EVIDENCE EVALUATIONS FOR AUSTRALIAN DRINKING WATER GUIDELINES CHEMICAL FACT SHEETS - LEAD REPLACEMENTS IN PLUMBING

Silicon Evaluation Report

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BASIS OF REPORT

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EXECUTIVE SUMMARY

The National Health and Medical Research Council (NHMRC) has contracted SLR Consulting Australia Pty Ltd (SLR) to evaluate the existing guidance and evidence for several substances that have been flagged as potential lead replacement alloys in plumbing products in Australia, specifically bismuth, silicon, and selenium; lead is also included as an additional substance for review. The evidence reviews have been undertaken in line with a new methodological framework intended to implement best practice methods for evidence evaluations as per the 2016 *NHMRC Standards for Guidelines*.

This Evaluation Report summarises the evaluation undertaken for silicon. The methodology of the review is also provided in more detail in an accompanying Technical Report.

Although the targeted screening of existing health-based guidance using the agreed research protocol did not identify any candidate guidance/guideline values for silicon for potential adoption/adaptation, consultation of bibliographies of some of the agency reports did reveal the existence of an existing guidance value from EVM (2003). Nevertheless, a detailed review of the health-based literature was done.

From evaluation of the balance of the available information, it was concluded that oral silicon exposure appears to be of low hazard to humans. However, considering the limited toxicological database for silicon, additional studies which clarify the dose response for development of renal calculi in humans would be useful to confirm the likely low hazard to humans from silicon in drinking water.

The existing guidance value is considered relevant to the Australian context for potential adaptation. The candidate silicon drinking water guideline (DWG) derived by adapting the existing guidance value for silicon is 123 mg/L. In Australian drinking waters, mean source-water derived silicon concentrations may range from 0.6 to 90 mg/L depending on the region; these concentrations are all below the candidate DWG. However, exposure to silicon may also theoretically occur from leaching of silicon from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for silicon from lead replacements in plumbing products be generated for Australian conditions to inform this matter. Nevertheless, it is noted that no adverse effects were observed in the study used to derive the candidate DWG.

The concentration of the candidate DWG of 123 mg/L would be achievable with existing treatment technologies in distributed water and readily measurable with current commercial analytical techniques. Its achievability in waters at the tap is currently unknown due to lack of leachability data from lead replacements in plumbing products.

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Abbreviations/Definitions

Acronym	Definition
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
DWG	Drinking Water Guideline
EFSA	European Food Safety Authority
FSANZ	Food Standards Australia New Zealand
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg bw	Kilogram of Body Weight
L/day	Litres per Day
LOAEL	Lowest Observed Adverse Effect Level
LOR	Limit of Reporting
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
OEHHA	Californian Office of Environmental Health and Hazard Assessment
OHAT	United States Office of Health Assessment and Translation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB	Risk of Bias
RR	Relative Risk
RSC	Relative Source Contribution
SAS	Synthetic Amorphous Silica
SCC	Stress Corrosion Cracking
Si	Silicon
SiO_2	Silicon Dioxide
The Committee	NHMRC Water Quality Advisory Committee
The Guidelines	NHMRC and NRMMC (2011). Australian Drinking Water Guidelines 6 2011; Version 3.8 updated September 2022, National Health and Medical Research Council and Natural Resource Management Ministerial Council, Commonwealth of Australia, Canberra.
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

1 Introduction and Background

The National Health and Medical Research Council (NHMRC) has contracted SLR Consulting Australia Pty Ltd (SLR) to evaluate the existing guidance and evidence for several substances that have been flagged as potential lead replacement alloys in plumbing products in Australia, specifically bismuth, silicon, and selenium; lead is also included as an additional substance for review. The findings of these reviews are intended to be used by NHMRC to develop public health advice and/or health-based guideline values (if required) for inclusion in the *Australian Drinking Water Guidelines* (2011) (the Guidelines). The evidence reviews undertaken by SLR were governed by a newly designed methodological framework intended to implement best practice methods for evidence evaluations as per the 2016 *NHMRC Standards for Guidelines*. For each of the four substances, SLR was asked to:

- Customise and apply the 'Research Protocol' template provided by NHMRC to answer research questions. The research questions and specific requirements for the review varied slightly according to the substance being evaluated.
- Produce a Technical Report and an Evaluation Report for each substance.
    - The Technical Report is to capture the details and methods used to undertake each review.
    - The Evaluation Report is to interpret, synthesise and summarise the existing guidance and evidence pertaining to the research questions.

These tasks were performed in consultation with the NHMRC Water Quality Advisory Committee (the Committee) and NHMRC.

For bismuth and silicon (which currently do not have existing chemical factsheets in the Guidelines), the requirements of the evaluation were as follows:

1. Screen any existing guidance/guidelines on bismuth/silicon, and bismuth/silicon brasses (if available).
2. Review all primary studies and other relevant data.
3. Collate and review any useful supporting information for a potential chemical factsheet.

For the other two substances (lead and selenium), requirements 1 and 3 were completed in July 2022.

The report herein is the Evaluation Report for silicon.

1.1 Objectives

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.

The overarching objective of this review is to identify relevant information on the potential impact of exposure to silicon in drinking water on human health outcomes.

Another objective of the review is to undertake an evidence scan to inform development of supporting information (e.g. monitoring and treatment guidance) that is typically provided in a fact sheet.

2 Research Questions

Research questions for this review were drafted by SLR and peer reviewed and agreed upon by the Committee and NHMRC prior to conducting the literature searches. The research questions guiding the review are provided in **Table 1**.

Table 1 Research Questions for Evidence Evaluation of Silicon

#	Research Questions
Health-based	
1	What level of silicon in drinking water causes adverse health effects?
2	What is the endpoint that determines this value?
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?
4	Is there a knowledge gap from the time at which existing guideline values were developed?
5	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)?
6	What are the key adverse health hazards from exposure to silicon in Australian drinking water?
7	Are there studies quantifying the health burden (reduction or increase) due to silicon?
8	What is the critical human health endpoint for silicon?
9	What are the justifications for choosing this endpoint?
Exposure Profile	
10	What are the typical silicon levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?
11	Are there any data for silicon levels leaching into water from in-premise plumbing?
Risk Summary	
12	What are the risks to human health from exposure to silicon in Australian drinking water?
13	Is there evidence of any emerging risks that require review or further research?
Supporting Information on Factsheet	
14	What is silicon used for and how might people be exposed?
15	How is the concentration of silicon measured in drinking water?
16	What are the indicators of the risks? How can we measure exposure?
17	What analytical methods are currently used to measure silicon in drinking water?
18	What are the limits of quantification or limit of reporting for silicon in drinking water?
19	How is drinking water treated to minimise silicon concentrations?
20	What are the current practices to minimise or manage the risks identified?

3 Methodology Overview

As part of the review, a number of literature searches were undertaken to target specific information relevant to answering the research questions. They consisted of the following:

- A targeted literature search of existing health-based guidance/guidelines. Jurisdictions included in this search were those previously identified by ToxConsult (2019) as providing reliable information and meeting a large proportion of pre-determined technical and administrative criteria. They included the 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 Environmental Health and Hazard Assessment (OEHHA), Food Standards Australia New Zealand (FSANZ), and the Australian Pesticides and Veterinary Medicines Authority (APVMA).
- An additional literature search was undertaken in two scientific databases for published studies relevant to addressing the health-related research questions. One relevant existing health-based guidance value was identified for silicon from national and international agencies, but it was identified as a result of consulting the bibliographies of papers identified in the full review of the literature. A full review of the literature was undertaken (as opposed to simply undertaking an evidence scan for any recent health-based information that could impact the guidance/guideline value).
- An additional evidence scan of recent publicly available literature for supporting information in the fact sheet (e.g. general description, uses, measurement techniques and limits of reporting in drinking water, treatment options, etc).

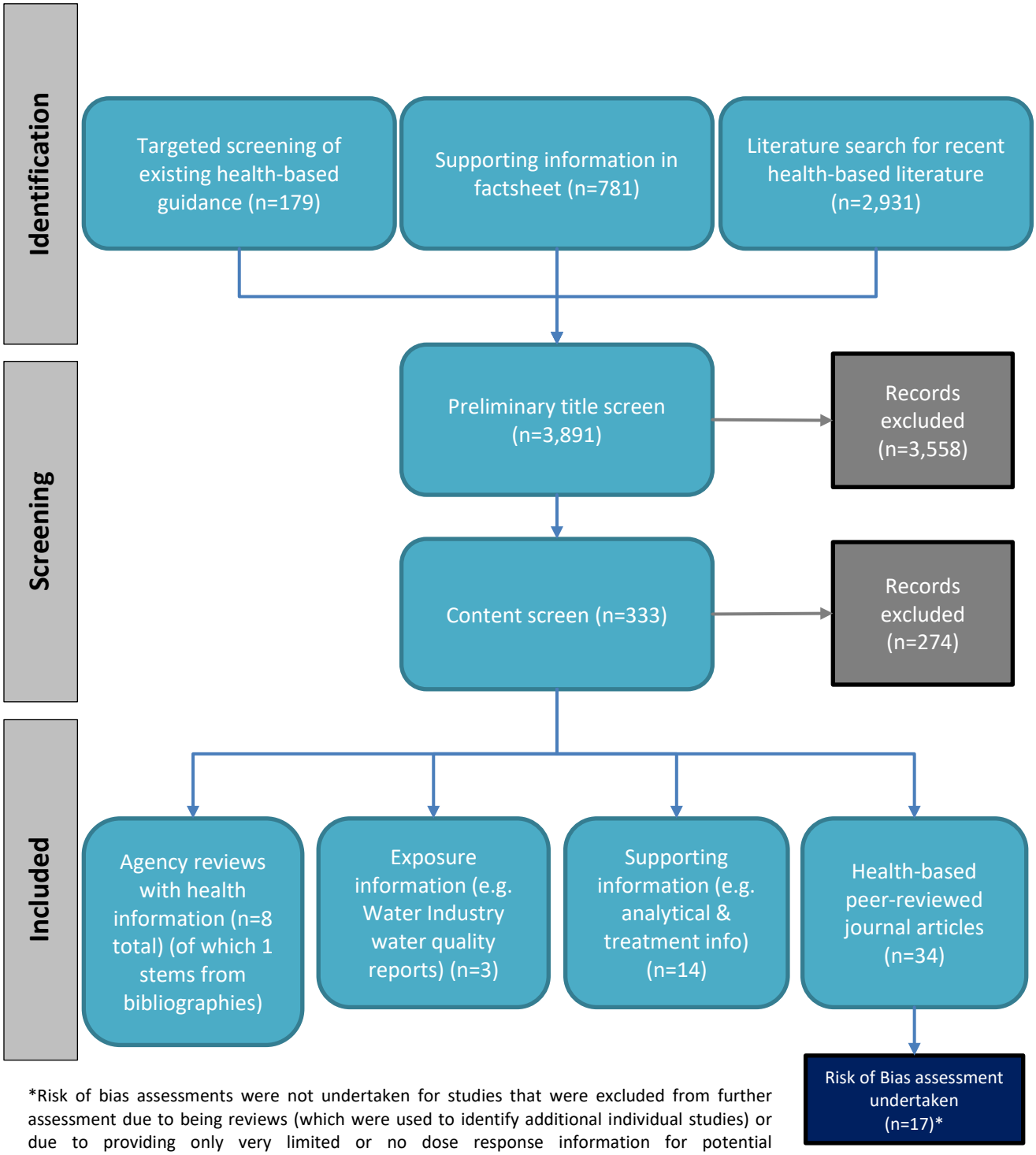
Results were subjected to the following steps in order to identify the most relevant information:

- A preliminary title screen where titles of results were scanned by a researcher and a decision recorded regarding relevance of the result; and
- A content screen where full text content of reports/reviews/articles selected to be included from the preliminary title screen step were reviewed in relation to the research questions by a subject expert to determine which to include in data extraction.

Relevant data were extracted by populating various pre-constructed tables which focused on data needed to answer the research questions. Synthesis was conducted by presenting summarised extracted data in tabular format for each individual research question. For each candidate jurisdiction's guideline/guidance value identified for silicon (note only one was identified in the search conducted), an evaluation of existing jurisdiction guidelines was undertaken with respect to a defined list of administrative and technical criteria (previously defined by ToxConsult 2019 and NHMRC). All critical studies deemed relevant for defining the dose response of silicon were subjected to a risk of bias (RoB) assessment with the use of a RoB tool (i.e. modified Office of Health Assessment and Translation, or OHAT, tool). Outcomes of these assessments were provided as a RoB rating. The reader is referred to the accompanying Technical Report for the detailed methodology, records of the literature screening process (including all records that were excluded) and all data extraction, Assessment Tool and RoB tables. This Evaluation Report also presents summary tables for the following:

- Threshold doses of silicon associated with no adverse effects and critical adverse health effects. This was presented along with study bias/quality.
- Overall certainty of evidence for different health endpoints / evidence streams where possible. This considered the overall confidence of the body of evidence with regard to RoB, indirectness/applicability, imprecision, inconsistency between studies and publication bias, with information provided as an overall confidence rating.

Figure 1 shows an overview of the literature search process followed for silicon. This is presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that describes the study selection process and numbers of records at each stage of screening (Moher et al. 2009).



*Risk of bias assessments were not undertaken for studies that were excluded from further assessment due to being reviews (which were used to identify additional individual studies) or due to providing only very limited or no dose response information for potential guidance/guideline value development.

Figure 1 Overview of literature search process followed for Silicon

This report provides the summary of the findings (**Section 4**), a discussion of the results (**Section 5**), and conclusion (**Section 6**). Where health-based information was considered reasonable for potential derivation of a guideline value, calculations of prospective drinking water guidelines (DWGs) were undertaken using the methodology and default assumptions outlined in the Guidelines (NHMRC and NRMMC 2011).

The default equation is outlined in NHMRC and NRMMC (2011, Section 6.3.3) and has been adapted below as **Equation 1**. In this instance, units have been added in to show how they cancel out and the 'animal dose' in the equation can in fact be an animal or human dose, since both data types may be used to derive DWGs. In some instances, if adaptation of existing guidance values was considered, these guidance values may already incorporate the safety factor shown in the denominator of **Equation 1**.

Guideline value (µg/L) =

$$\frac{animal\ or\ human\ dose\ (\mu g/kg\ bw/d)\ x\ human\ weight\ (kg\ bw)\ x\ proportion\ of\ intake\ from\ water\ (fraction)}{volume\ of\ water\ consumed\ (L/d)\ x\ safety\ factor\ (unitless)}$$

……**Equation 1**

Default assumptions typically used in the Guidelines are 70 kg bw for adult human body weight (or 13 kg bw for 2-year old child or 5 kg for an infant), 10% (0.1) for the proportion of intake from drinking water (apart from bottle-fed infants, where 100% is used), and 2 L/day of water consumed by an adult (1 L/day by a child, 0.75 L/day by a bottle-fed infant).

It is noted that various experimental studies have used different forms of silicon (e.g. silicate salts, silica-based food additives, etc). It is unknown what species of silicon would likely be present in drinking water as a result of leaching from plumbing materials; due to the paucity of information on soluble silica salts, oral health effects information for silicates and silica was also considered relevant for the purposes of this review.

4 Results

The targeted screening of existing health-based guidance using the agreed research protocol identified no existing health-based guidance/guideline values for silicon in the literature consulted, however upon consultation of the bibliographies of the available agency reviews for silicon, one report from the United Kingdom (UK) Expert Group on Vitamins and Minerals (EVM 2003) was identified which provides a health-based guidance value for silicon. In addition to the agency reports consulted, responses to research questions were informed by the data extractions conducted for the various experimental animal (EA) studies, cross-sectional (CrSe), cohort (Co) and human controlled trials (HCT) found in the literature reviewed.

Detailed summary findings tables for each research question are provided in the Technical Report. In this Evaluation Report, the research question tables have been condensed to highlight differences between the various studies where they have been identified.

4.1 Health-based aspects

Research Questions 1-9 all cover health-based aspects of the review; this is considered to be the central information of a potential fact sheet. **Table 2** provides a synthesis of the results.

Table 2 Summary of findings from data extraction for health-based research questions

#	Research Questions	Response
1	What level of silicon in drinking water causes adverse health effects?	No existing health-based guideline values were found for silicon in drinking water. However, EVM (2003) derived an oral guidance value of 25 mg/kg bw/day supplemental silica (equivalent to 12 mg/kg bw/d elemental silicon) from chronic / carcinogenicity studies in rats and mice in which no treatment-related adverse effects were observed at the highest dose of amorphous silica administered via the diet (i.e. 2,500 mg/kg bw/day in rats; 7,500 mg/kg bw/d in mice) (Takizawa et al. 1988). This guidance value has been used to derive a candidate guideline value for silicon in drinking water in **Section 5.2.2**.
2	What is the endpoint that determines this value?	The highest dose tested in a dietary chronic / carcinogenicity study in rats where no adverse treatment-related effects were observed (i.e. NOAEL = 2,500 mg/kg/d).
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?	The available guidance value from EVM (2003) is likely relevant to the Australian context for dietary exposures to food-grade amorphous silica. Although EFSA (2004) commented that the extrapolation of these data to other forms of silicon (such as silicates) is inappropriate, EFSA (2009, 2018a) later used the guidance value from EVM (2003) in an evaluation of the safety of various silicates (calcium silicate, silicon dioxide, silicic acid gel, orthosilicic acid-vanillin complex) as sources of silicon in food. It is unknown what form silicon from silicon brasses will likely be in if it were to leach from lead-replacement plumbing, but it likely will be in the form of solubilised silicon (e.g. orthosilicic acid)); if this is assumed to be correct, the EVM (2003) guidance value is likely relevant to the Australian context. It is noted the form of silicon does not appear to have any marked bearing on the oral toxicity of silicon, since no adverse effects have been identified in experimental animal studies conducted with various forms of silicon.
4	Is there a knowledge gap from the time at which existing guideline values were developed?	A detailed literature review of primary studies was undertaken for health-based information for silicon. The literature review identified numerous studies however the majority of the critical information would have been available to EVM (2003) at the time the EVM guidance value was derived. Thus, the additional information would be unlikely to alter the assessment done by EVM (2003).
5	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)?	

#	Research Questions	Response
6	What are the key adverse health hazards from exposure to silicon in Australian drinking water?	In humans, apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon (EFSA 2010, FAO/WHO 1974, EFSA 2018c). EFSA (2018c) also indicates the occurrence of urinary silicate calculi is seldom (0.1-0.2% of all urinary stones) and the association between silicate antacid use and renal calculi is 'possible' but not 'definite', which means it cannot be excluded that the occurrence of renal calculi and intake of silicates is a chance finding. Indeed, available epidemiological information (albeit limited) and some animal studies suggests a potential protective effect of silicon in drinking water to various health endpoints (see the response to Question 7). Experimental studies in rats have also found no treatment-related adverse effects from dietary administration of various silicon compounds, whereas one study in dogs (diet bolus dose, Newberne and Wilson 1970) and two in guinea pigs (drinking water, Dobbie and Smith 1982; Markovic and Arambasic 1971) found renal histopathological findings when animals were administered sodium silicate or magnesium trisilicate or suspended quartz (but not aluminium silicate). EFSA (2018c) commented that kidney effects observed in dogs were most probably related to the large amount of test compound consumed as a bolus dose by the animals. The effects on the kidney reported in guinea pigs could be due to higher concentrations of silicate in the primary urine because of lower glomerular filtration rates in guinea pigs (2.29 mL plasma/min per kg) compared to rats (4.63 mL plasma/min per kg). EFSA (2018c) noted that, in humans, the glomerular filtration rate (3.56 mL plasma/min per kg) is higher than in guinea pigs and kidney effects have generally not been found in humans despite the wide and long-term use of high doses of magnesium trisilicate (up to 4 g/person per day) as an antacid over decades. Other toxicological studies conducted in rats with micronised synthetic amorphous silica (SAS) have found no treatment-related adverse effects in these animals (e.g. Lewinson et al. 1994, Wolterbeek et al. 2015, Yoo et al. 2022, Liang et al. 2018).
7	Are there studies quantifying the health burden (reduction or increase) due to silicon?	Available epidemiological information (albeit limited) suggests a potential protective effect of silicon in drinking water for a few different endpoints (e.g. age-adjusted death rate from cancer, cognitive decline, dementia, and Alzheimer's disease, mortality for cardiovascular disease) (Burton et al. 1980, Gillette-Guyonnet et al. 2007, Jacqmin-Gadda et al. 1996, Najda et al. 1991).
8	What is the critical human health endpoint for silicon?	As indicated in the response to Question 6, most publications have not identified any adverse effects from exposure to silicon in humans, rats, mice, and rabbits. In humans, according to EFSA (2010) and FAO/WHO (1974) apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon. Indeed, this may still be a chance finding and definite causality has not been established. Nevertheless, one study with dogs and another two with guinea pigs found histopathological renal lesions after administration of some forms of silicates (sodium and magnesium silicate, suspended quartz). This may be the critical health endpoint for silicon exposure, but from the available information, humans appear to be markedly less sensitive to these effects compared to dogs or guinea pigs.
9	What are the justifications for choosing this endpoint?	

#	Research Questions	Response
NOAEL = No Observed Adverse Effect Level.		

4.2 Exposure-related aspects

Another important aspect the potential fact sheet would cover is exposure-related considerations. This is important for consideration of whether exposures by Australians to the chemical evaluated are potentially approaching a health-based guidance value that will be used for deriving a candidate DWG. It is also important for considerations of whether typical levels of the chemical considered in Australian drinking water supplies would generally remain below any derived DWG. Research Questions 10-11 cover exposure-related aspects of the review. For these aspects, drinking water quality reports from various water corporations around Australia were consulted in addition to the literature sourced as part of the health-based review and the supporting information. **Table 3** provides a synthesis of the results.

Table 3 Summary of findings from data extraction for exposure-related research questions

#	Research Questions	Findings
10	What are the typical silicon levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?	Concentrations of silicon measured around Australia appear to vary depending on remoteness of the region and potentially therefore source of drinking water. • In Victoria in 2020, concentrations in drinking water ranged from 2.3 to 7.2 mg/L (Melbourne Water 2021). • In Northern Territory in 2019-2020, mean values ranged from 5.2 to 49 mg/L (PWNT 2020). • In Western Australia in 2019-2020, mean values ranged from 0.6 to 90 mg/L (WCWA 2020). Data were also found for other countries with silicon concentrations in drinking water typically ranging from 0.4 to 72 mg/L.
11	Are there any data for silicon levels leaching into water from in-premise plumbing?	One study (Choucri et al. 2021) investigated the corrosion behaviour and stress corrosion cracking (SCC) susceptibility of two leaded alloys and one lead-free silicon brass and investigated this in simulated drinking water solutions containing different chloride concentrations. All brass types, particularly one of the two leaded alloys, exhibited susceptibility to SCC. However, no relevant quantitative data for silicon was found in the literature consulted. It is suggested that leachability data for silicon from lead replacements in plumbing products be generated for Australian conditions to provide information on the form/species of silicon in lead replacements and leachates as well as potential exposure concentrations.

4.3 Risk-based aspects

Research Questions 12 and 13 are risk-based considerations. The publications subjected to detailed data extraction mentioned at the start of **Section 4** were also consulted to answer these questions. **Table 4** presents a summary of the findings.

Table 4 Summary of findings from data extraction for risk-based research questions

#	Research Questions	Findings
12	What are the risks to human health from exposure to silicon in Australian drinking water?	No risks to human health from exposure to silicon in drinking water identified in any of the publications reviewed. Most publications did not identify any adverse effects from exposure to silicon in humans, rats, mice, and rabbits. In humans, apart from occasional case reports of renal stones (for which no dose response information was found in the literature consulted), mainly associated with long-term use of silicate-containing antacids (e.g. as magnesium trisilicate), there is little evidence of adverse effects of orally ingested silicon. Therefore, the human health risks from exposure to silicon in Australian drinking water at the source are likely low, but this is based on limited information. It is also noted exposure to silicon may also theoretically occur from leaching of silicon from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. Therefore the extent of exposure to silicon at the tap is technically unknown. It is suggested that leachability data for silicon from lead replacements in plumbing products be generated for Australian conditions to inform this.
13	Is there evidence of any emerging risks that require review or further research?	None identified, however the toxicological database for silicon is limited. Clarification of the dose response for development of renal calculi in humans would be useful to confirm the likely low risk of harm to humans from silicon in drinking water.

4.4 Supporting information

Supporting information in fact sheets for chemicals in the Guidelines (NHMRC and NRMMC 2011) typically consist of a brief general description of the chemical (i.e. uses of silicon, sources in drinking water), typical values in Australian drinking water, treatment of drinking water, and measurement (i.e. analytical) considerations. The remaining Research Questions 14-20 cover the supporting information of the review. For these aspects, in addition to consulting the previously mentioned sources (e.g. the drinking water quality reports from various water corporations and utilities around Australia, the health-based literature identified in the targeted search), additional targeted searches were undertaken (for details, refer to Technical Report). **Table 5** provides a summary of the results.

Table 5 Summary of findings from data extraction for supporting information

#	Research Questions	Findings
14	What is silicon used for and how might people be exposed?	Silicon is a ubiquitous element present in the environment. Silicon occurs naturally in foods as silicon dioxide (SiO_2, silica) and silicates. High levels of silicon are found in foods derived from plants, and particularly cereals, whereas silicon levels are lower in foods from animal sources. Silica is mainly found as insoluble silicates, but small amounts of soluble silicon are naturally present in water, chiefly as orthosilicic acid, $Si(OH)_4$ which is the most bioavailable source of silicon. Amorphous silica is used as a food additive, in particular as an anti-caking agent, but also to clarify beverages, control viscosity and as an anti-foaming agent and dough modifier. It is also used as an anti-caking agent and as an excipient in pharmaceuticals for various drug and vitamin preparations. Silicon brasses with various compositions have also been developed to induce grain refining and strength increase or to produce lead- and arsenic-free alloys with good machinability for plumbing product purposes. As mentioned under the exposure-related aspects (see **Section 4.2**), theoretically silicon could leach from lead replacements in plumbing albeit no quantitative published data were found to ascertain the form of silicon nor the concentrations found in tap waters in households as a result of leaching.
15	How is the concentration of silicon measured in drinking water?	Most commonly this is by inductively coupled plasma-mass-spectrometry (ICP-MS), Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) or Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) according to USEPA Methods SW-846, 3005A, 3010A, 3015A, 3051A, 6010, 6020, 6020A & 29. Other methods cited in the literature include the use of spectrophotometric analysis using specialised processes.
16	What are the indicators of the risks? How can we measure exposure?	Silicon (or silica) can be monitored in drinking water, but there are also concomitant intakes in food and dietary supplements. Exposure in drinking water can be measured using the techniques outlined in the response to Research Question 15.
17	What analytical methods are currently used to measure silicon in drinking water?	See response to Question 15.
18	What are the limits of quantification or limit of reporting for silicon in drinking water?	In Australian commercial laboratories this is 0.05 to 0.5 mg/L, depending on the laboratory. In other published literature, the limits of quantification are cited as 0.003-0.01 mg/L (Ghaffari et al. 2021, Selianova et al. 2010).
19	How is drinking water treated to minimise silicon concentrations?	Very limited information was found to answer this Research Question. One study mentions a strongly basic anion exchange resin in the deionisation process by distillation or reverse osmosis (Dayanand et al. 2019). Another paper also found reverse osmosis to reduce tap water silicon concentrations by about ~55% (from 2.2 to 0.95 mg/L) (Dobbie and Smith 1986). Silicon exposure could theoretically occur post-treatment due to leaching from lead replacements in plumbing.
20	What are the current practices to minimise or manage the risks identified?	No data were found to answer this Research Question.

DWG = Drinking Water Guideline. LOR = Limit of Reporting. ICP = Inductively Coupled Plasma. MS = Mass Spectrometry. AES = Atomic Emission Spectroscopy.

5 Discussion

This section provides an overview of the dose response for silicon along with a discussion of the overall confidence in the health-based literature for possible use in derivation of a potential guideline value for silicon. This includes consideration of RoB of individual studies (see **Appendix D** – Technical Report). A RoB analysis for two example study types (one case report, one experimental animal study) was independently conducted by two content experts. Although there was disagreement between the two content experts for 1-2 of the evaluated aspects, the disagreement did not markedly change the overall RoB rating for the two studies. This gave reasonable confidence that the RoB ratings would be reasonably reproducible. Due to the resources available for this project, one of the content experts conducted the remaining RoB evaluations.

Individual RoB assessments were summarised in tables for each body of evidence by study design. The findings for individual studies were grouped together as much as possible based on the reported health outcomes. Overall RoB ratings for each body of evidence by health outcome were determined using guidance from OHAT (2019) and considered alongside aspects such as imprecision, unexplained inconsistency, indirectness, publication bias, dose response, etc. to determine overall confidence ratings.

5.1 Dose response and overall confidence by evidence stream

5.1.1 Existing health-based guidance

Although the targeted screening of existing health-based guidance using the agreed research protocol did not identify any candidate guidance/guideline values for silicon for potential adoption/adaptation, consultation of bibliographies of some of the agency reports did reveal the existence of an existing guidance value from EVM (2003).

EVM (2003) derived an oral guidance value (termed a 'safe upper level' of intake)[1] of 25 mg/kg bw/day supplemental silica (equivalent to 12 mg/kg bw/d elemental silicon) from chronic / carcinogenicity studies in rats and mice in which no treatment-related adverse effects were observed at the highest dose of amorphous silica administered via the diet (i.e. 2,500 mg/kg bw/day in rats; 7,500 mg/kg bw/d in mice) (Takizawa et al. 1988). In this study, groups of forty B6C3F1 mice and forty Fisher rats were fed 0, 12,500 (1.25%), 25,000 (2.5%) or 50,000 ppm (5%) SYLOID (food grade micronised silicon dioxide) in the diet for up to 21 months in mice and 24 months in rats. Although doses were not provided by Takizawa et al. (1988), EVM (2003) indicates this was equivalent to 1,900 – 7,500 mg/kg bw silica or 900 to 3,500 mg Si/kg/d in mice. In rats, EVM (2003) states the top dose is equivalent to 2,500 mg/kg/d as silica. EVM (2003) applied an uncertainty factor of 100 (10x for inter-species variation, 10x for human variability) to the top dose in rats (2,500 mg silica/kg/d) to derive the guidance value of 25 mg silica/kg/d (i.e. 12 mg Si/kg/d). At a body weight of 70 kg, this would equate to a 'safe upper level' of intake of 840 mg Si/day for an adult.

[1] This is an intake of silicon that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence (EVM 2003).

No significant treatment-related effects were seen at any dose on mortality, body weight, food consumption, clinical signs, clinical laboratory examinations, gross or histopathology. The occasional presence of some neoplasms did not reveal any consistent, dose-related trends in any group. In mice, tumours attributed to the treatment of SYLOID were found in the haematopoietic organs, particularly malignant lymphoma/leukaemia, which occurred in 7/20 (35%) females of the 2.5% dosage group as opposed to 2/16 (12.5%) in controls. However, a Cochran-Armitage test for positive dose-related trends in the incidence of tumours was not significant. In rats, the incidence of tumours showed no significant differences between the control and treated groups (with controls frequently having higher incidences, but not significantly so). A RoB summary table for the critical study underpinning the EVM (2003) oral guidance value is presented in **Table 6** below.

Table 6 RoB summary for critical experimental animal study used by EVM (2003) to derive guidance value for silicon

Health outcome:	**All health endpoints (no adverse effects)**
Study ID:	**Takizawa et al. 1988**
Selection bias	
Randomization	--
Allocation concealment	NR (2)
Comparison groups appropriate	
Confounding bias	
Confounding (design/analysis)	
Performance Bias	
Identical experimental conditions	--
Blinding of researchers during study?	NR (2)
Attrition/Exclusion Bias	
Missing outcome data	--
Detection Bias	
Exposure characterisation	NR (1)
Outcome assessment	NR
Selective Reporting Bias	
Outcome reporting	--
Other Sources of Bias	
Other threats	
Overall risk of bias across studies (not likely/serious/very serious)	Not likely (1)

-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Although the criterion of low RoB was not met for exposure characterisation (considered to be one of the key domains), this was not considered to be serious since this was due to the study not reporting the purity of the test substance, but there being no cause for concern that could lead to large bias in exposure.
2. This was conservatively assigned 'NR', however due to the study outcomes being objective measures, it may be considered unlikely that these domains would have markedly biased the study outcomes. Thus bias for these domains could potentially be interpreted as 'probably low RoB' instead of 'NR'.

It was also considered by SLR whether the derived guidance value would likely be protective of urinary calculi which are seldom found in humans, which may or may not be associated with silicon exposure (see **Section 5.2.1**). EFSA (2018c) describe a few case reports: i) one case with renal colic from taking 2 g (i.e. 2,000 mg, or 640 mg Si) magnesium trisilicate (as an antacid) with every meal for many years (i.e. ~1,920 mg Si/day)[2], ii) cases are mostly found in adults but have been described in rare cases in children where they were associated with consumption of milk thickener containing 5.5% silicates in one case of a 6-month old boy (Si intake unknown), or iii) milk powder dissolved in silicate-rich mineral water (estimated daily intake 200 mg silicate) in a 10-month old boy. The dose resulting in renal colic in the first case report (~1,920 mg Si/day)[3] is greater than the dose associated with the EVM (2003) 'safe upper level' (i.e. 840 mg Si/day), which at least provides an indication that the EVM (2003) guidance value is also likely protective of renal effects in humans, albeit there is uncertainty whether such effects are due to silicon.

In addition, the existing health-based guidance value for silicon from EVM (2003) has been evaluated using the Assessment Tool provided in **Appendix F** of the Technical Report. This tool evaluates the document against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. The overall suitability of the guidance/guideline value for adoption/adaption can be gauged at least partially by examining the percentage of 'must-have', 'should-have', and 'may-have' criteria met by each jurisdiction. The EVM (2003) document met 75% (15/20)[4] of the 'must-have' criteria, 50% (5/10) of the 'should-have' criteria and 0% (0/2) of the 'may-have' criteria. This probably indicates moderate confidence in administrative and technical aspects in the EVM (2003) document. Most of the missing criteria related to limited or no information provided with respect to the literature search undertaken, which is not uncommon for agency documentation produced around that time.

5.1.2 Cross-sectional and cohort studies

A few cohort / cross-sectional / ecological studies investigating health effects of silicon in drinking water (or dialysis fluid) were identified in the literature consulted (see **Table 7**). None of these studies found overt adverse effects or positive associations between exposures and adverse health effects. Conversely, some suggested a significant protective effect for silica in drinking water.

Table 7 Summary of cross-sectional / cohort / ecologic studies on silicon in drinking water (or dialysis fluid)

Study	Findings	Concentration of silicon in water/ fluid (mg/L)
Neurological disorders (e.g. cognitive decline, dementia, Alzheimer's disease) (no effects observed)		
Prospective cohort: Rondeau et al. 2009	Large prospective cohort study (15-year follow-up) found no association for silica exposure in drinking water or bottled water [up to a silica (silicon) concentration of 22.4 (10.5) mg/L in tap water, 77.6 (36.5) mg/L in bottled water) and cognitive decline, dementia, and Alzheimer's disease in France.	Tap water = 10.5 Bottled water = 36.5

[2] If it is assumed three meals were ingested per day this would equate to an intake of ~1,920 mg Si/day.

[3] A more conservative approach of assuming two meals per day (i.e. 1,280 mg Si/day) would still be greater than the EVM (2003) 'safe upper level'.

[4] Note three of the 'must-have' criteria were technically not applicable, however they have been counted in the 'must-have' criteria. Hence one could also say that 12/17 (i.e. 71%) of 'must-have' criteria were met, with three additional sets of criteria not being applicable.

Study	Findings	Concentration of silicon in water/ fluid (mg/L)
Cross-sectional: Jacqmin-Gadda et al. 1996	No significant association between silica concentration (4.2-22.4 mg/L, i.e. 2.0 – 10.5 mg Si/L) in drinking water and cognitive impairment, suggested a **protective** effect of silica against aluminium from drinking water.	2.0 – 10.5
Mortality from cancer (protective effect)		
Cross-sectional: Burton et al. 1980	For Si concentrations 0 to 15 mg/L in drinking water, there was a significant regression and **negative** correlation with age-adjusted death rate from cancer in the USA. For the rest of the range of concentrations (15-70 mg/L), there was no further significant reduction in death rates.	0 – 15.0
Mortality from cardiovascular disease (no effect)		
Ecological study: Rapant et al. 2015 (1)	Study authors concluded that SiO_2 in drinking water (18.21 mg/L, i.e. 8.6 mg Si/L) is unlikely to be causally related to relative mortality for cardiovascular disease even though a statistical relationship between the two factors was observed.	8.6
No overt health effects		
Observational study: Gitelman et al. 1992(2)	Exposure to silicon in dialysis fluids (1.9-5.2 mg/L) can increase silicon levels in plasma. No overt adverse health effects from silicon exposure in dialysis fluid in end-stage renal disease but study limited by the limited endpoints examined.	1.9 – 5.2 (dialysis fluid)
Renal effects		
Ecological study: Mascarenhas et al. 2017	Study authors make a large claim in terms of silica exposure in groundwater (at 115.5 mg/L but not at ~13.5 mg/L) (i.e. 54 mg Si/L but not at ~6.3 mg Si/L) being the potential cause for chronic kidney disease observed in some villages in India. However, no statistical analysis or odds ratios were calculated in this study and no correction for confounders was undertaken. The authors used the results of *in vitro* cytotoxicity assays as the basis for such an association.	6.3 - 54

1. No RoB assessment has been undertaken on this study, as it provides limited information on the hazards of silicon in groundwater. The study authors concluded that SiO_2 is unlikely to be causally related to relative mortality for cardiovascular disease even though a statistical relationship between the two factors was observed. According to the study authors the relationship observed between Si concentration in drinking water and relative mortality of cardiovascular disease (ReI) is mediated by the relationship between calcium, magnesium, calcium plus magnesium and ReI rates. The SiO_2 content therefore does not have a causal relationship with ReI rather, the relationship is stochastic. In epidemiological terms, this is known as collinearity. Collinearity means that within a set of observations, some of the factors are (nearly) totally predicted by the other factors. While there are statistical methods to distinguish which factor is the truly influential factor, in the study by Rapant et al. (2015), the known biological links between calcium or magnesium and ReI give plausibility to the interpretation that SiO_2 does not have a causal relationship with ReI (Rapant et al. 2015). As the paper does not provide any useful dose response information for guidance/guideline value development, it was not subjected to RoB assessment.
2. This study shows that exposure to silicon in dialysis fluids can increase silicon levels in plasma. It suggests no overt adverse health effects from silicon exposure in dialysis fluid in end-stage renal disease but is obviously limited by the limited endpoints examined. As the study does not provide dose response information for potential derivation of a guidance/guideline value for drinking water, it was not subjected to RoB assessment.

A RoB summary table for the included studies is presented in **Table 8** below, separated into different health outcomes (neurological disorders, mortality, and renal effects). An overall RoB rating of 'not likely' (for no effect on neurological disorders), 'serious' (for a protective effect on mortality from cancer), or 'very serious' (for renal effects) was determined for the health outcomes based on varying RoB across the studies.

Table 8 RoB summary table for epidemiological studies investigating health effects of silicon exposure

Health outcome:	No neurological disorders		No increased mortality from cancer	Renal effects
Study ID:	**Rondeau et al. 2009 (Co)**	**Jacqmin-Gadda et al. 1996 (CrSe)**	**Burton et al. 1980 (CrSe)**	**Mascarenhas et al. 2017 (Ecol)**
Selection bias				
Randomization				
Allocation concealment				
Comparison groups appropriate	--	-	NR	-
Confounding bias				
Confounding (design/analysis)	--	-	-	++
Performance Bias				
Identical experimental conditions				
Blinding of researchers during study?				
Attrition/Exclusion Bias				
Missing outcome data	--	NR	-	NR
Detection Bias				
Exposure characterisation	-	-	--	--
Outcome assessment	-	NR	-	NR
Selective Reporting Bias				
Outcome reporting	--	-	NR	NR
Other Sources of Bias				
Other threats			++	++
Overall risk of bias across studies (not likely/serious/very serious)	Not likely [1]		Serious [2]	Very Serious [3]

Co = Cohort, CrSe = Cross-sectional, Ecol = Ecological.

-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Based on relatively consistent low RoB for the majority of key domains (potential RoB only identified for one of the two studies due to lack of information provided).
2. Based on high RoB from other threats (it is unclear from the publication whether statistical analysis used was appropriate, as no normality tests appear to have been conducted; in addition, the data do not appear to have been adjusted for many socioeconomic and lifestyle factors which could also influence outcome).
3. Based on high RoB for confounding and other threats. The study authors make a large claim in terms of silica exposure in groundwater (at 115.5 mg/L but not at ~13.5 mg/L) being the potential cause for chronic kidney disease (CKD) observed in some villages in India. However, no statistical analysis or odds ratios were calculated in this study and no correction for confounders was undertaken. The authors used the results of *in vitro* cytotoxicity assays as the basis for such an association.

The initial confidence rating for the prospective cohort is considered moderate, since there was no controlled exposure, but being prospective, exposure occurred prior to measuring the outcome, individual outcome data were assessed, and a comparison group was used. For the other studies initial confidence is low (or very low). **Table 9** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'moderate to high' (for no neurological effects), 'low' (for no mortality from cancer) or 'very low' (for renal effects) for the body of evidence for each health outcome.

Table 9 Confidence Rating for cross-sectional / cohort / ecologic studies on silicon exposure

Health outcome [number of studies]	No neurological effects [2]	No increased mortality from cancer [1]	Renal effects [1]	**Comment** [(1)]
Initial confidence rating	**LOW (CrSe) to MODERATE (Co)**	**LOW**	**VERY LOW**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence				
Risk of Bias	Not likely. Not downgraded.	Serious. Downgraded to **VERY LOW**.	Very serious. Cannot downgrade further.	Based on overall RoB across studies as per **Table 8.**
Unexplained inconsistency	Not serious.	Not serious.	Not serious. Only one study.	Studies appear to be consistent in terms of their findings (i.e. no adverse effects noted), with the exception of the study by Mascarenhas et al. 2017 for renal effects (study was deemed to have very serious RoB). Confidence not downgraded as it was only one study.
Indirectness	Not serious.	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Not serious.	Serious. Cannot downgrade further.	No large standard deviations or large ratios for RR in cohort study. Serious for observational study by Mascarenhas et al. (2017), as study does not clearly meet the guidance for 'not serious' or 'very serious'.
Publication bias	Undetected.	Undetected.	Detected. Cannot downgrade further.	Undetected (no downgrade) for most studies, except Mascarenhas et al. (2017) for which publication bias was detected from large unsubstantiated claims made.
Factors Increasing Confidence				
Magnitude	Not large.	Not large.	Not large.	No effect noted, so confidence not upgraded for large magnitude of effect.
Dose response	No. Confidence not upgraded.	No. Confidence not upgraded.	No. Confidence not upgraded.	No dose response found, except with respect to potential protective effect (up to a certain threshold).
Residual confounding	No.	No.	No.	No residual confounding identified. Confidence not upgraded.

Health outcome [number of studies]	No neurological effects [2]	No increased mortality from cancer [1]	Renal effects [1]	**Comment** [(1)]
Consistency across species	Yes. Upgraded to **MODERATE to HIGH.**	Yes. Upgraded to **LOW.**	No. Not upgraded.	Results of no adverse effects reported for the endpoints examined in these studies (except for Mascarenhas et al. 2017) is consistent with findings in most experimental animal studies (see **Section 5.1.4**). Confidence upgraded in these studies.
Final confidence rating	**MODERATE to HIGH**	**LOW**	**VERY LOW**	-

Co = Cohort; CrSe = Cross-sectional; RR = Relative Risk.

1. As per guidance provided in OHAT (2019, Table 7)

5.1.3 Human (un)controlled study

In a human, single blinded, (un)controlled, first-in-man study, although a limited number of endpoints were monitored, no overt adverse health effects were seen in any of the 20 healthy male subjects (18-35 years of age) after oral administration of 9 grams/day of precisely engineered mesoporous silica[5] (for use as a food additive) for 21 days in normal weight individuals or an additional 10 weeks for obese individuals (Hagman et al. 2020). Using the body weights reported in the paper, the daily dose equates to a NOAEL for overt health outcomes of 80 to 110 mg Si/kg bw/d, taking into consideration very limited health outcomes were assessed in this study. The study was considered to have a 'very serious' RoB (see **Table 10** below) based on high RoB for lack of blinding of research personnel, and potential RoB for one of the key domains (i.e. exposure characterisation), as there is indirect evidence that exposure may not have been consistently administered across treatment groups.

Table 10 RoB summary for human (un)controlled trial

Health outcome:	**No clinical signs or changes in biochemical parameters, creatinine, or serious adverse events**
Study ID:	**Hagman et al. 2020**
Selection bias	
Randomization	-
Allocation concealment	+
Comparison groups appropriate	
Confounding bias	
Confounding (design/analysis)	
Performance Bias	
Identical experimental conditions	
Blinding of researchers during study?	++
Attrition/Exclusion Bias	
Missing outcome data	--
Detection Bias	
Exposure characterisation	+
Outcome assessment	-
Selective Reporting Bias	

[5] Mesoporous materials are special types of nanomaterials with ordered arrays of uniform nanochannels. It is recognised this study is likely not entirely relevant to the research questions of this project which relate to the silicon that may leach from silicon brasses used for lead-replacement plumbing.

Outcome reporting	-
Other Sources of Bias	
Other threats	
Overall risk of bias across studies (not likely/serious/very serious)	Very serious [1]

-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Based on high RoB for lack of blinding of research personnel in a human (un)controlled trial, and potential RoB for one of the key domains (i.e. exposure characterisation), as there is indirect evidence that exposure may not have been consistently administered across treatment groups.

The initial confidence rating for the human uncontrolled study evidence is considered 'moderate', as it was an uncontrolled (not a controlled) trial. **Table 11** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'very low'.

Table 11 Confidence Rating for Human Uncontrolled Study on Silicon

Health outcome [number of studies]	**No clinical signs, or changes in biochemical parameters, creatinine, or serious adverse events [1]**	**Comment** [1]
Initial confidence rating	**MODERATE**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence		
Risk of Bias	Very serious. Downgraded to **VERY LOW.**	Confidence downgraded based on very serious overall RoB (see **Table 10**).
Unexplained inconsistency	Not serious.	No unexplained inconsistency identified. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Serious. Cannot be downgraded further.	Small sample size (n=20 exposed individuals) render the results imprecise.
Publication bias	Potential detected. Cannot be downgraded further.	Some of the authors of paper declared a commercial affiliation to the pharmaceutical manufacturer whereas other authors declare no competing interests. Single study.
Factors Increasing Confidence		
Magnitude	Not large.	This human uncontrolled trial investigated limited health outcomes and does not meet the classic consideration for magnitude of response. Confidence not upgraded.
Dose response	No.	No effects observed and only one dose administered. Confidence not upgraded.
Residual confounding	No.	No residual confounding identified that could have resulted in an overstating of the effect. Confidence not upgraded.
Consistency across species	N/A	Not applicable, since there is only one human (un)controlled trial. Confidence not upgraded.
Final confidence rating	**VERY LOW**	

1. As per guidance provided in OHAT (2019, Table 7)

5.1.4 Experimental animal studies

Numerous controlled experimental animal studies have been conducted with silicate compounds and soluble silicon (see **Table 12**).

Table 12 Summary of experimental animal studies with silicon

Study	Exposure circumstance	Effects observed	Endpoint (mg Si/kg bw/d unless otherwise stated)
No adverse effects			
Austin 1978	Soluble silicon ($Na_2SiO_3.9H_2O$) administered to mice (n=27), rabbits (n=3), monkey (n=1), or dog (n=1) in drinking water for 4 months at 50 or 1,000 mg/L.	No adverse effects	NOAEL = 1,000 mg Si/L
Jugdaohsingh et al. 2008, 2015a	Soluble silicon (as orthosilicic acid) administered to rats and mice in feed and water for 26 weeks (rats) or 15-19 weeks (mice).	No adverse effects at highest dose tested.	NOAEL = 4.08 (supplemented group rats), 18.51 (reference group rats), 57.4 (mice)
Najda et al. 1991 (1)	Reagent grade sodium metasilicate nonahydrate ($Na_2SiO_3.9H_20$—REACHIM) administered to rats in drinking water for 18 weeks (with progressively increasing concentrations, 6 weeks at each dose of 100, 200 or 400 mg Si/kg/d).	Suggested beneficial effect of silicon on lipid parameters (very limited parameters investigated).	NOAEL = 400
Takizawa et al. 1988	1.25-5% SYLOID (food grade micronised silica) administered in diet to rats or mice for ~2 years.	No adverse effects in rats or mice	NOAEL = 2,500 (rats) NOAEL = 3,500 (mice) (note doses of SYLOID were provided in the study, but not doses of Si; doses of Si ascertained from doses reported by EVM 2003).
Lewinson et al. 1994	Standard toxicological package for oral acute, subacute, chronic and carcinogenicity studies with hydrophobic amorphous nanosilicas (2)	No adverse effects	Lowest NOAEL (24-mth carcinogenicity study) was highest dose tested = 100
Liang et al. 2018	Silica microparticles administered via gavage to rats for 90 days.	No adverse effects	NOAEL = 1,500 (top dose)
Wolterbeek et al. 2015	Synthetic amorphous silica (SAS) administered via gavage to rats in a 2-generation toxicity study.	No adverse effects	NOAEL = 1,000 (top dose)
Yoo et al. 2022	Food grade SAS and precipitated SAS administered to rats via gavage for 28 days.	No adverse effects	NOAEL = 2,000 (top dose)
Gloxhuber et al. 1983	Zeolithe A (an aluminosilicate) fed to rats in diet for 2 years.	No adverse effects	NOAEL = 58.47 (males), 62.15 (females), corresponding to ~8.8 mg Si/kg/d (males) and ~9.3 mg Si/kg/d (females) (top dose)

Study	Exposure circumstance	Effects observed	Endpoint (mg Si/kg bw/d unless otherwise stated)
Renal effects			
Dobbie and Smith 1982	Magnesium trisilicate (7.5 mg/L, i.e. 16-32 mg Si/kg/d) administered to guinea pigs in tap water for 4 months. Other groups received crushed quartz or granite in tap water.	Focal tubule-interstitial nephritis in 6/6 guinea pigs. Similar but less intense lesions in 2/6 animals receiving crushed quartz. No lesions in crushed granite group.	LOAEL = 16-32 (single dose tested)
Newberne and Wilson 1970	Silicon dioxide, aluminium silicate, sodium silicate or magnesium trisilicate (~370 mg Si/kg/d) administered to rats or dogs for 4 weeks.	No adverse effects in rats	NOAEL = 370
		Renal lesions in dogs from sodium silicate and magnesium trisilicate	LOAEL = 370
Markovic and Arambasic 1971	Quartz suspension (at 50 and 250 mg SiO_2/L) given to guinea pigs for up to 6 months.	Nephropathy after 2-3 months	No NOAEL identified (amount of water ingested not provided). Effects observed at 50 mg SiO_2/L

NOAEL = No Observed Adverse Effect Level. LOAEL = Lowest Observed Adverse Effect Level.

1. This study suggests a beneficial effect of silicon. Very limited parameters were investigated (no pathology or histopathology done), therefore this study provides limited information regarding the silicon dose response. As this study is unlikely to be a key critical study for dose response assessment, it was not subjected to RoB assessment.
2. Information for nanosilicas may not be entirely relevant to silica subject of this report.

A RoB summary table for the included experimental animal studies is presented in **Table 13** below, separated into different health outcomes (no adverse effects or renal effects). A determination of 'serious' (no adverse effects) or 'very serious' (renal effects) RoB was reached depending on the health outcome, as there was substantial potential RoB across most of the studies composing the body of evidence for each health outcome [see Table 10 in OHAT (2019)].

Table 13 RoB summary for experimental animal studies with silicon

Health outcome:	No adverse effects									Renal effects		
Study ID:	**Austin 1978**	**Jugdaohsingh et al. 2008**	**Jugdaohsingh et al. 2015a**	**Takizawa et al. 1988**	**Lewinson et al. 1994**	**Liang et al. 2018**	**Wolterbeek et al. 2015**	**Yoo et al. 2022**	**Gloxhuber et al. 1983**	**Dobbie and Smith 1982**	**Newberne and Wilson 1970**	**Markovic and Arambasic 1971**
Selection bias												
Randomization	+	NR	-	--	NR	NR	--	NR	NR	NR	NR	NR
Allocation concealment	NR(3)	+	+	NR(3)	NR(3)	NR(3)	--	NR(3)	NR(3)	NR(3)	NR(3)	NR(3)
Comparison groups appropriate												
Confounding bias												
Confounding (design/analysis)												
Performance Bias												
Identical experimental conditions	-	--	--	--	--	-	--	--	--	-	-	-
Blinding of researchers during study?	NR(3)	-	-	NR(3)	NR(3)	NR(3)	NR(3)	NR(3)	-	NR(3)	NR(3)	-
Attrition/Exclusion Bias												
Missing outcome data	NR	--	--	--	--	-	+	--	-	NR	--	NR
Detection Bias												
Exposure characterisation	NR	-	-	NR	-	NR	+	NR	NR	NR	NR	+
Outcome assessment	NR	-	-	NR	NR	-	-	-	-	-	NR	NR
Selective Reporting Bias												
Outcome reporting	+	--	--	--	-	-	--	--	+	-	NR	+
Other Sources of Bias												
Other threats					++							
Overall risk of bias across studies (not likely / serious/ very serious)	Serious (1)									Very serious (2)		

-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Based on relatively consistent high selection bias and inconsistent detection bias (or these aspects generally not being reported in the studies) and other threats in one study.
2. Based on many aspects not being reported in the studies, and potentially high bias in one study, leading to potential selection, performance, attrition, detection and selective reporting bias.
3. This was conservatively assigned 'NR', however due to the study outcomes being objective measures, it may be considered unlikely that these domains would have markedly biased the study outcomes. Thus bias for these domains could potentially be interpreted as 'probably low RoB' instead of 'NR'.

The initial confidence rating for the experimental animal information is considered high for all studies, since each consisted of controlled exposures with exposures occurring prior to the outcome measurement, provided individual outcome data (in most instances) and used a comparison (or control) group. **Table 14** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'moderate' (no adverse effects) or 'very low' (renal effects) depending on the health outcome.

Table 14 Confidence Rating for Experimental Animal Studies with Silicon

Health outcome [number of studies]	**No adverse effects** [9]	**Renal effects** [3]	**Comment** [(1)]
Initial confidence rating	**HIGH**	**HIGH**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence			
Risk of Bias	Serious. Downgraded to **MODERATE.**	Very serious. Downgraded to **LOW.**	Serious or very serious for reasons specified in **Table 13**. Confidence downgraded accordingly.
Unexplained inconsistency	Not serious. Not downgraded.	Serious. Downgraded to **VERY LOW.**	Experimental studies in rats have consistently found no treatment-related adverse effects from dietary (or drinking water) administration of various silicon compounds. One study in dogs (diet bolus dose, Newberne and Wilson 1970) [(2)] and two in guinea pigs (drinking water, Dobbie and Smith 1982; Markovic and Arambasic 1971) found renal histopathological findings when animals were administered sodium silicate, magnesium trisilicate, or suspended quartz (but not aluminium silicate). EFSA (2018c) commented that kidney effects observed in dogs were most probably related to the large amount of test compound consumed as a bolus dose by the animals [(2)]. The effects on the kidney reported in guinea pigs could be due to higher concentrations of silicate in the primary urine because of lower glomerular filtration rates in guinea pigs compared to rats. EFSA (2018c) noted that in humans the glomerular filtration rate is higher than in guinea pigs and kidney effects have generally not been found in humans despite the wide and long-term use of high doses of magnesium trisilicate (up to 4 g/person per day) as an antacid over decades. Other toxicological studies conducted in rats with micronised SAS have found no treatment-related adverse effects in these animals. Hence inconsistency in studies finding renal effects is considered serious, as the inconsistency may be due to non-relevance to humans.
Indirectness	Not serious.	Not serious	Studies conducted in mammalian model systems are assumed to be relevant for humans (i.e. not downgraded) unless compelling evidence to the contrary is identified (which it was not). Confidence not downgraded.

Health outcome [number of studies]	**No adverse effects** [9]	**Renal effects** [3]	**Comment** [(1)]
Imprecision	Not serious.	Not serious.	No or minimal indications of large standard deviations, specifically in studies considered to be potentially critical for guideline value derivation. Confidence not downgraded.
Publication bias	Potentially detected in 1 of 9 studies. Not downgraded.	Not detected.	Unlikely. Mixture of studies with authors from different areas (industry, University research organisations, etc). Publication bias only potentially identified in 1 of 9 studies finding no adverse effects. Confidence not downgraded.
Factors Increasing Confidence			
Magnitude	Not large.	Not large.	Magnitude of response not really relevant to animal studies. Confidence not upgraded.
Dose response	No. No clear dose response as no treatment-related adverse effects were found in these studies.	No. Only limited dose groups and no clear indication of dose response.	No clear dose response. Confidence not upgraded.
Residual confounding	No.	No.	Not relevant for animal studies. Confidence not upgraded.
Consistency across studies	No.	No.	Most studies conducted in rats and mice showed consistency across studies and species. However, studies in guinea pigs and dogs were somewhat inconsistent with findings in mice and rats. Confidence not upgraded.
Final confidence rating	**MODERATE**	**VERY LOW**	-

(1) As per guidance provided in OHAT (2019, Table 7)

(2) It is noted, however, that in the Newberne and Wilson (1970) study, dogs were administered the test compound in a highly palatable diet. It is not completely clear from the study whether this was done by bolus capsule along with a palatable diet or mixed into the diet; according to EFSA (2018c) administration occurred via bolus dosing which suggests delivery by capsule together with the diet (also not an unusual form of administration in dog studies). SLR has relied partially on the EFSA (2018c) interpretation of this study.

5.2 Overall Evaluation

5.2.1 Hazard identification conclusions

The analysis in **Section 5.1** indicated a range of very low to high confidence in the overall body of evidence for the epidemiological and human (un)controlled study depending on the health outcome investigated whereas there was low to moderate confidence in the overall body of evidence for the experimental animal studies.

In accordance with the OHAT framework for systematic review and evidence integration (OHAT 2019, Figure 2), this indicates the conclusions shown in **Table 15**.

Table 15 Hazard identification conclusions for silicon

Health endpoint [number of studies]	Certainty rating	Conclusion	NOAEL/LOAEL (mg Si/kg/d unless otherwise stated)?
No neurological effects			
Cohort [1]	**HIGH**	There is moderate to high confidence in the body of evidence for no adverse association (i.e. no adverse effect) between exposure to silicon in drinking water and neurological effects. Indeed, a protective effect was observed in one of the two studies.	None identified (concentrations in water: 2-36.5 mg/L)
Cross-sectional [1]	**MODERATE**		
No increased mortality from cancer			
Cross-sectional [1]	**LOW**	There is low confidence in the body of evidence for no adverse association (i.e. no adverse effect) between exposure to silicon in drinking water and increased mortality from cancer in humans. Indeed, a protective effect was observed.	None identified (concentrations in water: 0-15 mg/L)
Renal effects			
Cross-sectional / observational [1]	**VERY LOW**	There is insufficient evidence available in humans to assess if exposure to silicon is associated with renal effects.	Insufficient
Experimental animal study [3]	**VERY LOW**	There is insufficient evidence in the body of evidence from experimental animal studies for an association between exposure to silicon (as magnesium trisilicate, sodium silicate or suspended quartz) and renal effects in guinea pigs and dogs (but not rats).	LOAEL = 16-32 (guinea pigs, single dose); 370 (dogs, single dose) NOAEL = 370 (rats, single dose)
No adverse effects			
Human uncontrolled trial [1]	**VERY LOW**	There is insufficient evidence available in humans to assess if exposure to silicon is associated with no adverse effects.	NOAEL = 80-110
Experimental animal study [9]	**MODERATE**	There is moderate confidence in the body of evidence from experimental animal studies for no adverse association (i.e. no adverse effect) between exposure to silicon (as soluble silicon, orthosilicic acid, sodium meta silicate nonahydrate, food grade micronized silica, hydrophobic amorphous nanosilica, silica microparticles, an aluminosilicate compound called Zeolithe A) and a range of standard toxicological endpoints investigated in these experiments.	Various NOAELs: from 2-yr chronic study, 2500 (rats), 3000 (mice) as silica

In summary, from **Table 15** there is:

- Moderate to high confidence from a prospective cohort study and a cross-sectional study of no adverse effects of silicon exposure on neurological effects (i.e. cognitive decline, dementia, and Alzheimer's disease). Note no NOAEL/LOAEL was identified in these studies, therefore this endpoint could not be used for potential guideline derivation.
- Low confidence from a cross-sectional study of no adverse effects of silicon exposure on mortality from cancer.

- Very low confidence (i.e. insufficient evidence) for renal calculi in humans from silicon exposure based on case report information (reviewed by other agencies), a cross-sectional/observational study, and from experimental animal studies for renal lesions observed in guinea pigs and dogs exposed to sodium silicate, magnesium trisilicate, or suspended quartz. It is noted the effects noted in animals are unlikely to be relevant to humans at the doses administered due to the exposure circumstances in those studies (potentially large bolus doses delivered in the diet) and the lower glomerular filtration rate of guinea pigs.
- Very low confidence (i.e. an inadequate level of evidence) for no health effects from a human (un)controlled study.
- A moderate level of confidence for no adverse health effects from most of the experimental animal studies (conducted in rats, mice, rabbits, a monkey, and a dog) with exposures to various silicon-containing compounds. The NOAEL from Takizawa et al. (1988), one of the experimental animal studies, was used for candidate guidance/guideline value derivation (see **Section 5.2.2**).

On the balance of the available information, silicon appears to be of low hazard to humans from oral exposure. Considering the limited toxicological database for silicon, additional studies which clarify the dose response for development of renal calculi in humans would be useful to confirm the likely low hazard to humans from silicon in drinking water.

5.2.2 Candidate guidance/guideline values

As indicated in **Section 5.1.1**, an existing guidance value was identified in the literature consulted which could potentially be adapted/adopted for the Guidelines. The potential resulting DWG using this guidance value is summarised in **Table 16**.

In potential adaptation of the guidance value of 12 mg Si/kg/d to the Australian context, the relative source contribution that drinking water can make to the total intake of silicon was considered. No data for typical exposures to silicon by Australians was found in the literature search undertaken. However, EVM (2003) indicated exposures in Europeans are likely to be as follows:

- Up to 50 mg/day from food (i.e. for a 70 kg adult this equates to 0.71 mg/kg/d).
- Up to 500 mg/day from supplements (i.e. for a 70 kg adult this equates to 7.14 mg/kg/d).

This leaves ~4 mg/kg/d (i.e. guidance value of 12 mg Si/kg/d minus total intake from food and supplements of 7.85 mg/kg/d) to be potentially attributed to drinking water exposures, i.e. ~30% of the guidance value. This indicates that use of 30% (0.3) as the relative source contribution factor for derivation of a drinking water guideline via adaptation of the EVM (2003) guidance value could be explored (rather than a default value of 10% or 0.1).

It is noted the critical study (Takizawa et al. 1988) selected by EVM (2003) for derivation of a guidance value is amongst the information for which there is moderate confidence (see **Table 15**) and for which a NOAEL is available.

Table 16 Potential drinking water guideline value (mg/L) resulting from adaptation of silicon guidance value from EVM (2003)

Parameter	EVM 2003
Critical study	Takizawa et al. 1988
Study population	Rats
Form of silicon studied	SYLOID (food grade micronised silicon dioxide)

Parameter		EVM 2003
Exposure route		Diet
Study timeframe		2 years
Critical Effect		No adverse effects reported
Point of Departure (mg/kg/d)		NOAEL: 2,500 (as silica), 1,175 (as silicon)
Uncertainty factors	UF_A	10
	UF_H	10
	$UF_{timeframe}$	-
	$UF_{database}$	-
	$UF_{composite}$	100
Health-based guidance value (mg/kg/d)		11.75 (as silicon)
Relative source contribution (RSC) to drinking water		30% (i.e. 0.3)
Resulting adaptation to a Health Based DWG(1) (mg/L)		123

DWG = Drinking Water Guideline; NOAEL = No Observed Adverse Effect Level; UF_A = Uncertainty factor for extrapolation from animals to humans; UF_H = Uncertainty factor for human variability; $UF_{timeframe}$ = Uncertainty factor for use of a short-term study; $UF_{composite}$ = Composite (i.e. total) uncertainty factor; $UF_{database}$ = Uncertainty factor to account for the limited database of toxicological studies (e.g. no reproductive/developmental toxicity studies and only limited experimental animal studies are available).

1. Adaptation of guidance value has been undertaken using the default assumptions for derivation of DWGs in Australia using the following equation as outlined in NHMRC (2021), with the exception of the relative source contribution of drinking water to overall intake which was adjusted from 10 to 30% (i.e. from 0.1 to 0.3) as outlined in the text preceding this table:

   DWG (mg/L) = [Guidance value (mg/kg bw/d) x 70kg (adult) x 0.3 for adult] ÷ 2 L/day for adult

The candidate silicon DWG derived by adapting an existing guidance value for silicon in the diet is 123 mg/L. In Australian drinking waters mean source-water derived silicon concentrations may range from 0.6 to 90 mg/L depending on the region. These concentrations are below the candidate DWG shown in **Table 16**, suggesting that silicon in distributed water is unlikely to present a human health risk in Australia. However, exposure to silicon may also theoretically occur from leaching of silicon from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. Thus the risk to human health from silicon in water at the tap is strictly speaking unknown. It is also nevertheless noted that no adverse effects were observed in the study used to derive the DWG. It is suggested that leachability data for silicon from lead replacements in plumbing products be generated for Australian conditions to inform this matter.

6 Conclusions

Although the targeted screening of existing health-based guidance using the agreed research protocol did not identify any candidate guidance/guideline values for silicon for potential adoption/adaptation, consultation of bibliographies of some of the agency reports did reveal the existence of an existing guidance value from EVM (2003). Nevertheless, a detailed review of the health-based literature was done.

From evaluation of the balance of the available information, it was concluded that oral silicon exposure appears to be of low hazard to humans. However, considering the limited toxicological database for silicon, additional studies which clarify the dose response for development of renal calculi in humans would be useful to confirm the likely low hazard to humans from silicon in drinking water.

The existing guidance value is considered relevant to the Australian context for potential adaptation. The candidate silicon DWG derived by adapting the existing guidance value for silicon is 123 mg/L. In Australian drinking waters mean source-water derived silicon concentrations may range from 0.6 to 90 mg/L depending on the region. These concentrations are below the candidate DWG shown in **Table 16**, suggesting that silicon in distributed water is unlikely to present a human health risk in Australia. However, exposure to silicon may also theoretically occur from leaching of silicon from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. Thus the risk of exposure to silicon in water at the tap is strictly speaking unknown. It is nevertheless noted that no adverse effects were observed in the study used to derive the DWG. It is suggested that leachability data for silicon from lead replacements in plumbing products be generated for Australian conditions to inform this matter.

The concentration of the candidate DWG of 123 mg/L would be achievable in distributed water with existing treatment technologies and readily measurable with current commercial analytical techniques. Its achievability in waters at the tap is currently unknown due to lack of leachability data from lead replacements in plumbing products.

7 Review Team

Name	Position	Responsibilities
Ms Tarah Hagen, MSc, DABT, RACTRA	Technical Director – Toxicology & Risk Assessment, SLR	Report author and technical oversight of literature review
Ms Maria Consuelo Reyes Campos, MSc	Project Consultant – Land Quality & Remediation	Literature searching, preliminary title screen, compilation of Appendices
Mr Giorgio De Nola, MSc, RACTRA	Principal Consultant – Toxicology & Risk Assessment, SLR	Internal peer review

8 Declared Interests

Team Member	Declaration of Interest
Ms Tarah Hagen	As part day-to-day consulting activities at SLR Consulting and ToxConsult Pty Ltd, Ms Hagen has: • Provided the report "Assessment of International and National Agency Processes for Deriving HBGVs and DWGs" to NHMRC. This has been used to inform the methodological framework for this review as described in the Research Protocol. • Been involved in preparation and/or review of draft and final technical and evaluation reports for a previous consultancy with NH&MRC (evidence evaluations for 11 inorganic chemicals).
Ms Maria Consuelo Reyes Campos	No interest to declare.
Mr Giorgio De Nola	As part day-to-day consulting activities at SLR Consulting Mr De Nola has: • Been involved in preparation and/or review of draft and final technical and evaluation reports for a previous consultancy with NH&MRC (evidence evaluations for 11 inorganic chemicals).

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