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

Bismuth 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 bismuth. The methodology of the review is also provided in more detail in an accompanying Technical Report.

No existing health-based guidance/guideline values relevant to bismuth were found in the literature search undertaken. Therefore, a detailed review of the health-based literature was done. The dose response information in the available human studies is considered insufficient for derivation of guidance/guideline values for bismuth. From the available experimental animal studies, there is one repeat dose study of sufficient quality which could be considered for guidance/guideline value derivation.

The candidate bismuth drinking water guideline (DWG) derived using the experimental animal study is 11.67 mg/L. The very limited information identified on potential source-water derived exposure concentrations of bismuth in drinking waters indicates exposures from these sources are likely to be orders of magnitude below the candidate DWG. However, exposure to bismuth may also theoretically occur from leaching of bismuth from low-lead plumbing materials, although no leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for bismuth from lead replacements in plumbing products be generated for Australian conditions to inform this matter.

The concentration of the candidate DWG of 11.67 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.

CONTENTS

DOCUMENT REFERENCES

TABLES

CONTENTS

FIGURES

Abbreviations/Definitions

Acronym	Definition
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
Bi	Bismuth
BiOCl	Bismuth Oxychloride
BIPP	Bismuth Iodoform Paraffin Paste
CaS	Case Study
CSF	Cerebrospinal Fluid
De-Nol	Refers to drug product containing Bismuth Tripotassium Dicitrate. De-Nol, TDB and colloidal bismuth subcitrate (CBS) are sometimes used interchangeably depending on the publication.
DWG	Drinking Water Guideline
EA	Experimental Animal (Study)
EFSA	European Food Safety Authority
F	Female
FSANZ	Food Standards Australia New Zealand
GI	Gastrointestinal
HCT	Human Controlled Trial
ICP-MS(AES)	Inductively Coupled Plasma Mass Spectrometry (Atomic Emission Spectroscopy)
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg bw	Kilogram of Body Weight
L/day	Litres per Day
LD_{50}	Median Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
LOR	Limit of Reporting
LTQ-MS	Linear Ion Trap Mass Spectrometer
M	Male
MPT	Microwave Plasma Torch
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
PUD	Peptic Ulcer Disease
RoB	Risk of Bias
TDB	Tripotassium Dicitrato Bismuthate

Acronym	Definition
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
WQAC	NHMRC Water Quality Advisory Committee

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 NHMRC's Water Quality Advisory Committee (WQAC) and NHMRC.

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

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

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 bismuth.

1.1 Objectives

There is currently no Australian drinking water guideline or existing Fact Sheet for bismuth. Nevertheless, bismuth 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 bismuth 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 WQAC 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 Bismuth

#	Research Questions
Health-based	
1	What level of bismuth 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 bismuth in Australian drinking water?
7	Are there studies quantifying the health burden (reduction or increase) due to bismuth?
8	What is the critical human health endpoint for bismuth?
9	What are the justifications for choosing this endpoint?
Exposure Profile	
10	What are the typical bismuth levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?
11	Are there any data for bismuth levels leaching into water from in-premise plumbing?
Risk Summary	
12	What are the risks to human health from exposure to bismuth in Australian drinking water?
13	Is there evidence of any emerging risks that require review or further research?
Supporting Information on Fact Sheet	
14	What is bismuth used for and how might people be exposed?
15	How does the specific chemical end up in drinking water and in what form?
16	How is the concentration of bismuth measured in drinking water?
17	What are the indicators of the risks? How can we measure exposure?
18	What are the limits of quantification or limits of reporting for bismuth in drinking water?
19	How is drinking water treated to minimise bismuth 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. As no relevant existing guidance/guideline values were identified for bismuth from national and international agencies, a full review of the literature was required (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).

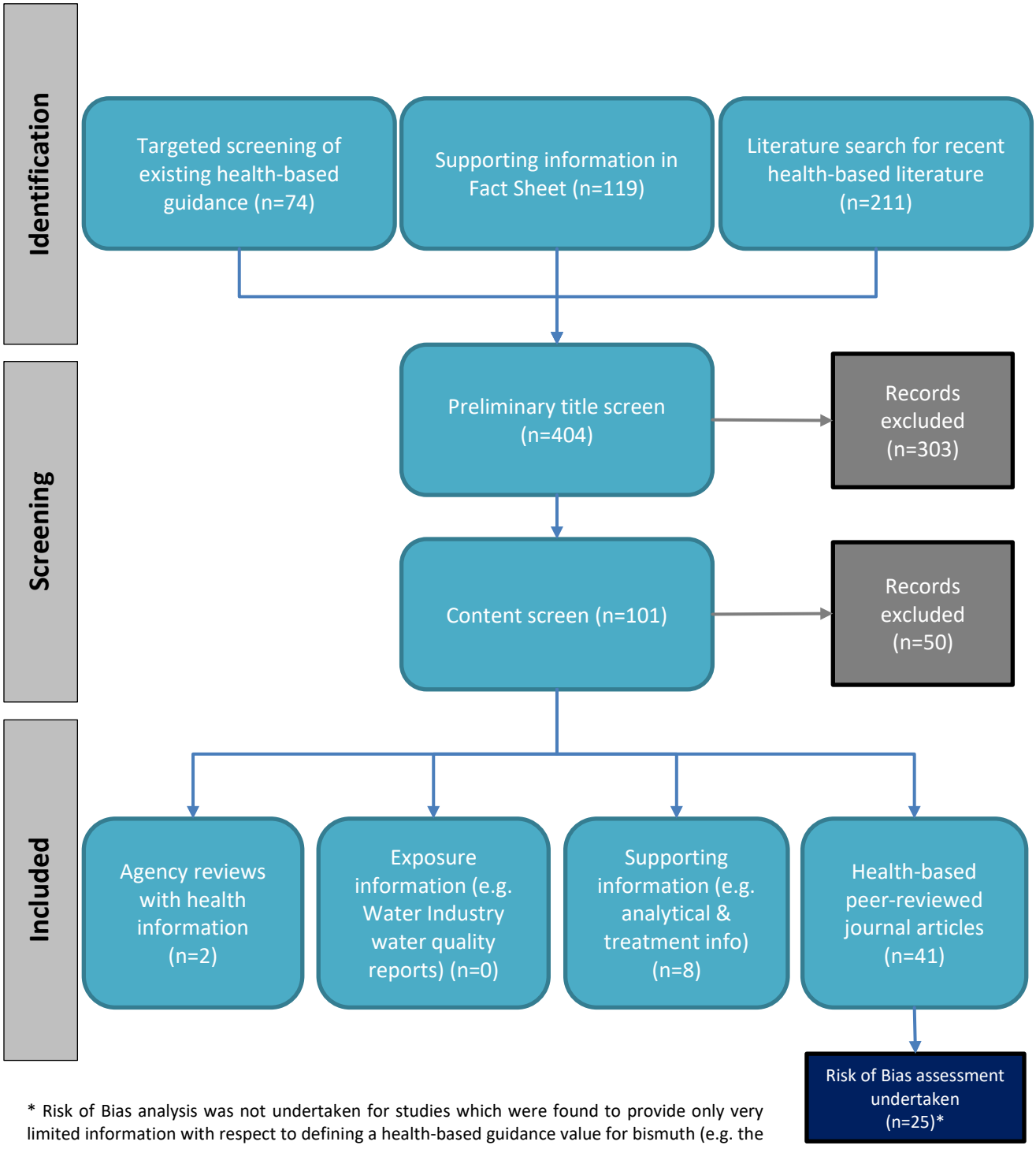
Results were subjected to the following steps in order to identify the most relevant information:

- 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. As no candidate jurisdiction's guideline/guidance values were identified for bismuth, there was no need to undertake evaluations of existing jurisdiction Guidelines 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 bismuth were subjected to a risk of bias (RoB) assessment with the use of a risk of bias tool (i.e. modified Office of Health Assessment and Translation, or OHAT, tool). Outcomes of these assessments were provided as a 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 and RoB tables. This Evaluation Report also presents summary tables for the following:

- Threshold doses of bismuth associated with no adverse effects and critical adverse health effects.
- RoB assessments across the body of evidence for each evidence stream and health outcome.
- Overall certainty of evidence for different health endpoints / evidence streams. This considered the overall confidence of the body of evidence with regard to risk of bias, indirectness/applicability, imprecision, inconsistency between studies and publication bias, with information provided as a certainty rating where possible using guidance from OHAT (2019).

Figure 1 shows an overview of the literature search process followed for bismuth. 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 analysis was not undertaken for studies which were found to provide only very limited information with respect to defining a health-based guidance value for bismuth (e.g. the study was an efficacy study examining very limited health outcomes, a review or administration timeframe and dose are both unknown).

Figure 1 Overview of Literature Search Process Followed for Bismuth

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 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).

4 Results

The targeted screening of existing health-based guidance identified no existing health-based guidance/guideline values for bismuth in the literature consulted. Thus, responses to research questions are based on the data extractions conducted for the various human case study (CaS) reports, experimental animal (EA) studies and human controlled trials (HCT) found in the literature reviewed. No other epidemiological information was found.

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 bismuth in drinking water causes adverse health effects?	No existing health-based guideline values were found for bismuth. No studies investigating the adverse health effects of bismuth in drinking water to humans were found. The oral dose response of bismuth along with a consideration of the RoB of individual studies and overall confidence by evidence stream has been summarised in **Section 5.1.** Candidate guideline values which consider the dose response information in human and experimental animal studies for bismuth via oral exposures (e.g. diet) have been derived in **Section 5.2.2.** US FDA (2023) set a recommended daily intake for adults and children 12 years of age and over for bismuth subgallate as an oral dose of 200-400 mg up to 4 times daily (i.e. 848 mg bismuth/day). At an adult body weight of 78 kg, this equates to 10.9 mg/kg/d (or 12.1 mg/kg/d at 70 kg bw). However, no further information, or derivation for this value, is provided, therefore it has not been used to derive a candidate guideline value for bismuth.
2	What is the endpoint that determines this value?	Not applicable. See response to Question 1.
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?	Not applicable. See response to Question 1.
4	Is there a knowledge gap from the time at which existing guideline values were developed?	Not applicable. See response to Question 1.
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)?	Not applicable. See response to Question 1.

#	Research Questions	Response
6	What are the key adverse health hazards from exposure to bismuth in Australian drinking water?	No data for bismuth in drinking water. In other studies key adverse health hazards appear to be neurotoxicity, and nephrotoxicity (see **Section 5.1.1** to **5.1.3**). • Case reports suggest the key potential adverse effects from exposure to bismuth are neurotoxicity (i.e. encephalopathy) or nephrotoxicity (acute renal failure or acute tubular necrosis) from oral exposure to various bismuth salts. • A human placebo-controlled trial (double-blinded) found no adverse events or drug-related changes in biochemical parameters in any of the subjects (all male) studied after oral administration of ranitidine bismuth citrate twice per day for 28 days at ~512 mg Bi/person (limited health outcomes were assessed). • Oral administration of various bismuth compounds to rodents for up to 60 days in the diet (various doses) did not result in overt adverse effects. • Bismuth orally administered as a single dose to rats at 627 mg/kg bw (as tripotassium dicitrato bismuthate (TDB)) caused nephrotoxicity in all rats and mortality in some (5/33). • Bismuth orally administered to rats at 313 or 627 mg/kg bw in a single oral dose (as TDB) caused dose-dependent nephrotoxicity. Acute NOAEL in this study was 157 mg Bi/kg bw. • In a 2-year chronic toxicity / carcinogenicity assay, BiOCl was administered in the diet to rats and no effects were observed [NOAEL in the study was the highest dose tested (i.e. presumably 1534/1918 mg Bi/kg bw/d in female/male rats, respectively)]. However, there is uncertainty with respect to the doses administered as the units reported in the study (g/kg bw) are nonsensical. • Bismuth metal (pure metal powder, mean particle diameter 10 µm) administered orally to rats resulted in a 28-day NOAEL at the highest dose tested (i.e. 1,000 mg Bi/kg bw/d in female/male rats).

#	Research Questions	Response
7	Are there studies quantifying the health burden (reduction or increase) due to bismuth?	No studies have quantified this in humans *per se*. However, the studies described in response to Question 6 have investigated adverse effects from bismuth exposure in medications and the diet. Reviews have also summarised bismuth health-based information. Key information includes the following: • In the mid-1970s, an outbreak of neurotoxicity occurred in France and Australia and was associated with intake of inorganic and organic bismuth salts (e.g. bismuth subnitrate, subcarbonate and subgallate) for treatment of gastrointestinal (GI) disorders. Some researchers have suggested that the outbreak was due to an increase in the prevalence of an otherwise benign group of gastro-intestinal microbes that promoted the methylation of bismuth, producing a more easily absorbed form. • Some researchers have suggested that maintaining blood bismuth concentration below a certain level (e.g. 100 µg/L) may prevent the occurrence of neurological effects, although the threshold concentration is debated among the scientific community. • One reviewer concluded that the uncontrolled and uninhibited ingestion of bismuth salts constituted misuse on such a scale that it would seem the factor most likely to have brought about the cases of neurotoxicity in the epidemic in France.
8	What is the critical human health endpoint for bismuth?	From the case studies of very high human intakes of soluble bismuth salts and reviews available (see response to Research Question 6), the critical human health endpoints for bismuth exposure appear to be neurotoxicity (i.e. encephalopathy) and nephrotoxicity (renal disease). From the experimental animal studies available (see response to Research Question 6), no adverse effects have been identified from chronic exposures at the doses (and compounds) tested. Acute exposures to high doses appear to potentially result in nephrotoxicity.
9	What are the justifications for choosing this endpoint?	Neurotoxicity and nephrotoxicity appear to be the two ailments potentially causally associated with high medicinal bismuth exposures in case study reports in humans. No adverse effects have been observed in a human controlled trial (albeit dose administered and bismuth form likely differs from those in case studies). Two experimental animal studies conducted in general accordance with standardised methods for conducting such studies have not identified critical adverse effects at the following doses. • Bismuth oxychloride (BiOCl) administered in diet of rats for 2 years did not result in adverse effects (NOAEL was highest dose tested = presumably 1534/1918 mg Bi/kg bw/day in female/male rats) (Preussman and Ivankovic 1975). However, there is uncertainty with respect to the doses administered as the units reported in this study (g/kg bw) are nonsensical. • Bismuth metal (pure metal powder, mean particle diameter 10 µm) administered orally via gavage to rats for 28 days did not result in adverse effects (NOAEL was highest dose tested = 1,000 mg Bi/kg bw/d) (Sano et al. 2005).

NOAEL = No Observed Adverse Effect Level. BW = Body weight. BiOCl = bismuth oxychloride. TDB = Tripotassium Dicitrato Bismuthate. GI = gastrointestinal.

4.2 Exposure-related aspects

Another important aspect in the potential Fact Sheet would cover 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 bismuth levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?	No relevant information for bismuth was found in the search conducted of water supplier websites to inform a response to this Research Question. Very limited other information was found and only one study in Australia (Hinwood et al. 2015). In that study 172 drinking water samples from non-smoking pregnant women >18 years in Western Australia recruited between 2008-2011 were analysed for numerous elements including bismuth. Concentrations of bismuth in drinking water: Median <0.005 µg/L, 100% of samples were lower than the LOR. Other studies (Malassa et al. 2014, Al-Khatib et al. 2019) were identified that measured bismuth in harvested rainwater in Hebron or Yatta, Palestine. Bismuth concentrations in Hebron ranging of 1.33-96.52 µg/L (Malassa et al. 2014) were considerably higher than the range of 0.01 – 0.75 µg/L reported in Yatta (Al-Khatib et al. 2019). The authors of the Hebron paper speculated the source of heavy metals in harvested water used for drinking may have been due to uncontrolled burning of solid wastes in illegal waste dumping sites. It is unknown how applicable these data would be to the Australian situation. Bismuth was also measured in rainwater (0.399 µg/L) and tap water (0.165 µg/L) samples collected from locations in Iran as part of validation of a novel method for determination of bismuth in water (Poursharifi and Moghimi 2011). It was also reported that bismuth concentrations in drinking water samples from the US are usually less than 0.01 mg/L (UK COT 2008) and in natural waters (which could be a proxy for raw waters used as a source of drinking water) usually less than 0.2 µg/L (Jaiswal et al. 2019).
11	Are there any data for bismuth levels leaching into water from in-premise plumbing?	No data for bismuth found in literature consulted. It is suggested that leachability data for bismuth from lead replacements in plumbing products be generated for Australian conditions to inform the form of bismuth in lead replacements (and chemical form leaching from lead replacements) as well as 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 bismuth in Australian drinking water?	No risks to human health from exposure to bismuth in drinking water were identified in any of the publications consulted. This may be due to the fact that no regulatory agency reviews could be found on the subject, although the analysis in **Section 5.2.2** indicates that risk of harm to humans from exposure to bismuth in drinking water at the source seems to be unlikely. However, exposure to bismuth may also theoretically occur from leaching of bismuth from low-lead plumbing materials although no leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for bismuth from lead replacements in plumbing products be generated for Australian conditions to inform this. The case studies and human controlled trials focused on oral intakes of bismuth from medicinal use. In these studies, the most important potential adverse health effects from bismuth exposure appear to be neurotoxicity (i.e. encephalopathy) and nephrotoxicity. Experimental animal studies with oral bismuth exposures have identified nephrotoxicity after acute administration of TDB, but otherwise no adverse effects have been found (see response to Research Question 6).
13	Is there evidence of any emerging risks that require review or further research?	None identified, however the toxicological database for bismuth is limited.

TDB = Tripotassium Dicitrato Bismuthate.

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 bismuth, 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 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 bismuth used for and how might people be exposed?	Numerous bismuth salts and complexes have been used in cosmetics and medicinally for over two centuries for a range of clinical conditions, including oral and upper respiratory tract infections, syphilis, diarrhoea, heartburn (pyrosis), dyspepsia (indigestion), gastroesophageal reflux, and peptic ulcer disease (PUD). Bismuth substances also have broad anti-microbial, anti-leishmanial and anti-cancer properties. The most commonly used bismuth forms include bismuth subsalicylate (Pepto Bismol®, Maalox®) and bismuth subcitrate, for the treatment of diarrhoea and PUD. These medicinal products contain high concentrations of bismuth. For instance, one form of Pepto Bismol®, pepto bismol ultra (bismuth subsalicylate) contains approximately 303 mg Bi/tablet, with a maximum suggested dose of 8 tablets a day for adults. Similarly, bismuth subcitrate contains 108 mg Bi/tablet. As a result of its medical use, bismuth has been found in low concentrations in biological and environmental samples including blood, urine, food and water.
15	How does the specific chemical end up in drinking water and in what form?	No information was found to answer this Research Question. Most of the studies available in the literature have focused on the medicinal exposures to bismuth from purposeful administration. However, as mentioned under the exposure-related aspects (see **Section 4.2**), theoretically bismuth could leach from lead replacements in plumbing albeit no published data were found to inform the form of bismuth nor the concentrations likely found in tap waters in households as a result of leaching.
16	How is the concentration of bismuth measured in drinking water?	Bismuth concentration in water can be determined by ICP-MS according to USEPA 6010/6020. Mentions of other analytical techniques were also made in the literature; these are ICP-AES and a novel method using microwave plasma torch (MPT) ion source coupled with linear ion trap mass spectrometer (LTQ-MS).
17	What are the indicators of the risks? How can we measure exposure?	No studies were found specifically evaluating the effects of exposure by humans to bismuth in drinking water. However, exposure concentrations in drinking water could be monitored using existing commercial analytical techniques (ICP-MS). In case studies, exposure to bismuth from medicinal use of various bismuth salts and compounds has been ascertained by measuring bismuth in blood, serum, plasma, urine and cerebrospinal fluid (CSF). A safety level of 50 µg/L bismuth in blood and an alarm level of 100 µg/L have been suggested in the past, but no evidence is available to support the choice of these levels.
18	What are the limits of quantification or limit of reporting for bismuth in drinking water?	In Australian commercial laboratories: • Standard LOR: 0.001-0.01 µg/L, depending on the laboratory. • Trace LOR (only offered by one commercial laboratory): 0.0001 µg/L

#	Research Questions	Findings
19	How is drinking water treated to minimise bismuth concentrations?	No data were found to answer this Research Question. However, bismuth 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 bismuth along with a discussion of the overall confidence in the health-based literature for possible use in derivation of a potential guideline value for bismuth. 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) to determine overall confidence ratings.

5.1 Dose response and overall confidence by evidence stream

5.1.1 Case reports

Numerous case reports for presumed bismuth intoxication resulting in either neurotoxicity or acute renal failure were identified in the literature consulted (see **Table 6**). The applied dose or dose of bismuth administered in these studies was often unknown, but some reported bismuth concentrations in blood, serum or urine.

Table 6 Summary of Case Reports on Bismuth Intoxication

Study	Exposure circumstance	Effects observed	Bismuth in biological fluid (µg/L)
Neurotoxicity			
Atwal and Cousin 2016	Buccal exposure to bismuth via BIPP antiseptic dressings (applied dose unknown)	Neurotoxicity (mild)	Case 1: 23 (blood) Case 2: 30 (blood)
Bridgeman and Smith 1994	Buccal exposure to bismuth via BIPP antiseptic gauze (applied dose unknown)	Neurotoxicity (mild)	41 (serum)
Jones 1990	Buccal exposure to bismuth via BIPP antiseptic gauze (applied dose unknown)	Neurotoxicity (mild)	30 (serum)

Study	Exposure circumstance	Effects observed	Bismuth in biological fluid (µg/L)
Morgan and Billings 1974	Two heaped teaspoons of bismuth subgallate ingested daily over 8 years (exact dose unknown)	Overt neurotoxicity (all symptoms reversible upon cessation of exposure)	No measurements
Ovaska et al. 2008	Sacral exposure to BIPP gauze (applied dose unknown)	Overt neurotoxicity (confusion, disorientation, delusion, aggression, tremor, myoclonic jerks)	340 (serum)
Buge et al. 1981	Examined clinical manifestations (presence or absence of seizures) in 70 patients with bismuth encephalopathy (patients ingested large doses of bismuth as bismuth subnitrate, i.e. 3.6-14.6g seemingly as a daily dose for 4 weeks to 30 years)	Overt neurotoxicity (all symptoms reversible upon cessation of exposure)	150-2,200 (serum)
Burns et al. 1974	Patients who had undergone abdominoperineal resection and were taking a third to one teaspoon of bismuth subgallate 2-3 times per day for a 'long time' (applied dose unknown)	Neurotoxicity	No measurement
Weller 1988	Oral ingestion of bismuth preparation bismuth tripotassium dicitrate (De-Nol) for 2 years, intermittently as needed (240-2,400 mg De-Nol/day)	Neurotoxicity (numbness and paraesthesia in hands, fatigue, irritability, memory impairment)	No measurement
Renal effects			
Urizar and Vernier 1966	Repeat dose bismuth ingestion as bismuth triglycollamate (younger sister took older sister's prescription without parents knowing) (applied dose unknown but estimated to be ~18 g over 5 months)	Acute renal failure	300-400 (plasma) 220 µg/24hr (urine)
Akpolat et al. 1996	Oral overdose (10-15 tablets) of tripotassium dicitrato bismuthate (containing 890-1,330 mg bismuth)	Acute tubular necrosis	No measurements
Huwez et al. 1992	Oral overdose of bismuth subcitrate (~1.4 g bismuth)	Acute renal failure	1,500 (serum), decreased rapidly to ~400 in first few hours, then 10 two weeks after dosing
Garrett and Chambers 1917 (1)	Wounds dressed with BIPP gauze (400 cases) (dose applied unknown)	No adverse effects	No measurements

BIPP = Bismuth iodoform paraffin paste.

1. Although this study was included in data extraction, a RoB assessment was not undertaken as this was not deemed to be a potential critical study. The primary objective of this study was to test the efficacy of a bismuth-containing drug (BIPP). Although the study provides supporting information that there were no clear adverse reactions from absorption of bismuth through the skin of these cases, it is an observational study and provides limited information with respect to defining a health-based guidance value for bismuth (dermal exposure, dose of bismuth applied to skin not provided, limited health outcomes monitored).

A RoB summary table for the included cases studies is presented in **Table 7** below, separated into different health outcomes (neurotoxicity and renal effects). An overall RoB rating of 'serious' was determined for both health outcomes based on a substantial RoB identified across most of the studies composing the body of evidence for case studies across both health outcomes.

Table 7 RoB Summary Table for Case Reports

Health outcome:	Neurotoxicity								Renal effects		
Study ID:	Atwal and Cousin 2016	Bridgeman and Smith 1994	Jones 1990	Morgan and Billings 1974	Ovaska et al. 2008	Buge et al. 1981	Burns et al. 1974	Weller 1988	Urizar and Vernier 1966	Akpolat et al. 1996	Huwez et al. 1992
Selection bias											
Randomization											
Allocation concealment											
Comparison groups appropriate											
Confounding bias											
Confounding (design/analysis)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Performance Bias											
Identical experimental conditions											
Blinding of researchers during study?											
Attrition/Exclusion Bias											
Missing outcome data											
Detection Bias											
Exposure characterisation	--	--	+	+	--	--	+	+	--	NR	--
Outcome assessment	+	+	+	-	-	-	-	-	-	-	-
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]								Serious [1]		

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

1. Based on no information provided for potential confounders in any of the studies (i.e. consistent potential confounding bias), and inconsistent detection bias across grouped case reports for each health outcome and high RoB for outcome reporting in one of the studies for each health outcome.

The initial confidence rating for the case reports is considered low, since there is no controlled exposure or comparison group in these studies. **Table 8** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'low' (neurotoxicity) or 'very low' (renal effects) for the body of evidence for each health outcome.

Table 8 Confidence Rating for Case Reports on Bismuth

Health outcome (number of studies)	Neurotoxicity (8)	Renal effects (3)	**Comment** [1]
Initial confidence rating	**LOW**	**LOW**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence			
Risk of Bias	Serious. Downgraded to **VERY LOW**.	Serious. Downgraded to **VERY LOW**.	Confidence downgraded due to consistent potential confounding and inconsistent detection bias across case studies for both health outcomes, as well as a high selective reporting bias in one study for each health outcome.
Unexplained inconsistency	Not serious.	Not serious.	Case reports appear to be consistent in terms of their findings (i.e. neurotoxicity or acute renal failure). Confidence not downgraded.
Indirectness	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Serious. Cannot downgrade further.	Serious. Cannot downgrade further.	Small sample sizes inherent of case reports render the results imprecise. Confidence remains very low.
Publication bias	Undetected.	Undetected.	No downgrade.
Factors Increasing Confidence			
Magnitude	Not large.	Not large.	Case reports with small sample sizes do not fit the classic consideration for magnitude of response. Confidence not upgraded.
Dose response	Yes. Confidence upgraded to **LOW**.	No. Confidence not upgraded.	Case reports with small sample sizes do not lend themselves to a dose response. However, for neurotoxicity, when examining the case reports as a whole in **Table 6**, it is evident that overt signs of neurotoxicity occur at higher measured serum/blood bismuth than mild signs of neurotoxicity. Such a dose response is not directly evident for renal effects.
Residual confounding	No.	No.	Not relevant for case reports. Confidence not upgraded.
Consistency across species	N/A	N/A	Not applicable for case reports. Confidence not upgraded.
Final confidence rating	**LOW**	**VERY LOW**	

1. Table adapted from guidance provided in OHAT (2019, Table 7)

5.1.2 Human controlled studies

In two human placebo-controlled trials (double-blinded) by Koch et al. (1996) and Dunk et al. (1990) no adverse events or drug-related changes in biochemical parameters were seen in:

- any of the 27 healthy male subjects (20-49 years of age) in the study by Koch et al. (1996) after oral administration of ranitidine bismuth citrate twice per day for 28 days, or

- any of the 34 male and female subjects with a history of duodenal ulceration in the study by Dunk et al. (1990) after oral administration of bismuth in the form of TDB tablets once per day for up to 12 months.

In the studies, the dose of bismuth administered per day was ~512 mg Bi/person (Koch et al. 1996) or ~108 mg Bi/person (Dunk et al. 1990). At an average male adult body weight of 85 kg or an average male and female adult body weight of 78 kg (enHealth 2012), this equates to NOAELs for overt health outcomes of 6 mg Bi/kg bw/d or 1.4 mg Bi/kg bw/d respectively, taking into consideration very limited health outcomes were assessed in the studies. The studies were considered to have a 'serious' RoB (see table below) as they did not satisfy the requirements for having low risk of bias for most domains.

Table 9 RoB Summary for Human Controlled Trials

Health outcome:	**Biochemical parameters, serious adverse events**	
Study ID:	**Koch et al. 1996**	**Dunk et al. 1990**
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	NR	NR
Outcome assessment	-	-
Selective Reporting Bias		
Outcome reporting	+	+
Other Sources of Bias		
Other threats		
Overall risk of bias across studies (not likely/serious/very serious)	Serious [1]	

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

1. Based on not meeting the criterion of low RoB for one of the key domains (i.e. outcome reporting).

The initial confidence rating for the human controlled study evidence is considered high. **Table 10** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'very low'.

Table 10 Confidence Rating for Human Controlled Studies on Bismuth

Health outcome (number of studies)	**Biochemical parameters, serious adverse events** (2)	**Comment** [1]
Initial confidence rating	**HIGH**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence		
Risk of Bias	Serious. Downgraded to **MODERATE**.	Confidence downgraded based on not meeting the criterion of low RoB for one of the key domains (i.e. outcome reporting).
Unexplained inconsistency	Not serious.	No unexplained inconsistency identified. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Serious. Downgraded to **LOW**.	Small sample size (n=17 or 34 exposed individuals) render the results imprecise. Confidence downgraded to **Low**.
Publication bias	Undetected across body of evidence but conflict of interest likely for Kock et al. (1996) study. Downgraded to **VERY LOW**.	Authors of Koch et al. (1996) paper are from Glaxo Wellcome Inc, i.e. the drug manufacturer. No conflict of interest statement is included in the article. Since this is a single study sponsored by the drug manufacturer, confidence is downgraded to **Very Low.**
Factors Increasing Confidence		
Magnitude	Not large.	These human controlled trials were conducted primarily to ascertain pharmacokinetics thus health outcomes are limited and do 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.	Confidence not upgraded.
Consistency across species	N/A	Not applicable, since there are only two human controlled trials. Confidence not upgraded.
Final confidence rating	**VERY LOW**	

1. Table adapted from guidance provided in OHAT (2019, Table 7)

5.1.3 Experimental animal studies

Numerous controlled experimental animal studies have been conducted with different forms of bismuth (see **Table 11**).

Table 11 Summary of Experimental Animal Studies with Bismuth

Study	Exposure circumstance	Effects observed	Endpoint (mg/kg bw/d as Bi unless otherwise specified)
Laval et al. 2018 [2]	Bi^{3+} orally administered to mice for 60 days (single dose = 141 mg/kg/d).	No overt toxicity (i.e. mortality or effects on haematological parameters) [2]	NOAEL = 141
Abbracchio et al. 1985 [1]	Oral repeat exposure (4 days) to Bi in rats (328 or 820 mg/kg TDB or 100 or 250 mg/kg Bi_2O_3) resulted in lower Bi concentrations in blood and brain of rats (compared to intraperitoneal injection).	No obvious signs of neurotoxicity observed	NOAEL = 233
Canena et al. 1998	Oral repeat exposure (15 days) to male Wistar rats of different compounds (Bi subcitrate: 13.7 mg/kg/d, ranitidine hydrochloride: 8.6 mg/kg/d, ranitidine bismuth citrate: 22.8 mg/kg/d)	No signs of encephalopathy	NOAEL = 13.7 (Bi subcitrate), 8.6 (ranitidine hydrochloride), 22.8 (ranitidine bismuth citrate)
Chaleil et al. 1981 [1]	Single oral administration of bismuth-cysteine complex to male Wistar rats	Mortality	LD_{50} = 156 ± 20 mg/kg (bismuth-cysteine complex)
Hanzlik et al. 1938	Single oral administration of sobisminol, a soluble bismuth product prepared from sodium bismuthate (3%), triisopropanolamine (8%), propylene glycol (50%) and water (balance) intended for oral and intramuscular uses in the treatment of syphilis to rats and rabbits	Mortality	NOAEL = 84 (rats), 252 (rabbits) LD_{50} = 294 (rats), 310.8 (rabbits)
Leussink et al. 2000	Bi administered as single oral dose (as TDB) to rats (0 or 627 mg/kg bw)	Nephrotoxicity (i.e. renal effects) and mortality in some rats (5/33)	LOAEL = 627 (only dose tested)
Leussink et al. 2001	Bi administered as single oral dose (as TDB) to rats (157, 313 or 627 mg/kg bw)	Dose-dependent nephrotoxicity (i.e. renal effects)	NOAEL = 157 LOAEL = 313
Tubafard and Fatemi 2008	Bi orally administered to rats in drinking water or food for 55 days (as bismuth nitrate) presumably at 20 or 40 mg/kg/d (although doses are unclear)	Reduced body weight & food consumption, clinical signs, decreased iron levels in food group	Uncertain (reporting lacks quality)
Preussman and Ivankovic 1975 [2]	2-year chronic toxicity / carcinogenicity study for BiOCl given in diet to rats. Doses: 1, 2, or 5% BiOCl (i.e. presumably M: 383, 767, or 1,918 mg/kg bw/d; F: 307, 614, or 1,534 mg/kg bw/d). Note there is uncertainty with respect to the doses administered as the units reported in the study (g/kg bw) are nonsensical.	No treatment-related adverse effects (on body weight, clinical signs, survival, macroscopic or histological findings) [2]	NOAEL = presumably 1,534/1,918 (F/M) (highest dose tested)

Study	Exposure circumstance	Effects observed	Endpoint (mg/kg bw/d as Bi unless otherwise specified)
Sano et al. 2005[2]	Acute and 28-day repeat dose oral (by gavage) toxicity study using bismuth metal (pure metal) in rats (acute study = 2,000 mg/kg, repeat doses = 0, 40, 200, or 1,000 mg/kg/d).	No treatment-related adverse effects (on clinical signs, body weight, food consumption, haematology, urinalysis, pathology) [2]	LD_{50} = >2,000 mg Bi/kg NOAEL = 1,000

TDB = Tripotassium dicitrato bismuthate. LD_{50} = Median lethal dose. BiOCl = Bismuth oxychloride. M = Males. F = Females

1. Excluded – Risk of bias assessment not undertaken as this was not deemed to be a potential critical study (see Appendix C in Technical Report for reasoning).
2. These studies are potentially the most relevant with respect to the exposure circumstances considered in this report (i.e. exposure to bismuth from bismuth-containing alloys used in lead-replacement plumbing). This has been denoted in the table using blue shading.

A RoB summary table for the included experimental animal studies is presented in **Table 12** below, separated into different health outcomes (general toxicity, renal effects, encephalopathy, mortality). A determination of 'serious' RoB was reached for each health outcome, apart from mortality where RoB was deemed 'very serious', as there was substantial RoB identified across most of the studies composing the body of evidence for each health outcome [see Table 10 in OHAT (2019)].

Table 12 RoB Summary for Experimental Animal Studies

Health outcome:	General toxicity				Renal effects		Encephalopathy	Mortality
Study ID:	**Tubafard and Fatemi 2008**	**Preussman and Ivankovic 1975**	**Laval et al. 2018**	**Sano et al. 2005**	**Leussink et al. 2000**	**Leussink et al. 2001**	**Canena et al. 1998**	**Hanzlik et al. 1938**
Selection bias								
Randomization	NR	NR	NR	-	--	--	-	NR
Allocation concealment	NR	NR	NR	NR	NR	NR	-	NR
Comparison groups appropriate								
Confounding bias								
Confounding (design/analysis)								
Performance Bias								
Identical experimental conditions	+	-	-	--	--	--	--	++
Blinding of researchers during study?	NR	+	+	+	NR	NR	+	NR
Attrition/Exclusion Bias								
Missing outcome data	NR	-	--	--	--	-	NR	--
Detection Bias								
Exposure characterisation	+	++	NR	-	NR	NR	NR	NR
Outcome assessment	NR	NR	NR	-	NR	NR	-	NR
Selective Reporting Bias								
Outcome reporting	+	-	--	--	--	-	-	-
Other Sources of Bias								
Other threats								

Overall risk of bias across studies (not likely / serious/ very serious)	Serious [1]	Serious [2]	Serious [3]	Very serious [4]

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

1. Based on consistent potentially high selection bias, inconsistent high performance bias, and relatively consistent detection bias.
2. Based on several aspects not being reported in the studies, leading to potential performance and detection bias.
3. Based on not meeting the criterion of low RoB for key domains (e.g. attrition/exclusion bias).
4. Based on most aspects not being reported in the study with very high performance bias.

The initial confidence rating for the experimental animal information is considered high for the majority of 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 13** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'low' (mortality), 'moderate' (general toxicity and encephalopathy) or 'high' (renal effects) depending on the health outcome.

Table 13 Confidence Rating for Experimental Animal Studies with Bismuth

Health outcome (number of studies)	**General toxicity** (4)	**Renal effects** (2)	**Encephalo-pathy** (1)	**Mortality** (1)	**Comment** [1]
Initial confidence rating	**HIGH**				Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence					
Risk of Bias	Serious. Downgraded to **MODERATE**.			Very serious. Down-graded to **LOW.**	Serious or very serious. Confidence downgraded to moderate or low for reasons specified in **Table 12**.
Unexplained inconsistency	Not serious.				Animal studies appear to be relatively consistent in their findings depending on the bismuth compound, with most showing no adverse effects or renal effects. Confidence not downgraded.
Indirectness	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.
Imprecision	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	Not detected.				Mixture of studies with authors from different areas (industry, University research organisations, etc). Confidence not downgraded.

Health outcome (number of studies)	**General toxicity** (4)	**Renal effects** (2)	**Encephalo-pathy** (1)	**Mortality** (1)	**Comment** [1]
Factors Increasing Confidence					
Magnitude	Not large.				Magnitude of response not really relevant to animal studies. Confidence not upgraded.
Dose response	No.	Yes. Upgraded to **HIGH**.	No.	No.	Some animal studies have shown a dose response for renal effects (Leussink et al. 2001). Most other animal studies found no treatment-related adverse effects.
Residual confounding	No.				Not relevant for animal studies. Confidence not upgraded.
Consistency across studies	No.				Most studies conducted in rats (a single species), with only a few in another species (rabbits). Confidence not upgraded.
Final confidence rating	**MODERATE**	**HIGH**	**MODERATE**	**LOW**	

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

5.2 Overall Evaluation

5.2.1 Hazard identification conclusions

The analysis in **Section 5.1** indicated low to very low confidence in the overall body of evidence for the case reports and human controlled study whereas the confidence in the overall body of evidence ranged from high to low 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 14**.

Table 14 Hazard Identification Conclusions for Bismuth

Health endpoint (number of studies)	Certainty rating	Conclusion	NOAEL/LOAEL (mg/kg/d)?
Neurotoxicity/Encephalopathy			
Case reports (8)	**LOW**	There is low confidence in the body of evidence for an association between exposure to bismuth (as bismuth iodoform paraffin paste, bismuth subgallate, bismuth subnitrate, or tripotassium dicitrate bismuthate) and neurotoxicity.	None identified
Experimental animal study (1)	**MODERATE**	There is moderate confidence in the body of evidence for no association (i.e. no effect) between exposure to bismuth (as bismuth subcitrate or ranitidine bismuth citrate) and encephalopathy (i.e. a form of neurotoxicity). Note single dose tested and no LOAEL identified.	NOAEL = 13.7 (Bi subcitrate), 8.6 (ranitidine hydrochloride), 22.8 (ranitidine bismuth citrate)
Renal effects			
Case reports (3)	**VERY LOW**	There is insufficient evidence available for an association between exposure to bismuth (as bismuth triglycollamate, tripotassium dicitrato bismuthate, or bismuth subcitrate) and renal effects in humans.	None identified
Experimental animal study (2)	**HIGH**	There is high confidence in the body of evidence for an association between exposure to tripotassium dicitrato bismuthate and renal effects. Note no repeat dosing studies available (single administration).	NOAEL = 157 mg/kg LOAEL = 313 mg/kg (acute - single administration)
General toxicity (all outcomes)			
Human controlled study (2)	**VERY LOW**	There is insufficient evidence available to assess if the exposure to bismuth (as ranitidine bismuth citrate or TDB) is associated with general toxicity. It is noted, however, no adverse effects were found in either study.	Insufficient (limited health outcomes assessed)
Experimental animal study (4)	**MODERATE**	There is moderate confidence in the body of evidence for an association between exposure to bismuth (as bismuth nitrate, bismuth oxychloride, bismuth metal, or Bi^{3+}) and no general toxicity (i.e. all health outcomes). No LOAEL identified as no adverse effects observed at top doses.	NOAEL = 141 (single dose tested), 1,000 or presumably 1,534/1,918 (Female/Male)
Mortality			
Experimental animal study (1)	**LOW**	There is low confidence in the body of evidence for an association between exposure to bismuth [as sobisminol, a soluble bismuth product prepared from sodium bismuthate (3%), triisopropanolamine (8%), propylene glycol (50%) and water] and mortality. Note no repeat dosing studies available (single administration).	NOAEL = 84 mg/kg (rats) 252 mg/kg (rabbits) (acute – single administration)

In summary, from **Table 14** there is:

- Low confidence for neurotoxicity/encephalopathy and renal effects in humans based on the case report information and insufficient evidence (i.e. very low confidence) for no health effects from the human controlled studies.
- Moderate confidence for no adverse health effects from most of the experimental animal studies (conducted with Bi^{3+}, bismuth subcitrate, ranitidine bismuth citrate, BiOCl, and bismuth metal), whereas there is high confidence for renal effects from single high dose exposures to TDB. This indicates there are certain bismuth compounds that may exert toxicity in experimental animals at high doses; although not explicitly stated, this is likely due to differences in solubility/bioavailability between different bismuth compounds.

5.2.2 Candidate Guidance/Guideline Values

No existing guideline/guidance values which could potentially be adapted/adopted into the Guidelines were found in the literature consulted. Nevertheless, as some bismuth compounds may exert toxicity (see **Section 5.2.1**) it seems reasonable to derive candidate guidance/guideline values *de novo* for potential inclusion in the Guidelines.

The dose response information in humans is insufficient for derivation of guidance/guideline values for bismuth. From the experimental animal studies, although there is high confidence in renal effects with exposures to TDB, this is based on single dose studies with TDB being of uncertain relevance for the form of bismuth potentially found in drinking water. Although three repeat dose experimental animal studies were considered for guidance/guideline value derivation (Laval et al. 2018, Preussman and Ivankovic 1975, Sano et al. 2005), the first two have limitations (e.g. only a single dose tested, uncertainty with dose units) that preclude them from use by themselves. The repeat dose study by Sano et al. (2005) is considered to be of sufficient quality for guidance/guideline value derivation.

- Sano et al. (2005) conducted an acute and repeat dose oral (gavage) toxicity study using bismuth metal (pure metal powder, mean particle diameter 10 µm) in rats (this is potentially a more relevant form of bismuth reminiscent of the type of bismuth exposure that might occur with bismuth alloys). The study was well conducted and included all standardised endpoints which are typically investigated in such studies. The repeat dose study established a 28-day NOAEL as the highest dose tested (i.e. 1,000 mg Bi/kg bw/d in female/male rats). On its own, the study is judged to not have a serious RoB based on the majority of key domains having a low RoB (see **Table 12**).

The use of the short-term (i.e. 28-day) study by Sano et al. (2005) is supported by the findings of the 2-year chronic toxicity / carcinogenicity NOAEL from Preussman and Ivankovic (1975), presuming it is in mg/kg bw/d rather than g/kg bw/d as reported in the paper, which was in a similar range to the NOAEL of 1,000 mg Bi/kg bw/d from the 28-day study by Sano et al. (2005).

The potential resulting DWG using this NOAEL *de novo* is summarised in **Table 15**.

It is noted the available experimental animal studies have identified lower LOAELs or LD_{50} values for complex bismuth compounds (e.g. TBD, sobisminol, bismuth-cysteine complex); although unclear from the information reviewed, the higher toxicity observed in acute toxicity tests with those compounds is likely due to higher solubility/bioavailability of bismuth in those forms. It is considered the form of bismuth potentially the most applicable to bismuth that may arise from bismuth alloys used in lead replacement plumbing, is bismuth metal or bismuth salts rather than the complex forms used for medicinal preparations.

It is also noted that the health-based guidance value of 3.3 mg Bi/kg/day derived in **Table 15** using the data from Sano et al. (2005) is approximately a factor of three lower than the health-based guidance value suggested by US FDA (2023) for bismuth subgallate (i.e. 848 mg Bi/day, or 10.9 mg Bi/kg/day for a 78 kg adult). The latter value was not used in deriving a candidate drinking water guideline for bismuth because no basis for the US FDA (2023) value was provided (see also **Section 4.1**).

Table 15 Potential Drinking Water Guideline Values (mg/L) Resulting from *De Novo* Derivation using Experimental Animal Studies

Parameter		Sano et al. 2005
Study population		Rats
Form of bismuth studied		Bi metal
Study timeframe		28 days
Critical Effect		No adverse effects reported
Point of Departure (mg/kg/d)		NOAEL: 1,000
Uncertainty factors	UF_A	10
	UF_H	10
	$UF_{timeframe}$	1 (1)
	$UF_{database}$	3
	$UF_{composite}$	300
Health-based guidance value (mg/kg/d)		3.3
Resulting adaptation to a Health Based DWG(1) (mg/L)		11.67

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. No additional uncertainty factor was applied for use of a short-term study, since the 2-year chronic toxicity / carcinogenicity NOAEL from Preussman and Ivankovic (1975), presuming it is in mg/kg bw/d rather than g/kg bw/d as reported in the paper, was in a similar range to the NOAEL from the 28-day study by Sano et al. (2005).
2. 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 (2011):

   DWG (mg/L) = [Guidance value (mg/kg bw/d) x 70 kg (adult) x 0.1 for adult] ÷ 2 L/day for adult

The candidate bismuth DWG derived using an experimental animal study is 11.67 mg/L. There is very limited information for bismuth exposure in Australian drinking waters, with a single study (Hinwood et al. 2015) detecting no bismuth in 172 drinking water samples in Western Australia (all concentrations <0.005 µg/L). Even in a region with potentially contaminated harvested rainwater in Hebron, Palestine, bismuth concentrations only ranged from 1.33 to 96.52 µg/L (Malassa et al. 2014). These concentrations are orders of magnitude below the candidate DWG shown in **Table 15**, suggesting that bismuth is unlikely to present a human health risk from drinking water at the source. Exposure to bismuth may also theoretically occur from leaching of bismuth from low-lead plumbing materials although no leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for bismuth from lead replacements in plumbing products be generated for Australian conditions to inform this matter.

6 Conclusions

No existing health-based guidance/guideline values relevant to bismuth were found in the literature search undertaken. Therefore, a detailed review of the health-based literature was done. The dose response information in the available human studies is insufficient for derivation of guidance/guideline values for bismuth. From the available experimental animal studies, there is one repeat dose study of sufficient quality which could be considered for guidance/guideline value derivation.

The candidate bismuth DWG derived using an experimental animal study is 11.67 mg/L. The very limited information identified on potential source-water derived exposure concentrations of bismuth in drinking waters indicates exposures from these sources are likely to be orders of magnitude below the candidate DWG. However, exposure to bismuth may also theoretically occur from leaching of bismuth from low-lead plumbing materials although no leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for bismuth from lead replacements in plumbing products be generated for Australian conditions to inform this.

The concentration of the candidate DWG of 11.67 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, FACTRA	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 NHMRC (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 NHMRC (evidence evaluations for 11 inorganic chemicals).

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