Australian Government
National Health and Medical Research Council

NHMRC

Evidence evaluation for *Australian Drinking Water Guidelines* chemical factsheet – PFOS, PFHxS, PFOA, PFBS, and GenX (Research Protocol Stage 1 – initial screen/adopt-adapt)

Organisation

SLR Consulting Australia Pty Ltd

Team

Tarah Hagen

Giorgio De Nola

Maria Consuelo Reyes Campos

Contact

Tarah Hagen; Level 11, 176 Wellington Parade, East Melbourne, VIC 3002;
thagen@slrconsulting.com

Date protocol completed

26/05/2023

IMPORTANT: This Research Protocol template is designed for reviews commissioned by NHMRC to inform the update or development of *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 3

Objectives of the review 4

Methods 4

Health-related advice in factsheet 5

Research questions 5

Evidence review for health-related advice in factsheets 6

Criteria for considering existing guidelines/guidance 6

Search and screening methods 8

Data collection and analysis 11

Supporting information in factsheet 13

Research questions 13

Evidence scan for supporting information 14

Criteria for considering evidence for supporting information 14

Search and screening methods 14

Data collection and analysis 17

Reporting 17

Acknowledgements 19

Declaration of interests 20

References 21

Appendix A – Search strategy and selection of evidence 23

Appendix B – Data extraction template 25

Appendix C – Criteria for assessing existing guidance or guidelines 27

Background

Per- and poly-fluorinated alkylated substances (PFAS) are a group of over four thousand manufactured chemicals that do not occur naturally in the environment. Some PFAS are very effective at resisting heat, stains, grease and water, making them useful chemicals for a range of applications. Their resistance to degradation in the environment makes some PFAS persist in the environment and therefore may lead to exposure in humans (e.g. via drinking water and food); as some PFAS also persist in human blood/tissues, it has been recommended as a precaution by the Australian Department of Health[2] that exposure be minimised.

In August 2018, NHMRC[3] published a chemical fact sheet for PFAS in drinking water, with health-based guideline values derived for perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS) and perfluorooctanoic acid (PFOA). The guideline values were based on the health-based tolerable daily intakes (i.e. guidance values) derived by Food Standards Australia New Zealand (FSANZ) in 2017.[4] The FSANZ health-based guidance values for PFOS and PFOA were based on toxicological findings in experimental animals since the available human epidemiology information at the time was deemed as not suitable to support the derivation of guidance values for these chemicals. Human equivalent doses (HEDs) of serum No Observed Adverse Effect Levels (NOAELs) for various effects (e.g. for PFOS, decreased body weight gains in a multigeneration reproductive toxicity study in rats; for PFOA, foetal toxicity in a development and reproductive toxicity study in mice) were derived using pharmacokinetic modelling to account for the marked variation in clearance of these chemicals in various species. FSANZ considered there was insufficient toxicological and epidemiological information to justify establishing a health-based guidance value for PFHxS and instead recommended that the use of the PFOS health-based guidance value is likely a conservative approach and protective of public health as an interim measure.

Australia has not recommended health-based guidance or guideline values for perfluorobutane sulfonate (PFBS) or for hexafluoropropylene oxide (HPFO) dimer acid and its ammonium salt ("GenX chemicals"). These two PFAS have been the subject of recently derived health advisories (in drinking water) overseas[5,6,7,8,9,10,11].

In recent years, several new health-based guidance/guideline values and health advisories for PFAS (in drinking water) have been derived by overseas jurisdictions. Some of these jurisdictions have based their guidance values on different endpoints to those used by FSANZ. In particular, in June 2022, the United States Environmental Protection Agency (US EPA) derived drinking water health advisories for PFOS, PFOA, PFBS and GenX chemicals[8,10]. The values for PFOS and PFOA are much lower than the Australian guidelines (there are no current Australian health-based guidance/guideline values for PFBS and GenX chemicals). This has resulted in growing community concern regarding exposure to PFAS chemicals.

For these reasons, NHMRC is prioritising the review of existing health-based guideline values for PFAS in drinking water. In particular, the PFAS chemicals in the current Australian drinking water fact sheet and the additional PFAS chemicals for which US EPA derived health advisories in 2022 are considered in this review.

Objectives of the review

To identify existing sources of guidance or guidelines on the impact of exposure to select PFAS (i.e. PFOS, PFOA, PFHxS, PFBS and GenX chemicals) in drinking water at levels higher or lower than the current health-based guideline values (where these exist) on human health outcomes.

An evidence scan to inform an update to the existing supporting information (e.g. levels detected in Australian drinking water, 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.

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

- A review of existing advice (guidelines/guidance) 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 relevant data from existing guidelines/guidance 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 or update (as applicable to each PFAS under consideration) of supporting information sections in a factsheet.

The overall approach to reviewing evidence for different sections of a 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* • Risk summary • Derivation of guideline value	• Search for relevant guidance/guidelines that can be used to update the existing PFAS factsheet including inclusion of two additional PFAS (PFBS and GenX chemicals) if appropriate • Screen and assess quality of existing guidance/guidelines 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**) • Present summary of findings (including the derivation of any potential options for guideline values for consideration by NHMRC and the Water Quality Advisory Committee) • Report details of methods used to search and 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 • Risk management options	• Review existing factsheet information for currency (if available) • Scan and collate evidence that could be used to update existing information or inform development of a new factsheet • Present summary of findings • Report details of literature search.
* 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.	

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 PFOS, PFOA, PFHxS, PFBS and GenX chemicals in drinking water causes adverse health effects? What is the critical human health endpoint that determines this value? What are the justifications for choosing this endpoint? What other recent guideline values exist? If there are existing guidance/guideline values, are the proposed option/s for health-based 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?
Health considerations	What are the key adverse health hazards from exposure to PFOS, PFOA, PFHxS, PFBS and GenX chemicals in Australian drinking water?
Typical Australian water levels or exposure profile [(a)]	What are the typical levels in Australian drinking water supplies, considering distributed drinking water and households using their own borewater, rainwater or surface water for drinking? Do they vary around the country or under certain conditions e.g. drought? What other factors should be considered (e.g. differences between groundwater versus surface water sources)?
Risk summary	What are the risks to human health from exposure to PFOS, PFOA, PFHxS, PFBS and GenX chemicals in Australian drinking water? Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review or further research?
(a) The level of detail involved in answering this question will be similar to that for the supporting information evidence scan.	

Evidence review for health-related advice in factsheets

Criteria for considering existing guidelines/guidance

Study designs for adopt/adapt approach	Guidelines/guidance on PFOS, PFOA, PFHxS, PFBS and GenX chemicals developed by Australian and international agencies will be considered, including:

	• 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) Existing guidance/guidelines from other sources may also be considered. Existing guidance/guidelines will be screened and assessed against the applicable criteria outlined in the Assessment Tool provided in **Appendix C**.
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 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); cells as surrogates for human exposure will not be considered.
Exposure	The chemical/s of interest: • PFOS (CASRN 1763-23-1) • PFOA (CASRN 335-67-1) • PFHxS (CASRN 355-46-4) • PFBS (CASRN 375-73-5) and related compound potassium perfluorobutane sulfonate (CASRN 29420-49-3) • GenX chemicals (CASRN 13252-13-6 and 62037-80-3) Exposure parameters that will be considered for the chemicals of interest 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, foetal) • Exposure through drinking, cooking, washing, skin contact
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 drinking water) 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 than those used for derivation of the Guidelines would be of interest. Comparison to no exposure may be of interest to demonstrate that a particular level is below the 'no observed adverse effect level'.
Outcome(s)	The human health outcomes of concern from exposure to the chemicals of interest 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 PFOS, PFOA, PFHxS, PFBS and GenX chemicals 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 PFOS, PFOA, PFHxS, PFBS and GenX chemicals in drinking water considered to be safe or acceptable to human health during a short-term event

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/guidelines	The following sources will be searched and 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 Standards Australia New Zealand (FSANZ) ☒ Australian Pesticides and Veterinary Medicine Authority (APVMA) ☒ Other Australian agencies [Australian Industrial Chemicals Introduction Scheme] ☒ Other international agencies [US State Health Departments including Minnesota, Washington, Maine, Alabama, Alaska, Connecticut, Vermont, New Jersey, Michigan, Massachusetts,; Health Canada; Dutch National Institute for Public Health and the Environment (RIVM); German Bundesinstitut für Risikobewertung (BfR – Federal Institute for Risk Assessment)] ☐ Other relevant sources [list any sources you intend to search]
Limits:	We will include: ☒ Publicly available documents of guidance/guidelines or evidence reviews supporting guidelines (near publication and consultation drafts will be accepted if available). ☐ Guidance/guidelines in languages other than English ☒ Superseded guidelines will not be considered unless requested (i.e. only the most current organisational guideline should be assessed in the first instance) ☒ Key publications provided by NHMRC and the Water Quality Advisory Committee will be considered ☐ Other [please specify]
Dates:	The search for existing guidance/guidelines will be conducted from December 15, 2016, corresponding to the cut-off date of the literature search conducted as part of the Australian derivation of health-based guidance values for PFOS, PFOA, and PFHxS[4]. No cut-off date will be used for PFBS and GenX.

Key search terms to be used:	• (PFAS) AND (drinking water) • (PFOS) OR (1763-23-1) AND (drinking water) OR (toxicity) • (PFOA) OR (335-67-1) AND (drinking water) OR (toxicity) • (PFHxS) OR (355-46-4) AND (drinking water) OR (toxicity) • (PFBS) OR (375-73-5) OR (29420-49-3) AND (drinking water) OR (toxicity) • (GenX) OR (13252-13-6) OR (62037-80-3) AND (drinking water) OR (toxicity) Note search terms may be refined depending on number of relevant hits.
Validation of search results	☐ Search results will be screened against key publications ☒ Other [no validation proposed as the searching will be conducted for existing health-based guidelines/guidance]
Screening search results:	☒ Screening of titles will be performed by researcher [MCRC] and verified by content expert [TH or GDN] 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
Discrepancy resolution:	☐ Consensus and/or third reviewer ☒ Other [no discrepancy resolution proposed, as single reviewer will screen records]
Excluded guidance/ guidelines	☒ All decisions taken during screening will be documented and outlined in the final report with a list of excluded guidance/guidelines and justification for their exclusion. (summary justification for title/abstract exclusions, full citations and justifications for full-text exclusions). ☐ Guidance/guidelines that are initially 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 GDN]. ☐ 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**). ☒ Health-based guideline values or equivalent guidance value for PFOS, PFOA, PFHxS, PFBS and GenX chemicals (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[12]]. ☒ 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 ☐ Other [please specify]
Data to be extracted from key studies underpinning guidance/ guidelines	☒ 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 (this will depend on the study)
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., combining raw data, meta-analysis or 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 each specified chemical, with associated additional considerations and assumptions. ☒ Table or Figure summarising findings of Assessment Tool (**Appendix C**) against all included guidelines [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 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 [please specify]
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 assessed by a content expert and a narrative summary provided ☒ Selected primary studies [(a)] underpinning derivation of existing guideline values will be assessed with a Risk of Bias tool [e.g., OHAT/modified OHAT[1] (**Appendix D**)], and information provided about the outcomes as a risk of bias rating ☐ 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	A summary of findings will be tabulated for consideration by NHMRC and the Water Quality Advisory Committee. See Reporting section below.
(a) Only selected studies will be subjected to a risk of bias assessment. The number of key studies subjected to such an assessment is dependent on available resources and will be agreed upon with NHMRC with advice from the Water Quality Advisory Committee.	

Supporting information in factsheet

Research questions

Supporting information	Research questions to consider
General description	Is the general description in the factsheet current for all 5 PFAS under review? What are the chemicals used for and how might people be exposed? How do the chemicals end up in drinking water and in what form?

[1] See Appendix D

Measurement	Is the measurement information in the factsheet current? What are the current analytical methods used to measure/detect the concentration of the specified chemicals in water? What are the limits of quantification or limit of reporting for these chemicals in drinking water? What are the indicators of the risks? How can we measure this exposure?
Treatment options	Is the information on treatment of drinking water in the factsheet current? What are the available options for removing the specified chemicals from drinking water?
Risk management options	What are the current practices to minimise or manage the risks identified?
Are there any additional sections that should be added to the factsheet? [Should anything be removed?]	

Evidence scan for supporting information

Criteria for considering evidence for supporting information

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

Search and screening methods

Expertise	The searches will be: ☒ verified by a content expert [TH or GDN] ☐ [conducted/informed/verified] by an information specialist [initials] ☐ independently peer reviewed.
Electronic databases	☒ MEDLINE/PubMed/TOXLINE ☐ EMBASE ☒ Scopus ☐ SciFinder ☐ Web of Science ☐ Other [please specify]

Other sources	☒ References identified in existing guideline reviews and/or key articles (backward searching) [(a)] ☐ Articles citing existing guideline reviews and/or key articles (forward searching) ☒ Systematic review references ☒ Data from government/ intergovernmental agencies [data contained within the reviews sourced as part of the health-related advice, Heads of EPA National Environment Management Plan, selected Department of Defence reports for contaminated sites] [(b)] ☒ 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, water corporations around Australia]
Limits:	Evidence to be considered will include: ☒ Peer reviewed published or in press studies ☒ Unpublished but publicly available studies (e.g. government reports) ☐ Ongoing studies (e.g. published water quality datasets) ☒ Key publications provided by NHMRC and the Water Quality Advisory Committee will be considered ☐ 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 health-based guideline/guidance value search will pick up reviews from which supporting information will be extracted. That search will be conducted from December 2016 for PFOS, PFOA and PFHxS to the present date, as this date coincides with the publication of the current NHMRC fact sheet for PFAS. No cut-off date will be used for PFBS and GenX. For the additional evidence scan for supporting information in the two scientific databases specified, a cut-off date of 2016 will be used for all 5 PFAS to ensure currency of the information.

Key search terms to be used:	• (PFOS) OR (1763-23-1) AND (treatment OR analysis) AND (drinking water) • (PFOA) OR (335-67-1) AND (treatment OR analysis) AND (drinking water) • (PFHxS) OR (355-46-4) AND (treatment OR analysis) AND (drinking water) • (PFBS) OR (375-73-5) OR (29420-49-3) AND (treatment OR analysis) AND (drinking water) • (GenX) OR (13252-13-6) OR (62037-80-3) AND (treatment OR analysis) AND (drinking water) Note search terms may be refined depending on number of relevant hits.
Validation of search results	☐ Search results will be screened against key publications [as understood by the reviewers/provided by NHMRC and/or the Water Quality Advisory Committee] ☒ Other [validation will not be undertaken due to resource constraints]
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 of titles will be performed by researcher [MCRC] and verified by content expert [TH or GDN] in Excel [note: might not be required for evidence scan] ☐ Screening will be performed by [initials] based on inclusion/exclusion criteria developed by [specify researcher/content expert/methodologist etc. and initials] in [specify software] and verified by [specify]
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.

(a) Key articles identified in this manner (i.e. from existing health-based reviews) will only be cited but not reviewed in detail (i.e. data extraction will not be undertaken separately for these key articles).

(b) The evidence scan will briefly collate relevant information to answer the research questions. A detailed review and data collation exercise for PFAS data at contaminated sites around Australia is outside the scope of the review. For example, this may involve selecting a few Department of Defence contaminated site reports (published online) and extracting concentration data for the relevant PFAS at offsite bores used for drinking water purposes.

Data collection and analysis

Expertise	☒ Data extraction will be performed by content expert [TH or GDN]. ☐ 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 [see **Appendix A** for the type of information that can be included in a search strategy]	☐	☒
	Process for selecting relevant guidance/guidelines (i.e. application of inclusion/exclusion criteria) and list of included and excluded guidance/guidelines (if any).	☐	☒
	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 key selected primary studies underpinning options for guideline values (i.e. use of risk of bias tool). Completed copy of risk of bias tool for each included key 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 (suitable guidelines) and potential options for Australian 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 NHMRC Water Team and members of 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 of day-to-day consulting activities at SLR Consulting and ToxConsult, Ms Hagen: • Has conducted numerous health risk assessments for clients where PFAS were the chemicals of potential concern requiring assessment. • 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. • Is currently preparing full evidence evaluations for the NHMRC for four inorganic chemicals considered as a result of lead replacement options in plumbing.
Mr Giorgio De Nola	As part of day-to-day consulting activities at SLR Consulting and ToxConsult, Mr De Nola: • Has conducted numerous health risk assessments as part of contaminated land audits as well as for other clients where PFAS were the chemicals of potential concern requiring assessment. • Has been involved in preparation and/or review of draft technical and evaluation reports for previous and/or current consultancies with NHMRC (evidence evaluations for 11 inorganic chemicals, full reviews for four inorganic chemicals).
Ms Maria Consuelo Reyes Campos	As part of day-to-day consulting activities at SLR Consulting and ToxConsult, Ms Reyes Campos: • Has been involved in literature searching for a current consultancy with NHMRC (full evidence evaluation for four inorganic chemicals considered as a result of lead replacement options in plumbing).

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. DoH (undated). Per- and Poly-fluoroalkyl substances (PFAS) Health Effects and Exposure Pathways. https://www.health.gov.au/sites/default/files/documents/2022/07/enhealth-guidance-health-effects-and-exposure-pathways-per--and-polyfluoroalkyl-substances-pfas.pdf

3. NHMRC (2018). Physical and Chemical Characteristics – Fact Sheets: Per-fluoroalkyl and poly-fluoroalkyl substances (PFAS). In: Australian Drinking Water Guidelines Version 3.5. National Health and Medical Research Council.

4. FSANZ (2017). Perfluorinated chemicals in food (and associated supporting documents). Food Standards Australia New Zealand. https://www.health.gov.au/resources/collections/perfluorinated-chemicals-in-food

5. OEHHA (2021). Notification Level Recommendation: Perfluorobutane Sulfonic Acid in Drinking Water. January 2021. California Office of Environmental Health Hazard Assessment. https://oehha.ca.gov/media/downloads/water/chemicals/nl/pfbsnl121820.pdf

6. MDH (2022). Toxicological summary for: Perfluorobutane sulfonate. Minnesota Department of Health. March 2022. https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf

7. Washington DoH (2021). Recommended State Action Levels for Per- and Polyfluoroalkyl Substances (PFAS) in Drinking Water: Approach, Methods and Supporting Information. Washington Department of Health. 331-673. Revised November 1, 2021. https://doh.wa.gov/sites/default/files/2022-02/331-673.pdf

8. US EPA (2022). Drinking water health advisory: Hexafluoropropylene oxide (HPFO) dimer acid (CASRN 13252-13-6) and HFPO dimer acid ammonium salt (CASRN 62037-80-3), also known as “GenX chemicals”. United States Environmental Protection Agency, Office of Water. EPA Publication # EPA/822/R-22/005. https://www.epa.gov/system/files/documents/2022-06/drinking-water-genx-2022.pdf

9. US EPA (2021). Human health toxicity values for hexafluoropropylene oxide (HPFO) dimer acid and its ammonium salt (CASRN 13252-13-6 and CASRN 62037-80-3). Also known as “GenX chemicals”. United States Environmental Protection Agency. October 2021. EPA Document Number 822R-21-010. https://www.epa.gov/system/files/documents/2021-10/genx-chemicals-toxicity-assessment_tech-edited_oct-21-508.pdf

10. US EPA (2022). Drinking water health advisory: Perfluorobutane sulfonic acid (CASRN 375-73-5) and related compound potassium perfluorobutane sulfonate (CASRN 29420-49-3). United States Environmental Protection Agency, Office of Water. EPA Publication # EPA/822/R-22/006. https://www.epa.gov/system/files/documents/2022-06/drinking-water-pfbs-2022.pdf

11. US EPA (2021). Human health toxicity values for perfluorobutane sulfonic acid (CASRN 375-73-5) and related compound potassium perfluorobutane sulfonate (CASRN 29420-49-3). United States Environmental Protection Agency. April 2021. EPA Document Number EPA/600/R-20/345F.

12. 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. 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? What will you do with publications that you aren't sure about?]
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 selected key study as agreed with NHMRC. 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 different study types can be removed 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**			
2.	**Allocation concealment**			
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 (++)	++