

Evidence evaluation for *Australian Drinking Water Guidelines* chemical factsheet – SELENIUM (Research Protocol Stage 2 – extended review)

Organisation

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Date protocol completed

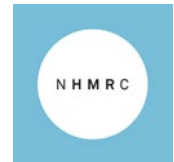
20/02/2023

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.

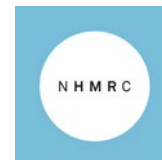
This template was developed to maximise quality and efficiency in the review process, and has been adapted from an existing template developed for rapid reviews by Cochrane.¹ All sections should be completed. Rationales should be provided throughout for all methodological decisions in the final Technical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



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Background

Selenium is an essential metalloid, usually found associated with sulphide minerals or with silver, lead, copper or nickel minerals. It is an essential trace element and is found in foodstuffs such as cereals, meat and fish³. Selenium and its compounds are also commercially produced as a by-product of copper refining, and used in some photographic devices, plastics, paints, vitamin and mineral supplements, anti-dandruff shampoos, fungicides and certain types of glass². Exposure to selenium primarily occurs via the diet; it would be unusual for drinking water to make a significant contribution to total selenium intake^{2,3}.

Most water-soluble selenium compounds are effectively absorbed by the gastrointestinal tract, and distributed to most organs, with highest concentrations found in the kidney, liver, spleen, testes and skeletal muscle^{4,7}.

Very low selenium status in humans has been associated with a juvenile, multifocal myocarditis called Keshan disease and a chondrodystrophy called Kaschin-Beck disease.

Selenium toxicity varies among selenium compounds. Selenite and selenate are more toxic than selenium sulfide⁴. Acute and chronic selenium toxicity from excessive intakes is rare. High selenium intakes over prolonged periods can cause gastrointestinal disturbances, discolouration of the skin, changes in peripheral nerves, tooth decay, lassitude, dizziness, dermatitis, garlic breath, and nail deformities (a condition termed selenosis)^{3,4}.

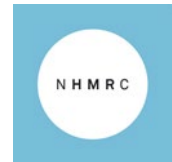
According to the International Agency for Research on Cancer (IARC) selenium is not classifiable as to its carcinogenicity in humans (Group 3, inadequate evidence in humans and in animals)⁵. A putative role for selenium as an anticarcinogen has been suggested⁷.

Due to health concerns associated with adverse effects resulting from excessive selenium concentrations in foods, WHO/FAO in 2011 and NHMRC in 2014 established an upper tolerable limit for selenium of 400 µg/day for adults^{3,8}.

An initial Stage 1 review of published guidelines and guidance documents relevant to selenium identified five existing guidance/guideline values from six jurisdictions that were suitable to adopt/adapt based on an assessment of administrative and technical criteria. Potential adaptation of these similar guidance values would result in a health-based DWG of 0.02 mg/L, which is higher than the current Australian DWG of 0.01 mg/L. However, the evidence scan undertaken for the Stage 1 review revealed a number of recently published studies which could potentially impact the conclusions made in the report. It was, however, beyond the scope of the Stage 1 review to undertake a detailed critical appraisal of the new information. As a result, a targeted search and review of relevant primary studies published since 2010 (determined to be the cut-off date for the most recent agency review from Stage 1) will be conducted. Details of methods are provided in later sections.

Objectives of the review

To identify relevant information on the impact of exposure to selenium in drinking water at levels higher or lower than the current health-based guideline value on human health outcomes. The process will involve searching for relevant information in primary studies and other evidence



sources based on findings from the initial Stage 1 review to derive up-to-date options for health-based guideline values for selenium in Australian drinking water supplies.

In particular, this will involve assessing evidence published since 2010. This date was estimated by consulting the bibliographies of the various agency reviews identified in Stage 1.

Methods

For the health-based guideline value and health-related advice in the factsheet where a targeted review of existing advice did not provide suitable guidance to adopt/adapt without further review, an expanded search and review of other relevant guidance will be undertaken. This will include primary studies published after 2010, which was determined to be the most appropriate cut-off date based on the bibliographies of the most recent health-based agency reviews found in Stage 1 which were found suitable for adoption/adaptation based on an assessment of administrative and technical criteria and a critical analysis of the underpinning studies.

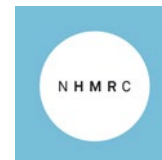
For supporting information in the factsheet (e.g. monitoring, treatment information) an evidence scan was conducted at Stage 1 (adopt/adapt) to assess the currency of the existing information in the factsheet. This information will be included, where relevant, in updates to the factsheets. The updates to factsheets are outside of the scope of the Stage 2 review.

The overall approach to reviewing health-related advice of the factsheet is summarised in the table below:

Section of factsheet	Key steps
<p>Health-related advice in chemical factsheet including:</p> <ul style="list-style-type: none"> Health-based guideline value Health considerations Typical Australian exposure levels⁽¹⁾ Risk summary Derivation of guideline value 	<ul style="list-style-type: none"> Screen and assess quality of primary studies and other relevant evidence relating to health-based guideline values or other relevant guidance values (if applicable) for drinking water using an appropriate risk of bias tool (see Appendix C) Present summary of findings (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.
<p>(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 presented in Stage 1 (adopt/adapt).</p>	

The methods outlined below will govern the searching, selecting, assessment and reporting of the evidence used to inform the update to 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

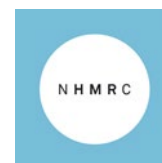
Research questions

Health-related advice	Research questions to consider
Health-based guideline value	What level of selenium in drinking water causes adverse health effects? What is the endpoint that determines this value? Is the proposed option for a health-based guideline value relevant to the Australian context?
Health considerations	<p>What are the key adverse health hazards from exposure to selenium in Australian drinking water?</p> <p>Are there studies in Australia quantifying the health burden (reduce or increase) due to selenium?</p> <p>What is the critical human health endpoint for selenium?</p> <p>What are the justifications for choosing this endpoint?</p>
Typical Australian water levels or exposure profile	<p>What are the typical levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought? (note this was already done in Stage 1)</p> <p>Are there any data for selenium levels leaching into water from in-premise plumbing?</p>
Risk summary	<p>What are the risks to human health from exposure to selenium in Australian drinking water?</p> <p>Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review or further research?</p>

Evidence review for health-related advice in factsheets

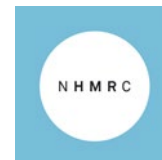
Criteria for considering evidence

Study designs	<p>Existing guidelines and guidance from national and international agencies have been considered in Stage 1. This review will consider:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Existing systematic reviews or literature reviews not considered in Stage 1 <input checked="" type="checkbox"/> Human epidemiological studies
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	<input checked="" type="checkbox"/> Animal studies ¹ <input type="checkbox"/> In vitro studies <input type="checkbox"/> Other relevant studies or data [please specify] Please specify any study types that will <i>not</i> be considered (if any).
Population	<input checked="" type="checkbox"/> Humans, including the general population as well as specific populations who may be at higher risk of adverse health outcomes such as: <ul style="list-style-type: none"> • Infants and children • People who are pregnant • Aboriginal and Torres Strait Islander peoples • People with low or very high nutritional status • People with pre-existing health conditions • People who ingest higher than average amounts of water (e.g. tropical locations, outdoor workers) • People with certain genetic polymorphisms <input checked="" type="checkbox"/> Animals or cells as surrogates for human exposure (see footnote 1)
Exposure	Exposure parameters that will be considered for selenium include: <ul style="list-style-type: none"> • Exposure over a lifetime • Short-term exposure (e.g. over days or weeks during a water contamination event) • Exposure through drinking, cooking, washing • Combination or reaction with other substances
Comparator(s)	Health-based guidance underpinning current NHMRC drinking water guideline value and threshold doses for different health effects.
Outcome(s)	The human health outcomes of concern from exposure to selenium include: <ul style="list-style-type: none"> • Mortality • Severe human health outcomes, including incidence of life-threatening illness, disability or chronic disease with ongoing impact on quality of life.

¹ Animal studies may only be consulted if there are insufficient human data. For selenium, as current health advice is already based on human epidemiological studies, it is unlikely animal studies will require detailed review.

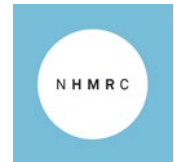


	<ul style="list-style-type: none"> • Less severe or short-term human health outcomes, e.g. irritation. <p>Consideration regarding these outcomes will be given to:</p> <ul style="list-style-type: none"> • The level of selenium in drinking water considered to be safe or acceptable to human health over a lifetime • If deemed relevant from the information reviewed, the level of selenium in drinking water considered to be safe or acceptable to human health during a short-term event
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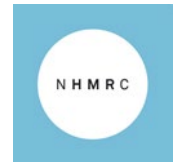
Search and screening methods

Expertise	<p>The searches will be:</p> <p><input checked="" type="checkbox"/> verified] by a content expert [TH]</p> <p><input type="checkbox"/> [conducted/informed/verified] by an information specialist [initials]</p> <p><input type="checkbox"/> independently peer reviewed.</p>
Electronic databases (to search for primary studies published in journal articles and reviews) (select at least two)	<p><input checked="" type="checkbox"/> MEDLINE/PubMed/TOXLINE</p> <p><input type="checkbox"/> EMBASE</p> <p><input type="checkbox"/> Scopus</p> <p><input checked="" type="checkbox"/> SciFinder</p> <p><input type="checkbox"/> Web of Science</p> <p><input type="checkbox"/> Trials registers [please specify]</p> <p><input type="checkbox"/> Other relevant databases [please specify]</p>
Other sources of evidence	<p><input checked="" type="checkbox"/> References identified in existing key reviews and/or key articles (backward searching) – limited by publication date (2010-onwards)²</p> <p><input type="checkbox"/> Articles citing existing reviews and/or key articles (forward searching)</p> <p><input checked="" type="checkbox"/> Systematic review references</p> <p><input checked="" type="checkbox"/> Data from government/ intergovernmental agencies [check for updates since Stage 1 – same agencies as searched in Stage 1]</p>

² This is to coincide with the apparent cut-off date for literature searches undertaken in the identified agency reviews. This date was estimated by consulting the bibliographies of the various agency reviews identified in Stage 1. Although one of the reviews is dated 2014 (by EFSA), the review does not appear to contain any updated information on selenium excess compared to the 2006 review by the same agency. The 2011 review by WHO is the next most-recent review which contained cited literature up to 2010.



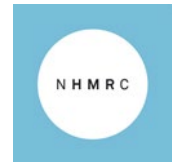
	<input checked="" type="checkbox"/> Data from industry [e.g. published peer-reviewed articles written by industry, industry reports for exposure information which may or may not have been peer-reviewed] <input type="checkbox"/> Contact experts for references <input type="checkbox"/> Other [please specify]
Limits:	<p>We will include:</p> <input checked="" type="checkbox"/> Publicly available documents of guidelines or evidence supporting guidelines (near publication drafts will be accepted if available). <input checked="" type="checkbox"/> Peer reviewed published or in press studies <input checked="" type="checkbox"/> Unpublished but publicly available studies (e.g., government reports) <input checked="" type="checkbox"/> Ongoing studies (e.g., published water quality datasets). <input type="checkbox"/> Abstracts and conferences proceedings <input type="checkbox"/> Studies in languages other than English [please specify]
Dates:	The search will be conducted from 2010 to the present date. This is to coincide with the approximate literature searching cutoff date from the second most recent agency review identified in Stage 1 (see footnote 2).
Key search terms to be used:	(Selenium) AND (toxicity) AND (oral) (Selenium) AND (health) AND (oral) (Selenium) AND (toxicity) AND (drinking water) (Selenium) AND (health) AND (drinking water) (Selenium) AND (plumbing) AND [leach(ing)] (search terms to be refined as project progresses)
Search strategy:	<input type="checkbox"/> The complete search strategy for [at least one database] is provided in [Appendix X – please attach]. <input checked="" type="checkbox"/> 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. <input type="checkbox"/> If available, the search strategies used to underpin an eligible guideline will be replicated.
Screening search results:	<input checked="" type="checkbox"/> 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 <input type="checkbox"/> Other [please specify]



Abstracts of primary studies:	<input checked="" type="checkbox"/> Single reviewer screens all records. <input type="checkbox"/> Dual; second reviewer checks all excluded records <input type="checkbox"/> Dual; second reviewer checks [X%] of excluded records <input type="checkbox"/> Dual; independent screen and cross check [X%] of records
Full text of primary studies:	<input checked="" type="checkbox"/> Single reviewer screens all records <input type="checkbox"/> Dual; second reviewer checks all excluded records <input type="checkbox"/> Dual; second reviewer checks [X%] of excluded records <input type="checkbox"/> Dual; independent screen and cross check [X%] of records
Screening other relevant data:	<input checked="" type="checkbox"/> Single reviewer screens all records <input type="checkbox"/> Dual; second reviewer checks all excluded records <input type="checkbox"/> Dual; second reviewer checks [X%] of excluded records <input type="checkbox"/> Dual; independent screen and cross check [X%] of records
Discrepancy resolution:	<input type="checkbox"/> Consensus and/or third reviewer <input checked="" type="checkbox"/> Other [note second reviewer, GDN, will independently check consistency in application of risk of bias tool for a couple of studies]
Excluded primary studies:	<input type="checkbox"/> 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]. <input type="checkbox"/> 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] <input checked="" type="checkbox"/> 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.

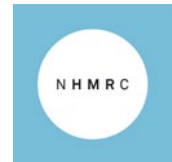
Data collection and analysis

Expertise	<input checked="" type="checkbox"/> Data extraction will be performed by content expert [TH]. <input type="checkbox"/> Data extraction will be performed by [initials] based on framework developed and demonstrated by [specify content expert/methodologist etc and initials].
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<p>Data to be extracted from primary studies or other relevant evidence</p>	<p><input checked="" type="checkbox"/> Details on the review/study [including citation information, publication status, type of study, sample size, and summary of methods]</p> <p><input checked="" type="checkbox"/> Population, setting, exposure, comparison and outcome characteristics (PECO) of the study</p> <p><input checked="" type="checkbox"/> 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.</p> <p><input type="checkbox"/> Other relevant information that should be considered by NHMRC and the Committee [please specify]</p>
<p>Data extraction methods</p>	<p><input checked="" type="checkbox"/> Single, no second reviewer</p> <p><input type="checkbox"/> Dual; second reviewer checks all data</p> <p><input type="checkbox"/> Dual; second reviewer checks [add proportion]</p> <p><input type="checkbox"/> Dual; independent extraction and cross check [add proportion]</p>
<p>Analysis</p>	<p><input checked="" type="checkbox"/> Results will be tabulated across studies, grouping together studies of relevance to each research question, and by study design.</p> <p><input checked="" type="checkbox"/> Synthesis will be conducted [e.g., presenting combined raw data for same health outcome].</p> <p>The following tables will be presented:</p> <p><input checked="" type="checkbox"/> Table to compare PECO characteristics/ study design features</p> <p><input checked="" type="checkbox"/> Table of potential guideline options, comparisons and assumptions</p> <p><input type="checkbox"/> 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.</p> <p><input checked="" type="checkbox"/> Other [Comparisons will likely be presented for:</p> <ul style="list-style-type: none"> • Overall certainty of evidence for different health endpoints. • Threshold doses of selenium 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.]
<p>Risk of Bias for included primary studies</p>	<p><input type="checkbox"/> Included primary studies will be assessed for Risk of Bias and a narrative summary provided</p> <p><input checked="" type="checkbox"/> Included primary studies will be assessed with a Risk of Bias tool [e.g., OHAT/modified OHAT³ (Appendix C)], and information provided about the outcomes as a rating</p>

³ See Appendix C



Overall confidence in results	<input type="checkbox"/> Overall confidence in body of evidence assessed by a content expert and a narrative summary provided <input checked="" type="checkbox"/> 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)
Reporting	<p>A summary of relevant studies will be tabulated for consideration by the Water Quality Advisory Committee.</p> <p>See Reporting section below.</p>

Supporting information in factsheet

Questions relating to currency and/or need to update the supporting information in factsheets were covered in the Stage 1 review and are not covered here. The information from the Stage 1 review will be integrated into the final factsheet updates.

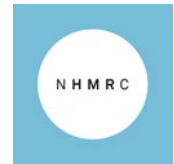
Reporting

Evidence Evaluation and Technical Reports

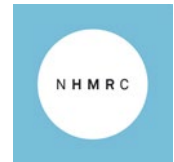
The Evidence Evaluation Report will interpret, synthesise and summarise the findings of the evidence review and address the research questions. This Report will contain high-level information only.

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Introduction and Background	Definitions (key terms, outcome measures, abbreviations), rationale for review and objectives.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Research question/s	Questions underpinning the review for health-related advice	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>



Evidence Evaluation Methods	Brief overview of the approach taken for evidence search and evaluation (reference complete details in Technical Report)	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Approach used to identify and retrieve relevant primary studies [see Appendix A for the type of information that can be included in a search strategy]	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Process for selecting studies (i.e. application of inclusion/exclusion criteria) and list of included and excluded studies.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Methods for data extraction and completed table of extracted data for each piece of evidence	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	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 C).	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Methods used to analyse/synthesise/summarise or compare data from different sources. Summary of findings tables directly comparing data from different sources and uncertainty.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Methods used for any calculations and explanatory text for any assumptions if used (can have different levels of information about this in each Report)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Results	Summary of findings tables for each research question. Easy to compare different studies in Evaluation Report, more detailed information in Technical Report if required.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Discussion	Strengths and limitations of the included studies, 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 required)	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Conclusion	Summary of recent evidence and options for guideline values (if any).	<input checked="" type="checkbox"/>	<input type="checkbox"/>



	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Declared interests	Documentation of the declared interest(s) of reviewers	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Acknowledgements	Documentation of any inputs from individuals not on the Team	<input checked="" type="checkbox"/>	<input type="checkbox"/>
References	Included references	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Appendices	Additional technical detail or examples of templates used in methods to be provided as required	<input type="checkbox"/>	<input checked="" type="checkbox"/>

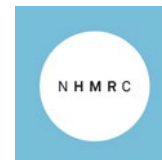
Acknowledgements

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](#)

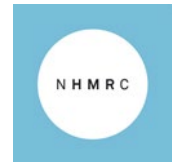
Declaration of interests

Team member	Declaration of interest
Ms Tarah Hagen	As part day-to-day consulting activities at SLR Consulting and ToxConsult, Ms Hagen has: <ul style="list-style-type: none"> • 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	As part day-to-day consulting activities at SLR Consulting, Mr De Nola was also involved in the Stage 1 review of the work described herein.
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. ATSDR (2003). Toxicological profile for Selenium, Department of Health and Human Services, Agency for Toxic Substances and Disease Registry <https://www.atsdr.cdc.gov/ToxProfiles/tp92.pdf>.
3. WHO (2017). Guidelines for drinking-water quality. Fourth edition incorporating the first Addendum, World Health Organization. Geneva. <https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=8A179F96A66DD2F070E785831CAB3180?sequence=1>.
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5. IARC (International Agency for Research on Cancer) (1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Overall Evaluations of Carcinogenicity. An updating of IARC monographs volumes 1 to 42. World Health Organization, IARC, Supplement 7.
6. 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.
7. WHO (2010). Selenium in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality, World Health Organization. WHO/HSE/WSH/10.01/14.
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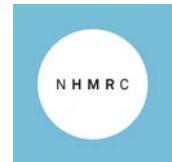


Appendix A – Search strategy and selection of evidence

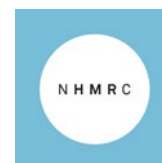
Example template of documenting a search strategy and how evidence is selected (if required).

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 retrieve thousands of publications). For example, will you only screen the titles or

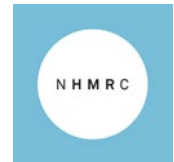


	abstracts for key words? Will publications that you aren't sure about be screened at full text?]
Quality check	[Methods for checking that key publications have been picked up the search – are there any omissions or missed papers from the database searches?]
Grey literature	[Detail how you will search 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 – Risk-of-bias tool – modified OHAT

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

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:	RoB: Yes/No	Notes		Risk of bias rating (--/-/+/>++)
Study Type:	Unknown N/A			
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 (++)	++
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