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

Lead Evaluation Report

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BASIS OF REPORT

This report has been prepared by SLR Consulting Australia Pty Ltd (SLR) with all reasonable skill, care and diligence, and taking account of the timescale and resources allocated to it by agreement with National Health and Medical Research Council (the Client). Information reported herein is based on the interpretation of data collected, which has been accepted in good faith as being accurate and valid.

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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*.

An initial Stage 1 review completed in May 2022 of published guidelines and guidance documents relevant to lead identified only one candidate health-based guidance/guideline value for potential adoption/adaptation from the Office of Environmental Health Hazard Assessment (OEHHA). Several other agency reviews summarised health-based information for lead, but none considered it appropriate to derive a health-based guidance or guideline value for lead. Two guidance/guideline values from the World Health Organization (WHO) and NHMRC were also identified in the literature which are not strictly health-based. All three guidance/guideline documents assessed were found to be suitable to adopt/adapt based on an assessment of their administrative and technical characteristics, however NHMRC (2015a,b) met the highest number of overall criteria. In addition, the guidance value from OEHHA was deemed unsuitable to adopt/adapt for other reasons. Although no guidance value was derived, NHMRC (2015a,b) concluded if a person has a blood lead level >5 µg/dL, their exposure to lead should be investigated and reduced. This blood lead level is currently referenced by public health services and applied in risk assessments of lead exposure undertaken in Australia. It is termed a 'target' blood lead level in this report. In the Stage 1 review, it was acknowledged that the 'target' blood lead level does not necessarily represent a threshold for the lack of adverse effects to lead, but the weight of evidence is less certain for effects of lead at blood lead <5 µg/dL than for effects between 5 and 10 µg/dL (NHMRC 2015a,b). It therefore was considered reasonable to consider deriving a candidate drinking water guideline for lead with the general aim of reduction / minimisation of lead exposures to a target of <5 µg/dL, consistent with current Australian science policy. In addition, the current Australian DWG of 10 µg/L is based on a Provisional Tolerable Weekly Intake (PTWI) that has since been withdrawn, so its basis is indeed in need of a review.

If it is accepted, as per the assumption in the current Guidelines (NHMRC and NRMMC 2011), that 20% of total lead intake can be attributable to water consumption, this translates to a blood lead level of 1 µg/dL. Using the Integrated Exposure Uptake Biokinetic (IEUBK) model for lead, a target geometric mean blood lead of 1 µg/dL would be attained in children between the ages of 6 months and 2 years if the concentration of lead in drinking water were 5 µg/L. Formula-fed infants would likely have a similar geometric mean blood lead although it is noted IEUBK is not designed to model formula-fed infant exposures. Since an infant would likely receive 100% of its lead intake from formula as opposed to only 20% used for young children, the exposure modelling done for young children is protective of infant exposures (refer to Stage 1 review). Therefore, in the Stage 1 review a candidate drinking water guideline for lead of 5 µg/L was suggested, which would mean the current Australian drinking water guideline for lead would be halved from 10 µg/L to 5 µg/L. This is to ensure consistency with Australian science policy to minimise lead exposure so that blood lead in the most sensitive population (i.e. young children) remains below 5 µg/dL.

However, because the evidence scan undertaken for the Stage 1 review revealed a number of recently published studies which were not previously considered in the NHMRC (2015a, b) review, a targeted search and review of relevant primary studies published since 2013 (determined to be the cut-off date for the literature included in the NHMRC 2015a, b publications identified in Stage 1) was conducted as part of this Stage 2 report.

EXECUTIVE SUMMARY

This Evaluation Report summarises the Stage 2 evaluation undertaken for lead. The methodology of the review is also provided in more detail in an accompanying Technical Report.

The updated targeted screening of existing health-based guidance did not identify any new potential candidate guidance/guideline values for lead for potential adoption/adaptation in addition to those completed in the Stage 1 reports. A detailed review of the health-based literature was done.

The detailed review undertaken in this Stage 2 evaluation showed that there is:

- High confidence in the body of evidence available for an association between exposure to lead and neurobehavioural effects. However, the results of the studies do not appear to alter the dose response relationship already established in NHMRC (2015a, b).
- Moderate confidence in the body of evidence available for an association between exposure to lead and blood pressure / hypertension, increased fasting plasma glucose, and increased incidence of fatty liver disease. The doses (or blood lead concentrations) at which these effects occur are uncertain but appear to be at blood lead levels >4.7 µg/dL which is similar to the previously established ‘target’ blood lead level of 5 µg/dL.
- Very low to low confidence in the association between exposure to lead and other health outcomes (i.e. markers of iron deficiency, birth outcomes, biochemical changes to sex hormones in males, behavioural effects, and adverse oral health outcomes) with insufficient confidence in the dose response for these effects.

Therefore the Stage 2 evaluation agrees with the findings in NHMRC (2015a, b) and does not alter the candidate drinking water guideline value of 5 µg/L derived in the Stage 1 reports.

Numerous studies were identified in the literature consulted as part of this Stage 2 evaluation quantifying potential concentrations of lead in tap waters as a result of lead leaching from lead-containing plumbing materials, predominately plumbing materials located in buildings and households, including taps. These data indicate that leaching of lead from lead containing plumbing materials, even when these are claimed to be ‘lead-free’ by the manufacturer, can be marked and can result in concentrations that approach or exceed the candidate drinking water guideline of 5 µg/L (refer to Stage 1 report for detail of derivation). This indicates that, in some households, exposure to lead from drinking water may be marked and could potentially increase the risk of those persons’ overall exposure exceeding the ‘target’ blood lead level of 5 µg/dL thereby increasing the risk of adverse health effects.

CONTENTS

DOCUMENT REFERENCES

TABLES

CONTENTS

FIGURES

Abbreviations/Definitions

Acronym	Definition
%ile	Percentile
ACT	Australian Capital Territory
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
CaCo	Case-control study
CAD	Coronary Artery Disease
CBLL	Cord Blood Lead Level
CDC	US Centre for Disease Control
CI	Confidence Interval
Co	Cohort
CPI	Community Periodontal Index
CrSe	Cross-sectional Study
CVD	Cardiovascular Disease
DALY	Disability-adjusted Life Years
DWG	Drinking Water Guideline
Ecol	Ecological Study
EFSA	European Food Safety Authority
ESA	Erythropoietin Stimulating Agent
ESKD	End-stage Kidney Disease
EU	European Union
FSANZ	Food Standards Australia New Zealand
GI	Gingival Index
IEUBK	Integrated Exposure Uptake Biokinetic Model for Lead
IQ	Intelligence Quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MAFLD	Metabolic Dysfunction-associated Fatty Liver Disease
MCL	US EPA Maximum Contaminant Level
NAFLD	Non-alcoholic Fatty Liver Disease
NHMRC	National Health and Medical Research Council
NT	Northern Territory
OEHHA	Californian Office of Environmental Health and Hazard Assessment
OHAT	United States Office of Health Assessment and Translation
OR	Odds Ratio
Pb	Lead

Acronym	Definition
PI	Plaque Index
QLD	Queensland
PR	Prevalence Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB	Risk of Bias
SA	South Australia
SD	Standard Deviation
SGA	Small for Gestational Age
TAS	Tasmania
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.
µg/dL	Micrograms Per Decilitre
µg/g	Micrograms Per Gram
µg/L	Micrograms per litre
US EPA	United States Environmental Protection Agency
VIC	Victoria
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 lead.

1.1 Objectives

An initial Stage 1 review of published guidelines and guidance documents for lead carried out by SLR Consulting in 2022 found one existing health-based guidance/guideline value (OEHHA 2009) that was suitable to adopt/adapt based on an assessment of administrative and technical criteria. A drinking water guideline (DWG) from WHO (2011) and current blood lead level guidance from NHMRC (2015a, b) were also identified and considered suitable for potential adaption/adoption in the Guidelines. However, the guidance value from OEHHA was deemed unsuitable to adopt/adapt for other reasons. It was found that potential adaptation of the NHMRC (2015a, b) advice on blood lead levels (with an aim of keeping blood lead levels under 5 µg/dL) would result in the current Australian drinking water guideline for lead being halved from 10 to 5 µg/L. An initial scan of evidence identified since publication of the NHMRC (2015a, b) advice was also undertaken and the key studies identified appeared to support the potential adoption of a DWG of 5 µg/L in the Guidelines. Critical assessment of the individual studies identified in the evidence scan was out of scope of the Stage 1 review. As a result, a targeted search and review of relevant primary studies published since the studies included in the NHMRC (2015a, b) publications was conducted as part of this Stage 2 report.

The overarching objective of this Stage 2 review is to identify relevant information on the impact of exposure to lead in drinking water at levels lower than the current health-based guideline value on human health outcomes, including consideration of available data in the context of leaching from low-lead replacement products. In particular, this involves assessing evidence published since the most recent and suitable review identified in Stage 1 (NHMRC 2015a, b) to determine whether a change in the NHMRC (2015a, b) blood lead investigation value is warranted. This will provide NHMRC and the Committee with further information to determine whether NHMRC (2015a, b) is suitable to derive a health-based guideline value for lead in the Guidelines or not.

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 Lead

#	Research Questions
Health-based	
1	What level of lead in drinking water causes adverse health effects?
2	What is the endpoint that determines this value?
3	Is the proposed option for a health-based guideline value relevant to the Australian context?
4	What are the key adverse health hazards from exposure to lead in Australian drinking water?
5	Are there studies in Australia quantifying the health burden (reduction or increase) due to lead?
6	What is the critical human health endpoint for lead?
7	What are the justifications for choosing this endpoint?
Exposure Profile	
8	What are the typical lead levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought? (note this aspect was already covered in a previous report)[1]

[1] This aspect was already covered in SLR Report entitled *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Lead Technical Report* (640.30242-R11-v4.0) and *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Lead Evaluation Report* (640.30242-R12-v2.0).

#	Research Questions
9	Are there any data for lead levels leaching into water from in-premise plumbing?
Risk Summary	
10	What are the risks to human health from exposure to lead in Australian drinking water?
11	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review or further research?

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:

- An update of the targeted literature search of existing health-based guidance/guidelines to capture any new information published since the search undertaken for the Stage 1 investigation (i.e. from 2021-2023). 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 Medicine Authority (APVMA).
- An additional literature search was undertaken in two scientific databases for published studies relevant to addressing the health-related research questions. A full review of the literature was intended to be undertaken (as opposed to simply undertaking an evidence scan for any recent health-based information that could impact the guidance/guideline value).

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

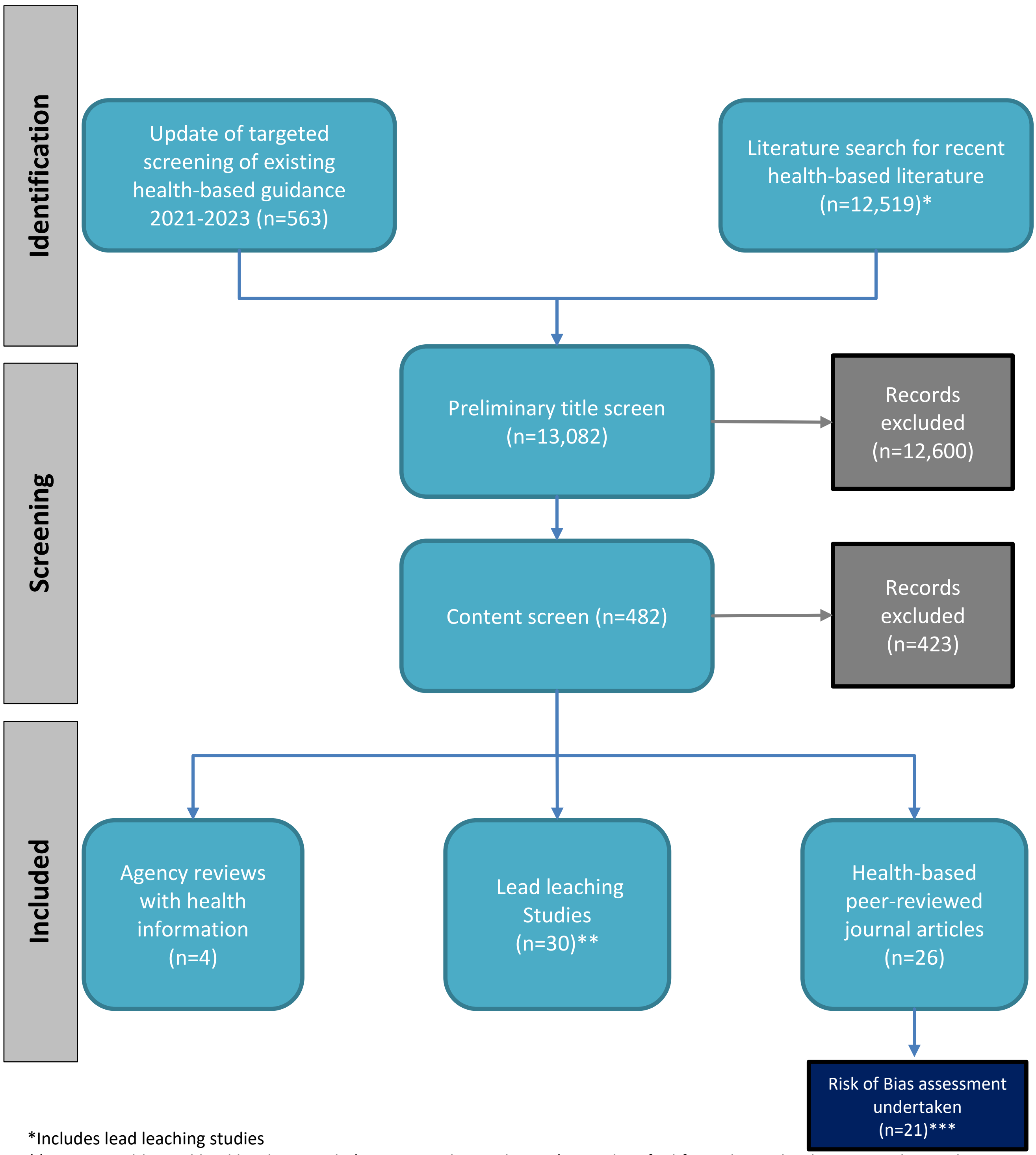
- A preliminary title screen where titles of results were scanned by a researcher and a decision recorded regarding relevance of the result; and
- A content screen where full text content of reports/reviews/articles selected to be included from the preliminary title screen step were reviewed in relation 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. Due to the large number of publications retrieved and the limited resources for this project, data extraction focused on those studies that may alter the conclusions made in the Stage 1 reports for lead. Specifically, this included human epidemiological studies investigating the blood lead dose response at relatively low (≤ 10 µg/dL) blood lead levels published since May 2013 (to coincide with the cut-off date for the literature included in NHMRC 2015a, b identified in the Stage 1 review).

Synthesis was conducted by presenting summarised extracted data in tabular format for each individual research question. All critical studies deemed relevant for defining the critical adverse health effects and dose response of lead 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 and RoB tables. This Evaluation Report also presents summary tables for the following.

- Blood lead / serum lead / water lead concentrations associated with adverse effects as identified in the Stage 2 literature retrieved. This is presented along with summaries of study bias/quality for each health endpoint/outcome.
- 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.

Figure 1 shows an overview of the literature search process followed for lead. 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). Four agency reviews with health information and 55 health-based peer-reviewed journal articles comprising 29 lead leaching studies and 26 health-based studies were evaluated. Twenty-one health-based studies were subjected to a RoB assessment.



*Includes lead leaching studies
** Note an additional lead leaching study (Weeramanthri et al. 2017) was identified for inclusion by the WQAC Chemical Subgroup in their review of the draft report.
*** Risk of Bias analysis was not undertaken for studies which were found to have no clear dose response analysis of utility at blood Pb <10 µg/dL.

Figure 1 Overview of literature search process followed for Lead

This report provides the summary of the findings (**Section 4**), a discussion of the results (**Section 5**), and conclusion (**Section 6**).

4 Results

The 2021-2023 targeted screening of existing health-based guidance identified no existing health-based guidance/guideline values for lead additional to those already identified in the Stage 1 review. A few additional agency reviews were found, but none provided a health-based guidance or guideline value. Responses to research questions were informed by these agency reviews as well as the data extractions conducted for the various cross-sectional (CrSe), cohort (Co), case-control (CaCo), and ecologic (Ecol) studies 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 1-7 all cover health-based aspects of the review; this is considered to be the central information in the factsheet. **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 lead in drinking water causes adverse health effects?	Although a few additional agency reviews were identified in the literature retrieved, no additional existing health-based guideline values were found for Pb in drinking water. US EPA (2023) cites Center of Disease Control (CDC 2022) as setting a new blood Pb reference value of 3.5 µg/dL in the United States corresponding to the 97.5th percentile of blood Pb in US children aged 1-5 years based on data collected in a national survey between 2015-2018. It is noted this is not a health-based guidance value, rather a reference value. EU revised their drinking water limit for Pb from 10 to 5 µg/L to come into effect by 2036 at the latest but do not provide the health basis of the value (EU 2020)[2]. It is noted this value is coincidentally the same as the candidate DWG derived in the Stage 1 Evaluation Report. In epidemiological studies retrieved as part of this Stage 2 review which have investigated Pb concentrations <u>in drinking water</u> and various health endpoints, elevated Pb in drinking water was found to be associated with an increased incidence of hip fracture in 66–85 year old men and women in Norway (Dahl et al. 2014); lower haemoglobin levels and higher erythropoietin stimulating agent (ESA) use among patients with end-stage kidney disease (ESKD) in the USA (Danziger et al. 2021); measures of iron deficiency (Danziger et al. 2022); increased incidence of miscarriages and foetal death in a town in Michigan with high Pb leaching from plumbing materials (Edwards et al. 2014); and increased incidence of low birth weight and preterm births in US children (Dave and Yang 2022). However, the overall confidence in these findings are low or very low and/or no clear dose response relationships could be established from the information in these studies (see **Section 5.1** and **5.1.8**). Other health-based studies examined associations of the principal accepted marker of Pb exposure, <u>blood Pb (or serum Pb)</u>, with a number of different health endpoints (see also response to Research Question 4).
2	What is the endpoint that determines this value?	None of the publications consulted have specifically proposed a new health-based guidance/guideline value for Pb in drinking water in addition to those identified in the Stage 1 report, apart from WHO (2022b) reporting of a revised EU drinking water limit for Pb of 5 µg/L but not providing the basis of the value. Nevertheless, numerous epidemiological studies have investigated and found statistically significant associations of Pb exposure (as Pb in drinking water, blood Pb or serum Pb) with various health endpoints (see also response to Research Question 4).
3	Is the proposed option for a health-based guideline value relevant to the Australian context?	Not applicable. No additional proposed health-based guideline values apart from those in the Stage 1 reports have been found in the Stage 2 searches.

[2] The EU Directive (EU 2020) states the following with respect to lead: "*In relation to lead, the WHO recommended retaining the current parametric value, but noted that concentrations should be as low as reasonably practicable. Therefore, it should be possible to retain the current value of 10 µg/l for 15 years after the date of entry into force of this Directive. By the end of this transitional period, at the latest, the parametric value for lead should be 5 µg/l. In addition, since existing lead pipes in houses and buildings are a persisting issue and since Member States do not always have the necessary authority to impose the replacement of those pipes, the value of 5 µg/l should remain aspirational when it comes to obligations related to domestic distribution systems. However, for all new materials that come into contact with water intended for human consumption, regardless of whether they are to be used in supply or domestic distribution systems, to be authorised in accordance with this Directive, the value of 5 µg/l should apply at the tap.*"

<table>
<tr><th>#</th><th>Research Questions</th><th>Response</th></tr>
<tr><td>4</td><td>What are the key adverse health hazards from exposure to lead in Australian drinking water?</td><td>The Stage 1 investigation reports indicated that jurisdictions generally agree that the evidence for Pb exposure (generally measured as blood Pb and representing total Pb exposure from all sources) and associations with adverse health endpoints is strongest for adverse cognitive effects (including reduced Intelligence Quotient - IQ) in children and cardiovascular effects (including increased blood pressure) in adults rendering these the most sensitive endpoints. The Stage 2 review identified several epidemiological studies not previously identified by NHMRC (2015a, b) that found associations of blood Pb, serum Pb, or Pb in drinking water with increases in various health-related endpoints including the following:
• Hip fractures in 66–85-year-old men (Dahl et al. 2014).
• Markers of iron deficiency (Danziger et al. 2021, 2022).
• Birth outcomes (including low birth weight, miscarriages/foetal death) (Dave and Yang 2022, Edwards et al. 2014, Cheng et al. 2017, Wang et al. 2017). In addition a number of studies (e.g. Sanders et al. 2014, Hanna-Attisha et al. 2021) found <u>no</u> association with Pb exposure and these endpoints.
• Blood pressure (De Almeida Lopes et al. 2017).
• Biochemical changes to sex hormones in males (Enehizena and Emokpae 2022).
• Neurodevelopmental outcomes in children and adults (the latter after childhood exposure) (Rodrigues et al. 2016, Vigeh et al. 2014, Reuben et al. 2017).
• Behavioural effects (Macdonald Gibson et al. 2022, Nkomo et al. 2018).
• Oral health status (Tort et al. 2018, Kim et al. 2017, Wu et al. 2019).
• Fasting plasma glucose (Wan et al. 2021).
• Fatty liver disease (Wan et al. 2022).
• Coronary artery disease (Asgary et al. 2017).
Overall there are varying levels of confidence in the health outcomes and the dose response for these associations at blood Pb levels <5 µg/dL is unclear (see Section 5.1 and 5.1.8). Therefore, the critical human health endpoints are consistent with the findings in NHMRC (2015a, b).</td></tr>
<tr><td>5</td><td>Are there studies quantifying the health burden (reduction or increase) due to lead?</td><td>Yes. Available epidemiological information found as part of the literature search undertaken in this Stage 2 investigation indicate Pb exposure may be associated with numerous adverse health outcomes in human populations; however, this was already known in the previous reviews undertaken by various agencies, including NHMRC (2015a, b). From the available information sourced in this Stage 2 investigation, the dose response for adverse outcomes at blood Pb concentrations <5 µg/dL is unclear, and the conclusions remain consistent with NHMRC (2015a, b).
According to WHO (2022a), nearly half of the 2 million lives lost to known chemical exposure in 2019 were due to Pb exposure. Pb exposure is estimated to account for 21.7 million years lost to disability and premature death (disability-adjusted life years, or DALYs) worldwide due to long-term effects on health, accounting for 30% of the global burden of idiopathic intellectual disability, 4.6% of the global burden of cardiovascular disease and 3% of the global burden of chronic kidney diseases.</td></tr>
<tr><td>6</td><td>What is the critical human health endpoint for lead?</td><td rowspan="2">See response to Research Question 4. The largest confidence exists for adverse cognitive effects (including reduced IQ) in children (‘high confidence’) and cardiovascular effects (including increased blood pressure) (‘moderate confidence’) in adults which is in line with the conclusions made by NHMRC (2015a, b) (see Section 5.2.1).</td></tr>
<tr><td>7</td><td>What are the justifications for choosing this endpoint?</td></tr>
</table>

4.2 Exposure-related aspects

Another important aspect of the fact sheet covers exposure-related considerations. This is important for consideration of whether exposures by Australians to the chemical evaluated are potentially approaching a candidate DWG. It is also important for considerations of whether typical levels of the chemical considered in Australian drinking water supplies (for lead, where leaching from plumbing products is the main lead source, the primary consideration is in water from the customers' tap) would adhere to any derived DWG. Research Questions 8-9 cover exposure-related aspects of the review; it is noted the response to Research Question 8 stems from the Stage 1 reports. **Table 3** provides a response to the exposure-related research questions.

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

#	Research Questions	Findings
8	What are the typical lead levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought? (note this aspect was already covered in previous reports as part of the Stage 1 review)	As per Stage 1 reports: Mean / range of means (minimum to maximum) concentrations of lead in drinking water in the distribution network: • ACT: 0.3 µg/L (<0.2-8.1 µg/L) • VIC: (<1-4 µg/L) • TAS: 0.2-2 µg/L (<0.1-2.7 µg/L) • NT: <1-20 µg/L (range not reported) • QLD: <1 µg/L (<1-<1 µg/L) • Rainwater tanks around Australia: Mean 3.8 µg/L (0.3 µg/L-13 µg/L) • SA (stored rainwater for drinking): 0.6 µg/L (max 22.4 µg/L). Main source of Pb in drinking water is leaching from household plumbing systems, therefore the Australian Environmental Health Standing Committee recommends flushing taps used for drinking and cooking for about 10 seconds first thing in the morning or after periods of absence (enHealth 2021). This will draw fresh water into the tap and reduce potential exposure to Pb. Pb is not detected above the current Australian drinking water guideline from most water samples taken from within distribution systems around Australia. In addition, due to soft and sometimes acidic nature of rainwater, when used in hot water systems, it leads to increases in Pb concentrations in the hot water (enHealth 2021).

#	Research Questions	Findings
9	Are there any data for lead levels leaching into water from in-premise plumbing?	Numerous studies were identified in the literature consulted as part of this Stage 2 report quantifying potential concentrations of Pb in tap waters as a result of Pb leaching from Pb-containing and low lead plumbing materials including taps. The concentrations varied markedly and can be summarised briefly as follows. Note that Pb has not been used in Australian water pipes (i.e. Pb service lines) since the 1930s therefore some of the sourced information is not directly applicable to the Australian context (note these studies are identified in *italics* below). • 30 to 44 µg/L from household installed pitcher pumps containing Pb (Akers et al. 2015). • *54 to 162 µg/L (no replacement of Pb plumbing materials), 17 µg/L (80% replacement of Pb plumbing materials) in service lines in Canada (Cartier et al. 2013).* • *37 µg/L (full Pb service line), 14 to 23 µg/L (partial replacement of Pb service line) in Canada (Deshommes et al. 2017).* • <1 to 2,870 (mean 22.3 µg/L) in pipes of a building in Hungary (Namrotee et al. 2022). • *2.3 to 9.9 µg/L for Pb service lines in the USA (Pieper et al. 2018b).* • 3.7 µg/L (mean) in NSW taps containing up to 2.84% Pb (Harvey et al. 2016). • 0.5 to 24.3 µg/L in 'Pb-free faucets' (i.e. ≤ 0.25% Pb w/w) (Parks et al. 2018). • Means of 6.37 and 7.97 µg/L (range: <1 to 62.5 µg/L) in samples collected from the drinking water supply in Perth's Children's Hospital as part of building commission stage (Weeramanthri et al. 2017).

4.3 Risk-based aspects

Research Questions 10 and 11 are risk-based considerations. The publications subjected to detailed data extraction 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
10	What are the risks to human health from exposure to lead in Australian drinking water?	WHO (2022a) states there is no known safe blood Pb concentration; as Pb exposure increases, the range and severity of symptoms and effects also increase. This is in line with the current understanding of the toxicological effects of Pb. **Section 5.2.1** provides an overall evaluation of the confidence in the data retrieved as part of this Stage 2 review for individual health endpoints. The overall confidence in the studies which found adverse associations with Pb exposure at blood Pb levels <5 µg/dL is mostly low; in other studies, the dose response for the health outcomes is unclear. Thus, there is insufficient health-based evidence to warrant a review of the position in NHMRC (2015a, b) that if a person has a blood Pb level >5 µg/dL, their exposure to Pb should be investigated and reduced, and also therefore insufficient evidence to alter the candidate guideline value of 5 µg/L suggested in the Stage 1 reports. Numerous studies were identified in the literature consulted as part of this Stage 2 report quantifying potential concentrations of Pb in tap waters as a result of Pb leaching from Pb-containing plumbing materials including taps (see response to Research Question 9). These data indicate that leaching of Pb from Pb containing plumbing materials, even when claiming these to be 'Pb-free' (i.e. ≤ 0.25% Pb w/w) can be marked and can result in concentrations that approach or exceed the candidate drinking water guideline of 5 µg/L. This indicates that, in some households, exposure to Pb from drinking water may be significant and could potentially increase the risk of those persons' overall exposure exceeding 5 µg/dL and thus increase the risk of adverse health effects.
11	Is there evidence of any emerging risks that require review or further research?	Plumbing fittings (<u>including taps</u>) that contain detectable Pb up to 2.84% are contributing to Pb levels in household drinking water. Even some plumbing fittings claimed to be 'Pb-free' (i.e. ≤ 0.25% Pb w/w) appear to be potentially contributing to relatively high levels of Pb in drinking water at the tap, with evidence of decreasing concentration over time. This aspect may warrant further research. Note in Australia, in 2022, the 'Pb free' threshold for plumbing materials in contact with drinking water was reduced to 0.25% (coming into effect from 1 May 2026) (ABCB 2023).

5 Discussion

This section provides an overview of the epidemiological information sourced in the Stage 2 review for lead which were considered to potentially influence the Stage 1 report findings along with a discussion of the overall confidence in the health-based literature for possible use in derivation of a potential guideline value for lead. This includes consideration of RoB of individual studies (see **Appendix D** – Technical Report) where appropriate. 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 reported health outcome. Overall RoB ratings for each health outcome were determined using guidance from OHAT (2019) to determine overall confidence ratings.

5.1 Dose response and overall confidence by evidence stream / health outcome

5.1.1 Hip fractures

A cohort study by Dahl et al. (2014) found 'elevated' lead in drinking water to be associated with an increased incidence of hip fracture in 66–85 year-old men and women in Norway. Average concentration of lead was 1.16 µg/L (range: 0.04–23.80 µg/L), and 'high' and 'low' lead exposures were defined as being above or below the measured average. As the range of lead concentrations in drinking water was large, and only two exposure stratification groups were examined, the study does not provide useful information with respect to defining a dose response for this effect. For this reason, a RoB analysis and confidence rating analysis was not undertaken for this study.

5.1.2 Markers of iron deficiency

The following two cross-sectional studies by the same research group examined the association of lead in drinking water and markers of iron deficiency.

- Danziger et al. (2021): Lead levels in drinking water below 15 µg/L were found to be associated with lower haemoglobin levels and higher erythropoietin stimulating agent (ESA) use among patients with end-stage kidney disease (ESKD) in the USA, with a 0.02 g/dL (95% confidence interval [95% CI], 0.01 to 0.02) lower haemoglobin concentration for each 10 µg/L increment in community water lead. A 10 µg/L increment in lead was associated with 0.03 g/dL (95% CI, 0.02 to 0.03) lower pre-ESKD haemoglobin concentration and 0.5% (95% CI, 0.2 to 0.7) higher prevalence of pre-ESKD ESA use.
- Danziger et al. (2022): Statistically significant associations were identified between lead concentration in water (≤ 15 µg/L) and measures of iron deficiency. However, the association/effect did not increase with increasing concentrations (i.e. there was no clear dose response with increasing Pb concentrations).

A RoB summary table for the included studies for the markers of iron deficiency outcome is presented in **Table 5** below. It is noted the associations were found between lead exposure in drinking water and a change in these markers but not the adverse health outcome *per se*. An overall RoB rating of 'not likely' was determined for the health outcome based on probably low or definitely low RoB across the majority of key domains and across both studies.

Table 5 RoB summary table for studies investigating an association between lead exposure in drinking water and markers of iron deficiency

Health outcome:	Markers of iron deficiency	
Study ID:	**Danziger et al. 2021 (CrSe)**	**Danziger et al. 2022 (CrSe)**
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	NR	NR
Detection Bias		
Exposure characterisation	-	-
Outcome assessment	-	-
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. CrSe = Cross-sectional study.		
1. Based on probably low or definitely low RoB across the majority of key domains and across both studies.		

The initial confidence rating for the studies investigating an association between lead exposure and markers of iron deficiency is considered 'low', since there was no controlled exposure, it is uncertain whether exposure occurred prior to measuring the outcome, individual outcome data were assessed, and a comparison (i.e. low-exposure - <1 µg/L) group was used. **Table 6** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'low'. There is therefore low confidence in the evidence to conclude that exposure to lead at relatively low levels (defined as blood Pb <5 µg/dL and water lead <5 µg/L)[3] can increase the risk of iron deficiency.

Table 6 Confidence Rating for cross-sectional study findings in relation to markers of iron deficiency and lead exposure

Health outcome [number of studies]	**Markers of iron deficiency** [2]	**Comment** (1)
Initial confidence rating	**LOW**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence		
Risk of Bias	Not serious.	Confidence not downgraded since overall RoB across studies for this endpoint is 'not likely' (see **Table 5**).
Unexplained inconsistency	Not serious.	No inconsistency between the two studies, except no clear dose response was observed. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	No large standard deviations [e.g. 95% CI for the Danziger et al. 2022 findings are 1.03-1.09, 1.02-1.10, 1.03–1.11 for transferrin saturation <20%, ferritin <200 ng/ml, and simultaneous transferrin saturation <20% and ferritin <200 ng/ml respectively. Danziger et al. (2021) confidence intervals for adjusted difference in haemoglobin and prevalence of ESA use were relatively narrow. Confidence not downgraded.

[3] These values correspond to the 'target' blood Pb level and candidate drinking water guideline summarised in the Stage 1 reports.

Health outcome [number of studies]	**Markers of iron deficiency** [2]	**Comment** (1)
Publication bias	Undetected.	Potential interests by specific authors of the papers were fully declared, but are considered unlikely to have influenced study outcomes. Confidence not downgraded.
Factors Increasing Confidence		
Magnitude	Not large.	Magnitude of effect in the two papers is not large (e.g. OR of ~1.05-1.1), so confidence not upgraded for large magnitude of effect.
Dose response	No.	No clear dose response observed for markers of iron deficiency in either study. Confidence not upgraded.
Residual confounding	No.	No residual confounding identified. Confidence not upgraded.
Consistency across species	N/A	Both cross-sectional studies found statistically significant associations between two different markers of iron deficiency. NHMRC (2015a, b) indicate abnormally low haemoglobin have been observed in humans at blood Pb levels between 10 and 60 µg/dL in adults and children. However, no blood Pb data were available to quantify internal exposures in the two cross-sectional studies. Therefore, consistency with this information across species, dissimilar populations and/or study types cannot be judged. Confidence not upgraded.
Final confidence rating	**LOW**	-
1. As per guidance provided in OHAT (2019, Table 7)		

5.1.3 Birth outcomes

The studies summarised in **Table 7** investigated the association between lead exposure and birth outcomes. The table presents the individual study findings.

Table 7 Summary of studies on lead exposure and risk of adverse birth outcomes

Study	Findings	Pb exposure
Co: Dave and Yang 2022	The study authors conclude increased likelihood of low birth weight and preterm births in children born in years in which Pb concentrations in tap water were greater than the US EPA Maximum Contaminant Level (MCL) at the time of 15 µg/L. The statistical analysis approach used in the study, i.e. difference in differences approach, renders the results difficult to interpret and confirm.	>15 µg/L (in drinking water)
Ecol: Sanders et al. 2014	No association was found between Pb levels in well water used for drinking in North Carolina and specific birth defects even though Pb levels in well water ranged from 2.5 to 1304.2 µg/L.	2.5-1,304.2 µg/L (in well water) (no association)
Ecol: Edwards et al. 2014 (1)	Increased Pb exposure from drinking water in Washington DC in 2006 resulted in a higher incidence of miscarriages and foetal death at blood Pb approaching 5 µg/dL. Partial service line replacement and removal of corrosion control resulted in high water Pb levels and increased risk of foetal deaths. However, the study provides no clear dose response for the effects investigated.	90th percentile water lead levels (WLL) spiked over 40 µg/L from 2001 to 2004, with peak WLL of 79 µg/L in 2001 (drinking water)

Study	Findings	Pb exposure
Co: Hanna-Attisha et al. 2021	There was no association found between cord blood lead levels (CBLLs) and birth outcomes (Gestational age, Birth weight, %Preterm, small for gestational age, Head circumference, and 5-min Apgar score) in 99 newborns born in Flint, Michigan compared to Detroit newborns even though there was higher prevalence of cord blood Pb levels ≥1 µg/dL in the Flint newborns. A CBLL ≥1 µg/dL was defined as the threshold for the higher Pb level group examined in this study.	≥ 1 µg/dL (cord blood) (no association)
Co: Cheng et al. 2017	High creatine adjusted urinary Pb (>4.06 µg/g) was found to be associated with a significant increase in the risk of preterm births in a Chinese cohort (adjusted OR 1.96, 95% CI 1.31, 2.44). Note blood lead levels were not measured, hence useful dose response data for guideline derivation may be difficult to establish from this study. Study split Pb exposure into the following tertiles: Low (≤2.29 µg/g creatinine), Medium (2.29–4.06 µg/g creatinine) and High (>4.06 µg/g creatinine).	>4.06 µg/g creatinine (urine)
Co: Wang et al. 2017	High maternal serum Pb level in the first trimester (≥1.71 µg/dL) of a Chinese cohort was found to be associated with an elevated risk of small for gestational age (SGA) in newborn infants when compared to low-Pb (<1.18 µg/dL) and medium Pb (1.18–1.70 µg/dL) (adjusted OR: 2.13, 95% CI 1.24, 3.38). Note that the maximum serum Pb level reported in this study was 5.46 µg/dL. It is noted serum, rather than whole blood Pb (which is typically measured in other studies) was reported in this study.	≥1.71 µg/dL (serum)

OR = Odds Ratio. CI = Confidence Interval.

1. No RoB analysis was undertaken on this study, since it was an ecological study with no clear dose response analysis of utility. It would therefore not alter the conclusions made by NHMRC (2015a, b) with respect to critical blood Pb levels.

A RoB summary table for the included studies for the birth outcomes is presented in **Table 8** below. An overall RoB rating of 'not likely' was determined for the birth outcome 'small for gestational age' based on probable or definite low RoB for the majority of domains, whereas a RoB rating of 'serious' was determined for the other outcomes (low birth weight and preterm births, birth defects) based on mixed results with probable or definite RoB for some domains and several instances where limited information was reported (i.e. NR).

Table 8 RoB summary table for epidemiological studies investigating birth outcomes and lead exposure

Health outcome:	Low birth weight & preterm births			Small for gestational age		Birth defects
Study ID:	**Dave and Yang 2022 (Co)**	**Hanna-Attisha et al. 2021 (Co)**	**Cheng et al. 2017 (Co)**	**Wang et al. 2017 (Co)**	**Hanna-Attisha et al. 2021 (Co)**	**Sanders et al. 2014 (Ecol)**
Selection bias						
Randomization						
Allocation concealment						
Comparison groups appropriate	-	NR	NR	-	NR	--
Confounding bias						
Confounding (design/analysis)	NR	-	--	-	-	NR
Performance Bias						
Identical experimental conditions						
Blinding of researchers during study?						
Attrition/Exclusion Bias						
Missing outcome data	NR	--	NR	-	--	-
Detection Bias						
Exposure characterisation	NR (1)	--	+	NR	--	+
Outcome assessment	-	-	-	-	-	-
Selective Reporting Bias						

Outcome reporting	--	--	--	--	--	-
Other Sources of Bias						
Other threats	+ [2]					
Overall risk of bias across studies (not likely/serious/very serious)	Serious [3]			Not likely [4]		Serious [5]

Pro Co = Prospective Cohort, HCT = Human Controlled Trial.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Although there was insufficient information provided about the validity of the exposure assessment method, there is no evidence for concern.
2. Unusual method of statistical analysis employed which makes it difficult to interpret and confirm significance of results.
3. Based on mixed results with probable RoB for exposure characterisation in one study, probable RoB for other threats in another study, and several instances where limited information was reported (i.e. NR).
4. Based on probable or definite low RoB for the majority of domains, apart from one aspect which was NR in each study.
5. Based on probable high RoB for exposure characterisation.

The initial confidence rating for the 'low birth weight and preterm births' health outcome is considered moderate, since there was no controlled exposure, but exposure occurred prior to measuring the outcome, individual outcome data were assessed, and a comparison group was used. The initial confidence rating for the other studies is considered low since there was no controlled exposure, exposure may not have occurred prior to the outcome, individual outcome data were assessed and a comparison group was used. **Table 9** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'low' for the low birth weight and preterm births and small for gestational age health outcomes, and 'very low' for the birth defects health outcome.

Table 9 Confidence Rating for epidemiological findings in relation to birth outcomes and lead exposure

Health outcome [number of studies]	**Low birth weight & preterm births** [3 x Co]	**Small for gestational age** [2 x Co]	**Birth defects** [1 x Ecol]	**Comment** [1]
Initial confidence rating	**MODERATE**	**LOW**	**LOW**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence				
Risk of Bias	Serious. Downgraded to **LOW**.	Not serious. Not downgraded.	Serious. Downgraded to **VERY LOW**.	Confidence not downgraded or downgraded based on overall RoB finding (see **Table 8**).
Unexplained inconsistency	No.	No.	No.	Inconsistency observed between the findings of the analyses for low birth weight and preterm births may be explained by the different comparators used (drinking water Pb in Dave and Yang 2022, cord blood Pb in Hanna-Attisha et al 2021 and urinary Pb in Cheng et al. 2017). Similarly inconsistency in findings for 'small for gestational age' can potentially be explained by different comparators (serum Pb vs. cord blood Pb). Confidence not downgraded.
Indirectness	Not serious.	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.

Health outcome [number of studies]	**Low birth weight & preterm births** [3 x Co]	**Small for gestational age** [2 x Co]	**Birth defects** [1 x Ecol]	**Comment** [(1)]
Imprecision	Not serious.	Not serious.	Not serious.	No large standard deviations. Confidence not downgraded.
Publication bias	Undetected	Undetected	Undetected	Not downgraded.
Factors Increasing Confidence				
Magnitude	Not large	Not large	No effect (i.e. not large)	For low birth weight and preterm births, magnitude of effect in Cheng et al. (2017) is not above 2 (OR 1.96), no association was observed in Hanna-Attisha et al. (2021) and an unconventional statistical analysis was used by Dave and Yang (2022). For small for gestational age, the adjusted OR observed by Wang et al. (2017) is just above 2 (i.e. 2.13) but no association was found in Hanna-Attisha et al. (2021). No association was found for birth defects in the Sanders et al. (2014) study. Confidence not upgraded for large magnitude of effect.
Dose response	No.	No.	No.	No clear dose response observed for birth outcomes in any of the studies. Confidence not upgraded.
Residual confounding	No.	No.	No.	No residual confounding identified. Confidence not upgraded.
Consistency across species	No.	No.	No.	No consistency across species and dissimilar populations identified, but potentially due to different measures of Pb exposure. Confidence not upgraded.
Final confidence rating	**LOW**	**LOW**	**VERY LOW**	

Co = Cohort; Ecol = Ecological.

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

5.1.4 Blood pressure/hypertension

A cross-sectional study by De Almeida Lopes et al. (2017) found a positive association between blood Pb in the highest quartile and diastolic blood pressure as well as a significant association of blood Pb in the highest quartile and hypertension in Brazilians aged 40 years or older, living in southern Brazil. It is noted however that the highest quartile (Q4) in this study had blood Pb >2.76 µg/dL whereas the maximum blood Pb was 45.62 µg/dL. Thus this study did not stratify the highest quartile blood Pb sufficiently to see whether significant associations for increased blood pressure and hypertension exist with blood Pb between 2.76 - 5 µg/dL.

A RoB summary table for the study is presented in **Table 10** below. An overall RoB rating of 'serious' was determined for the increased blood pressure / hypertension health outcome based on probable high exposure characterisation bias in the study.

Table 10 RoB summary table for epidemiological study investigating blood pressure/hypertension and lead exposure

Health outcome:	Increased blood pressure / hypertension
Study ID:	De Almeida Lopes et al. 2017 (CrSe)
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	
Outcome reporting	--
Other Sources of Bias	
Other threats	
Overall risk of bias across studies (not likely/serious/very serious)	Serious (1)

CrSe = Cross-sectional.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.
1. Based on probable high exposure characterisation bias in the study.

The initial confidence rating for the cross-sectional study investigating blood pressure/hypertension is considered low, since there was no controlled exposure, exposure may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. lowest quartile) group was used. **Table 11** shows an assessment of the confidence in the body of evidence, with a final confidence rating of 'moderate'. Consequently, based on the available information, there is moderate confidence to conclude that lead exposure is associated with increased blood pressure and/or hypertension in humans. This is consistent with the findings in the NHMRC (2015a, b) review. Although a dose response was observed for the health outcome, where the OR for hypertension increased with increasing blood Pb quartile (only statistically significant in Q4), the wide range of blood Pb values in the top quartile does not make it possible to determine whether significant associations for increased blood pressure and hypertension exist with blood Pb between 2.76 - 5 µg/dL.

Table 11 Confidence Rating for cross-sectional study findings in relation to risk of increased blood pressure / hypertension and lead exposure

Health outcome [number of studies]	**Increased blood pressure / hypertension** [1]	**Comment** (1)
Initial confidence rating	**LOW**	Based on study design as per OHAT (2019, Table 8).

Health outcome [number of studies]	**Increased blood pressure / hypertension** [1]	**Comment** (1)
Factors Decreasing Confidence		
Risk of Bias	Serious. Downgraded to **VERY LOW.**	Confidence downgraded due to probable high exposure characterisation bias in the study. Overall RoB was considered 'serious' (**Table 10**).
Unexplained inconsistency	Not serious.	Not applicable, since only one study investigating these health outcomes was retrieved in the Stage 2 literature search. Nevertheless, it is noted NHMRC (2015a, b) indicated increased blood pressure in adults was one of the most sensitive endpoints in epidemiological studies showing an association with blood Pb. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Confidence intervals for Q4 findings did not span >10 (i.e. 95% CI for Model 1: 1.12-4.66 for hypertension, 0.04-0.09 for change in diastolic blood pressure; for Model 2: 1.17-5.53 for hypertension, 0.04-0.09 for change in diastolic blood pressure). Confidence not downgraded for imprecision.
Publication bias	None detected.	None detected or obvious. Confidence not downgraded.
Factors Increasing Confidence		
Magnitude	Potentially large. Confidence upgraded to **LOW.**	Magnitude of effect in the study appears large (i.e. > 2) (OR for hypertension in Q4 was 2.28 in Model 1, 2.54 in Model 2) so confidence can be upgraded for large magnitude of effect.
Dose response	Yes. Confidence upgraded to **MODERATE**.	There appears to be a dose response for both increased blood pressure and hypertension with change in blood pressure higher in highest quartile blood Pb compared to other quartiles and OR for hypertension increasing with increasing blood Pb quartile (only statistically significant in Q4). Confidence upgraded.
Residual confounding	No.	No residual confounding that could increase confidence identified. Confidence not upgraded.
Consistency across species	N/A	Not applicable, since the review retrieved only one study for this health outcome. Consistency across species and dissimilar populations can therefore not be judged for this health outcome. Nevertheless, the findings are consistent with NHMRC (2015a, b). Confidence not upgraded.
Final confidence rating	**MODERATE**	

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

5.1.5 Biochemical changes to sex hormones in males

Enehizena and Emokpae (2022) conducted a case-control study in which a statistically significant difference in levels of follicle stimulating hormone and prolactin was observed in men with blood Pb levels of 4.00 ± 0.26 µg/dL (using hand dug water as drinking water) compared to those with 2.08 ± 0.42 µg/dL (using borehole water) and 1.64 ± 0.04 µg/dL (using treated water). However, it is noted these are biochemical changes, which on their own, are not adverse health outcomes *per se*.

A RoB summary table for the included study is presented in **Table 12** below. An overall RoB rating of 'serious' was determined for the biochemical changes outcome based on probable high attrition/exclusion bias in the study and minimal demographic data provided in the study.

Table 12 RoB summary table for epidemiological study investigating biochemical changes to sex hormones in males and lead exposure

Health outcome:	**Biochemical changes to sex hormones in males**
Study ID:	**Enehizena and Emokpae 2022 (CaCo)**
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	+
Detection Bias	
Exposure characterisation	-
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)

CaCo = Case control
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.
1. Based on probable high attriton/exclusion bias in the study and minimal demographic data provided in the study (i.e. NR for selection bias).

The initial confidence rating for the case-control study is considered 'moderate', since there was no controlled exposure, exposure appears to have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. treated water consumers) group was used. **Table 13** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'very low'. Consequently, based on the available information, there is insufficient information to conclude whether lead exposure is associated with biochemical changes in sex hormones in males.

Table 13 Confidence Rating for case-control findings in relation to risk of biochemical changes to sex hormones in males and lead exposure

Health outcome [number of studies]	**Biochemical changes to sex hormones** [1]	**Comment** (1)
Initial confidence rating	**MODERATE**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence		
Risk of Bias	Serious. Downgraded to **LOW.**	Confidence downgraded due to probable high attrition/exclusion bias in the study and minimal demographic data provided. Overall RoB was considered 'serious' (**Table 12**).

Health outcome [number of studies]	**Biochemical changes to sex hormones** [1]	**Comment** (1)
Unexplained inconsistency	Not serious.	Not applicable, since only one study investigating the health outcome was retrieved in the Stage 2 literature search. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Serious. Downgraded to **VERY LOW.**	Does not clearly meet guidance for 'not serious' or 'very serious'. Regression based results with only p values but no confidence intervals reported. Confidence downgraded for imprecision.
Publication bias	None detected.	None detected or obvious. Confidence not downgraded.
Factors Increasing Confidence		
Magnitude	No.	Magnitude of effect in the study unclear as there were no OR calculated. Confidence not upgraded.
Dose response	No.	There appears to be a dose response for exposure to Pb (as measured by mean Pb in water; treated water – 0.81 µg/L, borehole – 1.1 µg/L, hand-dug well – 1.81 µg/L) and decrease in follicle stimulating hormone and increase in prolactin. However study is hampered because the sex hormone comparison involved combining data for hand-dug well and borehole water consumers even though a statistically significant difference was observed in blood Pb levels between the two groups. It is also noted the outcome by itself is not adverse. Hence confidence was not upgraded for dose response.
Residual confounding	No.	No residual confounding that could increase confidence identified. Confidence not upgraded.
Consistency across species	N/A	Not applicable, since the review retrieved only one study for this health outcome. Consistency across species and dissimilar populations can therefore not be judged for this health outcome.
Final confidence rating	**VERY LOW**	
1. As per guidance provided in OHAT (2019, Table 7)		

5.1.6 Neurodevelopmental outcomes / behavioural effects

The studies summarised in **Table 14** investigated the association between lead exposure and neurodevelopmental outcomes in children and adults (the latter after childhood exposure) and behavioural effects. The table presents the individual study findings.

Table 14 Summary of studies on lead exposure and risk of neurodevelopmental / behavioural outcomes

Study	Findings	Pb exposure
Neurodevelopmental outcomes		
Co: Rodrigues et al. 2016	Found increased blood Pb in children was associated with decreased cognitive scores (p=0.05) in Sirajdikhan, Bangladesh (median blood Pb = 7.6 µg/dL, range = <3.3 – 43 µg/dL) compared to Pabna (median blood Pb = <3.3 µg/dL, range = <3.3 – 13.8 µg/dL). No OR calculated. As both groups included individuals with elevated blood Pb (i.e. ≥5 µg/dL), this study does not alter the dose response relationship already established in NHMRC (2015).	Blood Pb (median): 7.6 vs <3.3 µg/dL (range: <3.3-43 vs. <3.3-13.8 µg/dL)
Co: Vigeh et al. 2014	Increasing first trimester maternal blood lead levels (6.31 ± 1.95 µg/dL vs. 4.05 ± 2.4 µg/dL) found to be associated with lower developmental scores in early childhood after adjusting for multiple covariates (OR = 1.74, 95% CI 1.18-2.57, p=0.005). It is unlikely that a dose response relationship below 5 µg/dL can be established with the data in this paper.	Blood Pb: 6.31 ± 1.95 µg/dL vs. 4.05 ± 2.4 µg/dL
Co: Reuben et al. 2017	In this prospective cohort study in New Zealand, there was a statistically significant association between a 5 µg/dL increase in childhood (at age 11 years) in blood Pb from <5 µg/dL and lower cognitive function and socioeconomic status at adult age 38 years and with declines in IQ and downward social mobility. Associations with each 5 µg/dL increase in blood Pb above <5 µg/dL: • Fully-adjusted full scale adult IQ: -1.61 (95% CI -2.48, -0.74, p<0.001) • Fully-adjusted adult working memory IQ: -1.26 (95% CI -2.38, -0.14, p=0.03) • Fully-adjusted adult perceptual reasoning IQ: -2.07 (95% CI -3.14, -1.01, p<0.001) • Fully adjusted socioeconomic status: -1.79 (95% CI -3.17, -0.4, p=0.01)	Childhood blood Pb: 4-31 µg/dL (mean 10.99 ± 4.63 µg/dL)
Behavioural effects		
CrSe: Macdonald Gibson et al. 2022	Found an association between reported delinquency and small differences in mean blood Pb; 2.5 µg/dL for well users and 2.36 µg/dL for community water users (OR for any delinquency for full dataset: 1.13; 95% CI 1.05, 1.21). A dose response relationship cannot be established for this study as the study reports only a mean blood Pb concentration rather than stratified blood Pb.	Mean blood Pb: 2.5 vs. 2.36 µg/dL
Co: Nkomo et al. 2018	This study found a significant positive association between 'elevated' blood lead levels (≥10 µg/dL) and direct aggression in South African adolescents (β 0.37 ± 0.18, p=0.04), but no significant association for 5-9.99 µg/dL.	Blood Pb: ≥ 10 vs. <5 µg/dL
OR = Odds Ratio. CI = Confidence Interval.		

A RoB summary table for the included studies for the neurodevelopmental and behavioural outcomes is presented in **Table 15** below. An overall RoB rating of 'not likely' was determined for the neurodevelopmental outcomes based on definite low or probable low RoB for the vast majority of domains across all three studies, whereas a RoB rating of 'serious' was determined for the behavioural outcomes based on mixed results with probable or definite high RoB for some domains in one study but low RoB in the other study.

Table 15 RoB summary table for epidemiological studies investigating neurodevelopmental outcomes / behaviour and lead exposure

Health outcome:	Neurodevelopmental outcomes			Behavioural effects	
Study ID:	Rodrigues et al. 2016 (Co)	Vigeh et al. 2014 (Co)	Reuben et al. 2017 (Co)	Macdonald Gibson et al. 2022 (CrSe)	Nkomo et al. 2018 (Co)
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	-	-	-	-	-
Detection Bias					
Exposure characterisation	--	-	-	++	-
Outcome assessment	-	+ (1)	-	-	-
Selective Reporting Bias					
Outcome reporting	--	--	--	--	--
Other Sources of Bias					
Other threats					
Overall risk of bias across studies (not likely/serious/very serious)	Not Likely (2)			Serious (3)	

Pro Co = Prospective Cohort, HCT = Human Controlled Trial.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. There is indirect evidence that the outcome assessment method is an insensitive instrument (because blood lead levels were not stratified).
2. Based on definitely low or probably low RoB for the vast majority of domains across all three studies with the exception of probably high RoB for the outcome assessment in one of the three studies.
3. Based on definite high selection and exposure characterisation bias in one study, but no detected RoB in the other study.

The initial confidence rating for the studies investigating neurobehavioural outcomes is considered moderate, since there was no controlled exposure, exposure occurred prior to the outcome, individual outcome data were assessed, and a comparison group was used, whereas the initial confidence rating for the studies on behavioural effects was considered low (as exposure may not have occurred prior to the outcome). **Table 16** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'high' (for neurobehavioural outcomes) and 'low' (for behavioural effects).

Table 16 Confidence Rating for findings in relation to risk of neurodevelopmental and behavioural outcomes and lead exposure

Health outcome [number of studies]	**Neurobehavioural outcomes** [3]	**Behavioural effects** [2]	**Comment** (1)
Initial confidence rating	**MODERATE**	**LOW**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence			
Risk of Bias	Not likely.	Serious. Confidence downgraded to **VERY LOW**	Confidence downgraded for behavioural effects studies due to definite high selection and exposure characterisation bias in one of the two studies. Overall RoB was considered 'serious' (**Table 15**).

Health outcome [number of studies]	**Neurobehavioural outcomes** [3]	**Behavioural effects** [2]	**Comment** [(1)]
Unexplained inconsistency	Not serious.	Not serious.	Findings were consistent between the studies. Confidence not downgraded.
Indirectness	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Not serious.	No large standard deviations or large ratios for OR (95% CI for Vigeh et al. 2014 findings: 1.18-2.57; in Reuben et al. 2017: -2.48, -0.74; in Macdonald Gibson et al. 2022: 1.05, 1.21). Confidence not downgraded.
Publication bias	Not detected.	Not detected.	Not detected or obvious. Confidence not downgraded.
Factors Increasing Confidence			
Magnitude	Potentially large. Confidence upgraded to **HIGH.**	Not large.	Magnitude of effect in the studies does not appear to be large (OR for Vigeh et al. 2014: OR = 1.74; 1.13 in Macdonald Gibson et al. 2022), with exception of IQ (negative 1.26 to negative 2.07 for IQ in Reuben et al. 2017). As per OHAT (2019) guidance, this was still construed as a large magnitude of effect for neurobehavioural outcomes, as the effect on IQ could have detrimental consequences on a large population of individuals. Confidence upgraded for neurobehavioural outcomes.
Dose response	Yes. Cannot be upgraded further.	Yes. Upgraded to **LOW.**	Dose response observed for both health outcomes, but do not appear to alter the dose response relationship already established in NHMRC (2015a, b). Confidence upgraded.
Residual confounding	No.	No.	No residual confounding that could increase study confidence identified. Confidence not upgraded.
Consistency across species	Yes. Confidence cannot be upgraded further.	No.	There appears to be consistency across studies for neurobehavioural outcomes, and across studies previously reviewed by NHMRC (2015a, b). Confidence upgraded for this health outcome. Inconsistent findings for behavioural effects, as one study suggests a very steep dose response relationship at very low levels (2.5 vs. 2.36 µg/dL) whereas the other found no effects at these blood Pb concentrations (only at levels ≥10 µg/dL).
Final confidence rating	**HIGH**	**LOW**	-

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

5.1.7 Oral health status

The studies summarised in **Table 17** investigated the association between lead exposure and oral health outcomes. The table presents the individual study findings.

Table 17 Summary of studies on lead exposure and risk of adverse oral health outcomes

Study	Findings	Pb exposure
CrSe: Tort et al. 2018	Found a statistically significant association between adverse effects on oral health [periodontal index (CPI), gingival index (GI), and plaque index (PI)] and relatively low blood Pb levels (0.36 – 2.9 µg/dL). It is noted, however, confidence intervals were very large, likely due to the small size of the study [e.g. adjusted OR and 95% CI were 7.21 (1.72,30.19) for CPI; 6.13 (1.62,23.19) for GI; 3.37 (1.1, 10.34) for PI]. It is also unclear why associations were found in Quartile III but not in Quartile IV, the group with the highest blood Pb (although blood Pb in quartiles were not specifically reported).	Blood Pb: 0.36-2.9 µg/dL (mean 1.25 ± 0.43 µg/dL) (Quartile blood Pb not reported)
CrSe: Kim et al. 2017	Found a statistically significant increase in the risk of dental caries in deciduous teeth (adjusted PR 1.14, 95% CI 1.02-1.27) with an increase in blood Pb levels <5 µg/dL (but not in permanent teeth). There were negative associations between blood Pb levels and dental caries in permanent teeth even after adjustment for covariates (PR 0.83, 95% CI 0.69-0.99) however this is not discussed or outlined in the conclusions.	Blood Pb: 1.53 ± 1.57 µg/dL (geometric mean), maximum 4.89 µg/dL
Co: Wu et al. 2019	Found no significant association between decayed, missing and filled tooth (DMFT) scores at adolescence and blood Pb levels in the womb/early childhood (ranging from 3.34±2.68 to 15.48±7.29 µg/dL) in a prospective cohort study when adjustments for covariates were made. However, evidence from stratified analysis suggested a Pb-caries association among children with high sugar-sweetened beverage intake in adolescence.	Blood Pb (lowest and highest mean ± SD): 3.34 ± 2.68 (peri-puberty, females) to 15.48 ± 7.29 µg/dL (early childhood males)

OR = Odds Ratio. CI = Confidence Interval. PR = Prevalence ratio. SD = Standard deviation.

A RoB summary table for the included studies for the oral health outcomes is presented in **Table 18** below. An overall RoB rating of 'serious' was determined for the oral health outcomes based on definite low or probable low RoB for all domains across two of the three studies, with definite high risk of confounding bias and other threats in the study by Kim et al. (2017).

Table 18 RoB summary table for epidemiological studies investigating adverse oral health outcomes and lead exposure

Health outcome:	Oral health outcomes		
Study ID:	**Tort et al. 2018 (CrSe)**	**Kim et al. 2017 (CrSe)**	**Wu et al. 2019 (Co)**
Selection bias			
Randomization			
Allocation concealment			
Comparison groups appropriate	--	-	-
Confounding bias			
Confounding (design/analysis)	-	++ (2)	--
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			
Outcome reporting	--	-	--

Other Sources of Bias			
Other threats		++ (1)	
Overall risk of bias across studies (not likely/serious/very serious)	Serious (3)		

Pro Co = Prospective Cohort, HCT = Human Controlled Trial.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. The researchers did not discuss the negative associations (improvements) between blood Pb levels and dental caries in permanent teeth. This indicates a potential bias in the results.
2. There is indirect evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for (note that consumption of sugar-sweetened drinks was not accounted for).
3. Based on definitely low or probably low RoB for all domains across two of the three studies, with definite high risk of confounding bias and other threats in the study by Kim et al. (2017).

The initial confidence rating for the cohort study is considered moderate [decayed, missing and filled tooth (DMFT) scores at adolescence] and for the cross-sectional studies is low (adverse effects on oral health and an increase in the risk of dental caries in deciduous teeth), since there was no controlled exposure, exposure may or may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison group was used. **Table 19** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'low' for the cohort study (showing no association of lead exposure and DMFT scores at adolescence) and 'very low' for the cross-sectional study [showing increased dental caries in deciduous teeth and increased adverse effects on oral health (CPI, GI, and PI)]. Consequently there is insufficient information to conclude whether lead exposure is associated with adverse effects on oral health status.

Table 19 Confidence Rating for cohort and cross-sectional findings in relation to risk of adverse oral health outcomes and lead exposure

Health outcome [number of studies]	**Oral health outcomes** [2x CrSe, 1 x Co]	**Comment** (1)
Initial confidence rating	**LOW (CrSe)** **MODERATE (Co)**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence		
Risk of Bias	Serious. Confidence downgraded to **VERY LOW** (CrSe) or **LOW** (Co).	Confidence downgraded since overall RoB across studies for this health outcome is 'serious' (see **Table 18**) based on definite low or probable low RoB for all domains across two of the three studies, with definite high risk of confounding bias and other threats in the study by Kim et al. (2017).
Unexplained inconsistency	Not serious.	Some inconsistency observed between the findings in the cross-sectional study by Kim et al. (2017) where a statistically significant increase in the risk of dental caries in deciduous teeth with low blood Pb, whereas in the prospective cohort by Wu et al. (2019) there was no significant association with a similar measure (decayed, missing and filled tooth scores). This may potentially be explained by Kim et al. (2017) not accounting for an important potential confounder. As the inconsistency can potentially be explained, confidence was not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.

Health outcome [number of studies]	**Oral health outcomes** [2x CrSe, 1 x Co]	**Comment** [(1)]
Imprecision	Serious (for CrSe studies only). Confidence cannot be downgraded further.	The CI were very wide in the CrSe study by Tort et al. (2018) [i.e. 1.72,30.19 for CPI; 1.62,23.19 for GI; 1.1, 10.34 for PI]. CI in Kim et al. (2017) study were not wide, and no significant association was found in the cohort study. Confidence only downgraded for CrSe studies.
Publication bias	Undetected.	None detected or obvious. Confidence not downgraded.
Factors Increasing Confidence		
Magnitude	Not large.	Magnitude of effect in the Kim et al. (2017) paper that found a positive association is not large (e.g. PR of 1.14), whereas the OR in Tort et al. (2018) were very large (i.e. 7.21 for CPI; 6.13 for GI; 3.37 for PI), but this was accompanied by wide confidence intervals and study size was small. Confidence not upgraded for large magnitude of effect.
Dose response	No.	No clear dose response observed for adverse oral health found in any of the studies. Confidence not upgraded.
Residual confounding	No.	No residual confounding identified. Confidence not upgraded.
Consistency across species	N/A	There was inconsistency in the findings between studies in the same species (i.e. humans) but for different study types (CrSe vs. Co). Confidence not upgraded.
Final confidence rating	**VERY LOW** (CrSe) to **LOW** (Co)	-
1. As per guidance provided in OHAT (2019, Table 7)		

5.1.8 Fasting plasma glucose

A cross-sectional study by Wan et al. (2021) found blood lead levels >5.8 µg/dL (i.e. those in Quartile 4 only) in Chinese adults were positively associated with fasting plasma glucose levels (but not glycated haemoglobin) in a statistically significant manner after adjustment of potential confounders (OR of having 25% higher fasting plasma glucose = 1.25, 95% CI 1.05, 1.49). On its own, this is not an adverse effect *per se*.

A RoB summary table for the study is presented in **Table 20** below. An overall RoB rating of ‘not likely’ was determined for the increased fasting plasma glucose outcome based on probable or definite low RoB across all study domains.

Table 20 RoB summary table for epidemiological study investigating increased fasting plasma glucose and lead exposure

Health outcome:	**Increased fasting plasma glucose**
Study ID:	**Wan et al. 2021 (CrSe)**
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	
Outcome reporting	--
Other Sources of Bias	
Other threats	
Overall risk of bias across studies (not likely/serious/very serious)	Not likely [(1)]

CrSe = Cross-sectional.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.
1. Based on probable or definite low RoB across all domains.

The initial confidence rating for the cross-sectional study investigating fasting plasma glucose is considered low, since there was no controlled exposure, exposure may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. lowest quartile) group was used. **Table 21** shows an assessment of the confidence in the body of evidence, with a final confidence rating of 'moderate'. Consequently, based on the available information, there is moderate confidence to conclude that lead exposure is associated with increased fasting plasma glucose in humans, but the effect is a risk factor for disease, not necessarily an adverse effect *per se*. It was also only found in the fourth quartile at blood lead >5.8 µg/dL consistent with NHMRC (2015a, b) findings.

Table 21 Confidence Rating for cross-sectional study findings in relation to risk of increased fasting plasma glucose

Health outcome [number of studies]	**Increased fasting plasma glucose** [1]	**Comment** [(1)]
Initial confidence rating	**LOW**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence		
Risk of Bias	Not serious.	Confidence not downgraded as overall RoB was considered 'not likely' (**Table 20**).
Unexplained inconsistency	Not serious.	Not applicable, since only one study investigating this outcome was retrieved in the Stage 2 literature search. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Confidence intervals for Q4 findings did not span >10 (i.e. 95% CI 1.05, 1.49). Confidence not downgraded for imprecision.
Publication bias	None detected.	None detected or obvious. Confidence not down-graded.
Factors Increasing Confidence		
Magnitude	Not large.	Magnitude of effect in the study is not large (i.e. it is not > 2) (OR in Q4 was 1.25) so confidence was not upgraded for large magnitude of effect.
Dose response	Yes. Confidence upgraded to **MODERATE**.	There appears to be a dose response for the finding with OR increasing for increase in plasma fasting glucose with increasing blood Pb (Figure 1a in paper). Confidence upgraded.

Health outcome [number of studies]	Increased fasting plasma glucose [1]	Comment [(1)]
Residual confounding	No.	No residual confounding that could increase confidence identified. Confidence not upgraded.
Consistency across species	N/A	Not applicable, since the review retrieved only one study for this health outcome. Consistency across species and dissimilar populations can therefore not be judged for this outcome. Confidence not upgraded.
Final confidence rating	**MODERATE**	
1. As per guidance provided in OHAT (2019, Table 7)		

5.1.9 Fatty liver disease

A cross-sectional study by Wan et al. (2022) found blood lead levels >4.7 µg/dL (Quartile 3 and Quartile 4) in Chinese adults were associated with non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) in a statistically significant manner [OR and 95% CI, Quartile 3: 1.4 (1.13, 1.74) for NAFLD and 1.39 (1.12, 1.73) for MAFLD; Quartile 4: 1.54 (1.24, 1.91) for NAFLD and 1.52 (1.22, 1.89) for MAFLD].

A RoB summary table for the study is presented in **Table 22** below. An overall RoB rating of 'not likely' was determined for the increased fatty liver disease outcome based on probable or definite low RoB across all study domains.

Table 22 RoB summary table for epidemiological study investigating increased incidence of fatty liver disease and lead exposure

Health outcome:	Increased incidence of fatty liver disease
Study ID:	**Wan et al. 2022 (CrSe)**
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	
Outcome reporting	--
Other Sources of Bias	
Other threats	
Overall risk of bias across studies (not likely/serious/very serious)	Not likely [(1)]
CrSe = Cross-sectional. -- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB. 1. Based on probable or definite low RoB across all domains.	

The initial confidence rating for the cross-sectional study investigating fatty liver disease is considered low, since there was no controlled exposure, exposure may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. lowest quartile) group was used. **Table 23** shows an assessment of the confidence in the body of evidence, with a final confidence rating of ‘moderate’. Consequently, based on the available information, there is moderate confidence to conclude that lead exposure is associated with increased incidence of fatty liver disease in humans. The association was found in the third and fourth quartiles of blood lead at levels >4.7 µg/dL, which is very similar to the ‘target’ blood lead level from NHMRC (2015a, b).

Table 23 Confidence Rating for cross-sectional study findings in relation to risk of increased incidence of fatty liver disease

Health outcome [number of studies]	**Increased incidence of fatty liver disease** [1]	**Comment** (1)
Initial confidence rating	**LOW**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence		
Risk of Bias	Not serious.	Confidence not downgraded as overall RoB was considered ‘not likely’ (**Table 22**).
Unexplained inconsistency	Not serious.	Not applicable, since only one study investigating this outcome was retrieved in the Stage 2 literature search. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Confidence intervals for Q3 and Q4 findings did not span >10 (i.e. 95% CI ranged from ~1.12 to 1.91). Confidence not downgraded for imprecision.
Publication bias	None detected.	None detected or obvious. Confidence not down-graded.
Factors Increasing Confidence		
Magnitude	Not large.	Magnitude of effect in the study is not large (i.e. it is not > 2) (OR in Q3 and Q4 were 1.39-1.54) so confidence was not upgraded for large magnitude of effect.
Dose response	Yes. Confidence upgraded to **MODERATE**.	There appears to be a dose response for the finding with OR increasing for increase in fatty liver disease incidence with increasing blood Pb (Figure 1 in paper). Confidence upgraded.
Residual confounding	No.	No residual confounding that could increase confidence identified. Confidence not upgraded.
Consistency across species	N/A	Not applicable, since the review retrieved only one study for this health outcome. Consistency across species and dissimilar populations can therefore not be judged for this outcome. Confidence not upgraded.
Final confidence rating	**MODERATE**	

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

5.1.10 Coronary artery disease

A case-control study by Asgary et al. (2017) found serum levels of lead were associated with the presence of coronary artery disease (CAD) in cases with 8.19 ± 0.07 µg/L versus controls with 3.69 ± 0.08 µg/L [adjusted OR, 95% CI: 1.05 (1.009, 1.094), p=0.018]. It is noted, however, the lead serum levels seem very low or the units ascribed are incorrect (µg/L instead of µg/dL). In addition, serum is not typically measured (instead, whole blood lead is typically measured in epidemiological studies) therefore the relationship between the two is uncertain. It is also noted cadmium and mercury serum levels were also associated with the presence of CAD.

A RoB assessment was not undertaken for this study given the uncertainty in reported Pb serum levels, co-exposure with other heavy metals and difficulty in defining a dose response at blood Pb <5 µg/dL.

5.2 Overall Evaluation

5.2.1 Hazard identification conclusions

The analysis in **Section 5.1** indicates varying levels of confidence in the overall body of evidence with respect to different health outcomes and lead exposure.

In accordance with the OHAT framework for systematic review and evidence integration (OHAT 2019, Figure 2), this indicates the conclusions shown in **Table 24**.

Table 24 Hazard identification conclusions for lead

Health endpoint [number of studies]	Certainty rating	Conclusion	Pb exposures
Hip fractures in older adults			
Cohort [1]	**Not undertaken[(1)]**	As the range of lead concentrations in drinking water was large in this study, and only two exposure stratification groups were examined, the study does not provide useful information with respect to defining a dose response for this effect. For this reason, a RoB analysis and confidence rating analysis was not undertaken for this study.	Drinking water: 0.04–23.80 µg/L
Markers of iron deficiency			
Cross-sectional [2]	**LOW**	There is low confidence in the evidence to conclude that exposure to lead at relatively low levels (defined as blood lead <5 µg/dL and water lead <5 µg/L) can increase the risk of iron deficiency.	0.02 g/dL lower haemoglobin and 0.5% higher prevalence of pre-EKSD ESA use for each 10 µg/L increment in community water Pb.
Birth outcomes			
Low birth weight & preterm births			
Cohort [3]	**LOW**	There are inconsistent results and low confidence in the findings of low birth weight and preterm birth associations with lead exposures potentially due to different measures being used to describe exposure (drinking water Pb, cord blood Pb, or Pb in urine).	Drinking water: >15 µg/L (positive association) Cord blood: ≥ 1 µg/dL (no association) Urine: >4.06 µg/g (positive association)
Small for gestational age			
Cohort [2]	**LOW**	There are inconsistent results and low confidence in the findings for small for gestational age with lead exposures potentially due to different measures being used to describe exposure (cord blood Pb or serum Pb).	Cord blood: ≥ 1 µg/dL (no association) Serum: ≥1.71 µg/dL (positive association)

Health endpoint [number of studies]	Certainty rating	Conclusion	Pb exposures
Birth defects (no association)			
Ecological [1]	**VERY LOW**	There is very low confidence in the findings of no association for birth defects with lead exposures in drinking water.	Well water: 2.5-1,304.2 µg/L (no association)
Blood pressure / hypertension			
Cross-sectional [1]	**MODERATE**	There is moderate confidence in the body of evidence available for an association between exposure to lead and increased blood pressure / hypertension.	Blood: >2.76 µg/dL (positive association; note max was 45.62 µg/dL)
Biochemical changes to sex hormones in males			
Case-control [1]	**VERY LOW**	There is very low confidence in the body of evidence available for an association between exposure to lead and biochemical changes to sex hormones in males (note this is a biochemical change and by itself not an adverse effect *per se*).	Drinking water: Means of 1.81 µg/L (hand-dug well) and 1.1 µg/L (borehole) vs. 0.81 µg/L (treated water). Respective mean blood Pb was 4, 2.08, and 1.64 µg/dL.
Neurodevelopmental outcomes			
Cohort [3]	**HIGH**	There is high confidence in the body of evidence available for an association between exposure to lead and neurobehavioural effects. However, the results of the studies do not appear to alter the dose response relationship already established in NHMRC (2015a, b).	Blood Pb (median): 7.6 vs <3.3 µg/dL (range: <3.3-43 vs. <3.3-13.8 µg/dL) Blood Pb: 6.31 ± 1.95 µg/dL vs. 4.05 ± 2.4 µg/dL Childhood blood Pb: 4-31 µg/dL (mean 10.99 ± 4.63 µg/dL)
Behavioural effects			
Cross-sectional [1], cohort [1]	**LOW**	There is low confidence in the body of evidence available for an association between exposure to lead and behavioural effects in adolescents. Inconsistent findings in dose response, therefore data inappropriate for derivation of a candidate guideline value.	Mean blood Pb: 2.5 vs. 2.36 µg/dL Blood Pb: ≥ 10 vs. <5 µg/dL
Adverse oral health status			
Cross-sectional [2[, cohort [1]	**VERY LOW to LOW**	There is very low to low confidence in the body of evidence available for an association between exposure to lead and adverse oral health outcomes with inconsistent findings across the body of evidence.	Blood Pb: 0.36-~20 µg/dL
Increased fasting plasma glucose			
Cross-sectional [1]	**MODERATE**	There is moderate confidence in the body of evidence available for an association between exposure to lead and increased fasting plasma glucose, but the effect is a risk factor for disease, not necessarily an adverse effect *per se*. It was also only found in fourth quartile at blood Pb >5.8 µg/dL and therefore does not alter conclusions made in NHMRC (2015a, b) report.	>5.8 µg/dL
Increased incidence of fatty liver disease			
Cross-sectional [1]	**MODERATE**	There is moderate confidence in the body of evidence available for an association between exposure to lead and increased incidence of fatty liver disease (both non-alcoholic and metabolic dysfunction-associated fatty liver disease).	>4.7 µg/dL
Increased incidence of coronary artery disease			
Case-control [1]	**Not undertaken[(2)]**	A RoB and certainty assessment was not undertaken for this study given the uncertainty in reported Pb serum levels, co-exposure with other heavy metals and difficulty in defining a dose response at blood Pb <5 µg/dL.	Pb serum: 8.19 ± 0.07 µg/L (cases) vs. 3.69 ± 0.08 µg/L (controls)

Health endpoint [number of studies]	Certainty rating	Conclusion	Pb exposures

(1) As the range of lead concentrations in drinking water was large, and only two exposure stratification groups were examined, the study does not provide useful information with respect to defining a dose response for this effect. For this reason, a RoB analysis and confidence rating analysis was not undertaken for this study.

(2) A RoB assessment was not undertaken for this study given the uncertainty in reported Pb serum levels, co-exposure with other heavy metals and difficulty in defining a dose response at blood Pb <5 µg/dL.

In summary, from **Table 24** there is:

- High confidence in the body of evidence available for an association between exposure to lead and neurobehavioural effects. However, the results of the studies do not appear to alter the dose response relationship already established in NHMRC (2015a, b).
- Moderate confidence in the body of evidence available for an association between exposure to lead and blood pressure / hypertension, increased fasting plasma glucose, and increased incidence of fatty liver disease. The doses (or blood lead concentrations) at which these effects occur are uncertain but appear to be at blood lead levels >4.7 µg/dL.
- Very low to low confidence in the association between exposure to lead and other health outcomes (i.e. markers of iron deficiency, birth outcomes, biochemical changes to sex hormones in males, behavioural effects, and adverse oral health outcomes) with insufficient confidence in the dose response for these effects.

5.2.2 Candidate guidance/guideline values

The initial Stage 1 review of published guidelines and guidance documents for lead carried out by SLR Consulting in 2021 found one existing health-based guidance/guideline value that was suitable to adopt/adapt based on an assessment of administrative and technical criteria (OEHHA 2009). A drinking water guideline (DWG) from WHO (2011) and blood lead level guidance from NHMRC (2015a, b) were also identified and considered suitable for potential adaption/adoption in the Guidelines. It was found that potential adaptation of the NHMRC (2015a, b) advice on blood lead levels (with an aim of keeping blood lead levels under 5 µg/dL) would result in the current Australian drinking water guideline for lead being halved from 10 to 5 µg/L. It was acknowledged that the 'target' blood lead level of 5 µg/dL does not necessarily represent a threshold for the lack of adverse effects to lead, but the weight of evidence is less certain for effects of lead at blood lead <5 µg/dL than for effects between 5 and 10 µg/dL (NHMRC 2015a, b).

NHMRC (2015a, b) concluded that associations with adverse health endpoints are strongest for adverse cognitive effects (including reduced IQ) in children and cardiovascular effects (including increased blood pressure) in adults rendering these the most sensitive endpoints for lead exposure.

This Stage 2 evaluation report agreed with the findings in NHMRC (2015a, b) that there is high confidence in the body of evidence available for an association between exposure to lead and neurobehavioural effects (including reductions in IQ) and moderate confidence for an association with blood pressure / hypertension and increased incidence of fatty liver disease. However, the results of the studies retrieved in this Stage 2 evaluation do not appear to alter the dose response relationship and conclusions already established in NHMRC (2015a, b).

Therefore, the Stage 2 evaluation conducted herein does not alter the candidate guideline value of 5 µg/dL derived in the Stage 1 reports.

6 Conclusions

The detailed review undertaken in this Stage 2 evaluation showed that there is:

- High confidence in the body of evidence available for an association between exposure to lead and neurobehavioural effects. However, the results of the studies do not appear to alter the dose response relationship already identified in NHMRC (2015a, b).
- Moderate confidence in the body of evidence available for an association between exposure to lead and blood pressure / hypertension, increased fasting plasma glucose, and increased incidence of fatty liver disease. The doses (or blood lead concentrations) at which these effects occur are uncertain but appear to be at blood lead levels >4.7 µg/dL which is similar to the 'target' blood lead level of 5 µg/dL.
- Very low to low confidence in the association between exposure to lead and other health outcomes (i.e. markers of iron deficiency, birth outcomes, biochemical changes to sex hormones in males, behavioural effects, and adverse oral health outcomes) with insufficient confidence in the dose response for these effects.

Therefore the Stage 2 evaluation report is consistent with the findings in NHMRC (2015a, b) and does not alter the candidate guideline value of 5 µg/dL derived in the Stage 1 reports.

Numerous studies were identified in the literature consulted as part of this Stage 2 report quantifying potential concentrations of lead in tap waters as a result of lead leaching from lead-containing plumbing materials including taps. These data indicate that leaching of lead from lead containing plumbing materials, even when claiming these to be 'lead-free' (i.e. ≤ 0.25% Pb w/w), can be marked and can result in concentrations that approach or exceed the candidate drinking water guideline of 5 µg/L (refer to Stage 1 report for detail of derivation). This indicates that, in some households, exposure to lead from drinking water may be significant and could potentially increase the risk of those persons' overall exposure exceeding the 'target' blood lead level of 5 µg/dL thereby increasing the risk of adverse health effects.

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, data extraction, RoB assessments
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, data extraction, assistance with RoB assessments

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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