ Trials registers [please specify] ☐ Other relevant databases [please specify]
Other sources	☐ References identified in existing reviews and/or key articles (backward searching) ☐ Articles citing existing reviews and/or key articles (forward searching) ☐ Systematic review references ☐ Data from government/ intergovernmental agencies [please specify] ☒ Data from industry [contact Australian laboratories: National Measurement Institute, SGS, ALS, Eurofins] ☐ Contact experts for references ☒ Other [Water Services Association of Australia; Standard Methods for the Examination of Water and Wastewater (https://www.standardmethods.org/); US EPA Drinking Water Treatability Database (https://tdb.epa.gov/tdb/home); discussion/consultation with WQAC or Chemical Subgroup]
Limits:	Evidence to be considered will include: ☒ Peer reviewed published or in press studies ☒ Unpublished studies (e.g., government reports) ☐ Ongoing studies (e.g., government studies of water quality).

	☐ Abstracts and conferences proceedings ☐ Studies in languages other than English [please specify] ☒ Other appropriate search limits [Australian laboratory information sheets on measurement methods and limits of reporting, general correspondence with laboratories]
Dates:	The search will be conducted from 2008 to the present date. This would cover the last 15 years of information and is considered appropriate for supporting information, as older information is likely outdated (especially in terms of treatment and analytical methods).
Key search terms to be used:	(Silicon) AND (treatment) AND (drinking water) (Silicon) AND (analysis) AND (drinking water) (Silicon) AND (testing) AND (drinking water)
Search strategy:	☐ The complete search strategy for [at least one database] is provided in [Appendix X]. ☒ Complete search strategies for all electronic sources will be documented in sufficient detail to enable reasonable replication and will be provided in the final Technical Report.
Screening search results:	☒ Screening will be performed by researcher [MCRC] in Excel and verified by content expert [TH] ☐ Screening will be performed by [initials] based on inclusion/exclusion criteria developed by [specify content expert/methodologist etc. and initials] in [specify software]
Excluded studies	All decisions taken during screening will be documented and outlined in the final report with a list of excluded studies and justification for exclusion.

Data collection and analysis

Expertise	☒ Data extraction will be performed by researcher [MCRC] and verified by content expert [TH]. ☐ Data extraction will be performed by [initials] based on framework developed and demonstrated by [specify content expert/methodologist etc and initials].

Data to be extracted	☐ Study design details (including citation information, publication status, sample size, summary of methods). [see **Appendix B** for example] ☒ Data relevant to answering the research questions, along with definitions of outcomes measured, measurement instruments/tools used and the main conclusions of the study. Where multiple relevant numerical results are presented, all will be extracted. ☐ Other [please specify]
Data extraction methods	☒ Single, no second reviewer ☐ Dual; second reviewer checks all data ☐ Dual; second reviewer checks [add proportion] ☐ Dual; independent screen and cross check [add proportion]
Analysis	☐ Results will be tabulated across studies, grouping together studies of relevance to each research question, and by study design. ☒ Synthesis will not be conducted. The following tables will be presented: ☒ Table of relevant extracted data to answer research questions. Where multiple eligible numerical results are reported from a single study, all will be reported. ☐ Other [please specify]

Reporting

Evidence Evaluation and Technical Reports

The Evidence Evaluation Report will interpret, synthesise and summarise the findings of the evidence review and address the research questions. This Report will contain high-level information only.

The Technical Report will contain technical information about the review methodology and any other details relating to the Evidence Evaluation Report. The Technical Reports will describe all details of the methodology used that would be too exhaustive for the Evidence Evaluation Report.

Section	Description of content	Evaluation Report	Technical Report
Executive summary	Overarching statement about review and findings	☒	☐

Introduction and Background	Definitions (key terms, outcome measures, abbreviations), rationale for review and objectives.	☒	☐
Research question/s	Questions underpinning the review for: • Health-related advice • Supporting information	☒	☒
Evidence Evaluation Methods	Brief overview of the approach taken for evidence search and evaluation (reference complete details in Technical Report)	☒	☐
	Approach used to identify and retrieve existing guidelines/guidance or primary studies [see **Appendix A** for the type of information that can be included in a search strategy]	☐	☒
	Process for selecting studies (i.e. application of inclusion/exclusion criteria) and list of included and excluded studies.	☐	☒
	Methods for data extraction and completed table of extracted data for each piece of evidence	☐	☒
	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 C**).	☐	☒
	Methods of assessing quality of primary studies (i.e. use of risk of bias tool). Completed copy of risk of bias tool for each included primary study (**Appendix D**).	☐	☒
	Methods used to analyse/synthesise/summarise or compare data from different sources. Summary of findings tables directly comparing data from different sources and uncertainty.	☒	☒
	Methods used for any calculations and explanatory text for any assumptions if used (can have different levels of information about this in each Report)	☒	☒
Results	Summary of findings tables for each research question or section of factsheet. Easy to compare different guidelines/studies in Evaluation Report,	☒	☒

	more detailed information in Technical Report if required.		
Discussion	Strengths and limitations of the included studies/guidance, comparison of existing literature, a discussion of gaps in the evidence (if identified during the evaluation of the evidence) and a suggestion of areas for further research (if applicable)	☒	☐
Conclusion	Summary of recent evidence and options for guideline values (if any). Note: a recommendation is not part of the process. Recommendations will be made by the Water Quality Advisory Committee.	☒	☐
Review team	List members of Review Team	☒	☐
Declared interests	Documentation of the declared interest(s) of reviewers	☒	☐
Acknowledgements	Documentation of any inputs from individuals not on the Team	☒	☐
References	Included references	☒	☒
Appendices	Additional technical detail or examples of templates used in methods to be provided as required	☐	☒

Acknowledgements

Thanks to the members of the NHMRC Water Team and the NHMRC Water Quality Advisory Committee (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

Team member	**Declaration of interest**
Ms Tarah Hagen	As part day-to-day consulting activities at SLR Consulting and ToxConsult, Ms Hagen has: • Provided the report “Assessment of International and National Agency Processes for Deriving HBGVs and DWGs” to the

	NHMRC and also conducted the Stage 1 review of the work described herein.
Mr Giorgio De Nola	No interest to declare.
Ms Maria Consuelo Reyes Campos	No interest to declare.

References

1. Cochrane (2021). COVID Rapid Review Protocol Template. Accessed 19 February 2021. Available from: https://covidreviews.cochrane.org/sites/covidreviews.cochrane.org/files/public/uploads/covid-19_rr_protocol_template_v4.docx

2. Hao P, Wang Y, Sun X, Wang J and Zhang LW (2022). Derivation of the toxicological threshold of silicon element in the extractables and leachables from the pharmaceutical packaging and process components. Toxicology and Industrial Health 38(12): 819-834.

3. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD, Grade Working Group (2016). GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 353.

Appendix A – Search strategy and selection of evidence

Example template of documenting a search strategy and how evidence is selected (if required).

Outline specific steps that will be taken to search and select the evidence in enough detail that someone else could reasonably replicate the search, including details such as:

Search terms	[List and define keywords and suggested search string combinations that you will use to search for publications based upon the PECO elements and research questions (present in table if possible) – these will have to be used across all databases for consistency with minor adjustments as appropriate to each database. If there are multiple research questions to answer, several different searches may need to be undertaken.]
Databases	[List at least two databases that will be searched using the agreed search terms (e.g. PubMed, Scopus, Scifinder).]
Publication date	[Specify the publication date range that will be searched across all databases including justifications for any specific date ranges (e.g. for a guideline update NHMRC usually searches from the date of the last literature search so there is no duplication of effort, but if some key pieces of evidence were not considered in the last review these may also be included with justification)]
Language	[Specify the language of publications that the search will be limited to (this is important when there are limited resources to translate publications)]
Study Type	[State what types of publications will be accepted to answer the research question, or what hierarchy will be used by the reviewer in the event that limited evidence is available. State what types of publications will not be accepted.]
Inclusion and exclusion criteria	[Define any other criteria that can be applied to the evidence to select studies for appraisal; and importance (priority rating) of outcomes to be considered as part of the review.]
Validation methods used (if any)	[Details on how you will validate the search strategy and check that it works before you undertake a full search, e.g. performing an initial search based upon the chosen search terms and checking against key publications as determined by the reviewer or expert committee. Include a description of how you will refine the process based on these initial results (e.g. adding/modifying criteria or filters)]
Screening methods	[Details on how you will efficiently screen the results of your search (which can sometimes retrieved thousands of publications). For example, will you only screen the titles or

	abstracts for key words? Will publications that you aren't sure about be screened at full text?]
Quality check	[Methods for checking that key publications have been picked up the search – are there any omissions or missed papers from the database searches?]
Grey literature	[Detail how you will search and retrieve any grey literature (e.g. define what kind of grey literature you will be looking for, what search engines or websites you will use, list any agencies/organisations that will be contacted for information and how this will be done).]
Documentation of search	[Explain how this process will be recorded (e.g. using a PRISMA diagram (Moher et al. 2009)). Explain how you will record which publications were found but excluded with justification.]
Retrieval of publications	[Describe how you will obtain publications, collate papers for review into a literature database (e.g. Endnote) and store in secure backup storage]

Appendix B – Data extraction template

General information	Study ID	
	Date template completed	
	Authors Publication date Publication type Peer reviewed Country of origin Source of funding Possible conflicts of interest	
Study characteristics	Aim/objectives of study Study type/design Study duration Type of water source (if applicable)	
Population characteristics	Population/s studied Selection criteria for population (if applicable) Subgroups reported Size of study	
Exposure and setting	Type of water source (if applicable) Exposure pathway Source of chemical/contamination Comparison group(s)	
Study methods	Water quality measurement used Water sampling methods (monitoring, surrogates)	
Results **(for each outcome)**	Definition of outcome How outcome was assessed Method of measurement	

	Number participants (exposed/non-exposed, missing/excluded) (if applicable)	
Statistics (if any)	Statistical methods used Details on statistical analysis Relative risk/odds ratio, confidence interval?	
Author's conclusion	Interpretation of results Assessment of uncertainty (if any)	
Reviewer comments	Results included/excluded in review (if applicable) Notes on study quality e.g. gaps, methods	

Appendix C – 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?		
	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?		
	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?		

Appendix D – Risk-of-bias tool – modified OHAT

To be completed for each study. To discuss with the NHMRC project team before applying modified tool.

Table x: Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort, Case studies and Observational studies greyed out – this can be amended as required. Refer to OHAT Handbook for more information.

Study ID: **Study Type:**		**RoB:** **Yes/No** **Unknown** **N/A**	**Notes**	**Risk of bias rating** **(--/-/+/++)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	- Comparison groups appropriate			
	Confounding bias			
4.	- Confounding (design/analysis)			
	Performance Bias			
5.	**Identical experimental conditions**			

6.	**Blinding of researchers during study?**			
	Attrition/Exclusion Bias			
7.	**Missing outcome data**			
	Detection Bias			
8.	**Sample characterisation**			
9.	**Outcome assessment**			
	Selective Reporting Bias			
10.	**Outcome reporting**			
	Other Sources of Bias			
11.	**Other threats** (e.g. statistical methods appropriate; researchers adhered to the study protocol)			
	Overall risk of bias rating:			

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+)	+	Definitely high risk of bias (++)	++