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

Lead Technical Report

Prepared for:

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PREPARED BY

SLR Consulting Australia Pty Ltd
ABN 29 001 584 612
Level 11, 176 Wellington Parade
East Melbourne VIC 3002 Australia

T: +61 3 9249 9400
E: melbourne@slrconsulting.com   www.slrconsulting.com

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DOCUMENT CONTROL

Reference	Date	Prepared	Checked	Authorised
640.30609-R07-v4.0 (FINAL, with minor updates)	15 December 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
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Abbreviations/Definitions

Acronym	Definition
%ile	Percentile
ACT	Australian Capital Territory
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARB	Antibiotic Resistant Bacteria
As	Arsenic
ATSDR	US Agency for Toxic Substances and Disease Registry
BLL	Blood Lead Level
BLRV	Blood Lead Reference Value
$BMDL_{10}$	Benchmark Dose Limit at 10% for 10% extra risk
CaCo	Case-control study
CAD	Coronary Artery Disease
CBLL	Cord Blood Lead Level
Cd	Cadmium
CDC	US Centre for Disease Control
CI	Confidence Interval
Co	Cohort
CPI	Periodontal Index
Cr	Chromium
CrSe	Cross-sectional Study
Cu	Copper
DALY	Disability-adjusted Life Years
DWDS	Drinking Water Distribution System
DWSD	Detroit Water and Sewerage Department
EBLL	Elevated Blood Lead Level
Ecol	Ecological Study
EFSA	European Food Safety Authority
ESA	Erythropoietin Stimulating Agent
ESKD	End-stage Kidney Disease
EU	European Union
F	Flushed (sample)
FDR	Foetal Death Rate
FPG	Fasting Plasma Glucose
FSANZ	Food Standards Australia New Zealand
FSH	Follicle Stimulating Hormone

Acronym	Definition
GI	Gingival Index
h	hour
Hg	Mercury
HGP	Hepatic Glucose Production
ICP-MS(OES)	Inductively Coupled Plasma Mass Spectrometry (Optical Emission Spectroscopy)
IEUBK	Integrated Exposure Uptake Biokinetic Model for Lead
IPC	International Plumbing Code
IPCS	International Programme on Chemical Safety
IQR	Interquartile Range
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LCR	US Lead Copper Rule
LMIC	Low- and Middle- Income Countries
LOAEL	Lowest Observed Adverse Effect Level
LSL	Lead Service Line
MAFLD	Metabolic Dysfunction-associated Fatty Liver Disease
MCL	US EPA Maximum Contaminant Level
MRL	Minimum Reporting Level
NAFLD	Non-alcoholic Fatty Liver Disease
NHANES	US National Health and Nutrition Examination Survey
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
NSF	US National Science Foundation
NT	Northern Territory
OCCT	Optimal Corrosion Control Treatment
OEHHA	Californian Office of Environmental Health and Hazard Assessment
OHAT	United States Office of Health Assessment and Translation
OR	Odds Ratio
orthoP	Orthophosphate
Pb	Lead
PI	Plaque Index
PLSLR	Partial Lead Service Line Replacement
PVC	Polyvinyl Chloride
QLD	Queensland
RDT	Random Daytime (sample)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB	Risk of Bias

Acronym	Definition
SA	South Australia
SD	Standard Deviation
SEM	Scanning Electron Microscopy
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.
TM	Toxic Metals
TRV	Toxicity Reference Value
µg/dL	Micrograms Per Decilitre
µg/L	Micrograms Per Litre
µg/g	Micrograms Per Gram
US EPA	United States Environmental Protection Agency
VIC	Victoria
WHO	World Health Organization
WLL	Water Lead Level
XRD	X-ray Diffraction

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* (NHMRC 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 fact sheets in the Guidelines), the requirements of the evaluation were as follows:

1. Screen any existing guidance/guidelines on bismuth / bismuth brasses and silicon / 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 (referred to as 'Stage 1' in this report).

The report herein is the Technical Report for lead.

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 search. They 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?

#	Research Questions
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]
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 Evidence Evaluation Methods

3.1 Overview

This section summarises the methods followed to undertake the evidence evaluation review for lead. The intention is to provide enough detail for a third party to reproduce the search.

It was evident that some flexibility was required in adapting the methodology recorded in the final Research Protocol for lead to maximise efficiency in sourcing relevant information. Deviations from the final Research Protocol methodology have been recorded in this report. **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).

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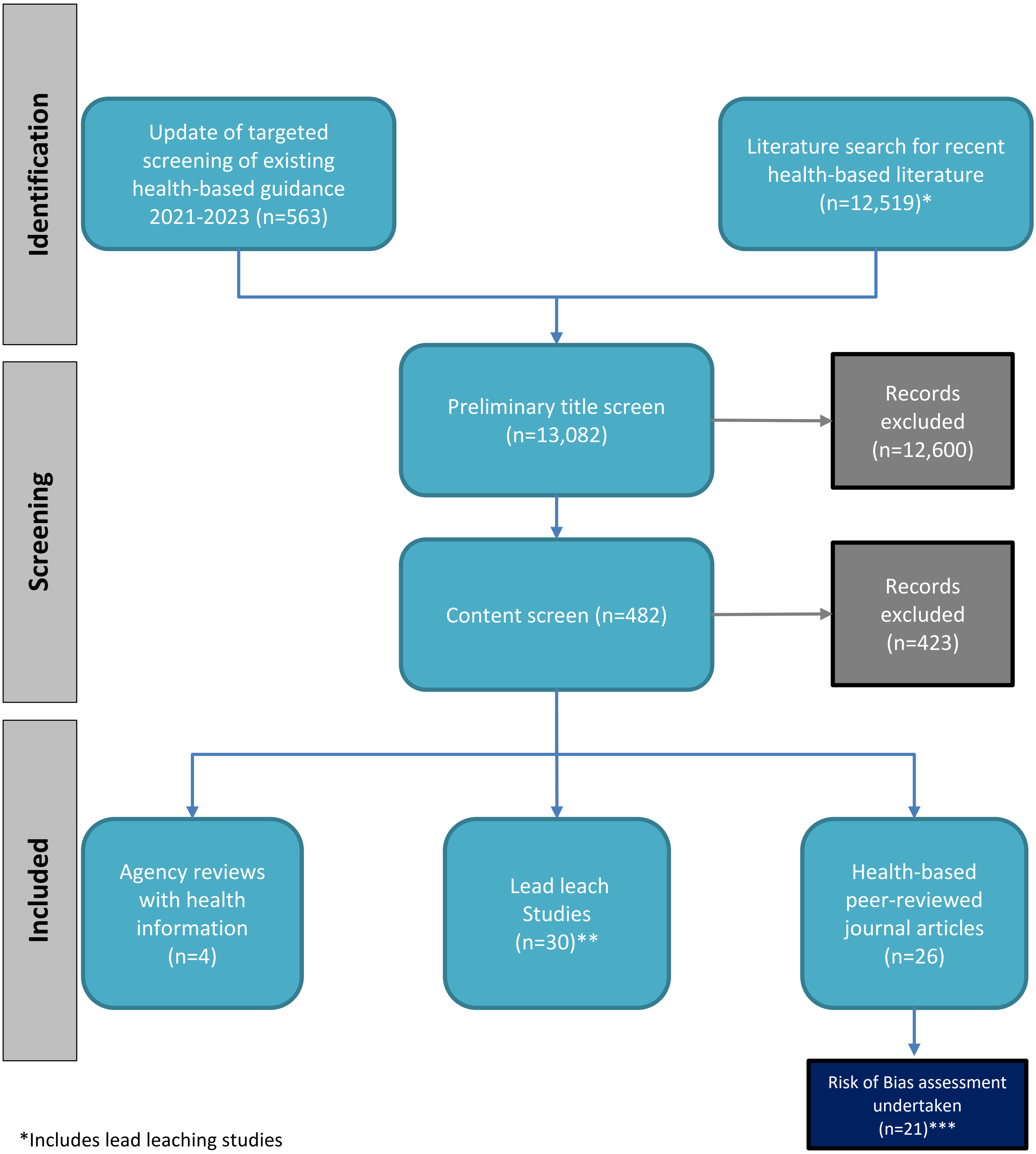
[1] This aspect was already covered in SLR Report entitled *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Lead Technical Report* (640.30242-R11-v4.0) and *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Lead Evaluation Report* (640.30242-R12-v2.0).



*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

3.2 Update of targeted screening of existing health-based guidance

Literature search strategy

Existing guidelines and guidance from national and international agencies were already considered in Stage 1. Nevertheless, an updated literature search was undertaken from January 2021- June 2023 to identify any additional health-based agency reviews published since the date of completion of the Stage 1 reports. The literature search strategy for existing health-based guidance documentation for lead is summarised in **Table 2** below.

Table 2 Search strategy for Existing Guidance/Guidelines

Parameter	Comments
Search terms	The selected search term was: • (lead)
Databases/Agency websites	The following sources were searched: • World Health Organization (WHO): https://www.who.int/ • International Programme on Chemical Safety (IPCS Inchem): http://www.inchem.org/#/search • Joint FAO/WHO Expert Committee on Food Additives (JECFA): (Included in IPCS Inchem search) • European Food Safety Authority (EFSA): https://www.efsa.europa.eu/en • United States Environmental Protection Agency (US EPA): • US Agency for Toxic Substances and Disease Registry (ATSDR): https://www.atsdr.cdc.gov/ • Californian Office of Environmental Health and Hazard Assessment (OEHHA) Public Health Goals (in Drinking Water): https://oehha.ca.gov/water/public-health-goals-phgs • Food Standards Australia New Zealand (FSANZ) • Australian Pesticides and Veterinary Medicines Authority (APVMA) Health Based Guidance Values: https://apvma.gov.au/node/26596
Publication Date	January 2021- June 2023 (to capture any updated health-based guidelines/guidance released since completion of the Stage 1 reports for lead).
Language	English
Study Type	Publicly available agency/industry reports and reviews of guidelines or evidence supporting guidelines (near publication drafts are included if available).

Parameter	Comments
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of agency reports/reviews: • NR = Not Relevant. Information not directly relevant to answering research questions. Rationale for non-relevance was provided for transparency. E.g. ○ Not HH related = Not human health related (e.g. criteria are for protection of aquatic life). ○ Not a relevant exposure pathway = Since lead is not volatile, guidelines for non-oral and non-dermal routes of exposure are not considered relevant (e.g. inhalation). ○ Not relevant to substance of interest. • DB = Dated before 2021 • AR = Already reviewed (in Stage 1 reports) • NPA = Basis of guideline value or information underpinning review conclusions are Not Publicly Available, e.g. health-based guideline value has used unpublished proprietary information which could not be verified. • L = Language other than English.
Validation methods used	As per the Stage 1 reports, preliminary searches were previously undertaken with more specific search terms [(Lead) AND (toxicity or health) AND (oral); (Lead) AND (health) AND (oral)]. Upon scanning preliminary search results for the Stage 1 reports, the reviewer found these search terms to be too specific, as very low numbers of agency reports appeared in the results. The search terms were consequently refined (see **Appendix A**).
Screening methods	Results were screened as follows: *Preliminary title screen* • Titles of results for each search were recorded in an Excel spreadsheet. • The researcher scanned the titles. In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The full text content of reports/reviews selected to be included from the preliminary title screen were reviewed by a subject expert to determine which reports/reviews to include in the data extraction step. Only reports/reviews which provided information relevant to answering the research questions were taken through to the data extraction step.
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

Data Collection and Quality Assessment

For each relevant result for which the full text was sourced:

- The full text was skimmed by a content expert.
- Where existing health-based guidance (in the form of drinking water guidelines or toxicity reference values, i.e. TRVs) was identified, relevant data on the guidance value in relation to the research questions were collected using the format shown in **Table 3.** The individual data collection tables are provided in **Appendix B**. Although a few new reviews were identified in the targeted search, none provided a health-based guidance value[2].

Table 3 Example of data extraction table format for existing health-based guidance

Agency Report Reference: ***Insert full bibliographical reference for report***		
General Information	Date of data extraction	
	Authors	
	Publication date	
	Literature search timeframe	
	Publication type	
	Peer reviewed?	
	Country of origin	
	Source of funding	
	Possible conflicts of interest	
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	
	Exposure timeframe	
	Critical human health endpoint	
	Justification provided by agency for critical endpoint	
	Critical study(ies) underpinning point of departure	
	Species for critical study(ies)	
	Point of departure type (e.g. NOAEL, LOAEL, $BMDL_{10}$, etc)	
	Point of departure value (include units)	
	Uncertainty factor(s) & rationale	
	Guideline value (include units)	
	Mode of action for critical health endpoint	
	Genotoxic carcinogen?	

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[2] US EPA (2023) cites CDC (2022) who have set a new blood lead reference value of 3.5 µg/dL in the United States as this corresponds to the 97.5th percentile of blood lead in US children ages 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. WHO (2022b) reports of a revised EU drinking water limit for lead of 5 µg/L but does not provide the basis of the value.

Agency Report Reference: ***Insert full bibliographical reference for report***		
	Identified sensitive sub-populations	
	Any non-health based considerations?	
Exposure considerations	Principal routes of exposure in general population	
	Levels in drinking water supplies (include location)	
	Any special considerations to exposure levels (e.g. higher in drought?)	
	Typical exposure in general population (include units for intakes & location)	
Risk Summary	Any risks to human health from drinking water identified in agency document?	
	Any emerging risks identified?	

Data summary/synthesis

The data from the various existing health-based guidance/guideline value reviews was summarised in tabular format for each individual research question.

Expert judgement was used to highlight areas of uncertainty or areas where an organisation's methods/interpretation differs from Australian science policy.

3.3 Detailed full evidence review of health-related studies

Literature search strategy

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 undertaken as recommended in the Stage 1 reports for literature published from May 2013 to April 2023.

The literature search strategy for undertaking the full review in scientific databases is summarised in **Table 4** below.

Table 4 Search strategy for full review of health-based studies

Parameter	Comments
Search terms	The selected search terms were: • (Lead) AND (toxicity) AND (oral) • (Lead) AND (health) AND (oral) • (Lead) AND (toxicity) AND (drinking water) • (Lead) AND (health) AND (drinking water) • (Lead) AND (plumbing) AND (leaching)
Databases	The following sources were searched: • MEDLINE/PubMed/TOXLINE • SciFinder
Publication Date	The search was conducted from May 2013 to April 2023. This is to coincide with the cut-off date for the literature included in the NHMRC (2015) publication identified in the Stage 1 review. The NHMRC (2015) publication represents the latest comprehensive review which derived a health-based guidance value in the form of a concentration of lead in blood.
Language	English
Study Type	Peer-reviewed published, in press, unpublished (but publicly available) and ongoing studies were included. In addition, publicly available documents of guidelines or evidence supporting guidelines (including near publication drafts) were included (see also **Section 3.2**). Study types may include existing systematic reviews or literature reviews not considered in Stage 1 and human epidemiological studies. *In vitro* studies and animal studies were not included, as the existing guideline value is already based on human information.
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of information: • NR = Not Relevant. Information not directly relevant to answering research questions. • Provides little or no useful information about substance of interest (lead). • Language = Language other than English. • Non-human = Animal or *in vitro* study (non-human study).
Validation methods used	Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened (see **Appendix A**).

Parameter	**Comments**
Screening methods	Results were screened as follows: *Preliminary title and abstract screen* • Titles of results for each search were recorded in an Excel spreadsheet. The results for each combination of search terms were exported into a separate tab of the spreadsheet. To readily eliminate duplicate records, results from all search term combinations were subsequently collated into one spreadsheet. • The researcher scanned the titles (and abstracts, if required). In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The abstracts first (and full text if required) of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data extraction and analysis step. • Due to the large number of publications sourced 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. *Additional search of relevant bibliographies* In addition to the primary search, the bibliographies of critical review papers were consulted if required to source additional papers of potential relevance. The latter papers were only subjected to the content screen.
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

Data Collection

For each relevant result for which the full text was sourced:

- Where deemed to be relevant to the research questions, relevant data were extracted using the example format shown in **Table 5.** The format was more applicable to epidemiological studies and was adapted slightly for reviews. The individual data extraction tables are provided in **Appendix C**.

Table 5 Example of data collection table format for full review of health-based studies

Publication Reference: ***Insert full bibliographical reference for report***		
General Information	Date of data extraction	
	Authors	

Publication Reference: ***Insert full bibliographical reference for report***		
	Publication date	
	Publication type	
	Peer reviewed?	
	Country of origin	
	Source of funding	
	Possible conflicts of interest	
Study characteristics	Aim/objectives of study	
	Study type/design	
	Study duration	
	Type of water source (if applicable)	
Population characteristics	Population/s studied	
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Type of water source (if applicable)	
	Exposure pathway	
	Source of chemical/contamination	
	Exposure concentrations (if applicable)	
	Comparison group(s)	
Study methods	Water quality measurement used	
	Water sampling methods (monitoring, surrogates)	
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	
Statistics (if any)	Statistical method used	
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	

Publication Reference: ***Insert full bibliographical reference for report***		
Author's conclusions	Interpretation of results	
	Assessment of uncertainty (if any)	
Reviewer comments	Results included/excluded in review (if applicable)	
	Notes on study quality, e.g. gaps, methods	

Data analysis

All critical studies deemed relevant for defining the dose response of lead at relatively low blood lead levels (i.e. ≤10 µg/dL) were subjected to a risk of bias (RoB) assessment with the use of a RoB tool (i.e. modified OHAT tool, shown in **Table 6**)[3]. The justification for excluding some studies from RoB assessments can be found in the individual data extraction summary tables in **Appendix C.** Outcomes of the RoB assessments are provided as a rating for each parameter; individual assessments are provided in **Appendix D**.

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[3] The example of the modified OHAT tool provided in this section is for a case study report. The table was amended to include fields deemed applicable to other study types.

Table 6 Modified OHAT risk of bias tool (example: case study report) adapted from OHAT 2019

Study ID: **Study Type:**		**RoB:** **Yes/No, Unknown, N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	Confounding (design/analysis)			
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	**Missing outcome data**	**N/A**	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation			
9.	Outcome assessment			
	Selective Reporting Bias			
10.	Outcome reporting			
	Other Sources of Bias			
11.	Other threats	N/A		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Relevant data were summarised in tabular format by research question, and by health endpoint. Where possible, synthesis was conducted by presenting combined data for the same health outcome. Due to resource constraints and data limitations, meta-analysis of the study findings was not undertaken.

Summary tables (or summary text) were provided for the following:

- Blood lead levels associated with critical adverse health effects, focusing on findings at ≤10 µg/L.
- RoB assessments across the body of evidence for each health outcome, focusing on findings at ≤10 µg/L.
- Overall certainty of evidence for different health endpoints at relatively low blood lead levels (i.e. ≤10 µg/dL). This considered the overall confidence of the body of evidence with regard to RoB, indirectness/applicability, imprecision, inconsistency between studies and publication bias, with information provided as a certainty rating where possible using guidance from OHAT (2019). Note hazard identification conclusions were not developed.

These aspects are presented in the Evidence Evaluation Report.

4 Results

A summary of the responses to the research questions for lead is provided the tables below.

No additional existing health-based guidance/guideline values were found in the updated literature search of agency reviews. Responses to research questions are based on agency reviews and data extractions conducted for the various cross-sectional (CrSe), cohort (Co), case-control (CaCo), and ecological (Ecol) found in the literature reviewed.

4.1 Health-based research question analysis

Table 7 Synthesis of extracted data for health-based research questions

#	Research Questions	Publications	Response to Research Questions
1	What level of lead in drinking water causes adverse health effects?	**Agency reviews (US EPA 2023, WHO 2022a, b; CDC 2022)**	Although a few additional agency reviews were found since the Stage 1 reports were written, none provided a health-based guidance or guideline value. US EPA (2023) cites CDC (2022) who have set a new blood lead reference value of 3.5 µg/dL in the United States as this corresponds to the 97.5th percentile of blood Pb in US children ages 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. WHO (2022b) reports of a revised EU drinking water limit for Pb of 5 µg/L but does not provide the basis of the value.
		Dahl et al. 2014 (Co), Danziger et al. 2021, 2022 (CrSe); Dave and Yang 2022 (Co); Edwards et al. 2014 (Ecol)	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. 2013); 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) (see also response to Research Question 4 for details). However, no clear dose response relationships could be established from the information in these studies (refer also to Evaluation Report).
		Other studies	Other health-based studies examined associations of the principal accepted marker of Pb exposure, blood Pb (or serum Pb), with a number of different health endpoints. These are summarised in the response to Research Question 4.

#	Research Questions	Publications	Response to Research Questions
2	What is the endpoint that determines this value?	Not applicable. No health-based guidance or guideline value, in addition to those identified in the Stage 1 reports, were found in the literature reviewed for this Stage 2 report.	
3	Is the proposed option for a health-based guideline value relevant to the Australian context?	Not applicable. See response to Research Question 1 and 2.	
4	What are the key adverse health hazards from exposure to lead in Australian drinking water?	**WHO 2022a**	There is no known safe blood Pb concentration; even blood Pb concentrations as low as 3.5 µg/dL may be associated with decreased intelligence in children, behavioural difficulties and learning problems. As Pb exposure increases, the range and severity of symptoms and effects also increase.
		Hip fractures (drinking water): Dahl et al. 2014 (Co)	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 however a dose response relationship cannot be established from the information in the study. Average concentration of Pb was 1.16 µg/L (range: 0.04–23.80 µg/L).
		Markers of iron deficiency (drinking water): Danziger et al. 2021, 2022 (CrSe)	• Danziger et al. (2021): Pb levels in drinking water below 0.015 mg/L (i.e. <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 0.01 mg/L (i.e. 10 µg/L) increment in community water Pb. A 0.01 mg/L increment in Pb 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 Pb 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).
		Low birth weight (drinking water): Dave and Yang 2022 (Co)	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.

#	Research Questions	Publications	Response to Research Questions
		Birth defects (drinking water): Sanders et al. 2014 (Ecol)	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.
		Foetal deaths (drinking water): Edwards et al. 2014 (Ecol)	According to the study authors, 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.
		Blood pressure (Blood Pb): De Almeida Lopes et al. 2017 (CrSe)	A positive association was identified between blood lead level (BLL) in the highest quartile and diastolic blood pressure and a significant association of BLL 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) had BLL of >2.76 µg/dL and that the maximum BLL was 45.62 µg/dL. It would have been ideal if there were five BLL ranges (i.e. quintiles) to see whether significant associations for hypertension were identified with BLL between 2.76 – 5 µg/dL.
		Anaemia (Blood Pb): Domeneh et al. 2014 (CrSe)	Higher BLL were observed in opium dependents (oral, mean = 11.75 µg/dL) compared to the control group (mean = 6.05 µg/dL). It is noted however that BLL was not correlated with anaemia (1.026, 95% CI 0.93-1.12). It is also noted that BLL in the control group was relatively high (6.05 µg/dL).
		Biochemical changes to sex hormones (Blood Pb): Enehizena and Emokpae 2022 (CaCo)	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 effects *per se*.
		Behavioural effects (Blood Pb): Macdonald Gibson et al. 2022 (CrSe), Nkomo et al. 2018 (Co)	• Macdonald Gibson et al. (2022) provides an association between reported delinquency and small differences in mean BLL; 2.5 µg/L for well users and 2.36 µg/L for community water users. A dose response relationship cannot be established for this study as the study reports only a mean BLL concentration rather than stratified BLL. • This study found a significant positive association between 'elevated' blood lead levels (*≥10 µg/dL*) and direct aggression in South African adolescents.

#	Research Questions	Publications	Response to Research Questions
		Foetal outcomes (cord blood Pb): Hanna-Attisha et al. 2021 (Co)	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.
		Foetal outcomes (urinary Pb): Cheng et al. 2017 (Co)	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. Note blood lead levels were not measured hence a useful dose response data for guideline derivation may be difficult to establish from this study.
		Oral health status (Blood Pb): Tort et al. 2018 (CrSe), Kim et al. 2017 (CrSe), Wu et al. 2019 (Pro Co)	• 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. It is also unclear why associations were found in Quartile III but not in Quartile IV, the group with the highest BLL. • Kim et al. (2017) found a statistically significant increase in the risk of dental caries in deciduous teeth 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 however this is not discussed or outlined in the conclusions. • In Wu et al. (2019), an association between dental caries and blood Pb levels (ranging from 3.34±2.68 to 15.48±7.29 µg/dL) was not established 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.
		Neurodevelopmental outcomes in children (Blood Pb): Rodrigues et al. 2016 (Co), Vigeh et al. 2014 (Co)	• Rodrigues et al. (2016) found increased blood Pb in children was associated with decreased cognitive scores in Sirajdikhan, Bangladesh (median BLL = 7.6 µg/dL, range = <3.3 – 43 µg/dL) compared to Pabna (median BLL = <3.3 µg/dL, range = <3.3 – 13.8 µg/dL). As both groups included individuals with elevated BLL (i.e. ≥5 µg/dL) this study does not alter the dose response relationship already established in NHMRC (2015). • Vigeh et al. (2014) found increasing maternal blood lead levels (mean < 6.5 µg/dL) were found to be associated with lower developmental scores in early childhood. It is unlikely that a dose response relationship below 5 µg/dL can be established with the data in this paper.

#	Research Questions	Publications	Response to Research Questions
		Neurodevelopmental outcomes in adults from childhood exposure (Blood Pb): Reuben et al. 2017 (Co)	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) BLL 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.
		Increased fasting glucose (Blood Pb): Wan et al. 2021 (CrSe)	Blood Pb levels >5.8 µg/dL (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.
		Fatty liver disease (Blood Pb): Wan et al. 2022 (CrSe)	Blood Pb 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.
		Small for Gestational Age (Serum Pb): Wang et al. 2017 (Co)	High 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). 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.
		Coronary artery disease (Serum Pb): Asgary et al. 2017 (CaCo)	Serum levels of Pb 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. However, the Pb 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).
5	Are there studies quantifying the health burden (reduction or increase) due to lead?	See response to Research Question 4. 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 effects in human populations; however, this was already known in the previous reviews undertaken by various agencies, including NHMRC (2015). From the available information sourced in this Stage 2 investigation, the dose response for adverse effects at blood Pb concentrations <5 µg/dL is unclear. According to WHO (2022a), nearly half of the 2 million lives lost to known chemicals exposure in 2019 were due to Pb exposure. Pb exposure is estimated to account for 21.7 million years lost to disability and death (disability-adjusted life years, or DALYs) worldwide due to long-term effects on health, with 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.	

#	Research Questions	Publications	Response to Research Questions
6	What is the critical human health endpoint for lead?	The Stage 1 investigation reports indicated that jurisdictions generally agree that the evidence is strongest for adverse cognitive effects (including reduced IQ) in children and cardiovascular effects (including increased blood pressure) in adults being the most sensitive endpoints. The Stage 2 review identified several epidemiological studies not previously reviewed by NHMRC (2015) that found associations of blood Pb, serum Pb, or Pb in drinking water with increases in various health-related endpoints including the following (see also response to Research Question 4 for individual references): • Hip fractures in 66–85-year-old men. • Markers of iron deficiency. • Birth outcomes (including low birth weight, miscarriages/foetal death). • Blood pressure. • Biochemical changes to sex hormones. • Neurodevelopmental outcomes in children and adults (the latter after childhood exposure). • Behavioural effects. • Oral health status. • Fasting plasma glucose. • Fatty liver disease. • Coronary artery disease. However, as discussed in the accompanying Evidence Evaluation Report, causality of exposure for some of the effects and the dose response for these associations at blood Pb levels <5 µg/dL is unclear. Therefore, the critical human health endpoints remain unchanged from NHMRC (2015).	
7	What are the justifications for choosing this endpoint?	As above	As above.
BLL = Blood Lead Level			

4.2 Exposure-related research question analysis

Table 8 Synthesis of extracted data for exposure-related research questions

#	Research Questions	Publications	Response to Research Questions
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)	The following information was summarised in the Stage 1 reports: Mean / range of means (minimum to maximum) concentrations of lead in drinking water: • 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 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. This will draw fresh water into the tap and reduce potential exposure to Pb. Pb is not detected from most water samples taken 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).	
9	Are there any data for lead levels leaching into water from in-premise plumbing?	**Akers et al. 2015**	Leaded components leach into water and equilibrate over time (4-12 hours) as a pitcher-pump system sits idle with Pb sourced from the Pb valve weights rather than the well screen or the solder. Maximum Pb measured: 30 – 44 µg/L (median 7 – 13.5). Median Pb concentrations in first draw samples are typically (slightly) higher than flushed samples.

#	Research Questions	Publications	Response to Research Questions
		Cartier et al. 2013	Release of Pb from 80% partially replaced service lines was compared to full Pb service lines using harvested-stabilised Pb pipes and field brass connectors. Partial replacement of Pb pipe by copper pipe over a 3-month period generated high Pb release attributed to galvanic corrosion and higher Pb concentrations (particularly at high flow rates) than with the full Pb pipe. Particulate lead is released mostly after stagnation periods >30 minutes. For the no treatment control condition (i.e. no partial replacement) Pb concentrations varied between 54 and 162 µg/L. For the 20%-Pb upstream and downstream pipes, mean dissolved Pb concentrations were respectively 17 ± 3 and 16 ± 3 µg/L, corresponding to 29% and 28% of the concentrations found for 100%-Pb.
		Liu et al. 2018	Pb accumulates in loose deposits and its release is influenced by water quality and sulfate.
		MacDonald Gibson et al. 2020	The lack of corrosion prevention leads to increased Pb exposure from private wells compared to the municipal water supply as a result of corrosion of household plumbing and well components.
		Chang et al. 2022	In a Pb leaching model from plumbing, Pb equilibrates in stagnant water after 6 hours with highest concentrations reported at the Pb solder interface (as high as 3 mg/L after 2 hours). Pb is also expected to leach out of copper pipes. Note this study may not be relevant to the Australian context since Pb solder is restricted in Australia.
		St Clair et al. 2016	Plumbing configurations representative of partial pipe replacements (with copper pipes) for potable water supply continued to release much more Pb than the full-Pb service pipe at moderate and high flow rates. This was significant for up to 48 months.
		Deshommes et al. 2017	Median Pb concentrations after 6 hours stagnation in Pb service lines (37 µg/L) were approximately double those observed with partial Pb line service replacement (14-23 µg/L) irrespective of whether the replacement was on the public side or private side and much higher than in areas with full Pb service line replacement (3 µg/L). Similar differences were observed after 30 minutes stagnation (median ranging from 1 to 18 µg/L) and after 5 minutes of flushing, concentrations were lower (median ranging from 1 to 8 µg/L). Full Pb service line replacement was required for Pb concentrations in water to be reduced consistently to below 10 µg/L irrespective of flushing and stagnation time.

#	Research Questions	Publications	Response to Research Questions
		Fisher et al. 2021	In analyses of drinking water in 3 countries in Africa, Pb concentration in drinking water was associated with copper, chromium, and zinc. The association of Pb with zinc may likewise implicate brass, but it could also arise from corrosion of galvanised steel. Of the metals samples, Pb most frequently occurred at levels of concern in sampled water system components and water samples. Pb mass fractions exceeded International Plumbing Code (IPC) recommended limits (0.25% w/w) for components in 82% (107/130) of systems tested. Brass components proved problematic, with 72% (26/36) exceeding IPC limits. Presence of a brass component in a water system increased expected Pb concentrations in drinking water samples by 3.8 times. Pb exceeded WHO guideline values in 9% (24/261) of drinking water samples across countries. Ensuring use of lead-free (<0.25%) components in new water systems and progressively remediating existing systems could reduce drinking water Pb exposures and improve health outcomes for millions.
		Jarvis et al. 2018	Water Pb levels were relatively high in both leaded and unleaded households and tended to be lower when phosphorus dosing was applied (although statistical significance of this was not assessed in the study).
		Knowles et al. 2015	In an experimental setup, dissolved water Pb levels in Pb pipes (96 – 203 µg/L) were much higher than observed in copper pipes with Pb solder (5.6 – 20 µg/L). Aluminium and iron coagulant residuals, at levels complying with recommended guidelines, can sometimes play a significant role in lead mobilisation from premise plumbing.
		Lei et al. 2018	Water Pb concentrations in this leaching study were much higher for brass/bronze (up to 800 µg/L) compared to other materials (<50 µg/L for copper, stainless steel and PVC).
		Namrotee et al. 2022	The mean Pb concentration from various taps in a 4-storey building was 22.3 µg/L (range <1–2,870) and 4.3 µg/L (range <1–412) in the first draw and flushed samples, respectively. Flushing of water and season influenced water Pb levels.
		Ng et al. 2016	Flushing of water and pH may influence water Pb levels.

#	Research Questions	Publications	Response to Research Questions
		Ng et al. 2016b	Brass fittings were identified as the source of Pb contamination in a plumbing system with Pb free components. Physical disturbance of the plumbing system resulted in spikes in water Pb levels. Continuous orthophosphate treatment was able to suppress total Pb levels below 10 µg/L but caused "blue water" problems. Concentrations of total Pb in water fluctuated in the simulated experiment in the first tap from approximately <5 to 83 µg/L (read off graphs). In the second tap (newly installed on Day 153 of the experiment) total Pb spiked at about 120 µg/L, followed by a marked reduction to <10 µg/L after ~20 days.
		Olson et al. 2017	Dissolution of Pb from lead service lines in Flint, Michigan, USA was attributed to the lack of corrosion controls in water treatment.
		Parks et al. 2018	Pb was shown to be released from "lead free faucets" and in this experiment water Pb levels (stagnant) ranged from 0.5 µg/L to 24.3 µg/L during the first week of the study and 1.5 µg/L to 3.0 µg/L after 19 days. Pb leaching from PVC controls was below detection (<0.5 µg/L).
		Pieper et al. 2015	• Households constructed pre-1988 had a significantly higher (p <0.05) median Pb concentration (5.4 µg/L, n = 600) compared to households constructed post-1988 (3.3 µg/L, n = 805). • The type of fittings used in the plumbing network (e.g. brass) is more important to predicting water Pb levels than the interior piping material (e.g. copper, plastic). • Homeowners who identified obvious signs of corrosion (OR = 1.72), blue-green staining on plumbing fixtures (OR = 2.78), and/or described the taste of water as metallic (OR = 2.29) were 1.7–2.8 times more likely to have elevated Pb concentrations compared to homeowners who did not identify these characteristics. • Flushing the system for 5 minutes appeared to reduce Pb concentrations to the recommended concentration at the time (i.e. below 15 µg/L) for most households in this study. • Participants who indicated the use of a water treatment device did not have significantly lower median Pb concentrations.
		Pieper et al. 2017	Elevated water Pb levels in households from Flint, Michigan were attributed to the mobilisation of particulate Pb from scale in service lines and not household "brass free" fittings and pipes.

#	Research Questions	Publications	Response to Research Questions
		Pieper et al. 2018a	Destabilised lead-bearing corrosion rust layers (scale) in galvanised iron pipe downstream of a Pb pipe was identified as the immediate cause of the high water Pb levels measured in 2014 in Macon County (North Carolina). Water Pb levels were highest in first draw samples and decreased with continued flushing. Sporadic spikes in particulate Pb occurred during continued water use. Problems with Pb release were associated with: • dissolution of Pb from plumbing during periods of stagnation; • scouring of leaded scales and sediments during initial water use; and • mobilisation of leaded scales during continued water use. Note: “lead-free” plumbing brass components could contain up to 8% Pb by weight and release Pb to water when exposed to more corrosive water conditions.
		Pieper et al. 2018b	The absence of corrosion control and more corrosive water resulted in increased water Pb levels in the Flint community in Michigan. Between August 2015 and November 2016, median water Pb reduced from • 3.0 to <1 µg/L for homes with copper service lines • 7.2 to 1.9 µg/L with galvanised service lines • 9.9 to 2.3 µg/L with Pb service lines. As of summer 2017, 90th percentile of 7.9 µg/L no longer differed from official results, which indicated Flint’s water Pb levels were below the action level.
		Zhang et al. 2015	Pb compounds that are used as the stabiliser in uPVC pipe may be released into drinking water. The use of uPVC pipes may result in Pb leaching into water with higher concentrations in stagnant leaching studies associated with increased exposure time, decreased pH value, and increased temperature. More Pb was released from three uPVC pipes (1.4-2.8% Pb) when there was chloramine in the water compared to chlorine. Level of Pb release was not linked to the weight percentage of Pb on the pipe inner surfaces.
		Tully et al. 2019	Modelling results of Pb leaching from leads service lines (LSLs) was inconsistent. Pilot studies and appropriate sampling regimes will be necessary to evaluate Pb leaching and optimise corrosion control.

#	Research Questions	Publications	Response to Research Questions
		Rockey et al. 2021	• Pb levels in premise plumbing water in Flint, Michigan did not change significantly within five weeks of replacement. • However, significant reductions were observed two weeks after service line replacement in flushed samples representative of distribution system water (pre-replacement median = 0.98 µg/L; two-week post-replacement median = 0.11 µg/L). • Multiple sequential samplings from one Flint residence before and 11 months after service line replacement revealed large reductions in Pb levels in all samples, indicating long-term benefits of service line replacement.
		Trueman et al. 2017	Corroded iron distribution mains may also need to be replaced when changing Pb service lines to reduce the possibility of elevated Pb in drinking water.
		Siu et al. 2020	Common thermo-mechanical treatment of brass piping installation may result in increased Pb leaching into water.
		Hannah-Attisha et al. 2015	Increased blood Pb levels were observed in Flint, Michigan following a change in the water supply. No significant change was observed outside the city, but increases were more evident amongst socioeconomically disadvantaged neighbourhoods. Poor corrosion control may be responsible for elevated water Pb levels (as also indicated by other papers examining this cohort).
		Harvey et al. 2016	Plumbing fittings (including taps) that contain detectable lead up to 2.84% are contributing to Pb levels in household drinking water. Mean Pb concentration found in first draw samples (n=212) of tap water collected from NSW households was 3.7 µg/L (median 1.3 µg/L). Samples collected following a 2-minute flush period returned variable lead concentrations.

#	Research Questions	Publications	Response to Research Questions
		Zahran et al. 2020	• Samples taken from homes in Flint, Michigan with Pb service lines were significantly more likely to exceed specified thresholds of water Pb than homes without Pb service lines. • Regardless of service line material type, sampled homes experienced significant reductions in water Pb with elapsed time from Flint's switchback to water provided by the Detroit Water and Sewage Department. • At 90 weeks from the switchback in water source, the quantity of water Pb consumed by children in homes with Pb service lines decreased 93%, as compared to 16 weeks. • Pb exposure benefits of service line replacement have declined in time, with modest differences in Pb uptake across homes with different service lines. • The Flint experience suggests that optimal corrosion control treatment (OCCT) techniques are effective in reducing water Pb levels, implying that lead service line replacement may not be necessary (at least in the short run).

4.3 Risk-based research question analysis

Table 9 Synthesis of extracted data for risk-associated research questions

#	Research Questions	Publication	Response to Research Questions
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. However, the dose response relationships for adverse effects at blood Pb levels <5 µg/dL are uncertain (refer to Evidence Evaluation report). Thus, there is insufficient health-based evidence to revise the position in NHMRC (2015) 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 revise 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. 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).* • 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; thought to be from brass fittings at the Perth Children's Hospital (Weeramanthri et al. 2017)[4]. • 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' (Parks et al. 2018). These data, especially the latter three reports which are likely relevant to the Australian context, indicate that leaching of Pb from Pb containing plumbing materials, even when claiming these to be 'Pb-free' can be marked and can result in concentrations that approach or exceed the candidate drinking water guideline of 5 µg/L.	

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[4] Note this study is not included in data extraction tables, since the study was identified by the Committee for inclusion after the first draft of this report was issued to NHMRC.

#	Research Questions	Publication	Response to Research Questions
11	Is there evidence of any emerging risks that are not mentioned in the current fact sheet that require review or further research?	Plumbing fittings (including taps) 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.	

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APPENDIX A

Literature search screening outcome spreadsheets

Appendix A contents here

APPENDIX B

Data extraction tables – Health-based guidance/guidelines

USEPA 2023

Agency Report Reference: USEPA (2023). Basic Information about Lead in Drinking Water, United States Environmental Protection Agency.		
General Information	Date of data extraction	19 June 2023
	Authors	United States Environmental Protection Agency (USEPA)
	Publication date	31 August 2022
	Literature search timeframe	Not stated
	Publication type	Agency Factsheet
	Findings	• The Centers for Disease Control and Prevention (CDC) recommends that public health actions be initiated when the level of lead in a child's blood is 3.5 micrograms per deciliter (µg/dL) or more. • It is important to recognise all the ways a child can be exposed to lead. Children are exposed to lead in paint, dust, soil, air, and food, as well as drinking water. If the level of lead in a child's blood is at or above the CDC action level of 3.5 micrograms per deciliter, it may be due to lead exposures from a combination of sources. EPA estimates that drinking water can make up 20 percent or more of a person's total exposure to lead. Infants who consume mostly mixed formula can receive 40 percent to 60 percent of their exposure to lead from drinking water.

WHO 2022a

Agency Report Reference: WHO (2022a). Lead factsheet, World Health Organization.		
General Information	Date of data extraction	19 June 2023
	Authors	World Health Organization (WHO)
	Publication date	31 August 2022
	Literature search timeframe	Not stated
	Publication type	Agency Factsheet

Agency Report Reference: WHO (2022a). Lead factsheet, World Health Organization.		
	Findings	• There is no known safe blood lead concentration; even blood lead concentrations as low as 3.5 µg/dL may be associated with decreased intelligence in children, behavioural difficulties and learning problems (1). As lead exposure increases, the range and severity of symptoms and effects also increase. • The World Health Organization's 2021 update of the Public health impact of chemicals: knowns and unknowns estimate that nearly half of the 2 million lives lost to known chemicals exposure in 2019 were due to lead exposure. Lead exposure is estimated to account for 21.7 million years lost to disability and death (disability-adjusted life years, or DALYs) worldwide due to long-term effects on health, with 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.

WHO 2022b

Agency Report Reference: WHO (2022b). Lead in drinking water. Health risks, monitoring and corrective actions. Technical brief., World Health Organization. ISBN 978-92-4-002086-3		
General Information	Date of data extraction	19 June 2023
	Authors	World Health Organization (WHO)
	Publication date	2022
	Literature search timeframe	Not stated
	Publication type	Agency Technical Brief
	Findings	• Accordingly, exceeding the WHO provisional guideline value of 10 µg/L does not necessarily constitute an emergency unless concentrations are continuously very high (e.g. over 100 µg/L). Where concentrations are high and vulnerable groups (foetuses, infants and children) are exposed, interim remedial actions should be considered – for example, flushing if the source is suspected to be in the plumbing system or use of an alternative safe drinking water supply if the water source is contaminated. • In 2021, a new EU drinking water directive lowered the limit further to 5 µg/L, which must be met by 12 January 2036 at the latest. This is in line with legislation in several other countries. The parametric value for lead until that date is 10 µg/L. However, caution is needed when comparing limits because interpretation should be informed by the sampling regime, which may or may not be specified in the regulation.

CDC 2022

Agency Report Reference: CDC (2021). CDC updates blood lead reference value, Centers for Disease Control and Prevention.		
General Information	Date of data extraction	19 June 2023
	Authors	Centers for Disease Control and Prevention (CDC)
	Publication date	Last reviewed: December 16, 2022.
	Literature search timeframe	Not applicable
	Publication type	Agency Website Update
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	Not stated
	Possible conflicts of interest	Not stated
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	On October 28, 2021, CDC updated the blood lead reference value (BLRV) from 5.0 µg/dL to 3.5 µg/dL. The value is based on the 97.5th percentile of the blood lead distribution in U.S. children ages 1 -5 years. By updating the BLRV to 3.5 µg/dL, children with blood lead levels (BLLs) within the range of 3.5-5 µg/dL can now also receive prompt actions to mitigate health effects and remove or control exposure sources.
	Exposure timeframe	Not applicable
	Critical human health endpoint	Not applicable (97.5th percentile of the blood lead distribution in U.S. children ages 1 -5 years)
	Justification provided by agency for critical endpoint	It is not a health-based standard or a toxicity threshold. The BLRV should be used as a guide to 1) help determine whether medical or environmental follow-up are recommended and 2) prioritise communities with the most need for primary prevention of exposure.
	Critical study(ies) underpinning point of departure	The BLRV is based on data from two consecutive cycles of the National Health and Nutrition Examination Survey (NHANES). The BLRV is updated periodically to reflect changes in the population. The current update is based on data from the 2015-2018 NHANES cycles.
	Species for critical study(ies)	Humans
	Point of departure type (e.g. NOAEL, LOAEL, $BMDL_{10}$, etc)	97.5th percentile of the blood lead distribution in U.S. children ages 1 -5 years
	Point of departure value (include units)	3.5 µg/dL
	Uncertainty factor(s) & rationale	Nil
	Guideline value (include units)	3.5 µg/dL

Agency Report Reference: CDC (2021). CDC updates blood lead reference value, Centers for Disease Control and Prevention.		
	Mode of action for critical health endpoint	Not applicable
	Genotoxic carcinogen?	Not applicable
	Identified sensitive sub-populations	Not applicable
	Any non-health based considerations?	Yes. A BLRV is intended to identify children with higher levels of lead in their blood compared with levels in most children.
Exposure considerations	Principal routes of exposure in general population	Not applicable
	Levels in drinking water supplies (include location)	Not applicable
	Any special considerations to exposure levels (e.g. higher in drought?)	Not applicable
	Typical exposure in general population (include units for intakes & location)	Not applicable
Risk Summary	Any risks to human health from drinking water identified in agency document?	No
	Any emerging risks identified?	No

APPENDIX C

Data extraction tables – Full Review for Health-based Studies

APPENDIX C1 Pb Leaching Studies

Recent Leaching Studies for Lead from plumbing

Akers et al. 2015

Publication Reference: Akers D. B., MacCarthy M. F., Cunningham J. A., Annis J. and Mihelcic J. R. (2015). Lead (Pb) contamination of self-supply groundwater systems in coastal Madagascar and predictions of blood lead levels in exposed children. Environ Sci Technol 49(5): 2685-2693.		
General Information	Date of data extraction	21/06/2023
	Authors	Akers, D.B., MacCarthy, M.F., Cunningham, J.A., Annis, J., Mihelcic, J.R.
	Publication date	Published: January 21, 2015
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	US
	Source of funding	This material is based upon work supported by the National Science Foundation (NSF) under grants DUE 0965743 and DUE 1200682.
	Possible conflicts of interest	The authors declare no competing financial interest.
Study characteristics	Aim/objectives of study	The objectives of this paper are to: (1) conduct a survey of Pb concentrations in water drawn from pitcher pumps at a set of households in Tamatave, Madagascar; (2) determine if Pb concentrations in pumped water decrease after flushing the systems; (3) perform an analysis of the correlation between Pb concentrations and pump-system characteristics such as age, depth to water table, manufacturer, season, and/or water quality; (4) assess whether replacing Pb check valves with iron check valves decreases Pb concentrations; (5) make a preliminary estimate of the blood lead levels (BLLs) that Malagasy children may experience as a result of exposure to Pb in their household water.
	Study type/design	Pb leach study
	Study duration	Three sampling campaigns

Publication Reference: Akers D. B., MacCarthy M. F., Cunningham J. A., Annis J. and Mihelcic J. R. (2015). Lead (Pb) contamination of self-supply groundwater systems in coastal Madagascar and predictions of blood lead levels in exposed children. Environ Sci Technol 49(5): 2685-2693.		
	Type of water source (if applicable)	Groundwater wells using a pitcher pump
Population characteristics	Population/s studied	• City of Tamatave in Eastern Madagascar was selected as the study area for its long history and current scale of pitcher-pump use. • Households were selected to provide a range of pump ages and well depths, and all pump systems included in the sampling campaigns were fabricated and installed by one of six area manufacturers.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	A survey about pitcher pump use was conducted at 53 households, from which 18 were selected for water quality sampling.
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	Metal in pitcher pumps components: (a) pure Pb valve weight; (b) leather valve providing a sliding seal; (c) brass well screen; (d) lead–tin solder. Sea water infiltration
	Exposure concentrations (if applicable)	Maximum: Pb 30 – 44 µg/L (median 7 – 13.5). Median Pb concentrations in the first draw samples are typically (slightly) higher than flushed samples
	Comparison group(s)	Flushed vs first flush
Study methods	Water quality measurement used	Concentrations above the WHO provisional guideline of 10 µg/L
	Water sampling methods (monitoring, surrogates)	• This study collected samples of 10 L, then analysed 5 mL drawn from the fully mixed 10 L bucket. • At each household, samples were collected under both "first-draw" conditions (i.e. after the pump had been inactive for 1 h) and "flushed" conditions (i.e. after a predetermined volume of water had first been flushed from the pump).
Results (for each outcome)	Definition of outcome	• Concentrations of Pb frequently exceeded the World Health Organization's provisional guideline for drinking water of 10 µg/L. • A blood lead level (BLL) greater than 5 µg/dL in children is considered "elevated". Note that the U.S. Environmental Protection Agency (U.S. EPA) developed Internal Exposure Uptake Biokinetic Model for Lead in Children (IEUBK model) was used to estimate BLL
	How outcome was assessed	
	Method of measurement	Anodic stripping voltammetry28 (ASV)
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	18 households

Publication Reference: Akers D. B., MacCarthy M. F., Cunningham J. A., Annis J. and Mihelcic J. R. (2015). Lead (Pb) contamination of self-supply groundwater systems in coastal Madagascar and predictions of blood lead levels in exposed children. Environ Sci Technol 49(5): 2685-2693.		
Statistics (if any)	Statistical method used	To determine if measured Pb concentration is correlated with other factors, Spearman's correlation was determined for the interrelationship of each variable. The six variables included in this multivariate analysis are Pb concentration (in µg/L), pump age (in years), manufacturer (assigned an integer value of 1 through 6), depth to well screen (in meters below ground surface), season of sampling campaign (assigned an integer value of 1 through 3), and contact time (i.e. flushed or first-draw conditions, assigned an integer value of 1 or 2).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable Some relevant results include: • At a low Pb concentration of 3.95 µg/L (corresponding to the 10th percentile of measured household concentrations), the percentage of children predicted to experience an elevated BLL increases to about 15% • Under first-draw conditions (i.e. after a pump had been inactive for 1 h), 67% of samples analysed were in excess of 10 µg/L Pb, with a median concentration of 13 µg/L. • Flushing the pump systems before collecting water resulted in a statistically significant ($p < 0.0001$) decrease in Pb concentrations: 35% of samples collected after flushing exceeded 10 µg/L, with a median concentration of 9 µg/L. • Based on measured Pb concentrations, a biokinetic model estimates that anywhere from 15% to 70% of children living in households with pitcher pumps may be at risk for elevated blood lead levels (>5 µg/dL).

Publication Reference: Akers D. B., MacCarthy M. F., Cunningham J. A., Annis J. and Mihelcic J. R. (2015). Lead (Pb) contamination of self-supply groundwater systems in coastal Madagascar and predictions of blood lead levels in exposed children. Environ Sci Technol 49(5): 2685-2693.		

Author's conclusions	Interpretation of results	• Time-Release Characterisation of Pb
		  ◦ Leaded components leach into water and equilibrate over time as a pitcher-pump system sits idle.
		  ◦ Equilibrium between water and leaded components is reached in approximately 4–12 h
		  ◦ It can take days of stagnation time for water to fully equilibrate with lead pipe, but Pb concentrations often begin to level off in the range of 6–16 h
		  ◦ There were measurable levels of Pb even in samples drawn immediately after flushing the pump (contact time = 0 h).
		  ◦ Most of the soluble Pb present in pitcher-pump systems is drawn from the nominally pure Pb valve weights rather than the well screen or the solder.
		• Estimation of BLLs
		  ◦ Even if the water does not contain any lead ("baseline" scenario of 0 µg/L), the IEUBK model predicts that about 10% of children may experience an elevated BLL (>5 µg/dL).
		  ◦ The concentration of Pb in household water is 23.5 µg/L, approximately 60% of children are estimated to have a BLL below 5 µg/dL.
		  ◦ Thus about 40% of children are estimated to have an elevated BLL above 5 µg/dL, at which point negative health outcomes are expected.
		  ◦ Relatively straightforward operational changes on the part of the pump-system manufacturers and pump users might reduce Pb exposure, thereby helping to ensure the continued sustainability of pitcher pumps in Madagascar.

	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	• Leaded components leach into water and equilibrate over time (4-12 hours) as a pitcher-pump system sits idle with Pb sourced from the Pb valve weights rather than the well screen or the solder. • Estimated BLL >5 µg/dL in 10% of children with no Pb in water and 60% at 23.5 µg/dL. • This study was not subject to a RoB assessment as it is not a health study.
	Notes on study quality, e.g. gaps, methods	

Cartier et al. 2013

Publication Reference: Cartier C., Doré E., Laroche L., Nour S., Edwards M. and Prévost M. (2013). Impact of treatment on Pb release from full and partially replaced harvested Lead Service Lines (LSLs). Water Res 47(2): 661-671.		
	Date of data extraction	21/06/2023

Publication Reference: Cartier C., Doré E., Laroche L., Nour S., Edwards M. and Prévost M. (2013). Impact of treatment on Pb release from full and partially replaced harvested Lead Service Lines (LSLs). Water Res 47(2): 661-671.		
General Information	Authors	Cartier, C., Dore, E., Laroche, L., Nour, S., Edwards, M., Prevost, M.
	Publication date	Available online 2 November 2012
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Canada
	Source of funding	This study was funded by the Canadian Water Network within the framework of a larger research effort carried out by the Natural Sciences and Engineering Research Council of Canada (NSERC) Industrial Chair on Drinking Water at E'cole Polytechnique.
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	The main objective of this study is to measure the impact of pH adjustment, phosphate addition and mass ratio or concentration ratio of chloride to sulfate (CMSR) increase, relative to particulate and dissolved/colloidal lead release from both full and partially replaced Lead Service Lines (LSLs). Secondary objectives include evaluating the impact of the Cu to Pb connection sequence, flow rate and stagnation time.
	Study type/design	Pb Leach Study
	Study duration	> 4 months
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	• 100% Pb pipes, • 20%-Pb pipe (connected with PVC or Cu)
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Scale in LLS (Pb and Cu water pipes)
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	20%-Pb pipe (connected with PVC or Cu)
Study methods	Water quality measurement used	Inductively Coupled Plasma-Mass Spectrometer (ICP-MS)
	Water sampling methods (monitoring, surrogates)	Weekly samplings were performed. A volume of 2 L was collected in order to ensure full recovery of water that stagnated in the plumbing section studied given the low mixing during sampling (van der Leer et al., 2002). A 40 mL aliquot was also taken from the first draw 2 L samples for quantification of dissolved/colloidal Pb via syringe filtration through a 0.45 mm pore size PVDF filter (Millex, Millipore).
	Definition of outcome	

Publication Reference: Cartier C., Doré E., Laroche L., Nour S., Edwards M. and Prévost M. (2013). Impact of treatment on Pb release from full and partially replaced harvested Lead Service Lines (LSLs). Water Res 47(2): 661-671.		
Results (for each outcome)	How outcome was assessed	Release of lead from 80% partially replaced service lines was compared to full lead service lines using harvested stabilised lead pipes and field brass connectors.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	• Release from 100%-Pb pipes ○ For the no treatment control condition Pb concentrations varied between 54 and 162 µg/L (phases 1 and 2) with a mean of 70±20 µg/L (phase 2), of which 58 ± 9 µg/L was dissolved lead. ○ OrthoP treatment significantly reduced (64%) lead release from a mean of 72 ± 14 to 26 ± 9 µg/L within 8 days after the onset of treatment (mean: 24 ± 4 µg/L) • Release from 20%-Pb pipe (connected with PVC or Cu) ○ For the 20%-Pb upstream and downstream pipes without treatment, mean dissolved Pb concentrations were respectively 17 ± 3 and 16 ± 3 µg/L, corresponding to 29% and 28% of the concentrations found for 100%-Pb. • Extending stagnation from 30 min to 16 h resulted in marked increases in the release of dissolved/colloidal Pb (Pbdiss).

Publication Reference: Cartier C., Doré E., Laroche L., Nour S., Edwards M. and Prévost M. (2013). Impact of treatment on Pb release from full and partially replaced harvested Lead Service Lines (LSLs). Water Res 47(2): 661-671.		
Author's conclusions	Interpretation of results	• Partial 80% replacement of a Pb pipe with copper pipe causes sustained lead release (at least up to 12 weeks), mostly in the particulate form which is almost entirely caused by galvanic corrosion between aged LSLs to new copper. Resulting concentrations released from the remaining 20% section of the LSL approach and sometimes exceed those observed from 100%-Pb pipe (without partial replacement) at a flow of 5LPM. • Flow conditions affect total Pb release and especially impact particulate Pb (Pb_{part}) release from both 100%-Pb and 20%-Pb/Cu configurations. Occasional high flows are associated with sustained and elevated Pb spikes over several months that calls into question the often assumed benefits of partial LSL replacement with copper. • In comparison to a full 100%-Pb pipe without treatment, orthophosphate reduced total Pb release by 64% at a flow of 5LPM and did not aggravate Pb release at high flow rate. However, Pb release from galvanic Pb-Cu configurations is not improved by the addition of orthoP, and created significant Pb spikes especially at higher flow rate. • Sulfate treatment had limited impact on Pb release from 100%-Pb rigs but effectively decreased Pb release from galvanic connections between aged Pb and new copper (20%-Pb/Cu partial pipes). After 3 months, Pb concentrations in the high sulfate water, were comparable to those before the connection between Pb and Cu was created. • The impact of stagnation varies for dissolved and particulate Pb release. Particulate Pb fraction increases systematically following stagnation. Protocols based on a short stagnation of 30-min stagnation may not be adequate to assess total Pb release over longer stagnation.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Replacement of lead pipe by copper pipe over a 3-month period generated high lead release attributed to galvanic corrosion and higher lead concentrations (particularly at high flow rates). Particulate lead is released mostly after stagnation periods >30 minutes. As this study does not consider lead toxicity (it is a leaching study) it was not subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Chang et al. 2022

Publication Reference: Chang L., Lee J. H. W. and Fung Y. S. (2022). Prediction of lead leaching from galvanic corrosion of lead-containing components in copper pipe drinking water supply systems. J Hazard Mater 436: 129169.		
General Information	Date of data extraction	27 June 2023
	Authors	Chang, L., Lee, J.H.W., and Fung, Y.S.
	Publication date	Available online 20 May 2022

Publication Reference: Chang L., Lee J. H. W. and Fung Y. S. (2022). Prediction of lead leaching from galvanic corrosion of lead-containing components in copper pipe drinking water supply systems. J Hazard Mater 436: 129169.

	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	China
	Source of funding	This research is supported by a grant from the Research Grants Council of Hong Kong (Project 16216717).
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	This paper reports an electrochemistry based model to predict lead leaching from a copper pipe fitted with leaded connections.
	Study type/design	Pb leach study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Copper pipe with lead connections, brass valve copper pipe and pure copper pipe
	Exposure concentrations (if applicable)	-
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	-
	Water sampling methods (monitoring, surrogates)	-
Results (for each outcome)	Definition of outcome	Stagnant leaching test, Corrosion measurements of plumbing materials
	How outcome was assessed	
	Method of measurement	Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES)
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Chang L., Lee J. H. W. and Fung Y. S. (2022). Prediction of lead leaching from galvanic corrosion of lead-containing components in copper pipe drinking water supply systems. J Hazard Mater 436: 129169.		
Author's conclusions	Interpretation of results	• Lead and copper ions are released out from the solder and copper surface and diffused to the bulk water via molecular diffusion. • The Pb concentration at the solder material surface can be as high as 3 mg/L after 2 h • Pb concentrations approach 300 µg/L and stabilise after 6 hours stagnation
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Lead equilibrated in stagnant water after 6 hours with highest concentrations reported at the Pb solder interface. Lead is also expected to leach out of copper pipes. As this study does not consider lead toxicity (it is a leaching study) it was not subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

De Santis et al. 2018

Publication Reference: DeSantis M. K., Triantafyllidou S., Schock M. R. and Lytle D. A. (2018). Mineralogical Evidence of Galvanic Corrosion in Drinking Water Lead Pipe Joints. Environ Sci Technol 52(6): 3365-3374.		
General Information	Date of data extraction	27 June 2023
	Authors	DeSantis, M.K., Triantafyllidou, S., Schock, M.R., Lytle, D.A.
	Publication date	March 20, 2018
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	US
	Source of funding	None disclosed (USEPA)
	Possible conflicts of interest	The authors declare no competing financial interest.
Study characteristics	Aim/objectives of study	To explore the hypothesis that active galvanic corrosion at lead-containing joints could result in local environments that could aggravate lead release
	Study type/design	Pb leach study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	

Publication Reference: DeSantis M. K., Triantafyllidou S., Schock M. R. and Lytle D. A. (2018). Mineralogical Evidence of Galvanic Corrosion in Drinking Water Lead Pipe Joints. Environ Sci Technol 52(6): 3365-3374.		
	Subgroups reported	Corrosive patterns: - Pattern 1: no evidence of galvanic corrosion was present - Pattern 2: galvanic corrosion was evident and lead pipe was cathodic relative to the connected anodic brass or copper pipe; - Pattern 3: galvanic corrosion was evident and lead pipe was anodic relative to the connected cathodic brass pipe
	Size of study	Twenty-eight lead pipe joints, connected to either leaded brass or copper pipe, were obtained from eight water utilities after 60–114 years of use. Most pipes were connected with lead-tin solder (wiped or cup joint). A limited number of samples were connected with a leaded brass fitting (flare or compression joint).
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Lead pipes and solder and brass fittings
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	-
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Observational results of galvanic lead corrosion
	How outcome was assessed	
	Method of measurement	Observational results
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	- Despite joints being over 60 years old, galvanic zones in Pattern 3 were active and possibly posed an important source of lead to drinking water. - Importantly, Pattern 3 was not observed in samples from systems representing water qualities favouring PbO_2 formation
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This data will not assist in answering leaching questions. It was not subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Deshommes et al. 2017

Publication Reference: Deshommes E., Laroche L., Deveau D., Nour S. and Prévost M. (2017). Short- and Long-Term Lead Release after Partial Lead Service Line Replacements in a Metropolitan Water Distribution System. Environ Sci Technol 51(17): 9507-9515.		
General Information	Date of data extraction	27 June 2023
	Authors	Deshommes, E., Laroche, L., Deveau, D., Nour, S., and Prevost, M.
	Publication date	Published: August 9, 2017
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Canada
	Source of funding	This work was funded by the Canadian Water Network (proposal MW2012-1).
	Possible conflicts of interest	The authors declare no competing financial interest.
Study characteristics	Aim/objectives of study	The objective of this study was to investigate the short- and long-term impacts of partial lead service line replacements (PLSLRs) on water lead levels (WLLs), using extensive repeat sampling and innovative point-of-entry filtration monitoring of particulate lead release from the lead service lines (LSLs), in a real water distribution system.
	Study type/design	Pb leach study
	Study duration	2 years
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	• PLSLR: partial lead service line replacements • FLSLR: full lead service line replacements • full LSL: full lead service lines. • old PLSLR
	Size of study	Thirty-three households were monitored for WLLs in Montreal (Canada) for a period of up to 20 months
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable

<table>
<tr><td colspan="3"><i>Publication Reference:</i> Deshommes E., Laroche L., Deveau D., Nour S. and Prévost M. (2017). Short- and Long-Term Lead Release after Partial Lead Service Line Replacements in a Metropolitan Water Distribution System. Environ Sci Technol 51(17): 9507-9515.</td></tr>
<tr><td rowspan="2"></td><td>Exposure concentrations (if applicable)</td><td>WLLs were significantly lower in households with PLSLRs as compared to no replacements, especially for PLSLRs > 2 years.
Median values (µg/L)
<table>
<tr><th></th><th>Full LSL
Pb-Pb</th><th>PLSLR
Cu-Pb
Recent</th><th>PLSLR
Cu-Pb
Old</th><th>PLSLR
Pb-Cu
Old</th><th>FLSLR
Cu-Cu
Recent</th></tr>
<tr><td>6HS:</td><td>37</td><td>23</td><td>14</td><td>22</td><td>3</td></tr>
<tr><td>30MS:</td><td>18</td><td>10</td><td>8</td><td>10</td><td>1</td></tr>
<tr><td>5MF:</td><td>8</td><td>6</td><td>3</td><td>6</td><td>1</td></tr>
</table>
Total Pb mass per meter of LSL - µg/m
<table>
<tr><th></th><th>N</th><th>Med</th><th>10th-90th</th><th>Max</th><th>K–W test</th></tr>
<tr><td>Before PLSLRb</td><td>25</td><td>1.4</td><td>0.17-3.4</td><td>4.0</td><td>-</td></tr>
<tr><td>Recent PLSLRb</td><td>27</td><td>1.7</td><td>0.44-6.3</td><td>8.6</td><td>p = 0.42f</td></tr>
<tr><td>Old PLSLRc</td><td>20</td><td>0.62</td><td>4.5–14</td><td>15</td><td>p < 0.01e</td></tr>
<tr><td>Recent FLSLRd</td><td>-</td><td>n/a</td><td>n/a</td><td>n/a</td><td>-</td></tr>
</table>
Particulate Pb mass per meter of LSL - µg/m
<table>
<tr><th></th><th>N</th><th>Med</th><th>10th-90th</th><th>Max</th><th>K–W test</th></tr>
<tr><td>Before PLSLRb</td><td>25</td><td>15</td><td>5.0–21</td><td>4.0</td><td>-</td></tr>
<tr><td>Recent PLSLRb</td><td>27</td><td>14</td><td>6.7–37</td><td>8.6</td><td>p = 0.42f</td></tr>
<tr><td>Old PLSLRc</td><td>20</td><td>7.7</td><td>4.5–14</td><td>4.1</td><td>p < 0.01e</td></tr>
<tr><td>Recent FLSLRd</td><td>-</td><td>n/a</td><td>n/a</td><td>n/a</td><td>-</td></tr>
</table></td></tr>
<tr><td>Comparison group(s)</td><td>• 6HS: ≥6 h but <24 h of stagnation
• 30MS (2L): after 30 min of stagnation
• 5MF (2L): flushed for 5 min</td></tr>
<tr><td rowspan="2">Study methods</td><td>Water quality measurement used</td><td>Not applicable</td></tr>
<tr><td>Water sampling methods (monitoring, surrogates)</td><td>Twenty-six households were monitored by repeat sampling at the tap. Sampling was carried out by the homeowner, who was trained by the team and had access to tutorial materials.</td></tr>
<tr><td rowspan="4">Results (for each outcome)</td><td>Definition of outcome</td><td rowspan="2">Pb water concentrations</td></tr>
<tr><td>How outcome was assessed</td></tr>
<tr><td>Method of measurement</td><td>ICP/MS</td></tr>
<tr><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>The study included households monitored before/after PLSLR (n = 6 households) or FLSLR (n = 2); households sampled following recent PLSLR (n = 8) or FLSLR (n = 1); households with a full LSL (n = 7); households with an old PLSLR (n = 9), including configurations with copper on the public (n = 4) or private side (n = 5)</td></tr>
<tr><td rowspan="3">Statistics
(if any)</td><td>Statistical method used</td><td rowspan="2">Not applicable</td></tr>
<tr><td>Details on statistical analysis</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>Not applicable</td></tr>
</table>

Publication Reference: Deshommes E., Laroche L., Deveau D., Nour S. and Prévost M. (2017). Short- and Long-Term Lead Release after Partial Lead Service Line Replacements in a Metropolitan Water Distribution System. Environ Sci Technol 51(17): 9507-9515.		
Author's conclusions	Interpretation of results	• Mean concentrations increased immediately after PLSLRs and erratic particulate lead spikes were observed over the 18 month post-PLSLR monitoring period. • The mass of lead released during this time frame indicates the occurrence of galvanic corrosion and scale destabilisation. • Systemwide, lead concentrations were however lower in households with PLSLRs as compared to those with no replacement, especially for old PLSLRs. • Nonetheless, 61% of PLSLR samples still exceeded 10 µg/L, reflecting the importance of implementing full LSL replacement and efficient risk communication. • Acute concentrations measured immediately after PLSLRs demonstrate the need for appropriate flushing procedures to prevent lead poisoning.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Median Pb concentrations after 6 hours stagnation in lead service lines (37 µg/L) were approximately double those observed with partial Pb line service replacement (14-23 µg/L) irrespective of whether the replacement was on the public side or private side and much higher than in areas with full Pb service line replacement (3 µg/L). Similar differences were observed after 30 minutes stagnation (median ranging from 1 to 18 µg/L) and after 5 minutes of flushing. Concentrations were lower (median ranging from 1 to 8 µg/L). Full Pb service line replacement was required for Pb concentrations in water to be reduced consistently to below 10 µg/L irrespective of flushing and stagnation time. As this study does not consider lead toxicity (it is a leaching study) it was not subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Fisher et al. 2021

Publication Reference: Fisher M. B., Guo A. Z., Tracy J. W., Prasad S. K., Cronk R. D., Browning E. G., Liang K. R., Kelly E. R. and Bartram J. K. (2021). Occurrence of Lead and Other Toxic Metals Derived from Drinking-Water Systems in Three West African Countries. Environ Health Perspect 129(4): 47012.		
General Information	Date of data extraction	28 June 2023
	Authors	Fisher, M.B., Guo, A.Z., Wren Tracy, J., Prasad, S.K., Cronk, R.D., Browning, E.G., Liang, K.R., Kelly, E.R. and Bartram, J.K.
	Publication date	Published 20 April 2021.
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	This work was supported by a grant from World Vision.
	Possible conflicts of interest	The authors declare they have no other actual or potential competing financial interests.

Publication Reference: Fisher M. B., Guo A. Z., Tracy J. W., Prasad S. K., Cronk R. D., Browning E. G., Liang K. R., Kelly E. R. and Bartram J. K. (2021). Occurrence of Lead and Other Toxic Metals Derived from Drinking-Water Systems in Three West African Countries. Environ Health Perspect 129(4): 47012.		
Study characteristics	Aim/objectives of study	Authors characterised the occurrence and investigated sources of toxic metals (TMs) contamination in 261 rural water systems in three West African low- and middle- income countries (LMICs) to inform prevention and management.
	Study type/design	Lead leaching study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Water samples were collected from 261 community water systems (handpumps and public taps) across rural Ghana, Mali, and Niger.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Drinking water
	Exposure concentrations (if applicable)	Arithmetic Mean Pb = 7.74 µg/L (95% CI 0.46, 15.01), maximum = 935.84 µg/L.
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Samples were analysed by inductively coupled plasma (ICP) mass spectrometry or ICP optical emission spectroscopy.
	Water sampling methods (monitoring, surrogates)	• At each of the randomly selected water systems, enumerators visited the water system and observed a 1 h stagnation period, during which the water system was not used (median = 1:0 h, [interquartile range (IQR)= 0:83–1:34 h]). • Enumerators collected a 1 L first-draw sample immediately after the stagnation period, using a new 1 L high-density polyethylene bottle. Samples were preserved with 2 mL of trace metal–grade nitric acid per litre to achieve a final pH of <2:5. After preservation, 10 mL duplicate aliquots were removed and samples were delivered to commercial laboratories in each country for analysis (with the exception of Niger, where samples were shipped to a laboratory in Ghana). • Scrapings were collected from accessible components of a subset of these systems using a drill with acid-washed diamond-tipped bits.
Results (for each outcome)	Definition of outcome	Predictors of Lead Concentration in Drinking Water were identified.
	How outcome was assessed	
	Method of measurement	-

Publication Reference: Fisher M. B., Guo A. Z., Tracy J. W., Prasad S. K., Cronk R. D., Browning E. G., Liang K. R., Kelly E. R. and Bartram J. K. (2021). Occurrence of Lead and Other Toxic Metals Derived from Drinking-Water Systems in Three West African Countries. Environ Health Perspect 129(4): 47012.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	261 community water systems
Statistics (if any)	Statistical method used	• Summary statistics were calculated. • In addition, univariable and multivariable ordinary least squares (OLS) regressions were calculated to determine the association between log TM concentration and country, source type, implementer, and/or system age, controlling for relevant covariates (e.g. stagnation period duration, water sample pH, conductivity). • Independent model variables included were those likely to relate to observable sources of TM contamination from water system corrosion or groundwater contamination (i.e. presence of water system materials of interest, such as brass, galvanised steel; or occurrence of lead in flushed groundwater samples), likely to influence the solubility/extent of corrosion of TMs of concern (pH, conductivity, stagnation time) or to be indicative of the occurrence of corrosion of materials of interest [e.g. copper (bronze, brass), zinc (brass, galvanised steel), tin (bronze)]. • Regression diagnostics were used to identify collinearity. • Influential observations and variables demonstrating multicollinearity were removed from models (although none were found). • Multivariable regressions were conducted to determine associations between the log-transformed concentrations of each TM of interest and all other TMs analysed (controlling for relevant covariates). • Longitudinal analyses were also conducted to determine the extent to which measured concentrations of lead and other TMs in an initial sample (e.g. TM concentration greater than WHO drinking water guideline) predicted similar results for a second sample from the same site. Statistical analyses were conducted using Stata (version 14.2; Stata Corporation).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	-

Publication Reference: Fisher M. B., Guo A. Z., Tracy J. W., Prasad S. K., Cronk R. D., Browning E. G., Liang K. R., Kelly E. R. and Bartram J. K. (2021). Occurrence of Lead and Other Toxic Metals Derived from Drinking-Water Systems in Three West African Countries. Environ Health Perspect 129(4): 47012.		
Author’s conclusions	Interpretation of results	• Lead concentration in drinking water was associated with copper, chromium, and zinc. The association of lead with zinc may likewise implicate brass, but it could also arise from corrosion of galvanised steel. • Of the TMs, lead most frequently occurred at levels of concern in sampled water system components and water samples. • Lead mass fractions exceeded International Plumbing Code (IPC) recommended limits (0.25% wt/wt) for components in 82% (107/130) of systems tested. • Brass components proved most problematic, with 72% (26/36) exceeding IPC limits. Presence of a brass component in a water system increased expected lead concentrations in drinking water samples by 3.8 times. • Overall, lead exceeded World Health Organization (WHO) guideline values in 9% (24/261) of drinking water samples across countries; these results are broadly comparable to results observed in many HICs. • Results did not vary significantly by geography or system type. • Ensuring use of lead-free (<0.25%) components in new water systems and progressively remediating existing systems could reduce drinking water lead exposures and improve health outcomes for millions.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Brass fittings in water system were responsible for elevated lead levels in drinking water. Ensuring use of lead-free (<0.25%) components in new water systems and progressively remediating existing systems could reduce drinking water lead exposures. As this is not a health study it is not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Hannah-Attisha et al. 2016

Publication Reference: Hanna-Attisha M., LaChance J., Sadler R. C. and Champney Schnepp A. (2016). Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response. Am J Public Health 106(2): 283-290.		
General Information	Date of data extraction	07 Julyn2023
	Authors	Hanna-Attisha, M., LaChance, J., Sadler, R.C., Schnepp, A.C.
	Publication date	Accepted November 21, 2015.
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	US
	Source of funding	Not stated
	Possible conflicts of interest	Not stated

Publication Reference: Hanna-Attisha M., LaChance J., Sadler R. C. and Champney Schnepp A. (2016). Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response. Am J Public Health 106(2): 283-290.		
Study characteristics	Aim/objectives of study	Authors analysed differences in paediatric elevated blood lead level incidence before and after Flint, Michigan, introduced a more corrosive water source into an aging water system without adequate corrosion control.
	Study type/design	Pb leaching study
	Study duration	2 years
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Children younger than 5 years who had a blood lead level (BLL) processed through the Hurley Medical Center's laboratory, which runs BLLs for most Genesee County children.
	Selection criteria for population (if applicable)	The pre time period (before the water source change) was January 1, 2013, to September 15, 2013, and the post time period (after the water source change) was January 1, 2015, to September 15, 2015.
	Subgroups reported	Pre and Post change, outside Flint, all Flint, High water lead level (WLL) Flint and lower WLL Flint
	Size of study	The primary study group comprised children living within the city of Flint (n = 1473; pre = 736; post = 737) who received water from the city water system. Children living outside the city where the water source was unchanged served as a comparison group (n = 2202; pre = 1210; post = 992).
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Service lines
	Exposure concentrations (if applicable)	Not stated
	Comparison group(s)	Comparison group (see above)
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• Authors reviewed blood lead levels for children younger than 5 years before (2013) and after (2015) water source change in Greater Flint, Michigan.
	How outcome was assessed	• They assessed the percentage of elevated blood lead levels in both time periods, and identified geographical locations through spatial analysis.
	Method of measurement	• Presumably direct measurement
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1473 children living within the city of Flint (pre = 736; post = 737) and 2202 in the comparison group (pre = 1210; post = 992).
Statistics	Statistical method used	

Publication Reference: Hanna-Attisha M., LaChance J., Sadler R. C. and Champney Schnepp A. (2016). Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response. Am J Public Health 106(2): 283-290.		
(if any)	Details on statistical analysis	Examined differences in overall socioeconomic disadvantage scores from the pre to post time periods by using the independent t test. Finally, they used both c2 analysis with continuity correction and 1-way ANOVA to assess demographic differences by area. Used post hoc least significant difference analysis following statistically significant 1-way ANOVAs.
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Incidence of elevated blood lead levels increased from 2.4% to 4.9% (P <.05) after water source change. • Neighbourhoods with the highest water lead levels experienced a 6.6% increase. • No significant change was seen outside the city. • Geospatial analysis identified disadvantaged neighbourhoods as having the greatest elevated blood lead level increases and informed response prioritisation during the now-declared public health emergency. • The percentage of children with elevated blood lead levels increased after water source change, particularly in socioeconomically disadvantaged neighbourhoods. Water is a growing source of childhood lead exposure because of aging infrastructure.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	• Increased blood lead levels were observed following a change in the water supply. No significant change was observed outside the city but was more evident amongst socioeconomically disadvantaged neighbourhoods. Poor corrosion control may be responsible for elevated water lead levels. • Pb leaching study so no RoB assessment was undertaken.
	Notes on study quality, e.g. gaps, methods	

Jarvis et al. 2018

Publication Reference: Jarvis P., Quy K., Macadam J., Edwards M. and Smith M. (2018). Intake of lead (Pb) from tap water of homes with leaded and low lead plumbing systems. Sci Total Environ 644: 1346-1356.		
General Information	Date of data extraction	29 June 2023
	Authors	Jarvis, P., Quy, K., Macadam, J., Edwards, M., Smith, M.
	Publication date	Available online 13 July 2018
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	UK
	Source of funding	Not stated
	Possible conflicts of interest	Not stated

Publication Reference: Jarvis P., Quy K., Macadam J., Edwards M. and Smith M. (2018). Intake of lead (Pb) from tap water of homes with leaded and low lead plumbing systems. Sci Total Environ 644: 1346-1356.		
Study characteristics	Aim/objectives of study	
	Study type/design	The duplicate intake study (Pb leach study)
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Two different water company regional areas (WC1 and WC2), selected to represent high risk situations in England
	Selection criteria for population (if applicable)	
	Subgroups reported	Four groups: • Leaded properties phosphorous dosed (P-dosed) • Leaded properties not phosphorous dosed (Non-P Dose) • Unleaded properties P-dosed • Unleaded properties Non-P Dose
	Size of study	48 individuals (7 of these aged under 16) were recruited to the lead study from 23 properties, providing 539 and 570 duplicate water intake samples from drinking water events in winter and summer respectively
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Lead or unleaded pipes It is acknowledged that these properties may have contained lead in the water from other sources, such as the brass in water meters and fixtures and fittings and solder containing lead.
	Exposure concentrations (if applicable)	**Median Lead concentrations (µg/L; winter, summer)** Leaded: WC1, WC2; Unleaded: WC1, WC2 Non-p dosed: 4.5, 3.7 | 5.7, 8.5 | 3.2, 9.7 | 0.5, 0.9 P-dosed: 0.1, 0.2 | 1.7, 2.9 | 0.2, 2.1 | 0.1, 0.3
	Comparison group(s)	Unleaded groups in WC1 and WC2 (P-dosed vs non P dosed also considered)
Study methods	Water quality measurement used	Lead concentrations were measured using inductively coupled plasma mass spectroscopy (ICP-MS)
	Water sampling methods (monitoring, surrogates)	Sampling was achieved following a duplicate water intake protocol, whereby a duplicate water sample was taken from each drink the participant of the study was about to consume. Participants filled the cup or glass with the amount of water used for making the drink. If the drink used boiled water, the sample was taken after the water had boiled. The water from the drinking vessel was poured into a measuring jug, and the volume of water was recorded. 125 mL Azlon sample bottles were then filled with water from the measuring jug. The rest of the water from the measuring jug was then returned to the cup or glass and topped up from the tap or kettle and the drink prepared as usual.
Results (for each outcome)	Definition of outcome	• Water lead levels in four types of households.
	How outcome was assessed	

Publication Reference: Jarvis P., Quy K., Macadam J., Edwards M. and Smith M. (2018). Intake of lead (Pb) from tap water of homes with leaded and low lead plumbing systems. Sci Total Environ 644: 1346-1356.		
	Method of measurement	• Note that lead consumption and BLL in children were also predicted (not measured). • Observations
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	539 and 570 duplicate water intake samples
Statistics (if any)	Statistical method used	Mann-Whitney U tests were carried out for comparisons between data in the sample groupings. Wilcoxon's matched pair tests for differences between winter and summer lead values were carried out for each participant. Kruskal-Wallis tests were carried out for non-parametric comparisons of particulate and soluble lead.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable. WC1 Leaded: non-p dosed
Author's conclusions	Interpretation of results	Results relevant to leaching study: • Variability in lead concentrations in household tap water was high and did not follow an obvious pattern with respect to stagnation or consumer drinking behaviour. • The effectiveness of P dosing was very different in the two regions studied, with some very high lead concentrations observed. • Water consumption increased in summer by 24% and lead concentrations were lower in winter.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Water lead levels were relatively high in both leaded and unleaded households and tended to be lower when phosphorus dosing was applied (although statistical significance of this was not assessed in the study). This is a lead leaching study hence was not subjected to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Knowles et al. 2015

Publication Reference: Knowles A. D., Nguyen C. K., Edwards M. A., Stoddart A., McIlwain B. and Gagnon G. A. (2015). Role of iron and aluminum coagulant metal residuals and lead release from drinking water pipe materials. J Environ Sci Health A Tox Hazard Subst Environ Eng 50(4): 414-423.		
General Information	Date of data extraction	29 June 2023
	Authors	Knowles, A.D., Nguyen, C.K., Edwards, M.A., Stoddart, A., Mcilwain, B., Gagnon, G.A.
	Publication date	Published online: 27 Feb 2015
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Canada

Publication Reference: Knowles A. D., Nguyen C. K., Edwards M. A., Stoddart A., McIlwain B. and Gagnon G. A. (2015). Role of iron and aluminum coagulant metal residuals and lead release from drinking water pipe materials. J Environ Sci Health A Tox Hazard Subst Environ Eng 50(4): 414-423.		
	Source of funding	The authors would like to acknowledge and thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support to the NSERC/ Halifax Water Industrial Research Chair. Additionally Alisha Knowles's graduate work was funded by a NSERC Postgraduate Studies Doctoral award (NSERC PGS-D).
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	Lead leaching was examined for two lead-bearing plumbing materials, including harvested lead pipe and new lead: tin solder after exposure to water with simulated aluminium sulfate (Alum X), polyaluminium chloride (PACl) and ferric sulfate coagulation treatments with 1-25-mM levels of iron or aluminium residuals in the water
	Study type/design	Pb leach study
	Study duration	27 weeks
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	• Lead pipe was harvested from a lead service line (LSL) • Copper-to-copper pipe connection using a simulated 40:60 lead:tin solder joint
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Lead pipes and solder
	Exposure concentrations (if applicable)	Not Applicable.
	Comparison group(s)	Copper pipes with lead/tin solder.
Study methods	Water quality measurement used	Atomic absorption graphite furnace or Induced Coupled Plasma Mass Spectrometry (ICP-MS)
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• During testing, the two pipe set-ups were exposed to the 3 water conditions. • Each test was performed in duplicate to obtain statistical confidence in trends. • Over the 27-week duration of the experiment, the samples obtained after each water change were analysed for bulk water pH, total lead content and chloride and sulfate levels.
	How outcome was assessed	
	Method of measurement	Not Applicable.

Publication Reference: Knowles A. D., Nguyen C. K., Edwards M. A., Stoddart A., McIlwain B. and Gagnon G. A. (2015). Role of iron and aluminum coagulant metal residuals and lead release from drinking water pipe materials. J Environ Sci Health A Tox Hazard Subst Environ Eng 50(4): 414-423.

	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not Applicable.
Statistics (if any)	Statistical method used	Not Applicable.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	**Average bulk water total and dissolved lead release concentrations (µg/L) for each water condition during Weeks 17 through 27 of this study (±standard deviation).** *Pb pipe –Pb:Sn solder - Cu pipe* Total / Dissolved Ferric Sulfate 916±332 203±81 PACl 497±352 96±21 Alum 422±302 128±45 *Cu pipe - Pb:Sn Solder - Cu pipe* Ferric Sulfate 27±28 5.6±11 PACl 37±27 20±11 Alum 47±19 2 7±17
Author's conclusions	Interpretation of results	• The release of lead from systems with harvested lead pipe was highly correlated with levels of residual aluminium or iron present in samples (R^2 = 0.66–0.88), consistent with sorption of lead onto the aluminium and iron hydroxides during stagnation. • The results indicate that aluminium and iron coagulant residuals, at levels complying with recommended guidelines, can sometimes play a significant role in lead mobilisation from premise plumbing.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	In an experimental setup, dissolved water lead levels in lead pipes (96 – 203 µg/L) was much higher than observed in copper pipes with lead solder (5.6 – 20 µg/L). This is a lead leaching study hence was not subjected to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Lei et al. 2018

Publication Reference: Lei I. L., Ng D. Q., Sable S. S. and Lin Y. P. (2018). Evaluation of lead release potential of new premise plumbing materials. Environ Sci Pollut Res Int 25(28): 27971-27981

General Information	Date of data extraction	29 June 2023
	Authors	Lei, I., Ng, D., Sable, S.S., and Lin, Y.
	Publication date	Published online: 31 July 2018
	Publication type	Journal article

Publication Reference: Lei I. L., Ng D. Q., Sable S. S. and Lin Y. P. (2018). Evaluation of lead release potential of new premise plumbing materials. Environ Sci Pollut Res Int 25(28): 27971-27981		
	Peer reviewed?	Not stated
	Country of origin	Taiwan
	Source of funding	This research was funded by the Taiwan Ministry of Science and Technology (MOST 105-2628-E-002-001-MY3), Taiwan Ministry of Education (NTU-107L901003), and National Taiwan University (103L891302).
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	The objective of this study is to investigate the extents of lead release from commonly used premise plumbing materials into drinking water.
	Study type/design	Pb Leach Study
	Study duration	Experiment period = 30 days
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	(1) brass/bronze, (2) stainless steel (SS), (3) copper (Cu), and (4) PVC
	Size of study	21 samples including 7 pipes (SS, CU and PVC), 4 tee fittings (SS, PVC and PVC/Bronze), 6 L-fittings (SS, PVC and PVC/Bronze), 2 valve/others (Brass and PVC) and 2 faucets (Brass)
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Pipes and fittings
	Exposure concentrations (if applicable)	-
	Comparison group(s)	Different material types (SS, Cu, PVC and Brass)
Study methods	Water quality measurement used	ICP-OES
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	-
	How outcome was assessed	
	Method of measurement	-
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Lei I. L., Ng D. Q., Sable S. S. and Lin Y. P. (2018). Evaluation of lead release potential of new premise plumbing materials. Environ Sci Pollut Res Int 25(28): 27971-27981		
Author's conclusions	Interpretation of results	• Brass- and bronze-based plumbing materials were found to release dangerous levels of lead. • Surface lead weight percentage obtained using SEM-EDX and lead weight percentages of the material body obtained using strong acid digestion were found to positively correlate with lead release. • A re-examination of the appropriateness of current certified leaching tests and a more stringent regulation on the use of lead as an additive for plumbing materials should be considered.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Water lead concentrations were much higher for brass/bronze (up to 800 µg/L) compared to other materials (<50 µg/L for copper, stainless steel, and PVC). This is a lead leaching study hence was not subjected to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Liu et al. 2018

Publication Reference: Liu Q., Han W., Han B., Shu M. and Shi B. (2018). Assessment of heavy metals in loose deposits in drinking water distribution system. Environ Monit Assess 190(7): 388.		
General Information	Date of data extraction	22/06/2023
	Authors	Liu, Q., Han, W., Han, B., Shu, M., Shi, B.
	Publication date	Published online: 9 June 2018
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	China
	Source of funding	This work was supported by the National Natural Science Foundation of China (51678558, 51378493) and the National Key R&D Program of China (2016YFC0400803)
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	In this work, the potential biological toxicity of heavy metals in loose deposits was calculated based on consensus-based sediment quality guidelines, and the effects of some of the main water quality parameters, such as the pH and bicarbonate and phosphate content, on the release behaviours of pre-accumulated heavy metals were investigated
	Study type/design	Pb Leach Study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water distribution system (DWDS)
	Population/s studied	Not applicable

Publication Reference: Liu Q., Han W., Han B., Shu M. and Shi B. (2018). Assessment of heavy metals in loose deposits in drinking water distribution system. Environ Monit Assess 190(7): 388.		
Population characteristics	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	DWDS
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively coupled plasma atomic emission spectrometry (ICP-OES) Scanning electron microscopy (SEM) and X-ray diffraction (XRD) analysis (loose deposits)
	Water sampling methods (monitoring, surrogates)	Loose deposits were obtained by unbolting fire hydrants at the chosen sample locations, and the suspended solids were captured from the discharge stream in a customised net assembly. (Loose deposits were collected from 11 different drinking water distribution system (DWDS) sites in a metropolitan city in northern China.)
Results (for each outcome)	Definition of outcome	Heavy metal accumulation and potential releases from loose deposits in drinking water distribution system
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The results showed that heavy metals (Cu, As, Cr, Pb, and Cd) significantly accumulated in all the samples. • Water quality can significantly influence the release of heavy metals from loose deposits. • The release of As, Cu, Pb, and Cr also accelerated with the addition of phosphate (from 1 to 5 mg/L).
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	Pb accumulates in loose deposits and its release is influenced by water quality and sulfate. As this study does not consider lead toxicity (it is a leaching study) it was not subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

MacDonald Gibson et al. 2020

Publication Reference: Gibson J. M., Fisher M., Clonch A., MacDonald J. M. and Cook P. J. (2020). Children drinking private well water have higher blood lead than those with city water. Proc Natl Acad Sci U S A 117(29): 16898-16907		
General Information	Date of data extraction	27 June 2023
	Authors	MacDonald Gibson, J., Fisher, M., Clonch, A., MacDonald, J.M., Cook, P.J.
	Publication date	First published July 6, 2020.
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This research was funded by the US Environmental Protection Agency Science to Achieve Results Program under Grant 83927901.
	Possible conflicts of interest	The authors declare no competing interest.
Study characteristics	Aim/objectives of study	Authors analysed the dataset for statistical associations between children's blood Pb and household drinking water source.
	Study type/design	Pb Leach Study
	Study duration	15 years
	Type of water source (if applicable)	Drinking water (municipal and private wells)
Population characteristics	Population/s studied	North Carolina children from Wake County, North Carolina. BLL from North Carolina's Childhood Lead Poisoning Prevention Program Wake County during 1985 to 2017. Since there were repeat analyses for some children, the authors' analysis focuses on the first blood Pb measurement for any one child. Blood Pb records were merged at the address level with residential property tax records obtained from the Wake County Geographic Information Systems Division. The house's water source (private well or community system), size (foot^2), and tax value were obtained. The merged dataset contained 77,969 unique records. All records for which blood Pb measurements or blood draw date were missing were dropped. In addition, all records prior to 2002 (the first year in which municipal water access data were available) were dropped. The final, curated dataset contained 59,483 unique records, corresponding to 41,871 unique addresses.
	Selection criteria for population (if applicable)	
	Subgroups reported	People drinking water from a private well or a regulated water utility
	Size of study	Final curated dataset contained 59,483 unique records.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Corroded pipes and fittings
	Exposure concentrations (if applicable)	Not applicable

Publication Reference: Gibson J. M., Fisher M., Clonch A., MacDonald J. M. and Cook P. J. (2020). Children drinking private well water have higher blood lead than those with city water. Proc Natl Acad Sci U S A 117(29): 16898-16907		
	Comparison group(s)	People drinking water from a regulated water utility
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Whether BLL are higher in children with private wells versus municipal water
	How outcome was assessed	
	Method of measurement	• BLL measured in North Carolina's Childhood Lead Poisoning Prevention Program Wake County during 1985 to 2017 • Lead in water was not measured
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	59,483: 7,709 in the private well group and 43,982 in the regulated water utility group
Statistics (if any)	Statistical method used	• Separate regression analyses were conducted to assess the influence of private well water on 1) the child's blood lead concentration and 2) the proportion of children for whom blood Pb concentrations exceeded the CDC's 5 µg/dL action level. • To control for the effects of multiple observations per residential address and the effects of left censoring on the dataset, a mixed-effects tobit regression of log-transformed blood lead levels was conducted using Stata's metobit function. • A mixed-effects logistic regression model clustered on street address with robust SEs clustered on census block group was also used to estimate the influence of independent variables on the risk of a blood Pb level equal to or greater than 5 µg/dL. • In both regressions (the mixed-effects tobit and logistic models), interactions between water source type and building age were also tested to assess whether the restriction on Pb content of plumbing to 8% or less by weight enacted under Section 1417 of the Safe Drinking Water Act Amendment of 1986.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	• The analysis shows that children in homes relying on private wells have 25% increased odds (95% CI 6.2 to 48%, P<0.01) of elevated blood Pb, compared with children in houses served by a community water system that is regulated under the Safe Drinking Water Act. • Blood Pb concentrations were significantly higher, on average, among children relying on private well water, compared with those served by a regulated water utility (1.75 versus 1.59 µg/dL, P <0.001).
Author's conclusions	Interpretation of results	This increased Pb exposure is likely a result of corrosion of household plumbing and well components, because homes relying on private wells rarely treat their water to prevent corrosion.

Publication Reference: Gibson J. M., Fisher M., Clonch A., MacDonald J. M. and Cook P. J. (2020). Children drinking private well water have higher blood lead than those with city water. Proc Natl Acad Sci U S A 117(29): 16898-16907		
	Assessment of uncertainty (if any)	A sensitivity analysis to test the robustness of any influence of water source on Pb exposure risk was performed by using a Monte Carlo permutation test in which the effects of randomly assigning households across census block groups were simulated with 1,000 repetitions.
Reviewer comments	Results included/excluded in review (if applicable)	The lack of corrosion prevention lead to increased Pb exposure from private wells compared to the municipal water supply as a result of corrosion of household plumbing and well components. As this study does not consider lead toxicity (it is a leaching study) it was not subject to RoB assessment.

Namrotee et al. 2022

Publication Reference: Namrotee Z., Bufa-Dőrr Z., Finta V., Izsák B., Sebestyén Á., Törő K. and Vargha M. (2022). Analysis and assessment of human lead exposure from drinking water and the influencing factors associated with lead. DESALINATION AND WATER TREATMENT 275: 306-312.		
General Information	Date of data extraction	29 June 2023
	Authors	Namrotee, Z., Bufa-Dőrr, Z., Finta, V., Izsák, B., Sebestyén, A., Törő, K., Vargha, M.
	Publication date	Accepted 29 July 2022
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Hungary
	Source of funding	Not stated
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	The objective of this study was to identify highest risk points within a 4-storey public building and gain better understanding of the drivers of in-building variations in lead concentration.
	Study type/design	Pb Leach Study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	First draw (Random daytime, RDT) and 1 min flushed (F) samples were taken at each tap (n = 56) in the building in two sampling periods (summer–spring).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	In total, 220 samples were analysed.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Pipes and fittings

<table>
<tr><td colspan="3"><i>Publication Reference:</i> Namrotee Z., Bufa-Dőrr Z., Finta V., Izsák B., Sebestyén Á., Törő K. and Vargha M. (2022). Analysis and assessment of human lead exposure from drinking water and the influencing factors associated with lead. DESALINATION AND WATER TREATMENT 275: 306-312.</td></tr>
<tr><td rowspan="2"></td><td>Exposure concentrations (if applicable)</td><td>The mean lead concentration of samples collected in August and March were similar, 8.8 and 8.9 µg/L</td></tr>
<tr><td>Comparison group(s)</td><td>Not applicable</td></tr>
<tr><td rowspan="2">Study methods</td><td>Water quality measurement used</td><td>The determination of the metal parameters was done by an inductively coupled plasma ion source mass spectrometer (ICP-MS)</td></tr>
<tr><td>Water sampling methods (monitoring, surrogates)</td><td>Sampling points were selected in every room in the four floors where there was a tap (n = 112), including the kitchens where most water is used for drinking and cooking purposes. To determine the lead concentration in water stagnating in the system, two samples were taken from each location, a random daytime (RDT) sample (i.e. taking the first litre of the water upon opening the tap) and a flushed (F) sample, taken after flushing the cold water for 1 min.</td></tr>
<tr><td rowspan="4">Results (for each outcome)</td><td>Definition of outcome</td><td rowspan="2">Determination of the metal parameters as well as pH, specific electrical conductivity, redox potential and temperature.</td></tr>
<tr><td>How outcome was assessed</td></tr>
<tr><td>Method of measurement</td><td>Not applicable</td></tr>
<tr><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>Not applicable</td></tr>
<tr><td rowspan="3">Statistics
(if any)</td><td>Statistical method used</td><td rowspan="2">Microsoft Excel™ and Statistica™ programs were used to analyse the data. Statistical analyses were carried out for the collected data to understand the relationship between the lead content and the other factors related to the seasonality, building and the water quality parameters. The impact of sampling method and the season of sampling was analysed by t-test, differences by floors and room types by Kruskal–Wallis non-parametric test and correlation with water quality parameters by Pearson correlation analysis.</td></tr>
<tr><td>Details on statistical analysis</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>Not applicable. Other results:
Results of the non-parametric Kruskal–Wallis test comparing flushed drinking water samples on different building levels
<table>
<tr><th></th><th>Street</th><th>Floor 1</th><th>Floor 2</th><th>Floor 3</th><th>Floor 4</th></tr>
<tr><td>Basement</td><td>1.0000</td><td>1.0000</td><td>1.0000</td><td>1.0000</td><td>0.2499</td></tr>
<tr><td>Street</td><td>1.0000</td><td>0.2861</td><td>1.0000</td><td>1.0000</td><td>0.0315*</td></tr>
<tr><td>Floor 1</td><td>1.0000</td><td>0.2861</td><td>1.0000</td><td>1.0000</td><td>1.0000</td></tr>
<tr><td>Floor 2</td><td>1.0000</td><td>1.0000</td><td>1.0000</td><td>1.0000</td><td>1.0000</td></tr>
<tr><td>Floor 3</td><td>1.0000</td><td>1.0000</td><td>1.0000</td><td>1.0000</td><td>1.0000</td></tr>
<tr><td>Floor 4</td><td>0.2499</td><td>0.0315*</td><td>1.0000</td><td>1.0000</td><td>1.0000</td></tr>
</table>
The mean lead concentration was 22.3 µg/L (range <1–2,870) and 4.3 µg/L (range <1–412) in the RDT and F samples, respectively. The difference was significant (dependent t-test, p < 0.001).</td></tr>
</table>

Publication Reference: Namrotee Z., Bufa-Dőrr Z., Finta V., Izsák B., Sebestyén Á., Törő K. and Vargha M. (2022). Analysis and assessment of human lead exposure from drinking water and the influencing factors associated with lead. DESALINATION AND WATER TREATMENT 275: 306-312.		
Author's conclusions	Interpretation of results	• Lead concentration exceeded the regulatory limit value (10 µg/L) in 62% and 32% of the RDT and F samples respectively. • Non-compliant samples were found in every storey of the building, indicating the extensive presence of lead pipes. • However, lead concentrations were significantly higher on the upper floors; flushing reduced lead concentration in the majority of the cases but was often insufficient for reaching compliance. • Other water quality parameters varied in a narrow range and had limited impact on lead leaching. • Results confirmed that in-building variability of lead in drinking water can exceed two orders of magnitude. • Representative sampling point in large buildings for single-sample monitoring schemes should be designated at a regularly used tap on the upper levels of the building. • Sampling in the warmer months and collecting pairs of first draw and flushed samples also assist reliable estimation of lead exposure via drinking water.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Flushing of water and season influences water lead levels.
	Notes on study quality, e.g. gaps, methods	This study was not subject to a RoB assessment

Ng et al. 2016a

Publication Reference: Ng D.-Q. and Yi-Pin L. (2016a). Effects of pH value, chloride and sulfate concentrations on galvanic corrosion between lead and copper in drinking water. Environmental chemistry (Online) 13(4): 602-610.		
General Information	Date of data extraction	29 June 2023
	Authors	Ng, D.Q. and Lin, Y.P.
	Publication date	Published online 23 November 2015
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Singapore/Taiwan
	Source of funding	The authors thank the Singapore Ministry of Education (project number R-302-000-049-112) and National Taiwan University (grant number NTU-CDP-103R7877) for financial support.
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	This study investigates the effects of pH value, chloride and sulfate concentrations on galvanic corrosion between lead and copper in drinking water.

Publication Reference: Ng D.-Q. and Yi-Pin L. (2016a). Effects of pH value, chloride and sulfate concentrations on galvanic corrosion between lead and copper in drinking water. Environmental chemistry (Online) 13(4): 602-610.

	Study type/design	Pb Leach Study
	Study duration	7-day test period
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	-
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively coupled plasma–optical emission spectrometry (ICP-OES)
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• It was found that enhanced lead release was indeed observed after the lead–copper couple was formed and the lead profiles after 48 h were strongly influenced by lead corrosion products formed in the system. • Under stagnant conditions, reducing pH and increasing either chloride or sulfate concentrations promoted lead release, leading to the formation of lead corrosion products such as cerussite and hydrocerussite as experiments proceeded. • The effect of chloride concentration on total lead concentration measured in the aqueous phase was similar to that of sulfate at the same molar concentration, showing that the chloride-to-sulfate mass ratio may not provide a good indication for total lead concentration in water.

Publication Reference: Ng D.-Q. and Yi-Pin L. (2016a). Effects of pH value, chloride and sulfate concentrations on galvanic corrosion between lead and copper in drinking water. Environmental chemistry (Online) 13(4): 602-610.		
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Flushing of water and pH may influence water lead levels. This study was not subject to a RoB assessment
	Notes on study quality, e.g. gaps, methods	

Ng et al. 2016b

Publication Reference: Ng D. Q. and Lin Y. P. (2016b). Evaluation of Lead Release in a Simulated Lead-Free Premise Plumbing System Using a Sequential Sampling Approach. Int J Environ Res Public Health 13(3).		
General Information	Date of data extraction	30 June 2023
	Authors	Ng, D.Q. and Lin, Y.P.
	Publication date	Published: 27 February 2016
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Singapore/Taiwan
	Source of funding	The authors thank the Singapore Ministry of Education (project number R-302-000-049-112) and National Taiwan University (grant number NTUCDP-103R7877) for financial support.
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	• To determine whether lead contamination in drinking water will occur in a “lead-free” premise plumbing system. • In this pilot study, a modified sampling protocol was evaluated for the detection of lead contamination and locating the source of lead release in a simulated premise plumbing system with one-, three- and seven-day stagnation for a total period of 475 days.
	Study type/design	Pb Leach Study
	Study duration	475 days
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable

Publication Reference: Ng D. Q. and Lin Y. P. (2016b). Evaluation of Lead Release in a Simulated Lead-Free Premise Plumbing System Using a Sequential Sampling Approach. Int J Environ Res Public Health 13(3).		
	Exposure concentrations (if applicable)	• 2.0±0.6 µg/L (prior to the test) • Conditioning phase: The highest lead concentration recorded was 83 µg/L on Day 31
	Comparison group(s)	-
Study methods	Water quality measurement used	Inductively coupled plasma mass spectrometer optical emission spectrometry (ICP-OES) (Note: Scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDX) (NovaTM NanoSEM 230) were used to investigate the morphology and chemical composition of the formed scales, respectively)
	Water sampling methods (monitoring, surrogates)	The sampling protocol requires sequential sampling of 50 and 100 mL for the first 200 mL after a stagnation period of one, three or seven days. Sequential sampling using 100 mL was sufficient for detecting lead contamination while using 50 mL could effectively locate the lead source.
Results (for each outcome)	Definition of outcome	Elevated water lead levels due to lead released from copper pipes, stainless steel taps and brass fittings used to assemble the "lead-free" system.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Elevated lead levels, far exceeding the World Health Organization (WHO) guideline value of 10 µg/L, persisted for as long as five months in the system. • "Lead-free" brass fittings were identified as the source of lead contamination. • Physical disturbances, such as renovation works, could cause short-term spikes in lead release. • Orthophosphate was able to suppress total lead levels below 10 µg/L but caused "blue water" problems. • When orthophosphate addition was ceased, total lead levels began to spike within one week, implying that a continuous supply of orthophosphate was required to control total lead levels. • Occasional total lead spikes were observed in one-day stagnation samples throughout the course of the experiments
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	

Publication Reference: Ng D. Q. and Lin Y. P. (2016b). Evaluation of Lead Release in a Simulated Lead-Free Premise Plumbing System Using a Sequential Sampling Approach. Int J Environ Res Public Health 13(3).		
	Notes on study quality, e.g. gaps, methods	Brass fittings were identified as the source of lead contamination in a plumbing system with lead free components. Physical disturbance of the plumbing system lead to spikes in water lead levels. This study was not subject to a RoB assessment

Olson et al. 2017

Publication Reference: Olson T. M., Wax M., Yonts J., Heidecorn K., Haig S.-J., Yeoman D., Hayes Z., Raskin L. and Ellis B. R. (2017). Forensic Estimates of Lead Release from Lead Service Lines during the Water Crisis in Flint, Michigan. Environmental Science & Technology Letters 4(9): 356-361.		
General Information	Date of data extraction	30 June 2023
	Authors	Olson, T.M., Wax, M., Yonts, J., Heidecorn, K., Haig, S., Yeoman, D., Hayes, Z., Raskin, L., Ellis, B.R.
	Publication date	Published: July 19, 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	Authors acknowledge financial support for this study from the University of Michigan’s Schlissel Research Fund for Flint and the University of Michigan’s MCubed and Dow Sustainability Fellows programs.
	Possible conflicts of interest	The authors declare no competing financial interest.
Study characteristics	Aim/objectives of study	In this report, the authors present scale characterisation data, a discussion of how these results differ from scale characterisations of lead service lines (LSLs) in cities without substantial corrosion, and an analysis of the potential mass of lead that was lost from the service lines in Flint during the corrosion event.
	Study type/design	Pb Leach Study
	Study duration	23 weeks and 47 weeks after Flint reconnected to the Detroit Water and Sewerage Department (DWSD) water supply.
	Type of water source (if applicable)	Not applicable. The mean lead content of the scale (±one standard deviation) was 12.4 ± 4.6% by weight.
Population characteristics	Population/s studied	Pipe coupons from Flint and 26 US cities
	Selection criteria for population (if applicable)	
	Subgroups reported	Flint and London pipe scale
	Size of study	27 US cities and 101 pipe coupons
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable

Publication Reference: Olson T. M., Wax M., Yonts J., Heidecorn K., Haig S.-J., Yeoman D., Hayes Z., Raskin L. and Ellis B. R. (2017). Forensic Estimates of Lead Release from Lead Service Lines during the Water Crisis in Flint, Michigan. Environmental Science & Technology Letters 4(9): 356-361.		
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	26 US cities
Study methods	Water quality measurement used	Not applicable. (Note: scale via inductively coupled plasma mass spectrometry (ICP-MS))
	Water sampling methods (monitoring, surrogates)	Not applicable. (Lead pipe segments were collected during the first (March−May 2016) and second (September−December 2016) phases of Flint's "FAST Start" LSL replacement program. Approximately 10 cm long coupons were cut radially using a tube cutter from each of the service line samples).
Results (for each outcome)	Definition of outcome	Pb content in scale from Flint LSL compared against Pb in LSL from other US cities
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	10 pipe coupons from Flint and 91 pipe coupons from 26 U.S. drinking water utilities
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• At Flint, scale was relatively depleted of lead compared to a literature survey of LSL scale from 26 U.S. utilities. • Flint LSL scale was also significantly enriched with aluminium and magnesium compared to reported literature LSL scale compositions. • The findings provide evidence that selective dissolution of lead phosphate minerals occurred because of the absence of orthophosphate during the crisis.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	The lack of corrosion controls in water treatment was attributed to dissolution of lead from lead service lines. As this is a Pb leaching study it is not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Parks et al. 2018

Publication Reference: Parks J., Pieper K. J., Katner A., Tang M. and Edwards M. (2018). Potential Challenges Meeting the American Academy of Pediatrics' Lead in School Drinking Water Goal of 1 µg/L. Corrosion 74(8): 914-917.		
General Information	Date of data extraction	30 June 2023
	Authors	Parks, J., Pieper, K.J., Katner, A., Tang, M., Edwards, M.
	Publication date	Preprint available online: June 2, 2018
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	The authors acknowledge Soil and Land Use Technology, Inc. for their financial support through the Technical Assistance Program at Virginia Tech.
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	The objective of this work was to determine whether kitchen faucets manufactured after 2014 could always satisfy the 1 µg/L goal of the American Academy of Pediatrics (AAP).
	Study type/design	Pb Leach Study
	Study duration	19 days
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Fourteen lead-free faucets and three PVC controls
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	• During the first week of the study, the average lead concentrations were relatively low by existing standards (>1 µg/L to 5.7 µg/L) for all faucets except Faucet C (average lead of 19.9 µg/L to 24.3 µg/L). • For PVC controls, the water lead levels were <0.5 µg/L. • Over the 19-day experiment, the average lead leaching from all faucets, including Faucet C, did decrease steadily.
	Comparison group(s)	Three PVC controls
Study methods	Water quality measurement used	Inductively coupled plasma mass spectrometer (ICP-MS)
	Water sampling methods (monitoring, surrogates)	Faucets were filled completely with the test water to exclude air and samples were collected per the schedule specified by the National Sanitation Foundation/American National Standards Institute (NSF/ANSI) standard. In brief, the test water was prepared fresh daily and five dump-and-fill water changes were conducted every 2 h over an 8-h period on Days 1 to 5, 8 to 12, and 15 to 18. After the overnight stagnation, the water from each faucet was collected in a high-density polyethylene bottle on Days 3, 4, 5, 10, 11, 12, 17, 18, and 19.

Publication Reference: Parks J., Pieper K. J., Katner A., Tang M. and Edwards M. (2018). Potential Challenges Meeting the American Academy of Pediatrics' Lead in School Drinking Water Goal of 1 µg/L. Corrosion 74(8): 914-917.

Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	Three styles of recently manufactured "lead-free" faucets were tested and average lead leaching ranged from 1.5 µg/L to 3.0 µg/L after 19 days. Given that the NSF/ANSI 61 test water is less aggressive than some potable waters, even newly manufactured "lead-free" faucets may not meet the standards recommended by AAP.
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	Lead is being released from "lead free faucets" and in this experiment water lead levels (stagnant) ranged from 0.5 µg/L to 24.3 µg/L during the first week of the study and 1.5 µg/L to 3.0 µg/L after 19 days. Pb leaching from PVC controls was below detection (<0.5 µg/L). This study was not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Pieper et al. 2015

Publication Reference: Pieper K. J., Krometis L. A., Gallagher D. L., Benham B. L. and Edwards M. (2015). Incidence of waterborne lead in private drinking water systems in Virginia. J Water Health 13(3): 897-908.

General Information	Date of data extraction	30 June 2023
	Authors	Pieper, K.J., Krometis, L.H., Gallagher, D.L., Benham, B.L., and Edwards, M.
	Publication date	2015
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This research was supported through the Rural Health and Safety Education Competitive Program of the USDA National Institute of Food and Agriculture (#2011-05026).
	Possible conflicts of interest	Not stated

Publication Reference: Pieper K. J., Krometis L. A., Gallagher D. L., Benham B. L. and Edwards M. (2015). Incidence of waterborne lead in private drinking water systems in Virginia. J Water Health 13(3): 897-908.		
Study characteristics	Aim/objectives of study	This study: (1) documents the occurrence of lead in water samples collected from the point of use (POU) of households dependent on private drinking water systems; (2) quantifies the relative amounts of dissolved and particulate lead in these samples; (3) identifies major system and environmental characteristics associated with high lead concentrations; and (4) evaluates associations between homeowner perception of water quality and the presence of high lead concentrations
	Study type/design	Pb Leach Study
	Study duration	Samples were collected between March 2012 and November 2013
	Type of water source (if applicable)	Municipal water, well water
Population characteristics	Population/s studied	Participation in the drinking water clinics was wholly voluntary and participants were therefore self-selected. Homeowners who wished to participate purchased a water sampling kit
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	2,146 samples submitted by private system homeowners from 61 of the 95 counties in Virginia.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Water Lead levels (mg/L) Standard Results Mean Median 90%ile 0.015 2,144 0.022 0.004 0.027 Lead concentrations in the first draws ranged from below detection (<1 µg/L) to 24,740 µg/L
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively coupled plasma-mass spectrometry (ICP-MS)
	Water sampling methods (monitoring, surrogates)	Per the instructions, homeowners collected samples from a non-swivel faucet on a predetermined morning. After a minimum of 6 hours of stagnation, homeowners removed the aerator and collected 250 mL of water at a pencil-thin flow ('first draw'). The system was then flushed for a minimum of 5 minutes, and three additional samples (two 250 mL and one 100 mL) were collected at a pencil-thin flow ('flushed samples').
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics	Statistical method used	

Publication Reference: Pieper K. J., Krometis L. A., Gallagher D. L., Benham B. L. and Edwards M. (2015). Incidence of waterborne lead in private drinking water systems in Virginia. J Water Health 13(3): 897-908.		
(if any)	Details on statistical analysis	All statistical analyses were conducted in R version 3.0.2 (R Development Core Team 2012) assuming an alpha of 0.05 as an indication of significance. Owing to the non-normal distribution of the lead data (Shapiro-Wilk; p <0.05), non-parametric statistics were used throughout this study. Potential associations between lead concentrations and the other water quality parameters (e.g. copper, zinc, and tin) were evaluated using the Spearman's rank correlation (ρ), while the Wilcoxon signed-rank test and Kruskal–Wallis test compared lead concentrations based on categorical household characteristics (e.g. income, education, piping material) and homeowner perception of water quality (e.g. taste, odour). Odds ratios (OR) were calculated to determine the odds of having elevated lead concentrations based on home-owners' perceptions of water quality.
	Relative risk/odds ratio, confidence interval?	• There was no significant difference (Wilcoxon signed-rank tests, p = 0.21) in lead concentrations between households that identified only having copper (n =514) versus plastic plumbing (n = 915). • Households constructed pre-1988 had a significantly higher (p <0.05) median lead concentration (5.4 µg/L, n = 600) compared to households constructed post-1988 (3.3 µg/L, n = 805). • Homeowners who identified obvious signs of corrosion (OR = 1.72), blue-green staining on plumbing fixtures (OR = 2.78), and/or described the taste of water as metallic (OR = 2.29) were 1.7–2.8 times more likely to have elevated lead concentrations compared to homeowners who did not identify these characteristics. • Homeowners who noted that their water had an odour (OR = 0.62), a sulfur odour (OR =0.49), a sulfur taste (OR = 0.42), identified white/chalk staining on plumbing fixtures (OR = 0.56), and/or noticed white flakes in the water (OR = 0.40) were 1.6–2.5 times less likely to have elevated lead concentrations compared to homeowners who did not identify these characteristics.

Publication Reference: Pieper K. J., Krometis L. A., Gallagher D. L., Benham B. L. and Edwards M. (2015). Incidence of waterborne lead in private drinking water systems in Virginia. J Water Health 13(3): 897-908.		
Author's conclusions	Interpretation of results	• Flushing the system for 5 minutes appeared to reduce lead concentrations to the recommended concentration (i.e. below 15 µg/L) for most households in this study. • On average, for the preselected first draws with detectable total lead concentrations (>1 µg/L, n = 55), 75% of the total lead was in the particulate form. • The median lead concentration for dug/bored wells (n = 248, 9.4 µg/L) was significantly higher (Kruskal–Wallis test, p <0.05) than drilled wells (n = 1,607, 3.6 µg/L) and springs (n = 77, 3.5 µg/L). • Participants who indicated the use of a water treatment device did not have significantly lower median lead concentrations. • Correlations between lead, copper, and zinc suggested brass components as a likely lead source. • Dug/bored wells had significantly higher lead concentrations as compared to drilled wells. • A random subset of samples selected to quantify particulate lead indicated that, on average, 47% of lead in the first draws was in the particulate form, although the occurrence was highly variable. • Some systems experienced an increase, perhaps attributable to particulate lead or lead-bearing components upstream of the faucet (e.g. valves, pumps).
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	The type of fittings used in the plumbing network (e.g. brass) is more important to predicting water lead levels than the interior piping material (e.g. copper, plastic)
	Notes on study quality, e.g. gaps, methods	This study was not subject to a RoB assessment.

Pieper et al. 2017

Publication Reference: Pieper K. J., Tang M. and Edwards M. A. (2017). Flint Water Crisis Caused By Interrupted Corrosion Control: Investigating "Ground Zero" Home. Environ Sci Technol 51(4): 2007-2014.		
General Information	Date of data extraction	30 June 2023
	Authors	Pieper, K.J., Tang, M., and Edwards, M.
	Publication date	Published: February 1, 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This research was supported by the National Science Foundation through a Rapid Research Response grant (#1556258) and funding from the Community Foundation of Greater Flint.

Publication Reference: Pieper K. J., Tang M. and Edwards M. A. (2017). Flint Water Crisis Caused By Interrupted Corrosion Control: Investigating "Ground Zero" Home. Environ Sci Technol 51(4): 2007-2014.		
	Possible conflicts of interest	The authors declare no competing financial interest.
Study characteristics	Aim/objectives of study	An intensive follow-up monitoring event at this home investigated patterns of lead release after progressively rising water lead levels (in Flint Michigan).
	Study type/design	Pb Leach Study
	Study duration	Not applicable
	Type of water source (if applicable)	Municipal water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	6 samples from "Resident Zero" On May 6, 2015, two 0.6–0.9 m (2–3 ft.) outdoor sections of the 58.5 m (192 ft.) galvanised iron service line (GSL; iron pipe with a protective "galvanized" surface coating composed of zinc, lead, and cadmium) were exhumed by a representative of EPA Region 5 and sent to Virginia Tech for analysis
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Flint, Michigan switched to the Flint River as a temporary drinking water source without implementing corrosion control in April 2014. Ten months later, water samples collected from a Flint residence revealed progressively rising water lead levels (104, 397, and 707 µg/L)
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively Coupled Plasma–Mass Spectrometry (ICP-MS)
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Nonparametric statistics were used in this study due to the non-normal distribution of the lead data (Shapiro-Wilk; $p < 0.05$). Spearman's rank correlation (ρ) was used to evaluate the associations between lead and other water quality parameters (e.g. copper and zinc). The Kruskal–Wallis test was used to compare lead and iron concentrations based on flow rate during the profiling effort
	Details on statistical analysis	

Publication Reference: Pieper K. J., Tang M. and Edwards M. A. (2017). Flint Water Crisis Caused By Interrupted Corrosion Control: Investigating "Ground Zero" Home. Environ Sci Technol 51(4): 2007-2014.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• EPA Region 5 Ground Water and Drinking Water Branch determined that the lead contamination was not associated with the interior household plumbing as it was primarily plastic plumbing with several "lead-free" fittings and fixtures. • An intensive follow-up monitoring event at this home investigated patterns of lead release by flow rate−all water samples contained lead above 15 µg/L and several exceeded hazardous waste levels (>5000 µg/L). • Forensic evaluation of exhumed service line pipes compared to water contamination "fingerprint" analysis of trace elements, revealed that the immediate cause of the high water lead levels was the destabilisation of lead-bearing corrosion rust layers that accumulated over decades on a galvanised iron pipe downstream of a lead pipe
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Elevated water lead levels in households from Flint Michigan were attributed to the mobilisation of particulate lead from scale in service lines and not household "brass free" fittings and pipes.
	Notes on study quality, e.g. gaps, methods	This study was not subject to a RoB assessment.

Pieper et al. 2018a

Publication Reference: Pieper K. J., Nystrom V. E., Parks J., Jennings K., Faircloth H., Morgan J. B., Bruckner J. and Edwards M. A. (2018a). Elevated Lead in Water of Private Wells Poses Health Risks: Case Study in Macon County, North Carolina. Environ Sci Technol 52(7): 4350-4357.		
General Information	Date of data extraction	30 June 2023
	Authors	Pieper, K.J., Nystrom, V.E., Parks, J., Jennings, K., Faircloth, H., Morgan, J.B., Bruckner, J. and Edwards, M.A.
	Publication date	March 14, 2018
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This research is supported by the Agriculture and Food Research Initiative (#2016-67012-24687) from the U.S. Department of Agriculture National Institute of Food and Agriculture and Edna Bailey Sussman Foundation.
	Possible conflicts of interest	The authors declare no competing financial interest.

Publication Reference: Pieper K. J., Nystrom V. E., Parks J., Jennings K., Faircloth H., Morgan J. B., Bruckner J. and Edwards M. A. (2018a). Elevated Lead in Water of Private Wells Poses Health Risks: Case Study in Macon County, North Carolina. Environ Sci Technol 52(7): 4350-4357.

Study characteristics	Aim/objectives of study	Authors evaluated water lead at the homes of two children with elevated blood lead in Macon County (North Carolina), which did not have identifiable lead paint or lead dust hazards, and examined water lead release patterns among 15 private wells in the county.
	Study type/design	Pb Leach Study
	Study duration	Not applicable
	Type of water source (if applicable)	Private well water
Population characteristics	Population/s studied	Select locations from Macon County (North Carolina).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	15 private wells, 2 case studies
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	**Table 1. First Draws and Flush Water Lead Levels (n = 15). Concentrations in µg/L.** Sample | % Measured | Mean | 90%ile | Max first draw | 100% | 247.8 | 945.8 | 1746.0 second draw | 73% | 5.7 | 11.5 | 34.0 1 min | 33% | 1.3 | 3.2 | 5.4 2 min | 20% | <1 | 1.1 | 1.4 3 min | 27% | 1.3 | 3.2 | 7.2 5 min | 20% | 1.6 | 4.3 | 10.7 10 min | 7% | <1 | <1 | 5.4 15 min | 20% | 1.2 | 2.9 | 6.2
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	ICP-MS
	Water sampling methods (monitoring, surrogates)	-
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics	Statistical method used	

Publication Reference: Pieper K. J., Nystrom V. E., Parks J., Jennings K., Faircloth H., Morgan J. B., Bruckner J. and Edwards M. A. (2018a). Elevated Lead in Water of Private Wells Poses Health Risks: Case Study in Macon County, North Carolina. Environ Sci Technol 52(7): 4350-4357.		
(if any)	Details on statistical analysis	Statistical analyses were performed in R v3.4.336 and significance was tested against an alpha of 0.05. Due to the non-normal distribution of the data (Sharpiro Wilk, p < 0.05), the Spearman's correlation was used to evaluate the association between lead and other water quality parameters. The Wilcoxon signed-rank paired and unpaired tests were used to compare water lead levels (WLLs) based on sample location and flushing interval.
	Relative risk/odds ratio, confidence interval?	Not applicable

Author's conclusions	Interpretation of results	• WLLs were highest in first draw samples and decreased with continued flushing.
		• Sporadic spikes in particulate lead occurred during continued water use.
		• Problems with lead release were associated with:
		  • (1) dissolution of lead from plumbing during periods of stagnation;
		  • (2) scouring of leaded scales and sediments during initial water use; and
		  • (3) mobilisation of leaded scales during continued water use.
		• Accurate quantification of water lead was highly dependent on sample collection methods, as flushing dramatically reduced detection of lead hazards.

	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Destabilised lead-bearing corrosion rust layers (scale) in galvanised iron pipe downstream of a lead pipe was identified as the immediate cause of the high water lead levels measured in 2014 in Macon County (North Carolina). Note: "lead-free" plumbing brass components could contain up to 8% lead by weight and release elevated lead to water when exposed to more corrosive water conditions. This study was not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Pieper et al. 2018b

Publication Reference: Pieper K. J., Martin R., Tang M., Walters L., Parks J., Roy S., Devine C. and Edwards M. A. (2018b). Evaluating Water Lead Levels During the Flint Water Crisis. Environ Sci Technol 52(15): 8124-8132.		
General Information	Date of data extraction	30 June 2023
	Authors	Pieper, K.J., Martin, R., Tang, M., Walters, L., Parks, J., Roy, S., Devine, C., Edwards, M.A.
	Publication date	Published: June 22, 2018
	Publication type	Journal article
	Peer reviewed?	Not stated

Publication Reference: Pieper K. J., Martin R., Tang M., Walters L., Parks J., Roy S., Devine C. and Edwards M. A. (2018b). Evaluating Water Lead Levels During the Flint Water Crisis. Environ Sci Technol 52(15): 8124-8132.		
	Country of origin	US
	Source of funding	This work was funded by discretionary funds (Round 1), EPA (Rounds 2, 3, and 4), and crowd sourcing, discretionary funds, and grant from the Greater Flint Community Foundation (Round 5).
	Possible conflicts of interest	The authors declare the following competing financial interest(s): *"The water crisis remains a contentious issue and is the subject of hundreds of lawsuits. We are not party to any of these lawsuits nor are we expert witnesses for any side in a lawsuit. However, our data and testimony has been subpoenaed.* *We were openly criticized by state and EPA for our data results in Round 1, and we have been attacked by activists for our data showing improving water quality through 2017."*
Study characteristics	Aim/objectives of study	This manuscript presents the longitudinal data collected between August 2015 and August 2017, which define the water lead levels (WLLs) during the Flint Water Crisis and subsequent water quality interventions. Specifically, the objectives of the study are to (1) evaluate system-wide lead contamination in August 2015 attributed to the switch to Flint River water and absence of corrosion control; (2) quantify the reduction in WLLs in 2016 and 2017 after MDEQ and USEPA interventions; and (3) examine variations in WLLs based on water quality parameters and service line characteristics.
	Study type/design	Pb leach study
	Study duration	-
	Type of water source (if applicable)	See above
Population characteristics	Population/s studied	Distributed sampling kits to Flint residents with response rates were very high: 92% (n = 277 of 300) of kits were returned in August 2015, 68% (n = 184 of 269) in March 2016, 98% (n = 176 of 180) in July 2016, 91% (n = 164 of 180) in November 2016, and 91% (n = 164 of 180) in August 2017. Participation in this testing was voluntary and residents were self-selected [i.e. high-risk homes with lead service lines (LSLs) were not targeted as required by the Lead Copper Rule (LCR)].
	Selection criteria for population (if applicable)	
	Subgroups reported	-
	Size of study	-
Exposure and setting	Exposure pathway	-
	Source of chemical/contamination	Note: Switching from drinking water with optimised corrosion control from the Detroit Water and Sewer Department (DWSD) to treated Flint River water resulting in an increase in water corrosivity (from the absence of corrosion control and higher chloride to sulfate mass ratio (CSMR)) that would be expected to dramatically increase lead and iron corrosion in Flint.

<table>
<tr><th colspan="3">Publication Reference: Pieper K. J., Martin R., Tang M., Walters L., Parks J., Roy S., Devine C. and Edwards M. A. (2018b). Evaluating Water Lead Levels During the Flint Water Crisis. Environ Sci Technol 52(15): 8124-8132.</th></tr>
<tr><td></td><td>Exposure concentrations (if applicable)</td><td>Pb (µg/L) Water Quality Data at 156 Homes That Participated in the Four Sampling Efforts between August 2015 and November 2016
<table>
<tr><th>Statistics</th><th>FD</th><th>1MF</th><th>3MF</th></tr>
<tr><td colspan="4">August 2015 Sampling (n = 268)</td></tr>
<tr><td>Above reporting level</td><td>92%</td><td>63%</td><td>50%</td></tr>
<tr><td>median</td><td>4.4</td><td>2.1</td><td><MRL</td></tr>
<tr><td>90th percentile</td><td>28.0</td><td>11.4</td><td>6.9</td></tr>
<tr><td colspan="4">March 2016 Sampling (n = 186)</td></tr>
<tr><td>Above reporting level</td><td>63%</td><td>42%</td><td>30%</td></tr>
<tr><td>median</td><td>1.9</td><td><MRL</td><td><MRL</td></tr>
<tr><td>90th percentile</td><td>22.4</td><td>9.0</td><td>3.2</td></tr>
<tr><td colspan="4">July 2016 Sampling (n = 176)</td></tr>
<tr><td>Above reporting level</td><td>56%</td><td>43%</td><td>33%</td></tr>
<tr><td>median</td><td>1.2</td><td><MRL</td><td><MRL</td></tr>
<tr><td>90th percentile</td><td>13.6</td><td>5.7</td><td>3.3</td></tr>
<tr><td colspan="4">November 2016 Sampling (n = 164)</td></tr>
<tr><td>Above reporting level</td><td>43%</td><td>32%</td><td>26%</td></tr>
<tr><td>median</td><td><MRL</td><td><MRL</td><td><MRL</td></tr>
<tr><td>90th percentile</td><td>8.4</td><td>3.9</td><td>2.6</td></tr>
</table>
FD = first draw; 1MF = 1 min flush; 3MF = 3 min flush; MRL = Minimum reporting level (1 µg/L)</td></tr>
<tr><td></td><td>Comparison group(s)</td><td>first draw, 1 min flush, 3 min flush</td></tr>
<tr><td>Study methods</td><td>Water quality measurement used</td><td>Inductively Coupled Plasma−Mass Spectrometry (ICP-MS)</td></tr>
<tr><td></td><td>Water sampling methods (monitoring, surrogates)</td><td>After a minimum of 6+hours of stagnation, residents were instructed to choose one drinking water tap (e.g. kitchen or bathroom faucet) to (1) collect 1 L of cold water at a normal flow (first draw sample); (2) flush the sample tap for 45 s and collect a 500 mL sample (1 min flush sample); and (3) flush the sample tap for an additional 2 min and collect a 125 mL sample (3 min flush sample). Along with water samples, residents provided sampling address, which was aggregated by the five primary zip codes for further analyses.</td></tr>
<tr><td>Results (for each outcome)</td><td>Definition of outcome</td><td>Not applicable</td></tr>
<tr><td></td><td>How outcome was assessed</td><td></td></tr>
<tr><td></td><td>Method of measurement</td><td>Not applicable</td></tr>
<tr><td></td><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>A total of 268 valid Flint samples were collected in August 2015. Of those 268 homes, a total of 186 participated in the next round in March 2016, and those who did not participate were dropped from later rounds. This approach led to 176 homes sampled in July 2016, 164 in November 2016, and 150 in August 2017</td></tr>
<tr><td>Statistics</td><td>Statistical method used</td><td></td></tr>
</table>

Publication Reference: Pieper K. J., Martin R., Tang M., Walters L., Parks J., Roy S., Devine C. and Edwards M. A. (2018b). Evaluating Water Lead Levels During the Flint Water Crisis. Environ Sci Technol 52(15): 8124-8132.		
(if any)	Details on statistical analysis	Statistical analyses on the citizen science sampling data (not reconstructed sampling pools) were conducted in R version 3.4.3 assuming an alpha of 0.05 as an indication of significance. Spearman's rho was used to evaluate correlations between lead and other metals and phosphate in water. The Kruskal–Wallis test was performed to examine relationships between WLLs and service line material. A test of proportions was used to compare WLLs among zip codes. The minimum reporting level (MRL) was 1 µg/L for lead, 0.01 mg/L for iron, and 0.03 mg/L as $PO^{4}{}_{3}$–-P, and all measurements below the MRL were set to half the MRL.
	Relative risk/odds ratio, confidence interval?	Not applicable

Author's conclusions	Interpretation of results	• The absence of corrosion control and use of a more corrosive source increased lead leaching from plumbing.
		• City-wide citizen science water lead results contradicted official claims that there was no problem– 90th percentile was 26.8 µg/L, which was almost double the Lead and Copper Rule action level of 15 µg/L.
		• Back calculations of a Lead and Copper Rule (LCR) sampling pool with 50% lead pipes indicated an estimated 90th percentile lead value of 31.7 µg/L (±4.3 µg/L).
		• Four subsequent sampling efforts were conducted to track reductions in water lead after the switch back to Lake Huron water and enhanced corrosion control. The incidence of water lead varied by service line material.
		• Between August 2015 and November 2016, median water lead reduced from
		  • 3.0 to <1 µg/L for homes with copper service lines
		  • 7.2–1.9 µg/L with galvanised service lines
		  • 9.9–2.3 µg/L with lead service lines.
		• As of summer 2017, 90th percentile of 7.9 µg/L no longer differed from official results, which indicated Flint's water lead levels were below the action level.

	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	The absence of corrosion control and more corrosive water resulted in increased water lead levels.
	Notes on study quality, e.g. gaps, methods	As this is a Pb leaching study it was not subject to a RoB assessment.

Rockey et al. 2021

Publication Reference: Rockey N. C., Shen Y., Haig S.-J., Wax M., Yonts J., Wigginton K. R., Raskin L. and Olson T. M. (2021). Impact of service line replacement on lead, cadmium, and other drinking water quality parameters in Flint, Michigan. Environmental Science: Water Research & Technology 7(4): 797-808.		
General Information	Date of data extraction	07 July 2023
	Authors	Rockey, N.C., Shen, Y., Haig, S., Wax, M., Yonts, J., Wigginton, K.R., Raskin, L., Olson, T.M.
	Publication date	Accepted 22nd February 2021
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	This work was funded by the University of Michigan (UM) MCubed program. NCR was partially supported by a U.S. National Science Foundation Graduate Research Fellowship (award no. 2015205675), and YS and SJH were supported by Alfred P. Sloan Foundation Microbiology of the Built Environment Fellowships (G-2016-7250 and G-2014-13739, respectively). Additionally, SJH was supported by a UM Dow Sustainability Fellowship
	Possible conflicts of interest	The authors declare no conflicts of interest.
Study characteristics	Aim/objectives of study	In this study, the short- and long-term impact of service line replacement on Flint drinking water quality was investigated.
	Study type/design	Pb leaching study
	Study duration	11 months
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	24 Flint homes.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Service lines
	Exposure concentrations (if applicable)	See Figure 2 and Figure 3 in study
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Ion coupled plasma mass spectrometry (ICP-MS)

Publication Reference: Rockey N. C., Shen Y., Haig S.-J., Wax M., Yonts J., Wigginton K. R., Raskin L. and Olson T. M. (2021). Impact of service line replacement on lead, cadmium, and other drinking water quality parameters in Flint, Michigan. Environmental Science: Water Research & Technology 7(4): 797-808.		
	Water sampling methods (monitoring, surrogates)	Homes were sampled following a stagnation period of at least six hours. At each home, four cold water samples were collected from the kitchen faucet at full flow. First litre samples were collected in accordance with the lead and copper rule sampling protocol. Point-of-use filters were removed from faucets prior to sampling, while aerators were left in place during sampling. After collecting the first litre sample, 30 mL was immediately aliquoted and stored on ice for total and dissolved metals analyses. Subsequently, the aerator was removed and 2 L of additional premise plumbing water was added to the remaining portion of the first litre sample to comprise a 3 L premise plumbing sample. This 3 L composite sample of stagnant water was collected so sufficient biomass could be obtained for microbial analyses.
Results (for each outcome)	Definition of outcome	Lead, cadmium and microbial organisms in water
	How outcome was assessed	
	Method of measurement	Changes in concentration
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	At 17 of the 24 homes, samples were also collected approximately two and five weeks after service line replacement. The seven remaining homes were not sampled after the initial sampling as a result of one of the following reasons: no pipe replacement occurred, service line material could not be confirmed, or homes were not accessible for post-replacement sampling.
Statistics (if any)	Statistical method used	Comparison tests, correlation analyses, and linear mixed-effects models were conducted in R (version 3.3.2) using R studio (version 0.99.902), with significance defined as p-value < 0.05.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Lead levels in premise plumbing water did not change significantly within five weeks of replacement. • However, significant reductions were observed two weeks after service line replacement in flushed samples representative of distribution system water (pre-replacement median = 0.98 µg/L; two-week post-replacement median = 0.11 µg/L). • Multiple sequential samplings from one Flint residence before and 11 months after service line replacement revealed large reductions in lead levels in all samples, indicating long-term benefits of service line replacement. • Results provide evidence that both lead service line and galvanised service line replacement benefit consumers in the long term by reducing drinking water lead concentrations, while short-term advantages of service line replacement in sites with prior lead seeding of in-home plumbing are less apparent.
	Assessment of uncertainty (if any)	-

Publication Reference: Rockey N. C., Shen Y., Haig S.-J., Wax M., Yonts J., Wigginton K. R., Raskin L. and Olson T. M. (2021). Impact of service line replacement on lead, cadmium, and other drinking water quality parameters in Flint, Michigan. Environmental Science: Water Research & Technology 7(4): 797-808.		
Reviewer comments	Results included/excluded in review (if applicable)	Long-term benefits were observed after lead service line replacement with large drops in water lead levels.
	Notes on study quality, e.g. gaps, methods	As this is a Pb leaching study it was not subject to a RoB assessment.

Siu et al. 2020

Publication Reference: Siu K. W., Kwok J. C. M. and Ngan A. H. W. (2020). Thermo-mechanical processing of brass components for potable-water usage increases risks of Pb leaching. Water Res 186: 116414.		
General Information	Date of data extraction	07 July 2020
	Authors	Siu, K.W. Kwok, J.C.M., and Ngan, A.H.W.
	Publication date	Available online 8 September 2020
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	China
	Source of funding	The work described in this paper was supported by funds from the Kingboard Endowed Professorship in Materials Engineering at the University of Hong Kong.
	Possible conflicts of interest	The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Study characteristics	Aim/objectives of study	In this study, the effects of lead segregation on brass surfaces and subsequent leaching to contacting water resulting from thermo-mechanical processing of the brass are studied.
	Study type/design	Pb leaching study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Fittings

Publication Reference: Siu K. W., Kwok J. C. M. and Ngan A. H. W. (2020). Thermo-mechanical processing of brass components for potable-water usage increases risks of Pb leaching. Water Res 186: 116414.		
	Exposure concentrations (if applicable)	Pb content in laboratory tests (µg/L) • Untreated: 3.9 – 23.7 • Flame Treated: 7.5 - 535 Pb content after scaling (µg/L) • Untreated: 0.6 – 3.7 • Flame Treated: 1.2 – 82.9
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively coupled plasma (ICP) Note: energy dispersive X-ray analysis (EDX) for metal surfaces
	Water sampling methods (monitoring, surrogates)	Not applicable (water was stagnant)
Results (for each outcome)	Definition of outcome	Effects of mechanical processing and flame treatment
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Statistical variance.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Mechanical milling and polishing that replicate the common processing involved in pipeline installation yield a significant increase in surface lead, and a strong correlation exists between lead leaching and the plastic deformation of the brass surface. • Flame-torch treatment that replicates the common brazing of brass also results in a significant increase in surface lead. • These results indicate that the common thermo-mechanical processing of brass piping components poses a real risk of lead contamination in potable water, and revision in the common protocols for handling lead components may be necessary.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Common thermo-mechanical treatment of brass piping installation may result in increased Pb leaching into water. As this is a Pb leaching study it was not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

St Clair et al. 2016

Publication Reference: St Clair J., Cartier C., Triantafyllidou S., Clark B. and Edwards M. (2016). Long-Term Behavior of Simulated Partial Lead Service Line Replacements. Environ Eng Sci 33(1): 53-64.		
General Information	Date of data extraction	27 June 2023
	Authors	St. Clair, J., Cartier, C., Triantafyllidou, S., Clark, B., and Edwards, M.
	Publication date	Accepted in revised form: October 29, 2015
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	Financial support of the Robert Wood Johnson Foundation (RWJF) under the Public Health Law Research Program
	Possible conflicts of interest	No competing financial interests exist.
Study characteristics	Aim/objectives of study	Long-term impacts of copper:lead galvanic connections on lead release to water were assessed without confounding differences in pipe exposure prehistory or disturbances arising from cutting lead pipe.
	Study type/design	Pb Leach (Pilot) Study
	Study duration	48 months
	Type of water source (if applicable)	Service lines (potable)
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Three lead service line configurations, including (1) 100% lead, (2) traditional partial replacement with 50% copper upstream of 50% lead, and (3) 50% lead upstream of 50% copper as a function of flow rate
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Lead pipes, solder and fittings
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	"ICP-MS"
	Water sampling methods (monitoring, surrogates)	Three sampling methodologies tested
Results (for each outcome)	Definition of outcome	Elevated lead in water
	How outcome was assessed	
	Method of measurement	Not applicable

Publication Reference: St Clair J., Cartier C., Triantafyllidou S., Clark B. and Edwards M. (2016). Long-Term Behavior of Simulated Partial Lead Service Line Replacements. Environ Eng Sci 33(1): 53-64.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Elevated lead from galvanic corrosion worsened with time, with 140% more lead release from configurations representing traditional partial replacement configurations at 14 months compared to earlier data in the first 8 months. • Conditions representing traditional partial service line configurations were significantly worse (~40%) when compared to 100% lead pipe. • 100% of samples collected from traditional partial replacement configurations exceeded thresholds posing an acute health risk versus a 0% risk for samples from 100% lead pipe. • Temporary removal of lead accumulations near Pb:Cu junctions and lead deposits from other downstream plastic pipes reduced risk of partial replacements relative to that observed for 100% lead. • When typical brass compression couplings were used to connect prepassivated lead pipes, lead release spiked up to 10 times higher
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Configurations representative of partial pipe replacements continued to release much more lead than the full-lead service pipe at moderate and high flow rates. This was significant for up to 48 months. As this study does not consider lead toxicity (it is a leaching study) it was not subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Tully et al. 2019

Publication Reference: Tully J., DeSantis M. K. and Schock M. R. (2019). Water quality-pipe deposit relationships in Midwestern lead pipes. AWWA Water Sci 1(2).		
General Information	Date of data extraction	10 July 2023
	Authors	Tully, J., DeSantis, M.K., Schock, M.R.
	Publication date	2019 March 4
	Publication type	Journal article
	Peer reviewed?	Yes

Publication Reference: Tully J., DeSantis M. K. and Schock M. R. (2019). Water quality-pipe deposit relationships in Midwestern lead pipes. AWWA Water Sci 1(2).		
	Country of origin	USA
	Source of funding	Funding support for this project was received through a Regional Applied Research Effort (RARE) program coordinated by Regional Science Liaison Carole Braverman (U.S. EPA Region 5).
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	In this study, model predictions are compared to lead service line (LSL) scales from 22 drinking water distribution systems.
	Study type/design	Pb leaching study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	• For this study, 22 public water systems (PWSs) in EPA's Region 5 supplied at least one lead service lines (LSLs) for analysis at EPA's Advanced Materials and Solids Analysis Research Core (AMSARC) within the National Risk Management Research Laboratory in Cincinnati, OH, and supplied corresponding water quality data representative of water the LSL was in contact with for evaluation. • Of the 22 PWSs participating in this study, 7 were ground water (GW) systems and 15 were surface water (SW) systems. Approximately half of the surface water systems used Lake Michigan as their source. These systems represent a broad, but not random, cross-section of PWSs in Region 5 and utilise different strategies to control corrosion within their drinking water distribution systems (DWDSs)
	Selection criteria for population (if applicable)	
	Subgroups reported	-
	Size of study	22 PWSs
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	-
Study methods	Water quality measurement used	Not applicable. Water quality parameters were collected by EPA. (Scale: Mineralogical analysis: powder X-ray diffraction (XRD), elemental composition by XRD, scanning electron microscopy/energy dispersive spectroscopy (SEM/EDS), Total Carbon/Total Sulfur by combustion (TC/TS), and X-ray Fluorescence (XRF))
	Water sampling methods (monitoring, surrogates)	Not applicable. Water quality parameters were collected by EPA.
Results (for each outcome)	Definition of outcome	Corrosion control effectiveness was evaluated by assessing various water lead concentration results from the PWSs.
	How outcome was assessed	
	Method of measurement	

Publication Reference: Tully J., DeSantis M. K. and Schock M. R. (2019). Water quality-pipe deposit relationships in Midwestern lead pipes. AWWA Water Sci 1(2).		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	22 PWSs
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The results show that only nine of the 22 systems had LSL scales that followed model predictions. • The remaining systems had unpredictable scales some with unknown lead release characteristics demonstrating that predicting scale formation and lead release solely by models cannot be relied on in all cases to protect human health. • Therefore, for many systems with LSLs, pilot studies with existing LSL scales will be necessary to evaluate and optimise corrosion control, and correspondingly, appropriate residential water sampling will be needed to demonstrate consistent and optimal system corrosion control.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Modelling results of Pb leaching from LSLs was inconsistent. Pilot studies and appropriate sampling regimes will be necessary to evaluate Pb leaching and optimise corrosion control. This is a Pb leaching study hence a RoB assessment is not undertaken.
	Notes on study quality, e.g. gaps, methods	

Trueman et al. 2017

Publication Reference: Trueman B. F., Sweet G. A., Harding M. D., Estabrook H., Bishop D. P. and Gagnon G. A. (2017). Galvanic Corrosion of Lead by Iron (Oxyhydr)Oxides: Potential Impacts on Drinking Water Quality. Environ Sci Technol 51(12): 6812-6820.		
General Information	Date of data extraction	07 July 2023
	Authors	Trueman, B.F., Sweet, G.A., Harding, M.D., Estabrook, H., Bishop, D.P., and Gagnon, G.A.
	Publication date	Published: May 30, 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Canada
	Source of funding	This work was funded by the Natural Sciences and Engineering Research Council (NSERC) Industrial Research Chair in Water Quality and Treatment (Grant No. IRCPJ 349838-11).
	Possible conflicts of interest	The authors declare no competing financial interest

Publication Reference: Trueman B. F., Sweet G. A., Harding M. D., Estabrook H., Bishop D. P. and Gagnon G. A. (2017). Galvanic Corrosion of Lead by Iron (Oxyhydr)Oxides: Potential Impacts on Drinking Water Quality. Environ Sci Technol 51(12): 6812-6820.		
Study characteristics	Aim/objectives of study	The goals were 2-fold: (1) to investigate galvanic corrosion of lead by iron oxides in the presence of chemical species that influence lead mobility and (2) to estimate the effect of upstream iron corrosion on lead release using residential field data
	Study type/design	Pb leaching study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	See Figure 1 in study.
	Comparison group(s)	iron distribution main, cement mortar-lined ductile iron
Study methods	Water quality measurement used	Inductively coupled plasma mass spectrometry (ICP-MS) (Note: Identification of the crystalline phases characterising iron-based cathodes and lead anodes was performed using an X-ray diffractometer)
	Water sampling methods (monitoring, surrogates)	Residents collected 5 × 1L sample profiles at single-unit residences before and after full or partial replacement of lead service lines with copper. Profiles were collected following a minimum 6 h standing period, and the final litre was collected after a 5 minute flushing period.
Results (for each outcome)	Definition of outcome	Three factors influencing lead release-humic acid (1.8 mg/L as total organic carbon), orthophosphate (2.0 mg/L as P), and iron (oxyhydr)oxide-were investigated using a two-level full factorial design.
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Statistical comparisons were made using two-tailed rank sum tests on log-transformed data.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Trueman B. F., Sweet G. A., Harding M. D., Estabrook H., Bishop D. P. and Gagnon G. A. (2017). Galvanic Corrosion of Lead by Iron (Oxyhydr)Oxides: Potential Impacts on Drinking Water Quality. Environ Sci Technol 51(12): 6812-6820.		
Author's conclusions	Interpretation of results	• Upstream iron corrosion was a significant determinant of lead release from lead service lines. • Point-of-use lead levels after lead service line replacement were greater by factors of 2.3–4.7 at sites supplied by unlined cast iron water mains compared with the alternative, cement mortar-lined ductile iron. • Elevated lead levels due to iron particles could be addressed by replacing corroded iron distribution mains or by implementing rehabilitation regimes that reduce the likelihood of particle release from iron scale.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Corroded iron distribution mains may also need to be replaced when changing Pb service lines to reduce the possibility of elevated lead. As this is a Pb leaching study it is not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Zahran et al. 2020

Publication Reference: Zahran S., Mushinski D., McElmurry S. P. and Keyes C. (2020). Water lead exposure risk in Flint, Michigan after switchback in water source: Implications for lead service line replacement policy. Environ Res 181: 108928.		
General Information	Date of data extraction	07 July2023
	Authors	Zahrana, S., Mushinskia, D., McElmurry, S.P., Keyes, C.
	Publication date	2021 February 01
	Publication type	Journal article
	Peer reviewed?	No
	Country of origin	US
	Source of funding	Research reported in this publication was supported by the National Institute of Environmental Health Sciences of the National Institutes of Health (NIH) under Award no. R21 ES027199-01.
	Possible conflicts of interest	After being served with a subpoena by the Flint Special Prosecutor, Todd Flood, Dr. McElmurry testified, under oath, at investigatory proceedings and at preliminary examinations brought against two former employees of the Michigan Department of Health and Human Services (MDHHS)
Study characteristics	Aim/objectives of study	In this paper, the authors evaluate the potential lead exposure benefits of service line replacement (SLR) efforts in Flint against optimal corrosion control treatment (OCCT), providing scientific evidence on the potential gains of undertaking such policies nationwide.
	Study type/design	Pb leaching study

Publication Reference: Zahran S., Mushinski D., McElmurry S. P. and Keyes C. (2020). Water lead exposure risk in Flint, Michigan after switchback in water source: Implications for lead service line replacement policy. Environ Res 181: 108928.		
	Study duration	90 weeks
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Wave I: The EPA and MDEQ identified 766 sampling sites to characterise lead exposure risk in the Flint water system. Five rounds of sampling. Wave II: Focused more exclusively on highest-risk residences. 10 rounds of additional sampling.
	Selection criteria for population (if applicable)	
	Subgroups reported	Galvanised service line, Lead service line, water copper (µg/L), Bathroom, Kitchen, Temperature (°F), Main break
	Size of study	Each of the 820 homes sampled over both waves was observed on average 7.94 times, with a range of 1–16 independent water samples.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Lead service lines
	Exposure concentrations (if applicable)	Not stated
	Comparison group(s)	Refer to subgroups
Study methods	Water quality measurement used	Not stated (EPA Method 200.8)
	Water sampling methods (monitoring, surrogates)	Site occupants/residents were trained in how to draw water samples scientifically and in accordance with protocols in the Lead and Copper Rule (LCR), requiring that the first-draw 1 L water sample be collected after 6 h of stagnation or suspension of water use
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not stated (EPA Method 200.8)
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Two sample T-tests, Binary dependent variable panel data techniques, discrete factor model
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Refer to Table 3 and Table 5 of Zharan et al. (2020)

Publication Reference: Zahran S., Mushinski D., McElmurry S. P. and Keyes C. (2020). Water lead exposure risk in Flint, Michigan after switchback in water source: Implications for lead service line replacement policy. Environ Res 181: 108928.		
Author's conclusions	Interpretation of results	• Samples taken from homes with lead service lines were significantly more likely to exceed specified thresholds of water lead (WL) than homes without lead service lines. • Second, regardless of service line material type, sampled homes experienced significant reductions in WL with elapsed time from Flint's switchback to water provided by the Detroit Water and Sewage Department. • Third, the risk of exceedance of WL > 15 µg/L was uncorrelated with service line material type. • At 90 weeks from the switchback in water source, the quantity of water lead consumed by children in homes with lead service lines decreased 93%, as compared to 16 weeks. • Lead exposure benefits of service line replacement have declined in time, with modest differences in lead uptake across homes with different service lines. • In light of results, policy considerations for Flint and nationwide are discussed. • The Flint experience suggests that OCCT techniques are effective in reducing water lead levels, implying that LSL replacement may not be necessary (at least in the short run). • The impact of changes in Flint's water supply – from Detroit water to the Flint River and back to Detroit water – on water lead exposure also suggests that OCCT techniques' ability to reduce water lead content depends on the technical competence of local water authorities. • IEUBK model results also indicate that the risk of child lead exposure in Flint is likely driven by sources other than water, regardless of the period observed. That is, the percent of child blood lead attributable to non-water sources like air and soil/dust is notably larger than water lead sources at both 16 and 90 weeks from Flint's switchback to Detroit water.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Water lead levels decreased in time over the study period in all homes with different service line materials. Replacement of lead service lines may not be cost effective and optimal corrosion control treatment (OCCT) is preferred (if done competently). Lead exposure was greater from non-water sources than from water. This leaching study was not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Zhang et al. 2015

Publication Reference: Zhang Y. and Lin Y. P. (2015). Leaching of lead from new unplasticized polyvinyl chloride (uPVC) pipes into drinking water. Environ Sci Pollut Res Int 22(11): 8405-8411.		
General Information	Date of data extraction	07 July 2023
	Authors	Zhang, Y., Lin, Y.

Publication Reference: Zhang Y. and Lin Y. P. (2015). Leaching of lead from new unplasticized polyvinyl chloride (uPVC) pipes into drinking water. Environ Sci Pollut Res Int 22(11): 8405-8411.

	Publication date	Published online: 25 December 2014
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Singapore/Taiwan
	Source of funding	Financial support from National University of Singapore (R-302-000-049-112) and National Taiwan University (NTU-CDP-103R7877).
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	The effects of various water quality parameters including pH value, temperature, and type of disinfectant on the rate of lead release were examined.
	Study type/design	Pb leaching study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Three uPVC pipes (designated as P1, P2, and P3) with an inner diameter of 25 mm designed for the conveyance of drinking water were purchased locally and used in this study.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	**Pipe Number** **P1** **P2** **P3** % Pb in PVC 1.4 2.8 1.9
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	ICP-MS (Note: Scanning electron microscopy-energy dispersive X-ray spectroscopy (SEM-EDX) was used to determine the elemental composition of the inner surfaces of the pipes).
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Change in water lead levels based on pH value, temperature, and type of disinfectant
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Three pipes

Publication Reference: Zhang Y. and Lin Y. P. (2015). Leaching of lead from new unplasticized polyvinyl chloride (uPVC) pipes into drinking water. Environ Sci Pollut Res Int 22(11): 8405-8411.		
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Lead compounds that are used as the stabiliser in uPVC pipe may be released into drinking water and cause elevated lead levels. • SEM-EDX elemental mapping confirmed the presence of lead on the inner surfaces of locally purchased uPVC pipes. • Stagnant leaching studies showed that lead release increased with increasing exposure time, decreasing pH value, and increasing temperature. • The presence of monochloramine was found to cause faster lead release than that in the presence of free chlorine. • Among the employed pipes, however, the level of lead release was not linked to the weight percentage of lead on the pipe inner surfaces. • Results indicate that precautions on lead contamination should be taken when new uPVC pipes are installed in the premise plumbing system.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	The use of uPVC pipes may result in lead leaching into water with higher concentrations associated with increased exposure time, decreased pH value, and increased temperature. More lead was released when there was chloramine in the water compared to chlorine. This is a Pb leaching study hence was not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

APPENDIX C2 Health Studies

Recent Health-Based Studies for Lead

Dahl et al. 2014

Publication Reference: Dahl C., Søgaard A. J., Tell G. S., Flaten T. P., Hongve D., Omsland T. K., Holvik K., Meyer H. E. and Aamodt G. (2014). Do cadmium, lead, and aluminum in drinking water increase the risk of hip fractures? A NOREPOS study. Biol Trace Elem Res 157(1): 14-23.		
General Information	Date of data extraction	27 June 2023
	Authors	Dahl, C., Søgaard, A.J., Tell, G.S., Flaten, T.P., Hongve, D., Omsland, T.K., Holvik, K., Meyer, H.E., Aamodt, G.
	Publication date	Published online: 29 November 2013
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Norway
	Source of funding	This study was supported by grants from the Research Council of Norway.
	Possible conflicts of interest	Professor Tell did not report receiving fees, honoraria, grants, or consultancies. Department of Global Public Health and Primary Care is, however, involved in studies with funding from a pharmaceutical company as a research grant to (and administered by) the University of Bergen. This study has no relation to the present study. All other authors declare that they do not have any financial conflicts of interest.
Study characteristics	Aim/objectives of study	The aim of this study was to investigate relations between cadmium, lead, and aluminium in municipality drinking water and the incidence of hip fractures in the Norwegian population.
	Study type/design	Cohort study
	Study duration	1994-2000 (6 years) plus a follow-up period between 3 and 14 years
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Norwegian Epidemiologic Osteoporosis Study (NOREPOS) Core Research Group
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	~19,000 men and women
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Drinking water
	Exposure concentrations (if applicable)	The average concentration of lead was 1.16 µg/L (range, 0.04–23.80).
	Comparison group(s)	Low and high (water concentration) groups

Publication Reference: Dahl C., Søgaard A. J., Tell G. S., Flaten T. P., Hongve D., Omsland T. K., Holvik K., Meyer H. E. and Aamodt G. (2014). Do cadmium, lead, and aluminum in drinking water increase the risk of hip fractures? A NOREPOS study. Biol Trace Elem Res 157(1): 14-23.		
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Incident hip fractures were identified and retrieved from all hospitalisation records
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	5,438 men and 13,629 women aged 50–85 years who suffered a hip fracture.
Statistics (if any)	Statistical method used	Poisson regression models were fitted, adjusting for age, region of residence, urbanisation, and type of water source as well as other possibly bone-related water quality factors. Effect modification by background variables and interactions between water quality factors were examined (correcting for false discovery rate).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	The association between relatively high lead and hip fracture risk was significant in the oldest age group (66–85 years) for both men (IRR=1.11; 95 % CI 1.02, 1.21) and women (IRR=1.10; 95 % CI 1.04, 1.16).
Author's conclusions	Interpretation of results	In summary, a relatively high concentration of cadmium, lead, and aluminium measured in drinking water increased the risk of hip fractures, but the associations depended on gender, age, and urbanisation degree.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Elevated lead in drinking water may result in increased incidence of hip fracture in 66–85 years for men and woman however a dose response relationship cannot be established from the information in the study. For this reason, a RoB assessment was not undertaken for this study.
	Notes on study quality, e.g. gaps, methods	

Danziger et al. 2021

Publication Reference: Danziger J., Mukamal K. J. and Weinhandl E. (2021). Associations of Community Water Lead Concentrations with Hemoglobin Concentrations and Erythropoietin-Stimulating Agent Use among Patients with Advanced CKD. J Am Soc Nephrol 32(10): 2425-2434.		
General Information	Date of data extraction	23/06/2023
	Authors	Danziger, J., Mukamal, K.J., Weinhandl, E.
	Publication date	Accepted March 21, 2021
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA

Publication Reference: Danziger J., Mukamal K. J. and Weinhandl E. (2021). Associations of Community Water Lead Concentrations with Hemoglobin Concentrations and Erythropoietin-Stimulating Agent Use among Patients with Advanced CKD. J Am Soc Nephrol 32(10): 2425-2434.		
	Source of funding	None
	Possible conflicts of interest	• D. Weinhandl reports having consultancy agreements with Fresenius Medical Care North America; reports being a scientific advisor or member of the Advisory Board of Home Dialyzors United, Board of Directors member of Medical Education Institute; and reports having other interests/relationships as member of the Scientific Methods Panel for the National Quality Forum. • J. Danziger reports having other interests/relationships as former Medical Director of NxStage Boston South Dialysis Unit, and ongoing medical legal consulting. • K.J. Mukamal reports having other interests/relationships with the US Highbush Blueberry Council and Wolters Kluwer.
Study characteristics	Aim/objectives of study	To investigate associations of lead in community water systems with haemoglobin concentrations and erythropoietin stimulating agent (ESA) use among incident patients with End-stage kidney disease (ESKD)
	Study type/design	Cross-sectional
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Using data from the United States Renal Data System (USRDS), the national registry of patients with ESKD, we identified all incident patients with ESKD who initiated dialysis between January 1, 2005 and December 31, 2017. Water systems from eight states that did not describe geographic service area by city were excluded, as were those with implausible lead levels (>100-fold more than the EPA-actionable level, >1.5 mg/L, n=60).
	Selection criteria for population (if applicable)	
	Subgroups reported	Five categories for lead in Community Water (mg/L) defined as follows: • <0.001 mg/L • 0.001 to <0.00375 mg/L • 0.00375 to <0.0075 mg/L • 0.0075 to <0.015 mg/L • ≥0.015 mg/L
	Size of study	Authors linked the USRDS and EPA's Safe Drinking Water Information System (SDWIS) datasets by city and state to create a complete dataset of 597,968 incident patients with ESKD residing in 9566 cities serviced by 21,113 water systems. CROWNWeb data were available for 208,912 patients.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	See subgroups

Publication Reference: Danziger J., Mukamal K. J. and Weinhandl E. (2021). Associations of Community Water Lead Concentrations with Hemoglobin Concentrations and Erythropoietin-Stimulating Agent Use among Patients with Advanced CKD. J Am Soc Nephrol 32(10): 2425-2434.		
	Comparison group(s)	<0.001 mg/L
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	The primary outcomes were pre-ESKD haemoglobin concentration (recorded up to 45 days before dialysis initiation) and pre-ESKD Erythropoietin stimulating agent (ESA) use, as recorded on the ESKD Medical Evidence Report. To account for the effect of pre-ESKD ESA use on haemoglobin, authors also examined corrected haemoglobin concentration, which was set by subtracting a fixed decrement of 2 g/dL from the observed haemoglobin concentration in ESA users. Secondarily, we examined uncorrected and corrected haemoglobin concentration and ESA use during the first month of dialysis; authors set corrected haemoglobin concentration analogously.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	597,968 patients across the United States who began dialysis between 2005 and 2017
Statistics (if any)	Statistical method used	In all models, authors assessed two parameterisations of lead levels: in five categories defined by breakpoints of <0.001 mg/L and at 25%, 50%, and 100% of the EPA-actionable lead level at the time (0.015 mg/L); as a cubic polynomial, with lead levels winsorized at 0.1 mg/L to limit the influence of outlying values on the shape of the association. In all regressions, the authors clustered by the combination of dialysis facility and year of dialysis initiation. Analyses were performed using JMP Pro and SAS (Cary, NC).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	0.001-<0.0037 0.0037-<0.0075 0.0075-<0.015 ≥0.015 Adjusted difference in pre-ESKD haemoglobin (H) concentration • H -0.02 -0.007 -0.05 -0.04 g/dL • Corrected -0.002 -0.01 -0.05 -0.09 g/dL Adjusted difference in haemoglobin concentrations during the first month of dialysis • H -0.04 -0.06 -0.12 -0.14 g/dL • Corrected -0.05 -0.04 -0.13 -0.14 g/dL Adjusted difference in ESA use • Pre-ESKD ESA use -0.3% 0.2% 0.04% 1.9% 0.4% • During first month 0.3% -0.5% 1.2% 0.8% 0.3%

Publication Reference: Danziger J., Mukamal K. J. and Weinhandl E. (2021). Associations of Community Water Lead Concentrations with Hemoglobin Concentrations and Erythropoietin-Stimulating Agent Use among Patients with Advanced CKD. J Am Soc Nephrol 32(10): 2425-2434.		
Author's conclusions	Interpretation of results	• Among 597,968 patients initiating dialysis in the United States in 2005 through 2017 those in cities with detectable lead levels in community water had significantly lower pre-ESKD haemoglobin concentrations and more ESA use per 0.01 mg/L increase in 90th percentile water lead. • Findings were similar for the 208,912 patients with data from the first month of ESKD therapy, with lower haemoglobin and higher ESA use per 0.01 mg/L higher lead concentration. • These associations were observed at lead levels below the EPA threshold (0.015 mg/L) that mandates regulatory action. • Authors also observed environmental inequities, finding significantly higher water lead levels and slower declines over time among Black versus White patients. • This first nationwide analysis linking EPA water supply records to patient data shows that even low levels of lead that are commonly encountered in community water systems throughout the United States are associated with lower haemoglobin levels and higher ESA use among patients with advanced kidney disease.
	Assessment of uncertainty (if any)	Covariates considered: Patient pre-ESKD characteristics included age, sex, race (white, Black, Asian, other/unknown), body mass index, eGFR (as calculated by the Modification in Diet in Renal Disease four-factor equation), insurance, and employment status, all at the time of ESKD onset, and the presence of diabetes mellitus, heart failure, hypertension, cancer, or tobacco use at any time during the 10 years before ESKD onset. Levels of air quality, as estimated by measures of fine particulate matter between 2003 and 2011 in outdoor air. Could not account for how much water an individual drank, the use of bottled or filtered water, and the length of primary residence. In addition, averaging the level of exposure for all residents in cities with multiple water systems likely introduces misclassification, although estimates were consistent in cities with only one water system and when restricted to larger water systems. Levels of lead in the blood would help clarify the risk of lead toxicity associated with water exposure, but have not been widely measured in the ESKD population
Reviewer comments	Results included/excluded in review (if applicable)	Lead levels in drinking water below 0.015 mg/L may be associated with lower haemoglobin levels and higher erythropoietin stimulating agent (ESA) use among patients with End-stage kidney disease (ESKD), with a 0.02 g/dL (95% confidence interval [95% CI], 0.01 to 0.02) lower haemoglobin concentration for each 0.01 mg/L increment in community water lead. A 0.01 mg/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. As this study is a health study (cohort) it was subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Danziger et al. 2022

Publication Reference: Danziger J. and Mukamal K. J. (2022). Levels of Lead in Residential Drinking Water and Iron Deficiency among Patients with End Stage Kidney Disease. Kidney360 3(7): 1210-1216.		
General Information	Date of data extraction	23 July 2023
	Authors	Danziger, J., and Mukamal, K.J.
	Publication date	July, 2022
	Publication type	Journal article
	Peer reviewed?	Yes.
	Country of origin	USA
	Source of funding	None
	Possible conflicts of interest	J. Danziger reports consultancy for Healthmap Solutions; ownership interest in Healthmap Solutions; and is the regional medical director at Healthmap Solutions. K.J. Mukamal reports other interests or relationships with US Highbush Blueberry Council and Wolters Kluwer.
Study characteristics	Aim/objectives of study	Examine whether municipal 90th percentile drinking water lead levels associate with iron deficiency among incident dialysis patients.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Using data from the United States Renal Data System (USRDS), the national registry of patients with ESKD, authors identified all patients who initiated dialysis between 2012 and 2017
	Selection criteria for population (if applicable)	
	Subgroups reported	Five categories for lead in Community Water (mg/L) defined as follows: • <0.001 mg/L • 0.001 to <0.00375 mg/L • 0.00375 to <0.0075 mg/L • 0.0075 to <0.015 mg/L • ≥0.015 mg/L
	Size of study	143,754 incident ESKD patients
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	See subgroups
	Comparison group(s)	<0.001 mg/L
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable (lead results from municipal utility water system)

<table>
<tr><td colspan="3">***Publication Reference:*** Danziger J. and Mukamal K. J. (2022). Levels of Lead in Residential Drinking Water and Iron Deficiency among Patients with End Stage Kidney Disease. Kidney360 3(7): 1210-1216.</td></tr>
<tr><td rowspan="4">Results (for each outcome)</td><td>Definition of outcome</td><td rowspan="2">Outcomes, including transferrin saturation <10% and <20%, ferritin <100 and <200 ng/mL, and simultaneous transferrin saturation <20% and ferritin <200 ng/mL.</td></tr>
<tr><td>How outcome was assessed</td></tr>
<tr><td>Method of measurement</td><td>Not applicable</td></tr>
<tr><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>143,754 incident ESKD patients</td></tr>
<tr><td rowspan="3">Statistics
(if any)</td><td>Statistical method used</td><td>Authors used logistic regression, including all patient characteristics and socioeconomic factors, to examine the adjusted association of city-wide lead levels with thresholds of iron deficiency.</td></tr>
<tr><td>Details on statistical analysis</td><td>Authors explored the significance of multiplicative interactions between race (Black versus non-Black, excluding those with missing race categorisation) and detectable drinking water lead and provide the stratified results. They also explored whether results differed according to pre ESKD ESA use or nephrology care, haemoglobin concentrations (pre-ESKD), and household income.</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>Adjusted association of residential water systems lead concentration (mg/L) and iron deficiency among patients starting dialysis
<table>
<tr><th></th><th><0.001</th><th>0.001-
<0.0037</th><th>0.0037-
<0.0075</th><th>0.0075-
<0.015</th><th>≥0.015</th></tr>
<tr><td>Transferrin <10%</td><td></td><td>1.02</td><td>1.01</td><td>1.02</td><td>1.08</td></tr>
<tr><td>Transferrin <20%</td><td></td><td>**1.07***</td><td>1.04</td><td>**1.05***</td><td>**1.09***</td></tr>
<tr><td>Ferritin 100ng/mL</td><td></td><td>**1.07***</td><td>**1.09***</td><td>0.97</td><td>1.08</td></tr>
<tr><td>Ferritin 200ng/mlL</td><td></td><td>**1.07***</td><td>**1.07***</td><td>0.99</td><td>1.09</td></tr>
<tr><td>Simultaneous</td><td></td><td>**1.1***</td><td>1.04</td><td>1.01</td><td>1.12</td></tr>
</table>
Bolded values with Asterix (*) had CI ranging from >1 hence associations are statistically significant.</td></tr>
<tr><td>Author's conclusions</td><td>Interpretation of results</td><td>• Those in cities with drinking water lead contamination had 1.06 (95% CI, 1.03 to 1.09), 1.06 (95% CI, 1.02 to 1.10), and 1.07 (95% CI, 1.03 to 1.11) higher adjusted odds of a transferrin saturation <20%, ferritin <200 ng/mL, and simultaneous transferrin saturation <20% and ferritin <200 ng/mL, respectively. These associations were apparent across the range of lead levels found commonly in the United States and were significantly greater among Black patients (multiplicative interaction P values between lead and race <0.05).
• Even exposure to low levels of lead contamination, as commonly found in US drinking water, may have adverse hematologic consequence in patients with advanced kidney disease.</td></tr>
</table>

Publication Reference: Danziger J. and Mukamal K. J. (2022). Levels of Lead in Residential Drinking Water and Iron Deficiency among Patients with End Stage Kidney Disease. Kidney360 3(7): 1210-1216.		
	Assessment of uncertainty (if any)	Without individual patient dietary practices, including use of tap versus bottled water, direct assay of water lead content, and residential stability, lead exposure cannot be accurately adjudicated. Further studies with direct measurement of household water are needed. Although authors could not accurately characterise determinants likely to affect iron metabolism, including iron supplementation, underlying inflammation, nutrition, and a range of other disease states, the overall levels of comorbidity burden, pre-ESKD care, and ESA use were generally similar across strata of lead exposure. In addition, given no standard definition of iron deficiency in patients with kidney disease and competing pathophysiologic forces that modify iron storage and handling, misclassification is possible.
Reviewer comments	Results included/excluded in review (if applicable)	Statistically significant relationships were identified between lead concentration in water and iron deficiency. However, the association/effect did not increase with increasing concentrations (i.e. there was not a dose response established) and the association is unclear. This study was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Dave and Yang 2022

Publication Reference: Dave D. M. and Yang M. (2022). Lead in drinking water and birth outcomes: A tale of two water treatment plants. J Health Econ 84: 102644.		
General Information	Date of data extraction	27 June 2023
	Authors	Dave, D.M., and Yang, M.
	Publication date	Available online 27 May 2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	The authors declare that they have no relevant material or financial interests that relate to the research described in this paper.
	Possible conflicts of interest	The authors declare that they have no relevant material or financial interests that relate to the research described in this paper.
Study characteristics	Aim/objectives of study	Using data on the exact home addresses of pregnant women residing in the city of Newark, New Jersey combined with information on the spatial boundary separating areas within the city serviced by two water treatment plants, the authors exploit an exogenous change in water chemistry that resulted in lead leaching into the tap water of one plant's service area, but not the other's, to identify a causal effect of prenatal lead exposure on foetal health.
	Study type/design	Cohort study

Publication Reference: Dave D. M. and Yang M. (2022). Lead in drinking water and birth outcomes: A tale of two water treatment plants. J Health Econ 84: 102644.		
	Study duration	Using data on all live births in New Jersey between 2011 and 2019.
	Type of water source (if applicable)	Drinking water (tap water) affected by lead leaching from lead pipes due to ineffective use of corrosion inhibitor.
Population characteristics	Population/s studied	Authors use the restricted version of the birth certificate data from the New Jersey Department of Health (NJDOH) for this study. The data include all live births that occurred in New Jersey between 2011 and 2019. In addition to the information typically reported in vital statistics data, such as birth outcomes and mothers' demographic characteristics, which are publicly available through, for example, the U.S. National Center for Health Statistics (NCHS), the NJDOH data they obtained contains information on mothers' home addresses, geocoded by latitudes and longitudes.
	Selection criteria for population (if applicable)	
	Subgroups reported	Pequannock (treated) and Wanaque (control) service areas.
	Size of study	There are 838,337 singleton live births in New Jersey over the analysis period, with 36,173 singleton live births occurring in Newark between 2011 and 2019.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Drinking water
	Exposure concentrations (if applicable)	Up to 30 µg/L
	Comparison group(s)	Wanaque (control) service area. Authors define birth years 2011–2015 as the pre-treatment period and birth years 2016–2019 as the post-treatment period. Prior to 2016, tests from both service areas indicated <10% of samples tested >15 µg/L. However, after 2016, there was a significant run-up in lead in tap water sampled from residences in the Pequannock service area.
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	Effects of prenatal exposure to lead on birth outcomes (Low birth weight, Preterm length, Birth weight, Gestational length)
	How outcome was assessed	
	Method of measurement	Data are from the New Jersey birth records on all live births collected by the New Jersey Department of Health.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	The numbers of observations are: • 5,497 (Control Pre 2011-2015) • 2,132 (Control Post 2016-2017) • 4,190 (Control Post 2016-2019) • 13,489 (Treatment Pre 2011-2015) • 4,987 (Treatment Post 2016-2017) • 10,171 (Treatment Post 2016-2017) • 33,347 (Full sample, 2011-2019).
Statistics	Statistical method used	

Publication Reference: Dave D. M. and Yang M. (2022). Lead in drinking water and birth outcomes: A tale of two water treatment plants. J Health Econ 84: 102644.

(if any)	Details on statistical analysis	Authors employ a generalised difference-in-differences (DID) research design to identify causal effects of exposure to lead in drinking water —the "treatment "—on foetal health.
	Relative risk/odds ratio, confidence interval?	No RR calculated. Used an unconventional DID approach to estimate effect size. Difficult to interpret.
Author's conclusions	Interpretation of results	• Authors found robust evidence that the increased *in utero* exposure to lead through water contamination in Newark significantly increased the prevalence of infants being born with low birth weight or preterm. There is little evidence to suggest that these effects are driven by selection into births. • The authors' estimates indicate an approximately 1.5 percentage point (or 18%) increase in the likelihood of low birth weight, and an approximately 1.9 percentage point (or 19%) increase in likelihood of a preterm birth associated with 'treatment' in which lead concentrations at the tap in drinking water exceeded 15 µg/L ~30% of the time. • Authors indicate this findings has important policy implications in light of the substantial number of lead water pipes that remain in use as part of the ageing infrastructure and the cost-benefit calculus of lead abatement interventions.
	Assessment of uncertainty (if any)	The estimates were derived from a city composed of a population of lower socioeconomic status compared to the USA as a whole (or even an average similarly-sized city), therefore the effects may not necessarily generalise due to variation in media exposure, information processing and mitigation behaviours.
Reviewer comments	Results included/excluded in review (if applicable)	The study authors conclude increased likelihood of low birth weight and preterm births in children born in years in which lead concentrations in tap water were greater than the US EPA MCL at the time of 15 µg/L. The statistical analysis approach, i.e. difference in differences approach, used in the study renders the results difficult to interpret and confirm. The study was subjected to RoB analysis.
	Notes on study quality, e.g. gaps, methods	

De Almeida Lopes et al. 2017

Publication Reference: Almeida Lopes A. C. B., Silbergeld E. K., Navas-Acien A., Zamoiski R., Martins A. D. C., Jr., Camargo A. E. I., Urbano M. R., Mesas A. E. and Paoliello M. M. B. (2017). Association between blood lead and blood pressure: a population-based study in Brazilian adults. Environ Health 16(1): 27.

General Information	Date of data extraction	22/06/2023
	Authors	de Almeida Lopes, A.C.B., Silbergeld, E.K., Navas-Acien, A., Zamoiski, R., da Cunha Martins, A. Jr., Camargo, A.E.I., Urbano, M.R., Mesas, A.E., and Paoliello, M.M.B.
	Publication date	Published online: 14 March 2017
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Brazil

Publication Reference: Almeida Lopes A. C. B., Silbergeld E. K., Navas-Acien A., Zamoiski R., Martins A. D. C., Jr., Camargo A. E. I., Urbano M. R., Mesas A. E. and Paoliello M. M. B. (2017). Association between blood lead and blood pressure: a population-based study in Brazilian adults. Environ Health 16(1): 27.		
	Source of funding	This work was supported by the Coordination for the Improvement of Higher Level or Education Personnel (CAPES), through the Ministry of Health, Brazil.
	Possible conflicts of interest	Authors declare they have no actual or potential competing financial interests.
Study characteristics	Aim/objectives of study	The goal of this study was to examine the association of blood lead levels (BLL) with blood pressure and hypertension in a population-based study in a city in Southern Brazil.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied Selection criteria for population (if applicable)	• The study population included adults aged 40 years or older who were residents in an urban area in southern Brazil. • The study had a census-based design, using data from the Population Count 2007, when the city of Cambé had a total of 92,888 people, of whom 30,710 (33.1%) were aged 40 or older (46% men and 54% women). • A total of 1180 (88.3%) of the selected persons completed the interview and 959 (81.3%) performed blood collection. For the present analysis, authors used data from 948 subjects who participated in the interviews, who had performed blood tests and had blood pressure measurements.
	Subgroups reported	Quartile 1 (≤1.32 µg/dL), Quartile 2 (1.32–1.93 µg/dL), Quartile 3 (1.93–2.76 µg/dL), and Quartile 4 (>2.76 µg/dL)
	Size of study	• A total of 92,888 people, of whom 30,710 (33.1%) were aged 40 or older. • A total of 1180 (88.3%) of the selected persons completed the interview and 959 (81.3%) performed blood collection
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable. Note: • The geometric mean of BLL was 1.97 µg/dL (95%CI:1.90-2.04 µg/dL). • Range in BLL = 0.46 – 45.62 µg/dL • Participants currently or formerly employed in lead industries had higher blood lead levels (2.65 µg/dL; 95% CI, 2.31–3.05) than those not employed
	Comparison group(s)	Lowest quartile (Quartile 1)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable

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Results (for each outcome)	Definition of outcome	• Change in blood pressure outcomes (increased systolic and diastolic blood pressures, hypertension) with BLLs • Dietary, lifestyle and occupational background was obtained by administered household interviews. • Systolic blood pressure (SBP, <140 mm Hg and ≥140 mm Hg) and diastolic blood pressure (DBP, <90 mm Hg and ≥90 mm Hg) were measured according to the guidelines VI Brazilian Guidelines on Hypertension.
	How outcome was assessed	
	Method of measurement	• BLL were measured by inductively coupled plasma mass spectrometry technique
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• 948 adults, aged 40 years or older. • Eleven participants (of 959 with blood results) had missing information on blood pressure and were excluded from this analysis.
Statistics (if any)	Statistical method used	For statistical analysis authors used the software Stata to perform descriptive and inferential statistical tests. BLL were left skewed and log transformed for analysis. Outcome variables, systolic and diastolic blood pressures were, respectively, inverse and log transformed to follow normal distribution. Multiple linear regression models were performed to examine associations of BLL with systolic and diastolic blood pressures comparing those participants in quartiles 2 to 4 of BLL with those in quartile 1. Multiple logistic regression analysis was used to evaluate the risk of hypertension also by categorising BLL in quartiles. They also performed Pearson correlation analysis to verify the correlations between systolic and diastolic blood pressure with blood lead levels. Regression models were constructed based on *a priori* knowledge and biologic association with blood pressure (age, sex, antihypertensive medication use and blood lead log transformed). Other covariates were added to the model in two separated blocks: Model 1 – sex, age, race, income, education, antihypertensive medication and blood lead level; Model 2 – model 1 + total cholesterol, triglycerides, glycemia, smoking, alcohol consumption and body mass index. A third model was further adjusted for occupation status. Additionally, they performed regression analyses with only the subgroup that was not taking antihypertensive medication to elucidate if they would find significant changes in results. After running each model, the distribution of the residuals was tested for normality. Statistical tests with p value < .05 were considered statistically significant.
	Details on statistical analysis	

Publication Reference: Almeida Lopes A. C. B., Silbergeld E. K., Navas-Acien A., Zamoiski R., Martins A. D. C., Jr., Camargo A. E. I., Urbano M. R., Mesas A. E. and Paoliello M. M. B. (2017). Association between blood lead and blood pressure: a population-based study in Brazilian adults. Environ Health 16(1): 27.

	Relative risk/odds ratio, confidence interval?	Change (95% CI) diastolic blood pressure by blood lead levels (µg/dL) • Quartile — Model 1 — Model 2 • Q2 (1.32–1.93) — 0.04 (0.01–0.05) — 0.03 (0.01–0.05) • Q3 (1.93–2.76) — 0.03 (0.01–0.06) — 0.02 (0.00–0.05) • Q4 (>2.76) — 0.07 (0.04–0.09) — 0.06 (0.04–0.09) (Note: No change in systolic blood pressure) OR (95% CI) of hypertension by blood lead quartiles (µg/dL) • Quartile — Model 1 — Model 2 • Q2 (1.32–1.93) — 0.22 (0.02–2.97) — 0.11 (0.01–1.59) • Q3 (1.93–2.76) — 0.58 (0.42–8.22) — 0.40 (0.02–6.87) • Q4 (>2.76) — **2.28 (1.12–4.66)** — **2.54 (1.17–5.53)** • 90th – 10th %ile — **2.62 (1.40–4.91)** — **2.77 (1.41–5.46)**
Author's conclusions	Interpretation of results	• Of the 948 participants in the sample, 519 (54.7%) were classified as hypertensive. • Participants in the Q4 of blood lead presented 0.06 mmHg (95%CI, 0.04-0.09) average difference in DBP comparing with those in Q1. • Participants in the 90th percentile of blood lead distribution had 0.07 mmHg (95% CI, 0.03 to 0.11) higher DBP compared with those participants in the 10th percentile of blood lead. • The adjusted OR for hypertension was 2.54 (95% CI, 1.17-5.53), comparing the highest to the lowest blood lead quartiles. • Compared with participants in the 10th percentile of blood lead, participants in the 90th percentile presented higher OR for hypertension (OR: 2.77; 95% CI, 1.41 to 5.46). • At low concentrations, BLL were positively associated with DBP and with the odds for hypertension in adults aged 40 or older. • It is important to enforce lead exposure monitoring and the enactment of regulatory laws to prevent lead contamination in urban settings.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	A positive association was identified between BLL in the highest quartile and diastolic blood pressure and a significant association of BLL 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) had BLL of >2.76 µg/dL and that the maximum BLL was 45.62 µg/dL. It would have been ideal if there were five BLL ranges (i.e. quintiles) to see whether significant associations for hypertension were identified with BLL between 2.76 – 5 µg/dL. As this study is a health study (cross-sectional) it was subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Domeneh et al. 2014

Publication Reference: Domeneh B. H., Tavakoli N. and Jafari N. (2014). Blood lead level in opium dependents and its association with anemia: A cross-sectional study from the capital of Iran. J Res Med Sci 19(10): 939-943.		
General Information	Date of data extraction	23/06/2023
	Authors	Domeneh, B.H., Tavakoli, N., Jafari, N.
	Publication date	Accepted: 05-03-2014
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Iran
	Source of funding	Nil
	Possible conflicts of interest	None declared.
Study characteristics	Aim/objectives of study	The aim of this study is to investigate the blood lead level (BLL) in oral and inhalational opium dependents and its association with anaemia.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Opium dependent patients who were referred to five large detoxification centres in Tehran city. Between January 2009 and February 2010, all referral opium-dependent patients were examined and participants who met the inclusion criteria were enrolled.
	Selection criteria for population (if applicable)	
	Subgroups reported	Oral opium dependent group and inhalation opium dependent group amongst opium dependent patients.
	Size of study	134
Exposure and setting	Exposure pathway	Oral and inhalation
	Source of chemical/contamination	Opium
	Exposure concentrations (if applicable)	Not applicable (Note: BLL measured)
	Comparison group(s)	Healthy control group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	BLL compared in three groups (two subgroups and controls).
	How outcome was assessed	

Publication Reference: Domeneh B. H., Tavakoli N. and Jafari N. (2014). Blood lead level in opium dependents and its association with anemia: A cross-sectional study from the capital of Iran. J Res Med Sci 19(10): 939-943.		
	Method of measurement	For the measurement of BLL, 5 mL of blood was obtained from the antecubital vein and was collected in heparinised lead-free tubes. BLL of participants was measured using graphite furnace atomic absorption spectrometry technique. The results were obtained as µg/dL. Haemoglobin and haematocrit of the participants were assessed using a coulter AcT Diff Hematology Analyzer
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	86 opium dependent patients who were referred to five large detoxification centres in Tehran city and 48 healthy individuals. Eligibility criteria included diagnosis of opium dependence based on diagnostic and statistical manual of mental disorder-IV criteria for at least 6 months, age more than 18 years and consenting to participate. Persons working in mines or manufacturing industries with lead exposure, such as battery factories, foundries, wire factories or working with batteries, solder, ammunitions, paint, car radiators, cable, wires, and ceramic with lead glazes were excluded. Control group was selected among healthy participants from five pre-marriage consultation centres in Tehran city near the detoxification centres. Participants who had no history of opium dependence and lead exposure with negative urine morphine test were included in the control group. Forty-seven participants consented to participate and were recruited for the control group.
Statistics (if any)	Statistical method used	Multivariate analysis of variance was used to compare the mean of BLL and other haematologic factors in three groups (oral opium dependent, inhalational opium dependent and healthy individuals). A post-hoc (LSD) analysis was then used to analyse differences between groups. Binary logistic regression analysis was applied to assess the predictors of anaemia. Anaemia was defined as by the World Health Organization (WHO) (haemoglobin ≤12 g/dL for women, ≤13 g/dL for men). Considering the presence of anaemia as the dependent variable, the independent (predictor) variables were entered in the model, starting from the age of participants and followed by the BLL and opium dependence. The level of significance was set at P < 0.05 and all tests were two-tailed. The analysis of data was performed by the predictive analytic software (PASW Statistics 18) for Windows.
	Details on statistical analysis	

<table>
<tr><td colspan="3"><i>Publication Reference:</i> Domeneh B. H., Tavakoli N. and Jafari N. (2014). Blood lead level in opium dependents and its association with anemia: A cross-sectional study from the capital of Iran. J Res Med Sci 19(10): 939-943.</td></tr>
<tr><td></td><td>Relative risk/odds ratio, confidence interval?</td><td>Mean of lead level (µg/dL)
<table>
<tr><th>Group</th><th>Mean</th><th>SD</th><th>Mean difference</th><th>P value</th></tr>
<tr><td>Oral-opium</td><td>11.75</td><td>6.06</td><td>5.70</td><td><0.001</td></tr>
<tr><td>Control group</td><td>6.05</td><td>1.83</td><td>1.02</td><td>0.235</td></tr>
<tr><td>Inhalational</td><td>7.07</td><td>3.61</td><td></td><td></td></tr>
</table>
Frequency of anaemia
<table>
<tr><th>Group</th><th>With anaemia</th><th>Without Anaemia</th><th>P value</th></tr>
<tr><td>Oral-opium</td><td>38%</td><td>62%</td><td>0.001</td></tr>
<tr><td>Control group</td><td>0%</td><td>100%</td><td></td></tr>
<tr><td>Inhalational</td><td>43%</td><td>57%</td><td></td></tr>
</table>
Logistic regression analysis for variables predicting anaemia
<table>
<tr><th>Predictors</th><th>β</th><th>SE</th><th>OR</th><th>CI</th><th>P value</th></tr>
<tr><td>Age</td><td>0.056</td><td>0.015</td><td>1.06</td><td>1.03-1.09</td><td><0.001</td></tr>
<tr><td>Opium dependant</td><td>1.277</td><td>0.383</td><td>3.59</td><td>1.69-7.59</td><td><0.001</td></tr>
<tr><td>BLL</td><td>0.026</td><td>0.046</td><td>1.026</td><td>0.93-1.12</td><td>0.067</td></tr>
</table></td></tr>
<tr><td rowspan="2">Author's conclusions</td><td>Interpretation of results</td><td>• The highest BLL was detected in oral opium dependent group (mean = 11.75, standard deviation (SD) = 6.06) in comparison to inhalational opium dependent group (mean = 7.07, SD = 3.61) and healthy control group (mean = 6.05, SD = 1.83).
• Anaemia was detected in 38% of oral-opium dependent and 43% of inhalational-opium dependent group.
• Age (odds ratio (OR): 1.06, 95% confidence interval (CI): 1.03-1.09) and opium dependence (OR: 3.59, 95% CI: 1.69-7.59), but not BLL, were significant predictors of anaemia in these patients (P < 0.001).</td></tr>
<tr><td>Assessment of uncertainty (if any)</td><td>-</td></tr>
<tr><td rowspan="2">Reviewer comments</td><td>Results included/excluded in review (if applicable)</td><td rowspan="2">Higher BLL were observed in opium dependents (oral, mean = 11.75 µg/dL) compared to the control group (mean = 6.05 µg/dL). It is noted however that BLL was not correlated with anaemia (1.026, 95% CI 0.93-1.12).
It is also noted that BLL in the control group was relatively high (6.05 µg/dL).
As this study is a health study (cross-sectional) it was subject to RoB assessment.</td></tr>
<tr><td>Notes on study quality, e.g. gaps, methods</td></tr>
</table>

Sanders et al. 2014

<table>
<tr><td colspan="3"><i>Publication Reference:</i> Sanders A. P., Desrosiers T. A., Warren J. L., Herring A. H., Enright D., Olshan A. F., Meyer R. E. and Fry R. C. (2014). Association between arsenic, cadmium, manganese, and lead levels in private wells and birth defects prevalence in North Carolina: a semi-ecologic study. BMC Public Health 14: 955.</td></tr>
<tr><td rowspan="2">General Information</td><td>Date of data extraction</td><td>22/06/2023</td></tr>
<tr><td>Authors</td><td>Sanders, A.P., Desrosiers, T.A., Warren, J.L., Herring, A.H., Enright, D., Olshan, A.F., Meyer, R.E. and Fry, R.C.</td></tr>
</table>

Publication Reference: Sanders A. P., Desrosiers T. A., Warren J. L., Herring A. H., Enright D., Olshan A. F., Meyer R. E. and Fry R. C. (2014). Association between arsenic, cadmium, manganese, and lead levels in private wells and birth defects prevalence in North Carolina: a semi-ecologic study. BMC Public Health 14: 955.

	Publication date	2014
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	This research was funded by grants from the NIEHS (T32-ES007018, P42-ES005948-18, P30-ES010126, and R01-ES019315).
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	To assess the association between metal concentrations in private well water and birth defect prevalence in North Carolina.
	Study type/design	Ecological study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	20,151 infants born between 2003 and 2008 with selected birth defects (cases) identified by the North Carolina Birth Defects Monitoring Program, and 668,381 non-malformed infants (controls).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	24,704 infants with birth defects (cases) and 725,690 non-malformed controls in North Carolina.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not stated
	Exposure concentrations (if applicable)	The range of average tract levels (well water) was 2.5 to 1304.2 ppb (µg/L) for lead.
	Comparison group(s)	668,381 non-malformed infants (controls).
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
	Definition of outcome	

Publication Reference: Sanders A. P., Desrosiers T. A., Warren J. L., Herring A. H., Enright D., Olshan A. F., Meyer R. E. and Fry R. C. (2014). Association between arsenic, cadmium, manganese, and lead levels in private wells and birth defects prevalence in North Carolina: a semi-ecologic study. BMC Public Health 14: 955.		
Results (for each outcome)	How outcome was assessed	Case infants with selected birth defects were identified by the North Carolina Birth Defects Monitoring Program (BDMP). Twelve structural defects or groups of defects were included in this study: (1) spina bifida without anencephaly (n = 218); (2) anotia and microtia (n = 94); (3) conotruncal heart defects including common truncus, Tetralogy of Fallot (TOF), and transposition of the great arteries (TGA) (n = 435); (4) atrioventricular septal defects (AVSD) and endocardial cushion defects (ECD) (n = 150); (5) hypoplastic left heart syndrome (HLHS) (n = 142); (6) cleft palate (CP) (n = 351); (7) cleft lip with or without CP (n = 516); (8) oesophageal atresia (EA) and tracheo-oesophageal fistula (TEF) (n = 140); (9) pyloric stenosis (n = 1,204); (10) reduction defects of the upper and lower limbs (n = 255); (11) gastroschisis (n = 215); and (12) hypospadias (n = 1,994). The average level of each metal was calculated among wells sampled within North Carolina census tracts. Individual exposure was assigned as the average metal level of the census tract that contained the geocoded maternal residence.
	Method of measurement	Not stated
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	20,151 infants with selected birth defects (cases) and 668,381 non-malformed infants (controls). Infants from non-singleton births (n = 25,069), without a geocoded residence at delivery (n = 38,206), or case infants with known chromosomal abnormalities (n = 1,472) were considered ineligible and excluded from this study.
Statistics (if any)	Statistical method used	• Crude and adjusted estimates of the association between metal concentrations in drinking water and the prevalence of each birth defect within census tracts were calculated by log-linear regression using SAS 9.3 (SAS Institute Inc., Cary, North Carolina). • Prevalence ratios (PR) with 95% confidence intervals (CI) were calculated to estimate the association between the prevalence of birth defects in the highest category (≥90th percentile) of average census tract metal levels and compared to the lowest category (≤50th percentile).
	Details on statistical analysis	

Publication Reference: Sanders A. P., Desrosiers T. A., Warren J. L., Herring A. H., Enright D., Olshan A. F., Meyer R. E. and Fry R. C. (2014). Association between arsenic, cadmium, manganese, and lead levels in private wells and birth defects prevalence in North Carolina: a semi-ecologic study. BMC Public Health 14: 955.

	Relative risk/odds ratio, confidence interval?	• Lead levels appeared to be randomly spatially distributed, had a high coefficient of variation, and were not strongly correlated with other metals. • RR and 95% CI for twelve defects and Pb in well water: 1. Spina bifida: 1.0 (0.5, 1.7) 2. Anotia/microtia: 1.0 (0.4, 2.6) 3. Conotruncals: 0.9 (0.6, 1.5) 4. AVSD/ECD: 0.7 (0.3, 1.8) 5. HLHS: 1.7 (0.9, 3.3) 6. Cleft palate: (CP) 0.9 (0.6, 1.5) 7. Cleft lip ± CP: 1.0 (0.7, 1.5) 8. EA/TEF: 1.1 (0.5, 2.3) 9. Pyloric stenosis: 0.8 (0.6, 1.1) 10. Limb reduction: 0.7 (0.4, 1.4) 11. Gastroschisis: 1.4 (0.8, 2.4) 12. Hypospadias: 1.1 (0.9, 1.4) • The lead-exposed category was associated with an increased prevalence of HLHS (PR: 1.7 95% CI: 0.9-3.3), but the finding was not statistically significant.
Author's conclusions	Interpretation of results	• There were no statistically significant positive relationships between birth defect prevalence and residence in areas of the highest cadmium or lead levels. • Note: The findings suggest an ecological association between higher manganese concentrations in drinking water and the prevalence of conotruncal heart defects.
	Assessment of uncertainty (if any)	A sensitivity analysis was conducted using the census block group as the ecological unit of analysis to determine whether the pattern of findings observed at the tract level was robust.
Reviewer comments	Results included/excluded in review (if applicable)	No association was found between lead levels in well water used for drinking and specific birth defects even though lead levels in well water ranged from 2.5 to 1304.2 µg/L. As this study is a health study (case-control) it was subject to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Edwards et al. 2014

Publication Reference: Edwards M. (2014). Fetal death and reduced birth rates associated with exposure to lead-contaminated drinking water. Environ Sci Technol 48(1): 739-746.

General Information	Date of data extraction	28 June 2023
	Authors	Edwards, M.
	Publication date	Published: December 9, 2013
	Publication type	Journal article

Publication Reference: Edwards M. (2014). Fetal death and reduced birth rates associated with exposure to lead-contaminated drinking water. Environ Sci Technol 48(1): 739-746.		
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	M.A.E. was supported by a MacArthur Fellowship and the Robert Wood Johnson Foundation (RWJF) under the Public Health Law Research Program Grant ID No. 68391.
	Possible conflicts of interest	The author has been subpoenaed to testify in lawsuits of children who were lead poisoned in Washington D.C. from 2001-2004. He has received no financial compensation for his testimony. DC Water was a financial contributor to a Robert Wood Johnson Foundation grant which supported this research.
Study characteristics	Aim/objectives of study	This research examines whether expectations of adverse pregnancy outcomes are evident in foetal death and birth rate data for Washington, DC from 2001 to 2003 when water lead levels (WLLs) were elevated throughout the city and consumers were unprotected, and if there are also links between foetal death rates and partial service line replacement (PSLR) activities from 2007 to 2009 before public health interventions protected the public from high WLLs.
	Study type/design	Ecological study
	Study duration	12 years (1999 – 2011)
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Washington DC, Baltimore City and the United States
	Selection criteria for population (if applicable)	
	Subgroups reported	- Washington DC (DC) - Baltimore - USA
	Size of study	Population - DC (DC): 601 723 - Baltimore: 620 961 - US: 308 700 000
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Lead service lines
	Exposure concentrations (if applicable)	The 90th percentile water lead levels (WLL) in DC spiked over 40 µg/L from 2001 to 2004 after the switch to chloramine disinfectant, with a peak WLL of 79 µg/L in calendar year 2001
	Comparison group(s)	Baltimore and USA
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
	Definition of outcome	

Publication Reference: Edwards M. (2014). Fetal death and reduced birth rates associated with exposure to lead-contaminated drinking water. Environ Sci Technol 48(1): 739-746.

Results (for each outcome)	How outcome was assessed	- The 90th percentile (90^{th} %ile) WLL data in DC from 1997 to 2000 were derived from a U.S. EPA report, data from 2001 to 2007 were derived from Edwards et al. and data for 2008–2011 were obtained from DC WASA consumer confidence reports. - DC WASA provided data on PSLRs from 2003 to 2011 and incidence of lead pipes by neighbourhood or ward. Baltimore City WLL data were obtained from consumer confidence reports (2001 onward) and from the U.S. EPA before 2001 (1997–2001). - DC blood leads were derived from prior published independent data due to acknowledged problems with the CDC data set and DC DOH reporting. Baltimore City and U.S. data on incidence of childhood lead poisoning were compiled from Baltimore City Health Department records or CDC's lead surveillance data. - Total foetal deaths (over 20 weeks) in Washington, DC reported and compiled by DC DOH, were taken from Vitalstats (1997–2005) and DC DOH reports (2003–2011). Data on Washington, DC birth rates, general fertility rates, and births by ward (neighbourhood) were obtained from DC DOH reports or Vitalstats. Foetal death rates, birth rates and general fertility rates for Baltimore City 1997–2011 were obtained from annual Maryland Vital Statistics reports, and similar data for the United States were obtained from National Vital Statistics reports when available.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable (ecological study). Since chloramine was only dosed in part of 2000, and no WLL data were collected for that time period (and the data were subject to revision and controversy), year 2000 data were excluded from any correlations between WLLs and adverse pregnancy outcomes.
Statistics (if any)	Statistical method used	Correlations, statistical testing, and upper and lower confidence intervals were calculated using a standard Microsoft EXCEL 2010 program with an assumption that data were normally distributed. All error bars in graphs represent 95% confidence intervals.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (ecological study).

<table>
<tr><th colspan="3"><i>Publication Reference:</i> Edwards M. (2014). Fetal death and reduced birth rates associated with exposure to lead-contaminated drinking water. Environ Sci Technol 48(1): 739-746.</th></tr>
<tr><td rowspan="2">Author’s conclusions</td><td>Interpretation of results</td><td>• During 2001, incidence of childhood lead poisoning (blood lead >10 µg/dL) increased from 0.5% up to 4.8% for children less than 1.3 years of age (Prior work)
• Changes in the DC foetal death rates vs neighbouring Baltimore City were correlated to DC WLL ($R^2 = 0.72$).
• Birth rates in DC also increased versus Baltimore City and versus the United States in 2004−2006, when consumers were protected from high WLLs.
• The increased births in DC neighbourhoods comparing 2004 versus 2001 was correlated to the incidence of lead pipes ($R^2 = 0.60$).
• DC birth rates from 1999 to 2007 correlated with proxies for maternal blood lead including the geometric mean blood lead in DC children ($R^2 = 0.68$) and the incidence of lead poisoning in children under age 1.3 years ($R^2 = 0.64$).
• After public health protections were removed in 2006, DC foetal death rate (FDR) spiked in 2007−2009 versus 2004−2006 ($p < 0.05$), in a manner consistent with high WLL health risks to consumers arising from partial lead service line replacements, and DC FDR dropped to historically low levels in 2010−2011 after consumers were protected and the PSLR program was terminated.
• Overall results are consistent with prior research linking increased lead exposure to higher incidence of miscarriages and foetal death, even at blood lead elevations (≈5 µg/dL) once considered relatively low.
Demarcation of Washington DC Lead in Water Risks into Calendar Years for Consideration of Impacts on Foetal Death, Birth Rates and General Fertility
<table>
<tr><th><u>Year</u></th><th><u>Risk to elevated lead in water</u></th><th>WLL (µg/L) <u>90%ile</u></th></tr>
<tr><td>1997/99</td><td>Low. Lead service line with chloramine.</td><td>7-12.5</td></tr>
<tr><td>2000</td><td>Uncertain. Chloramine dosed part of the year.</td><td>34</td></tr>
<tr><td>2001/02</td><td>Highest. High WLL.</td><td>79, 45</td></tr>
<tr><td>2003</td><td>High. High WLL.</td><td>51.5</td></tr>
<tr><td>2004/06</td><td>Low. High WLL. Public education, use of filters and flush.</td><td>59, 15, 11</td></tr>
<tr><td>2007/09</td><td>Low. Corrosion control, High PSLR activity
High. Public health protections removed in PSLR homes.</td><td>10.5, 7, 8</td></tr>
<tr><td>2010/11</td><td>Very low. Low WLL, corrosion control
Low in PSLR homes. CDC health advisory issued, filter.</td><td>5, 5</td></tr>
</table></td></tr>
<tr><td>Assessment of uncertainty (if any)</td><td>-</td></tr>
</table>

Publication Reference: Edwards M. (2014). Fetal death and reduced birth rates associated with exposure to lead-contaminated drinking water. Environ Sci Technol 48(1): 739-746.		
Reviewer comments	Results included/excluded in review (if applicable)	According to the authors, increased lead exposure results 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.
	Notes on study quality, e.g. gaps, methods	This is an ecological study and a dose response relationship cannot be established hence it is not subject to a RoB assessment.

Eggers et al. 2021

Publication Reference: Eggers S., Safdar N., Kates A., Sethi A. K., Peppard P. E., Kanarek M. S. and Malecki K. M. C. (2021). Urinary lead level and colonization by antibiotic resistant bacteria: Evidence from a population-based study. Environ Epidemiol 5(6): e175.		
General Information	Date of data extraction	28 June 2023
	Authors	Eggers, S., Safdar, Nasia, N., Kates, A., Sethia, A.K., Peppard, P.E., Kanareka, M.S., Malecki, K.M.C
	Publication date	Published online 3 November 2021
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	Funding for this work came from the University of Wisconsin School of Medicine and Public Health's (UWSMPH) Wisconsin Partnership Program and UWSMPH's Department of Medicine Pilot Award Program. Funding for SE's time comes from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (T32 HD049311). A.K. was supported by a National Library of Medicine training grant to the Computation and Informatics in Biology and Medicine Training Program, USA (T15 LM007359). Authors also acknowledge support from the National Institutes of Health core grant to the Center for Demography and Ecology at the University of Wisconsin-Madison (P2C HD047873). K.M.C.M. is also a member of the Center for Demography and Aging at the University of Wisconsin Madison (P30 AG017266) and supported by related NIH grant (R21 AI142481).
	Possible conflicts of interest	The authors declare that they have no conflicts of interest with regard to the content of this report.
Study characteristics	Aim/objectives of study	This study analyses the association between urinary lead level and colonisation by antibiotic resistant bacteria (ARB) in a nonclinical human population.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: Eggers S., Safdar N., Kates A., Sethi A. K., Peppard P. E., Kanarek M. S. and Malecki K. M. C. (2021). Urinary lead level and colonization by antibiotic resistant bacteria: Evidence from a population-based study. Environ Epidemiol 5(6): e175.		
Population characteristics	Selection criteria for population (if applicable)	The study sample includes 695 adults age 18 years or older who participated between 2016 and 2017 in the Survey of the Health of Wisconsin (SHOW) and its ancillary Wisconsin Microbiome Study (WMS).
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	ARB-, ARB+
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	The primary outcome was ARB colonisation as defined by presence of at least one of four different ARB: methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), fluoroquinolone resistant Gram-negative bacilli (RGNB), and *Clostridium difficile* (*C. diff)*. Urinary lead levels, adjusted for creatinine, were used to assess exposure.
	How outcome was assessed	
	Method of measurement	ARB included methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), fluoroquinolone resistant Gram-negative bacilli (RGNB), and *Clostridium difficile* (C. diff), from skin, nose, and mouth swabs, and saliva and stool samples.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	695 participants
Statistics (if any)	Statistical method used	Logistic regression, adjusted for covariates, was used to evaluate associations between Pb and ARB. Secondary analysis investigated Pb resistance from ARB isolates.
	Details on statistical analysis	

Publication Reference: Eggers S., Safdar N., Kates A., Sethi A. K., Peppard P. E., Kanarek M. S. and Malecki K. M. C. (2021). Urinary lead level and colonization by antibiotic resistant bacteria: Evidence from a population-based study. Environ Epidemiol 5(6): e175.

Relative risk/odds ratio, confidence interval?

Results of logistic regression of ARB colonisation, unadjusted and adjusted for covariates.

	OR (Confidence Interval, CI)
95%ile Pb (yes)	2.05 (0.95, 4.44)
Age	**1.01 (1.00, 1.03)**
Gender (female vs. male)	1.04 (0.71, 1.53)
Antibiotic use (yes vs. no)	0.92 (0.62, 1.37)
Race/ethnicity	1.47 (0.91, 2.39)
Education	
≤High-school	0.66 (0.41, 1.08)
Some college	0.77 (0.5, 1.18)
Dietary fibre	0.95 (0.91, 1.00)
Dietary vitamin C	1.01 (1.00, 1.01)
Urban (vs. rural)	0.94 (0.64, 1.39)
Length of residence (years)	
0–1	0.73 (0.36, 1.45)
1–3	1.06 (0.61, 1.86)
3–10	0.87 (0.53, 1.44)

Results of logistic regression of ARB colonization, stratified by urbanicity, adjusted for covariates.

	Urban	Suburban/Rural
	OR (CI)	OR (CI)
95 %ile Pb (yes)	**2.85 (1.07, 7.59)**	1.07 (0.28, 4.05)
Age	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Gender (female vs. male)	1.30 (0.82, 2.07)	0.60 (0.30, 1.23)
Antibiotic use (yes vs. no)	0.96 (0.60, 1.54)	0.82 (0.38, 1.77)
Race/ethnicity	1.76 (1.01, 3.05)	0.46 (0.10, 2.16)
Education		
≤High-school	0.83 (0.45, 1.53)	0.49 (0.20, 1.19)
Some college	0.87 (0.51, 1.48)	0.55 (0.26, 1.14)
Dietary fibre	0.98 (0.93, 1.03)	0.90 (0.80, 1.01)
Dietary vitamin C	**1.01 (1.00, 1.01)**	**1.01 (1.00, 1.02)**
Length of residence (years)		
0–1	0.74 (0.32, 1.69)	0.46 (0.10, 2.00)
1–3	1.30 (0.67, 2.53)	0.40 (0.12, 1.33)
3–10	0.84 (0.45, 1.60)	0.94 (0.38, 2.29)

Publication Reference: Eggers S., Safdar N., Kates A., Sethi A. K., Peppard P. E., Kanarek M. S. and Malecki K. M. C. (2021). Urinary lead level and colonization by antibiotic resistant bacteria: Evidence from a population-based study. Environ Epidemiol 5(6): e175.		
Author's conclusions	Interpretation of results	• 239 (34%) tested positive for ARB. • Geometric mean urinary Pb (unadjusted) was 0.286 µg/L (95% confidence intervals [CI] = 0.263, 0.312) for ARB negative participants and 0.323 µg/L (95% CI = 0.287, 0.363) for ARB positive participants. • Models adjusted for demographics, diet, and antibiotic use showed elevated odds of positive colonisation for those in the 95th percentile (vs. below) of Pb exposure (odds ratio [OR] = 2.05, 95% CI = 0.95, 4.44), and associations were highest in urban residents (OR = 2.85, 95% CI = 1.07, 7.59). • RGNB isolates were most resistant to Pb. • These novel results suggest that Pb exposure is associated with increased colonisation by ARB, and that RGNB are particularly resistant to Pb.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Pb exposure, as represented by urinary Pb levels was found to be associated with increased colonisation by antibiotic resistant bacteria (ARB), particularly for people in urban areas. A dose-response relationship with water lead levels or blood lead levels has not been established and it is unlikely this study could be used for guideline derivation due to the effect not being an adverse effect *per se*. Hence, this study was not subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Enehizena and Emokpae 2022

Publication Reference: Enehizena O. O. and Emokpae M. A. (2022). Toxic Metal Concentrations in Drinking Water and Possible Effect on Sex Hormones among Men in Sabongida-Ora, Edo State, Nigeria. Medicines (Basel) 9(1).		
General Information	Date of data extraction	28 June 2023
	Authors	Enehizena, O.O. and Emokpae, M.A.
	Publication date	Published: 7 January 2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Nigeria
	Source of funding	This research received no external funding.
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	This study determines the concentrations of lead (Pb), cadmium (Cd), zinc (Zn), copper (Cu) in drinking water (borehole, hand-dug well and treated water) and sex hormone levels [serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PROL), oestradiol (E2), progesterone (PROG), and testosterone (T)] in males who drink water mainly from these sources.
	Study type/design	Prospective case-control study

Publication Reference: Enehizena O. O. and Emokpae M. A. (2022). Toxic Metal Concentrations in Drinking Water and Possible Effect on Sex Hormones among Men in Sabongida-Ora, Edo State, Nigeria. Medicines (Basel) 9(1).		
	Study duration	Not applicable
	Type of water source (if applicable)	Dug-Well, Borehole and treated water
Population characteristics	Population/s studied	• The study was conducted at Sabongida Ora, Owan West Local Government Area of Edo State among men who drink water solely from hand-dug well, borehole and treated sources. • Healthy men within the reproductive age of 20–45 years and drank water solely from hand dug wells and consumed borehole water and treated water were included in the study.
	Selection criteria for population (if applicable)	
	Subgroups reported	Dug-Well, Borehole and treated water consumers
	Size of study	A minimum of 60 participants and 30 non-occupationally exposed healthy subjects were enrolled in the study. 90 water sampling locations (30 each for urban, suburban and rural locations)
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	Contamination of surface and ground waters by industrial sewage and agricultural runoff.
	Exposure concentrations (if applicable)	Water Lead Level (mg/L) — Blood Lead Level (µg/dL) Hand-dug well: 1.81 ± 0.10 — 4.00 ± 0.26 Borehole: 1.10 ± 0.02 — 2.08 ± 0.42 Treated water: 0.81 ± 0.10 — 1.64 ± 0.04 **Interrelationship of sex hormones with Pb in water.** Sex hormones — p-value FSH (miu/mL) — **0.045** LH (miu/mL) — 0.674 E2 (pg/L) — 0.84 PROG (ng/mL) — 0.287 PROL (ng/mL) — **0.006** TESTO (ng/mL) — 0.382
	Comparison group(s)	Treated water consumers
Study methods	Water quality measurement used	• Not stated for water. • Blood: The metal concentrations were determined by an Atomic Absorption Spectrophotometer
	Water sampling methods (monitoring, surrogates)	Water samples were randomly selected across ten (10) locations in Sabongida-Ora.
Results (for each outcome)	Definition of outcome	Circulating levels of the follicle stimulating hormone (FSH), the luteinizing hormone (LH), prolactin and testosterone are vital for spermatogenesis and sexual function. The accumulation of toxic metals in the body is harmful to sexual function and reproduction. Therefore, the evaluation of toxic levels in drinking water and the possible effect on reproductive hormones is important for public health information.
	How outcome was assessed	

Publication Reference: Enehizena O. O. and Emokpae M. A. (2022). Toxic Metal Concentrations in Drinking Water and Possible Effect on Sex Hormones among Men in Sabongida-Ora, Edo State, Nigeria. Medicines (Basel) 9(1).		
	Method of measurement	The sex hormones (luteinizing hormone, follicle stimulating hormone, prolactin, testosterone, oestradiol and progesterone) were assayed by ELISA technique
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Individuals on male contraceptives, or with testicular varicocele, had been on long-term medications, living with HIV, or had chronic and serious systemic illness, took steroid preparations, did not consent and were smokers were excluded from the study
Statistics (if any)	Statistical method used	Data analysis was done using the statistical software SPSS version 21 (SPSS Inc., Chicago, IL, USA). The Student's t-test and Chi-square test were used to compare variables where appropriate, and a p < 0.05 was considered statistically significant.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	-
Author's conclusions	Interpretation of results	• Blood Pb levels were significantly higher (p < 0.001) among subjects who consumed hand-dug and borehole water than treated water. • Blood Cd and Pb levels were significantly higher (p < 0.001) in hand-dug well water consumers than borehole water consumers. • The consumption of water from hand-dug wells may have adverse reproductive sequelae among consumers.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	A statistically significant difference in levels of FSH and prolactin was observed in men with blood Pb levels of 4.00 ± 0.26 µg/dL (hand dug water) compared to those with 2.08 ± 0.42 µg/dL (borehole water) and 1.64 ± 0.04 µg/dL (treated water). A RoB assessment was undertaken for this study as it is a health-based study showing an association between BLL and changes in an effect (albeit the latter is a biochemical change) and on its own not considered adverse.
	Notes on study quality, e.g. gaps, methods	

Macdonald Gibson et al. 2022

Publication Reference: Gibson J. M., MacDonald J. M., Fisher M., Chen X., Pawlick A. and Cook P. J. (2022). Early life lead exposure from private well water increases juvenile delinquency risk among US teens. Proc Natl Acad Sci U S A 119(6).		
General Information	Date of data extraction	29 June 2023
	Authors	MacDonald Gibson, J., MacDonald, J.M., Fisher, M., Chena, X., Pawlicka, A., and Cook, P.J.
	Publication date	Published January 31, 2022.
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US

Publication Reference: Gibson J. M., MacDonald J. M., Fisher M., Chen X., Pawlick A. and Cook P. J. (2022). Early life lead exposure from private well water increases juvenile delinquency risk among US teens. Proc Natl Acad Sci U S A 119(6).		
	Source of funding	This research was funded by the US Environmental Protection Agency Science to Achieve Results Program under Grant no. 83927901
	Possible conflicts of interest	The authors declare no competing interest.
Study characteristics	Aim/objectives of study	This study reports on how unregulated private well water is an underrecognised Pb exposure source that is associated with an increased risk of teenage juvenile delinquency
	Study type/design	Cross-sectional study
	Study duration	1998 to 2017 (BLL data collected over this time period)
	Type of water source (if applicable)	Drinking water (private wells versus municipal water)
Population characteristics	Population/s studied	• The cohort of children in this study was drawn from records of all children who were tested for blood Pb in Wake County, NC (population 1.1 million), between 1998 and 2011. • As of 2015, ~137,400 Wake County residents (about 13.4% of the population) relied on unregulated private wells for their drinking water, and the rest were connected to regulated community water systems.
	Selection criteria for population (if applicable)	
	Subgroups reported	Full sample, Community water users, and Private well users
	Size of study	• Children with Juvenile delinquency reports in the database of linked blood Pb measurements and drinking water sources were retrieved by the NC Department of Public Safety (DPS) for all children who reached at least age 14 by December 31, 2019 (n = 17,868). • Overall, NCERDC located teenage addresses for 76.0% (13,580 of 17,869) of the children.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Drinking water
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Municipal water users
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Authors estimate how early life Pb exposure from private well water influences reported delinquency.
	How outcome was assessed	

Publication Reference: Gibson J. M., MacDonald J. M., Fisher M., Chen X., Pawlick A. and Cook P. J. (2022). Early life lead exposure from private well water increases juvenile delinquency risk among US teens. Proc Natl Acad Sci U S A 119(6).		
	Method of measurement	• Blood Pb measurements were provided by the NC Childhood Lead Poisoning Prevention Program for all children tested between 1998 and 2017. Blood Pb measurements were matched to each child's drinking water source (private well or community system) at the time of their first blood Pb test. • Juvenile delinquency reports for the children in the database of linked blood Pb measurements and drinking water sources were retrieved by the NC Department of Public Safety (DPS) for all children who reached at least age 14 by December 31, 2019 (n = 17,868)
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• 13,580 children under age 6. • Early life water source information was available for 13,372 of the 13,580 children for whom early life blood Pb and teenage address were matched. • Full sample (n = 13,372), Community water (n = 11,209), Private well (n = 2,163).
Statistics (if any)	Statistical method used	The influence of water source on Pb exposure and of Pb exposure on delinquency risk was analysed using a two-stage, least-squares regression approach
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Mean results Full Sample / Community Water / Private Well / p-value BLL µg/dL 2.30 2.36 2.52 <0.001 # complaints 0.122 0.117 0.144 0.688 # Serious complaint 0.046 0.0435 0.0587 0.975 **Odds of being reported for juvenile delinquency after age 14 for children on private well water, compared to children with community water** Delinquency / Model 1 Full dataset / Model 2 Quasi-exp. dataset Any 1.13 (1.05 to 1.21) 1.21 (1.05 to 1.40) Serious 1.16 (1.06 to 1.27) 1.38 (1.10 to 1.73)

Author's conclusions	Interpretation of results	• On average, children in homes with unregulated private wells had 11% higher blood Pb than those with community water service.
		• This higher blood Pb was significantly associated with reported delinquency.
		• Compared to children with community water service, those relying on private wells had
		  • a 21% (95% CI: 5 to 40%) higher risk of being reported for any delinquency and
		  • a 38% (95% CI: 10 to 73%) increased risk of being reported for serious delinquency after age 14.
		• These results suggest that there could be substantial but as-yet-unrecognised social benefits from intervention programs to prevent children's exposure to Pb from private wells, on which 13% of the US population relies.

Publication Reference: Gibson J. M., MacDonald J. M., Fisher M., Chen X., Pawlick A. and Cook P. J. (2022). Early life lead exposure from private well water increases juvenile delinquency risk among US teens. Proc Natl Acad Sci U S A 119(6).		
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This report provides an association between reported delinquency and small differences in mean BLL; 2.5 µg/L for well users and 2.36 µg/L for community water users. A dose response relationship data cannot be established for this study as the study reports only a mean BLL concentration rather than stratified BLL. Nonetheless, a RoB assessment weas undertaken for this study.
	Notes on study quality, e.g. gaps, methods	

Hanna-Attisha et al. 2021

Publication Reference: Hanna-Attisha M., Gonuguntla A., Peart N., LaChance J., Taylor D. K. and Chawla S. (2021). Umbilical Cord Blood Lead Level Disparities between Flint and Detroit. Am J Perinatol 38(S 01): e26-e32.		
General Information	Date of data extraction	29 June 2023
	Authors	Hanna-Attisha, M., Gonuguntla, A., Peart, N., LaChance, J., Taylor, D.K., Chawla, S.
	Publication date	Published online March 6, 2020
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This research was partially supported by the Dr. and Mrs. Mathias Pediatric Research and Education Fund, Hurley Medical Center.
	Possible conflicts of interest	None declared.
Study characteristics	Aim/objectives of study	The objective of this study was to investigate and compare cord blood lead levels (CBLLs) in newborns in Flint, Michigan, after the Flint water crisis, to a group of Detroit newborns.
	Study type/design	Cohort study
	Study duration	3 Months (November 2015 to January 2016)
	Type of water source (if applicable)	Municipal supplied drinking water
Population characteristics	Population/s studied	Mothers and newborns from Flint and Detroit
	Selection criteria for population (if applicable)	
	Subgroups reported	Flint newborns, Detroit newborns
	Size of study	215 mothers and newborns from Flint and Detroit
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Drinking water (in Flint)
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Detroit newborns

<table>
<tr><th colspan="3"><i>Publication Reference:</i> Hanna-Attisha M., Gonuguntla A., Peart N., LaChance J., Taylor D. K. and Chawla S. (2021). Umbilical Cord Blood Lead Level Disparities between Flint and Detroit. Am J Perinatol 38(S 01): e26-e32.</th></tr>
<tr><td rowspan="2">Study methods</td><td>Water quality measurement used</td><td>Not applicable.
(NB: For blood, graphite furnace atomic absorption spectrometry was used)</td></tr>
<tr><td>Water sampling methods (monitoring, surrogates)</td><td>Not applicable.</td></tr>
<tr><td rowspan="4">Results (for each outcome)</td><td>Definition of outcome</td><td rowspan="3">• A CBLL greater than or equal to 1 µg/dL (0.05 µmol/L) was defined as the threshold for the higher lead level group.
• Mothers of 99 Flint newborns were surveyed about potential lead exposures. These neonates were born after the recognition of population-wide lead-in-water contamination. CBLLs were measured and maternal–foetal metrics were reviewed. CBLLs and maternal–foetal metrics were then compared with those of a retrospective cohort of 116 Detroit newborns who previously shared the same water source.</td></tr>
<tr><td>How outcome was assessed</td></tr>
<tr><td>Method of measurement</td></tr>
<tr><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>In Flint, 218 patients approached, 200 (91.7% consented), and of consenting patients 99 (49.5%) met inclusion criteria.
Inclusion criteria included newborns of women who consented to the study, lived in Flint, and had their cord blood analysed.</td></tr>
<tr><td rowspan="3">Statistics
(if any)</td><td>Statistical method used</td><td rowspan="2">Analysis involved descriptive statistics, independent t-test, and χ2 analysis.</td></tr>
<tr><td>Details on statistical analysis</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>
<table>
<tr><td>Newborn metrics</td><td>Flint
<u>(n=99)</u></td><td>Detroit
<u>(n=116)</u></td><td><u>p-Value</u></td></tr>
<tr><td>Gestational age, wk</td><td>38.8</td><td>39.9</td><td>0.79</td></tr>
<tr><td>Birth weight, g</td><td>3,081.7</td><td>3,191.1</td><td>0.09</td></tr>
<tr><td>Preterm, %</td><td>4.0</td><td>5.2</td><td>0.69</td></tr>
<tr><td>small for gestational age</td><td>12.1</td><td>11.3</td><td>0.85</td></tr>
<tr><td>Head circumference, cm</td><td>33.6</td><td>33.8</td><td>0.46</td></tr>
<tr><td>Head circumference
<10th percentile, %</td><td>17.7</td><td>17.1</td><td>0.91</td></tr>
<tr><td>5-min Apgar score</td><td>8.9</td><td>8.9</td><td>0.18</td></tr>
</table>
</td></tr>
<tr><td>Author's conclusions</td><td>Interpretation of results</td><td>• CBLLs greater than or equal to 1 µg/dL (0.05 µmol/L) were more prevalent among Flint newborns (14%), as compared with Detroit newborns (2%; p =0.001).
• This was a sevenfold disparity between Flint and Detroit newborns.
• No statistically significant differences were found in birth weight, head circumference, small for gestational age status, gestational age, or preterm status among the two groups.</td></tr>
</table>

Publication Reference: Hanna-Attisha M., Gonuguntla A., Peart N., LaChance J., Taylor D. K. and Chawla S. (2021). Umbilical Cord Blood Lead Level Disparities between Flint and Detroit. Am J Perinatol 38(S 01): e26-e32.		
	Assessment of uncertainty (if any)	Data were gathered after reported knowledge of the lead-in-water contamination and declaration of the public health emergency (October 1, 2015) and after the first water advisories were instituted (August 2014). Even though Pb was still present in Flint water well after this study, half of the surveyed Flint women had stopped drinking the tap water and had transitioned to alternatives at the onset of water quality concerns. Further research has suggested that the greatest water lead exposure was likely in the summer of 2014, before the mothers in this cohort were pregnant and before implementation of boil advisories and other general water quality concerns.
Reviewer comments	Results included/excluded in review (if applicable)	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 a population of 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. As this is a health study it was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Tort et al. 2018

Publication Reference: Tort B., Choi Y. H., Kim E. K., Jung Y. S., Ha M., Song K. B. and Lee Y. E. (2018). Lead exposure may affect gingival health in children. BMC Oral Health 18(1): 79.		
General Information	Date of data extraction	07 July 2023
	Authors	Tort, B., Choi, Y., Kim, E., Jung, Y., Ha, M., Song, K., and Lee, Y.
	Publication date	Published online: 04 May 2018
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	South Korea
	Source of funding	This research was supported by Grants-in-Aid for Children's Health and Environment Research from the Ministry of Environment of Korea. This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2016R1D1A3B03934825).
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	The aim of this study was to investigate the relationship between blood lead level (BLL) and oral health status of children.
	Study type/design	Cross-sectional
	Study duration	Not applicable

Publication Reference: Tort B., Choi Y. H., Kim E. K., Jung Y. S., Ha M., Song K. B. and Lee Y. E. (2018). Lead exposure may affect gingival health in children. BMC Oral Health 18(1): 79.		
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	A total of 351 children (aged 7–15 years) were recruited from the pilot data of the Korean Environmental Health Survey in Children and Adolescents, which was designed to examine environmental exposure and children's health status in South Korea.
	Selection criteria for population (if applicable)	
	Subgroups reported	The participants were divided equally into four quartiles, with quartile I comprised of children with the lowest BLLs.
	Size of study	351 children (aged 7–15 years)
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable (note: Overall mean BLL was 1.25 ± 0.43 µg/dL, ranging from 0.36 to 2.90 µg/dL).
	Comparison group(s)	Four quartiles: Quartile I, Quartile II, Quartile III, Quartile IV.
Study methods	Water quality measurement used	Not applicable (Note: Lead levels in blood were determined using atomic absorption spectrophotometry).
	Water sampling methods (monitoring, surrogates)	Not applicable (Note: Whole blood (3–5 mL) was drawn from the subjects and sealed in a heparin containing tube. Lead levels were determined using atomic absorption spectrophotometry)
Results (for each outcome)	Definition of outcome	Blood samples were taken to determine BLLs and oral examinations were performed to assess oral health parameters, including community periodontal index (CPI), gingival index (GI), and plaque index (PI). Information regarding socioeconomic status, oral hygiene behaviour, and dietary habits was collected from parents and guardians.
	How outcome was assessed	
	Method of measurement	Oral health examinations were conducted by 1 dentist and 2 dental hygienists
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	351 children (aged 7–15 years) Quartile I (n = 35), Quartile II (n = 34), Quartile III (n = 34), Quartile IV (n = 34)
Statistics (if any)	Statistical method used	Analysis of variance (ANOVA) and a Chi-square test were used to compare the covariates and oral health parameters among the quartiles. One crude and two adjusted logistic regression models were used to explore the relationship between BLL and oral health parameters. Two adjusted odds ratios (OR) were calculated.
	Details on statistical analysis	

Publication Reference: Tort B., Choi Y. H., Kim E. K., Jung Y. S., Ha M., Song K. B. and Lee Y. E. (2018). Lead exposure may affect gingival health in children. BMC Oral Health 18(1): 79.		
	Relative risk/odds ratio, confidence interval?	• The crude odds ratios for community periodontal index (CPI), gingival index (GI), and plaque index (PI) in the third quartile were 5.24 (95% CI: 1.48-18.56), 4.35 (95% CI: 1.36-13.9), and 4.17 (95% CI: 1.50-11.54), respectively. • The age and gender-adjusted odds ratios were 7.66 (95% CI: 1.84-31.91), 6.80 (95% CI: 1.80-25.68), and 3.41 (95% CI: 1.12-10.40), respectively. • After adjustments for age, gender, parent education level, and frequency of tooth brushing, the adjusted odds ratios were 7.21 (95% CI: 1.72-30.19), 6.13 (95% CI: 1.62-23.19), and 3.37 (95% CI: 1.10-10.34), respectively.
Author's conclusions	Interpretation of results	• There were significant differences for PI ($p < 0.05$) among the quartile groups. • Higher BLLs were positively correlated with worse oral health measurements, including CPI, GI, and PI. • A high BLL might be associated with oral health problems in children, including plaque deposition and gingival diseases.
	Assessment of uncertainty (if any)	• Since the subjects were recruited from only two cities in South Korea, the findings are not representative of the overall Korean population. • Since this is a cross-sectional study, the results must be cautiously interpreted because this is not causality but an association study. • Final sample size was not enough to have statistical power when including several confounders in logistic regression models resulting in non-significant associations at the stratum of the fourth quartile.
Reviewer comments	Results included/excluded in review (if applicable)	• This study found a statistically significant association between adverse effects on oral health and relatively low blood lead 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. It is also unclear why associations were found in Quartile III but not in Quartile IV, the group with the highest BLL. • As this study provides health effects information, it was subjected to RoB.
	Notes on study quality, e.g. gaps, methods	

Rodrigues et al. 2016

Publication Reference: Rodrigues E. G., Bellinger D. C., Valeri L., Hasan M. O., Quamruzzaman Q., Golam M., Kile M. L., Christiani D. C., Wright R. O. and Mazumdar M. (2016). Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. Environ Health 15: 44.		
General Information	Date of data extraction	10 July 2023
	Authors	Rodrigues, E.G., Bellinger, D.C., Valeri, L., Hasan, O.S.I., Quamruzzaman, Q., Golam, M., Kile, M.L., Christiani, D.C., Wright, R.O., Mazumdar, M.
	Publication date	Published Online: 12 March 2016
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US (with US and Bangladeshi researchers)
	Source of funding	This work was supported by the United States National Institute of Environmental Health Sciences grants # R01 ES011622, ES P42 ES016454, K23 ES017437, and P30 ES000002.
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	The objective of this study was to investigate associations between environmental exposure to metal contaminants and neurodevelopmental outcomes among Bangladeshi children.
	Study type/design	Cohort study
	Study duration	40 months
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	The women and children in this study were participants in a prospective birth cohort study conducted in the Sirajdikhan and Pabna regions of Bangladesh between 2008 and 2011, investigating the effects of arsenic- contaminated drinking water and reproductive health outcomes
	Selection criteria for population (if applicable)	
	Subgroups reported	Sirajdikhan and Pabna regions, Bangladesh
	Size of study	524 children
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not stated
	Exposure concentrations (if applicable)	Water lead concentration not reported. **Blood Lead, µg/dL by clinic** N · %<LOD · P25 · Median · P75 · Max Sirajdikhan · 239 · 6 · 5.5 · 7.6 · 10.4 · 43 Pabna · 286 · 67 · LOD · LOD · 3.8 · 13.8 *LOD for blood lead = 3.3 µg/dL
	Comparison group(s)	Sirajdikhan and Pabna regions
Study methods	Water quality measurement used	Not stated (presumably inductively coupled plasma-mass spectrometry as done for As and Mn) (BLL: The Lead-Care® II portable system)

Publication Reference: Rodrigues E. G., Bellinger D. C., Valeri L., Hasan M. O., Quamruzzaman Q., Golam M., Kile M. L., Christiani D. C., Wright R. O. and Mazumdar M. (2016). Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. Environ Health 15: 44.		
	Water sampling methods (monitoring, surrogates)	Water samples from the tube well used by the family as the primary drinking water source were collected during the first trimester of pregnancy and follow-up visits at age 1 month, 12 months and 20 to 40 months. Approximately 50 mL of water was collected in a polyethylene tube and preserved with ultrapure nitric acid. Water only analysed for arsenic and manganese (Pb concentration in water not reported).
Results (for each outcome)	Definition of outcome	Water was collected from the family's primary drinking source during the first trimester of pregnancy and at ages 1, 12 and 20–40 months. At age 20–40 months, blood lead was measured and neurodevelopmental outcomes were assessed using a translated, culturally-adapted version of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III).
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Full study n = 812, Current study n = 525, excluded n = 287. In that study, pregnant women were recruited from the Sirajikhan and Pabna Sadar Upazilas of Bangladesh. Gestational age was determined by first trimester (<16 weeks) ultrasound. When children were aged 12–40 months, authors re-contacted the parents in the birth cohort study and invited them and their children to participate in the current study investigating the effects of prenatal and early childhood exposure to arsenic, manganese and lead on early childhood development. Excluded data shown in Table 1 of the publication.
Statistics (if any)	Statistical method used	All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC). Demographic characteristics were calculated for the entire cohort as well as for those who were included and excluded from the final regression model due to missing data. Chi-square tests were used to compare categorical variables, and Wilcoxon signed rank tests were used to compare continuous variables, including water and blood concentrations that were right-skewed. Due to the lognormal distributions of the water and blood measurements, metal concentrations were natural log transformed for use in the linear regression models. Linear regression was used to assess the relationship between water As and Mn and blood Pb concentrations and children's age-adjusted BSID-III z-scores adjusting for several potential confounders identified by a review of the literature, including maternal and child characteristics such as maternal age, maternal education, exposure to environmental tobacco smoke, child's sex, HOME score, maternal Raven score, and child's haematocrit levels. Generalised additive models (GAM) were used to assess the shapes of the relationships between the exposure measures and the BSID-III z-scores to determine if additional terms (e.g. quadratic) would be appropriate in the regression models. Two-way interaction terms between the three exposures were also assessed to determine if the effect estimates of a single exposure differed by varying concentrations of an additional exposure.
	Details on statistical analysis	

Publication Reference: Rodrigues E. G., Bellinger D. C., Valeri L., Hasan M. O., Quamruzzaman Q., Golam M., Kile M. L., Christiani D. C., Wright R. O. and Mazumdar M. (2016). Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. Environ Health 15: 44.		
	Relative risk/odds ratio, confidence interval?	**Multivariate model between Pb exposures and BSID-III scores at 20–40 months** **Cognitive** β (SE) p-value Sirajdikhan −0.17 (0.09) 0.05 Pabna 0.02 (0.12) 0.87 **Fine Motor** β (SE) p-value Sirajdikhan 0.07 (0.11) 0.50 Pabna −0.07 (0.11) 0.50
Author's conclusions	Interpretation of results	• Median blood lead concentrations were higher in Sirajdikhan than Pabna (7.6 vs. <3.3 µg/dL, p <0.0001) and water arsenic concentrations were lower (1.5 vs 25.7 µg/L, p <0.0001). • Increased blood lead was associated with decreased cognitive scores in Sirajdikhan (β= −0.17, SE = 0.09, p = 0.05). • Water manganese was associated with fine motor scores in an inverse-U relationship in Pabna. • Where blood lead levels are high, lead is associated with decreased cognitive scores on the BSID-III, and effects of other metals are not detected.
	Assessment of uncertainty (if any)	None for lead.
Reviewer comments	Results included/excluded in review (if applicable)	Increased blood lead was associated with decreased cognitive scores in Sirajdikhan (Median BLL = 7.6 µg/dL, range = <3.3 – 43 µg/dL) compared to Pabna (Median BLL = <3.3 µg/dL, range = <3.3 – 13.8 µg/dL). This study was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Wan et al. 2021

Publication Reference: Wan H., Wang B., Cui Y., Wang Y., Zhang K., Chen C., Xia F., Ye L., Wang L., Wang N. and Lu Y. (2021). Low-level lead exposure promotes hepatic gluconeogenesis and contributes to the elevation of fasting glucose level. Chemosphere 276: 130111.		
General Information	Date of data extraction	10 July 2023
	Authors	Wan, H., Wang, B., Cui, Y., Wang, Y., Zhang, K., Chen, C., Xia, F., Ye, L., Wang, L,. Wang, N., Lu, Y.
	Publication date	Available online 1 March 2021
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China

Publication Reference: Wan H., Wang B., Cui Y., Wang Y., Zhang K., Chen C., Xia F., Ye L., Wang L., Wang N. and Lu Y. (2021). Low-level lead exposure promotes hepatic gluconeogenesis and contributes to the elevation of fasting glucose level. Chemosphere 276: 130111.		
	Source of funding	This study was supported by the National Natural Science Foundation of China (91857117, 81600614); Yunnan Province Lu Yingli Expert Workstation; Science and Technology Commission of Shanghai Municipality (20ZR1432500, 18410722300); the Major Science and Technology Innovation Program of Shanghai Municipal Education Commission (2019-01-07-00-01-E00059); Commission of Health and Family Planning of Pudong District (PWZxq2017-17); and Shanghai JiaoTong University School of Medicine (19XJ11007).
	Possible conflicts of interest	The authors declare that they have no competing or financial interests regarding to the submitted work.
Study characteristics	Aim/objectives of study	Authors aimed to investigate whether low-level Pb exposure causes elevated plasma glucose levels and the possible mechanisms involved.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Chinese citizens >18 years old who had lived in their current area for >6 months were included.
	Selection criteria for population (if applicable)	
	Subgroups reported	Quartile 1 (≤ 2.69 µg/dL), Quartile 2 (> 2.69, ≤ 4.0 µg/dL), Quartile 3 (>4.0, ≤ 5.8 µg/dL), and Quartile 4 (> 5.8 µg/dL)
	Size of study	5747 participants from 16 sites in China.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Quartile 1 (≤ 2.69 µg/dL)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Hypertension was defined as systolic blood pressure 140 mmHg, diastolic blood pressure >90 mmHg, or self-reported previous diagnosis of hypertension by physicians, as in the authors' previous studies (Wan et al., 2020a, 2020b). High fasting plasma glucose (FPG) and High Glycated haemoglobin (HbA1c) were defined as FPG >5.6 mmol/L and HbA1c > 5.7%, respectively, according to the diagnosis of prediabetes from the American Diabetes Association.
	How outcome was assessed	
	Method of measurement	The participants underwent measurements of anthropometric factors, blood lead level (BLL) and fasting plasma glucose (FPG).

Publication Reference: Wan H., Wang B., Cui Y., Wang Y., Zhang K., Chen C., Xia F., Ye L., Wang L., Wang N. and Lu Y. (2021). Low-level lead exposure promotes hepatic gluconeogenesis and contributes to the elevation of fasting glucose level. Chemosphere 276: 130111.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	After excluding participants who were missing BLL data or were currently taking hypoglycaemic medications, 5747 participants were involved in the final analyses. Quartile 1 (n = 1,438), Quartile 2 (n = 1,456), Quartile 3 (n = 1,434), and Quartile 4 (n = 1,419)
Statistics (if any)	Statistical method used	Data analyses were conducted with IBM SPSS Statistics, Version 22 (IBM Corporation, Armonk, NY, USA). Continuous variables are summarised as the mean ± standard deviation (SD) or median (interquartile range). Categorical variables are summarised as percentages (%). Linear or logistic regression analysis was used to test for trends of variable changes across the BLL quartiles, providing unadjusted P-values. Concentrations of BLL were logarithmically transformed to achieve a normal distribution if needed for the analyses. Statistical significance was assessed by one-way ANOVA. A P-value <0.05 indicated significance (two sided). BLLs were divided into quartiles, with the first quartile representing the lowest quartile and the fourth quartile representing the highest quartile. Linear regression was used to measure the association of BLL with FPG and HbA1c. Logistic regression was used to measure the association of BLL with High FPG and High HbA1c. The model was adjusted for age, sex, current smoking, BMI, total cholesterol, triglycerides, HDL, LDL and hypertension.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	In humans, after adjusting for confounders, the odds of having High FPG (≥5.6 mmol/L) were significantly increased by 25% in the participants in the fourth BLL quartile (OR 1.25, 95% CI 1.05, 1.49)
Author's conclusions	Interpretation of results	• Increased BLL was associated with increased FPG levels but not HbA1c levels after adjusting for age, sex, current smoking, body mass index, total cholesterol, triglycerides, HDL, LDL and hypertension. • Increased BLL was associated with increased FPG and HbA1c levels without adjusting for any confounders. • These findings support the possibility that low-level Pb exposure may increase hepatic glucose production (HGP) by affecting key enzymes of hepatic gluconeogenesis, eventually resulting in impaired FPG and hyperglycaemia.
	Assessment of uncertainty (if any)	Confounders adjusted for.
Reviewer comments	Results included/excluded in review (if applicable)	Blood lead levels >5.8 µg/dL (Quartile 4 only) were associated with fasting plasma glucose levels (but not glycated haemoglobin) in a statistically significant manner after adjustment of potential confounders. This study was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Wan et al. 2022

Publication Reference: Wan H., Wang Y., Zhang H., Zhang K., Chen Y., Chen C., Zhang W., Xia F., Wang N. and Lu Y. (2022). Chronic lead exposure induces fatty liver disease associated with the variations of gut microbiota. Ecotoxicol Environ Saf 232: 113257.		
General Information	Date of data extraction	10 July 2023
	Authors	Wan,H., Wang, Y., Zhang, H., Zhang, K., Chen, Y., Chen, C., Zhang, W., Xia, F., Wang, N., Lu, Y.
	Publication date	Available online 29 January 2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
	Possible conflicts of interest	
Study characteristics	Aim/objectives of study	Authors aimed to investigate the association of chronic Pb exposure with fatty liver disease and whether the variations of the gut microbiota are involved in the mechanism of fatty liver disease induced by chronic Pb exposure.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	The subjects were recruited from 23 sites in Shanghai, Zhejiang, Jiangxi, Jiangsu, and Anhui Province from February 2014 to May 2016. Chinese citizens ≥ 18 years old who had lived in their current area for ≥ 6 months were included.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	3066 rural participants in East China
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable. (Blood Lead Level: The median BLL was 4.7 µg/dL).
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Quartile 1 (≤ 3.1 µg/dL), Quartile 2 (> 3.1, ≤ 4.7 µg/dL), Quartile 3 (>4.7, ≤ 6.6 µg/dL), and Quartile 4 (> 6.6 µg/dL)
Study methods	Water quality measurement used	Not applicable. BLL by atomic absorption spectrometry or quadrupole ICP-MS
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Blood lead level (BLL) was detected, and abdominal ultrasonography was used to diagnose hepatic steatosis. Both the definition of non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) were used. Trained staff used a questionnaire to collect information, including information on sociodemographic characteristics, medical history and lifestyle factors, and conducted the physical examinations in accordance with the previous standard protocol.
	How outcome was assessed	
	Method of measurement	

Publication Reference: Wan H., Wang Y., Zhang H., Zhang K., Chen Y., Chen C., Zhang W., Xia F., Wang N. and Lu Y. (2022). Chronic lead exposure induces fatty liver disease associated with the variations of gut microbiota. Ecotoxicol Environ Saf 232: 113257.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	After excluding participants who were unable to diagnose NAFLD or MAFLD or missing BLL data, 3066 rural participants were involved in the final analyses.
Statistics (if any)	Statistical method used	Statistical analyses were conducted with IBM SPSS 22.0 (Chicago, USA) and R Studio software (Boston, USA). Continuous variables are expressed as the mean ± standard deviation (SD) or median (inter-quartile range). Categorical variables are expressed as percentages (%). Linear or logistic regression analysis was applied to detect the trends of variable changes across the BLL quartiles, providing unadjusted P- values. To achieve a normal distribution, BLL were logarithmically transformed for the analyses. BLL was divided into quartiles. The first quartile was defined as the lowest quartile and the fourth quartile was defined as the highest quartile. Logistic regression was applied to measure the association of BLL with NAFLD and MAFLD. The models were adjusted for age, sex, and current smoking. Stratified analysis by sex were further performed. Statistical significance between two groups were examined using independent samples t-tests. A P-value < 0.05 indicated significance (two sided).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	In humans, after adjusting for potential confounders, the odds of having NAFLD and MAFLD were significantly increased by 54% and 52% in the participants in the fourth BLL quartile (OR 1.54, 95% CI 1.24, 1.91 and OR 1.52, 95% CI 1.22, 1.89). **Associations of BLL with the prevalence of NAFLD and MAFLD** <u>All participants</u> <u>NAFLD</u> <u>MAFLD</u> Quartile 4 1.54 (1.24, 1.91) 1.52 (1.22, 1.89) Quartile 3 1.40 (1.13, 1.74) 1.39 (1.12, 1.73) Quartile 2 1.05 (0.84, 1.30) 1.08 (0.86, 1.34)
Author's conclusions	Interpretation of results	• Compared with the participants in the lowest BLL quartile, those in the highest quartile were older, were more likely to be men, had significantly higher BMI, waist circumference, FPG, total cholesterol, triglycerides, and LDL levels, and had a higher prevalence of current smoking, MAFLD, NAFLD, and hypertension (all P for trend < 0.05). • Increased BLL was associated with higher prevalence of NAFLD and MAFLD both in the total population and in stratified analysis by sex after adjusting for potential confounders. • Chronic Pb exposure could induce fatty liver disease.
	Assessment of uncertainty (if any)	Sensitivity analyses were performed. Authors further analysed the association between BLL and the prevalence of NAFLD after adjusting for potential confounders including age, sex, current smoking, waist circumference, TC, TG, HbA1c and hypertension.
Reviewer comments	Results included/excluded in review (if applicable)	Blood lead levels >4.7 µg/dL (Quartile 3 and Quartile 4) in Chinese adults were associated with fatty liver disease in a statistically significant manner. This study was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

APPENDIX C3 Additional Studies

Asgary et al. 2017

Publication Reference: Asgary S., Movahedian A., Keshvari M., Taleghani M., Sahebkar A. and Sarrafzadegan N. (2017). Serum levels of lead, mercury and cadmium in relation to coronary artery disease in the elderly: A cross-sectional study. Chemosphere 180: 540-544.		
General Information	Date of data extraction	11 July 2023
	Authors	Asgary, S., Movahedian, A., Keshvari, M., Taleghani, M., Sahebkar, A., Sarrafzadegan, N.
	Publication date	Available online 29 March 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Iran
	Source of funding	This study was financially supported by the Research Council at the Isfahan University of Medical Sciences, Isfahan, Iran.
	Possible conflicts of interest	None.
Study characteristics	Aim/objectives of study	Authors aimed to evaluate serum concentrations of lead (s-Pb), mercury (s-Hg) and cadmium (s-Cd) in patients with coronary artery disease (CAD) in comparison with those of healthy individuals. The correlation between serum levels of these heavy metals and lipid profile parameters was also investigated.
	Study type/design	Case control study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Subjects were selected from those with suspected CAD undergoing coronary angiography at the Cardiology Centers of Shahid Chamran and Sadi Hospitals (Isfahan, Iran)
	Selection criteria for population (if applicable)	
	Subgroups reported	Patients with CAD and healthy controls
	Size of study	65 patients (35 females) aged 50-70 years with angiographically-documented CAD and 65 healthy controls (43 females) matched for sex, age and place of residence.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable

Publication Reference: Asgary S., Movahedian A., Keshvari M., Taleghani M., Sahebkar A. and Sarrafzadegan N. (2017). Serum levels of lead, mercury and cadmium in relation to coronary artery disease in the elderly: A cross-sectional study. Chemosphere 180: 540-544.

	Exposure concentrations (if applicable)	**Serum heavy metal concentrations in the study groups.** CAD+ / CAD- / p-value S-Pb (μg/L): 8.19 ±0.07 / 3.69 ±0.08 / 0.015 S-Hg (μg/L): 8.12 ±0.05 / 4.11 ±0.05 / 0.012 S-Cd (μg/L): 2.44 ±0.002 / 1.15 ±0.003 / 0.126
	Comparison group(s)	Healthy controls
Study methods	Water quality measurement used	Not applicable (Blood lead levels: graphite furnace atomic absorption (GFAA))
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Subjects were indicated for diagnostic coronary angiography because of chest pain, breath shortness or previous history of myocardial infarction (MI). • Coronary angiography was performed in all subjects using a standard procedure through femoral artery. • According to the angiogram findings, subjects were divided into two groups. Coronary angiography was considered positive (CAD þ group) if more than 70% diameter reduction was observed in at least one of the major coronary arteries (left main, circumflex, left anterior descending and right coronary artery), or the subject was a candidate for angioplasty or coronary artery bypass surgery (CABG).
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Patients with significant valvular disease or heart failure were excluded.
Statistics (if any)	Statistical method used	Statistical analyses were performed using SPSS software (version 15). Data were presented as mean ± standard deviation (SD). Group comparisons were performed using independent sample t-test (for normally distributed continuous variables), Mann-Whitney U test (for normally distributed continuous variables) and chi-square test (for categorical variables). Association between serum concentrations of lipids and heavy metals was assessed using Spearman's correlation. In addition, binary logistic regression analysis was performed to assess the association between serum levels of heavy metals and presence of CAD in the presence of confounders such as age, gender, serum TC:HDL-C ratio, BMI and presence of hypertension and diabetes.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	**Logistic regression analysis assessing the association between serum heavy metal levels and the presence of CAD.** OR / CI / p-value S-Pb Crude: 1.052 / 1.016, 1.090 / 0.005 S-Pb Adjusted: 1.050 / 1.009, 1.094 / 0.018 S-Cd Crude: 1.046 / 1.009, 1.086 / 0.016 S-Cd Adjusted: 1.041 / 0.992, 1.093 / 0.105 S-Hg Crude: 1.057 / 1.010,1.106 / 0.017 S-Hg Adjusted: 1.064 / 1.018, 1.111 / 0.006

Publication Reference: Asgary S., Movahedian A., Keshvari M., Taleghani M., Sahebkar A. and Sarrafzadegan N. (2017). Serum levels of lead, mercury and cadmium in relation to coronary artery disease in the elderly: A cross-sectional study. Chemosphere 180: 540-544.		
Author's conclusions	Interpretation of results	• It was observed that the mean concentration of s-Pb (12.54 ±8.41 vs. 5.89 ±4.44 µg/L, p <0.05) and s-Cd (0.938 ±0.72 vs. 0.448 ±0.30, p <0.05; CI: 95%) and s-Hg (10.14 ±5.06 vs. 6.11 ±5.66, p <0.05) were significantly higher in CAD patients compared with control subjects. • The same result was also obtained after adjustment for cardiovascular risk factors including age, dyslipidaemia, diabetes mellitus and hypertension (p <0.05). • The mean concentration of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and TC:HDL-C ratio were significantly higher in CAD patients (p <0.05). • There was no significant association between serum metal concentrations with TC, HDL-C and TC:HDL-C ratio (p >0.05). • The present results showed that serum levels of heavy metals are associated with the presence of CAD. Long-term exposure to trace levels of Pb, Cd and Hg may play a role in the development of coronary atherosclerotic plaques.
	Assessment of uncertainty (if any)	Some confounders adjusted for. Binary logistic regression analysis was performed to assess the association between serum levels of heavy metals and presence of CAD in the presence of confounders such as age, gender, serum TC:HDL-C ratio, BMI and presence of hypertension and diabetes.
Reviewer comments	Results included/excluded in review (if applicable)	Serum levels of Pb 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. Cadmium and mercury serum levels were also associated with the presence of CAD. However, the Pb 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). A RoB assessment was not undertaken 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.
	Notes on study quality, e.g. gaps, methods	

Carpenter et al. 2019

Publication Reference: Carpenter C., Potts B., von Oettingen J., Bonnell R., Sainvil M., Lorgeat V., Mascary M. C., She X., Jean-Baptiste E., Palfrey S., Woolf A. D. and Palfrey J. (2019). Elevated Blood Lead Levels in Infants and Children in Haiti, 2015. Public Health Rep 134(1): 47-56.		
General Information	Date of data extraction	11 July 2023
	Authors	Carpenter, C., Potts, B., von Oettingen, J., Bonnell, R., Sainvil, M., Lorgeat, V., Mascary, M.C., She, X., Jean-Baptiste, E., Palfrey, S., Woolf, A.D., Palfrey, J.
	Publication date	2019
	Publication type	Journal article
	Peer reviewed?	Not stated

Publication Reference: Carpenter C., Potts B., von Oettingen J., Bonnell R., Sainvil M., Lorgeat V., Mascary M. C., She X., Jean-Baptiste E., Palfrey S., Woolf A. D. and Palfrey J. (2019). Elevated Blood Lead Levels in Infants and Children in Haiti, 2015. Public Health Rep 134(1): 47-56.

	Country of origin	USA
	Source of funding	All phases of this study were supported by the Kay Mackenson Center, which receives support from the Goldsmith Foundation. In-kind donation provided by Magellan Diagnostics Inc, Billerica, Massachusetts (LeadCare2® equipment and supplies).
	Possible conflicts of interest	The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Study characteristics	Aim/objectives of study	Authors sought to determine the prevalence of elevated blood lead levels (EBLLs) among healthy Haitian children.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	We conducted this cross-sectional study of Haitian infants and young children aged 9 months to 6 years from March 1 through June 30, 2015, in 3 diverse geographical departments of Haiti: an urban area in the Haitian capital (Port-au-Prince) in the Nord-Ouest Department (an administrative region in Haiti), a coastal area in the Artibonite Department, and a mountain area in the Centre Department.
	Selection criteria for population (if applicable)	
	Subgroups reported	Children from urban, coastal, and mountain areas in exposed and unexposed groups
	Size of study	273 children
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	The median BLL was 5.8 µg/dL, with higher levels in the mountain area than in the other areas (P < 0.001).
	Comparison group(s)	Exposed and unexposed groups
Study methods	Water quality measurement used	Not applicable BLLs: LeadCare II Blood Lead Analyzer
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Authors obtained anthropometric measurements, household income, potential sources of lead exposure, and fingerstick BLLs from 273 children at 6 churches in Haiti. They considered a BLL >5 µg/dL to be elevated.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Of 273 children enrolled in the study, 95 were from the coastal area, 78 from the urban area, and 100 from the mountain area.
Statistics	Statistical method used	

Publication Reference: Carpenter C., Potts B., von Oettingen J., Bonnell R., Sainvil M., Lorgeat V., Mascary M. C., She X., Jean-Baptiste E., Palfrey S., Woolf A. D. and Palfrey J. (2019). Elevated Blood Lead Levels in Infants and Children in Haiti, 2015. Public Health Rep 134(1): 47-56.

(if any)	Details on statistical analysis	Authors analysed characteristics of the study population as numbers and percentages, except for income and serum lead levels, which were reported as medians and interquartile ranges (IQRs). Authors stratified characteristics and analysed them for differences across the 3 geographic areas by using the Pearson w2 test; compared median incomes and serum lead levels by using the nonparametric Kruskal-Wallis test. Authors determined the prevalence of EBLLs by demographic and potential lead exposure characteristics, and calculated the prevalence ratios (PRs) of EBLLs by selected risk factors, with a predetermined reference category (in general, the category with the lowest prevalence of EBLLs). They tabulated PRs with 95% confidence intervals (CIs), and considered P < 0.05 to be significant.
	Relative risk/odds ratio, confidence interval?	**Exposure to lead from improperly discarded batteries among a convenience sample of children aged 9 months to 6 years (n = 258), by geographic area, Haiti, 2015** (Note: Only stats for exposed group shown) N — Prevalence Ratio (95% CI) — P Value Mountain area — 51 — 1.34 (1.07-1.66) — .004 Urban area — 35 — 1.09 (0.72-1.64) — .69 Coastal area — 46 — 1.30 (0.91-1.88) — .14
Author's conclusions	Interpretation of results	• BLLs were elevated in 180 (65.9%) children. • The prevalence of EBLL was significantly higher in the mountain area (82 of 100, 82.0%; P < 0.001) than in the urban area (42 of 78, 53.8%) and the coastal area (56 of 95, 58.9%; P < 0.001). • Twenty-eight (10.3%) children had EBLLs >10 µg/dL and 3 (1.1%) children had EBLLs >20 µg/dL. • Exposure to improperly discarded batteries (P = 0.006) and living in the mountain area (P < 0.001) were significant risk factors for EBLLs. • More than half of Haitian children in our study had EBLLs. Public health interventions are warranted to protect children in Haiti against lead poisoning.

Publication Reference: Carpenter C., Potts B., von Oettingen J., Bonnell R., Sainvil M., Lorgeat V., Mascary M. C., She X., Jean-Baptiste E., Palfrey S., Woolf A. D. and Palfrey J. (2019). Elevated Blood Lead Levels in Infants and Children in Haiti, 2015. Public Health Rep 134(1): 47-56.		
	Assessment of uncertainty (if any)	The investigation into potential sources of lead exposure in the environment was exploratory. One major limitation was reliance on parental reporting of environmental lead hazards, which may have introduced recall, social desirability, or aquiescence bias. The questionnaire also asked only about the presence or absence of certain exposures. Although the authors were able to identify improperly discarded batteries as one source of lead exposure, additional questionnaire details such as information on manioc consumption, lead-containing paint or pottery, household dust, plasters and dirt may have allowed for identification of additional potential sources of lead exposure in the child's home environment. Also unable to take into account exposures outside of the home, such as in schools. The study may also be biased by the use of a convenience sample. Although the authors chose to recruit children from churches within each area because of the high rate of Christianity across all socioeconomic levels in Haiti, they did not include in the sample children whose parents were not Christian or who were Christian but did not attend church.
Reviewer comments	Results included/excluded in review (if applicable)	This study showed that children in Haiti had elevated blood lead levels but did not attempt to associate the elevated blood lead levels with a health affect thus there is no relevant dose response relationships from this data that could reliably be used to derive criteria. Hence, a RoB assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Cheng et al. 2017

Publication Reference: Cheng L., Zhang B., Huo W., Cao Z., Liu W., Liao J., Xia W., Xu S. and Li Y. (2017). Fetal exposure to lead during pregnancy and the risk of preterm and early-term deliveries. Int J Hyg Environ Health 220(6): 984-989.		
General Information	Date of data extraction	11 July 2023
	Authors	Cheng, L., Zhang, B., Huoa, W., Caoc, Z., Liua, W., Liaoa, J., Xiaa, W., Xua, S., Li, Y.
	Publication date	Accepted 16 May 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	China
	Source of funding	This study was supported by the National Natural Science Foundation of China (81372959, 21437002, and 81402649), the National key Research and Development Plan (2016YFC0206700, 2016YFC0206203), and the Fundamental Research Funds for the Central Universities, HUST (2016YXZD043).
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	This prospective birth cohort study evaluated the risks of preterm and early-term births and its association with prenatal lead exposure in Hubei, China.

Publication Reference: Cheng L., Zhang B., Huo W., Cao Z., Liu W., Liao J., Xia W., Xu S. and Li Y. (2017). Fetal exposure to lead during pregnancy and the risk of preterm and early-term deliveries. Int J Hyg Environ Health 220(6): 984-989.

	Study type/design	Prospective cohort study
	Study duration	40 weeks
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Data of this research was obtained from the prospective Healthy Baby Cohort (HBC), conducted at the Wuhan Medical and Health Center for Women and Children, China.
	Selection criteria for population (if applicable)	Inclusion criteria in this study were: (1) Residents of Wuhan City during pregnancy; (2) singleton live birth without congenital malformation, and (3) ability to understand Chinese in order to complete the questionnaire independently.
	Subgroups reported	Tertiles: Low (≤2.29 μg/g Cr), Medium (2.29–4.06 μg/g Cr) and High (>4.06 μg/g Cr)
	Size of study	A total of 7299 pregnant women were selected from the Healthy Baby Cohort.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	The geometric mean of creatinine-adjusted urinary lead concentrations among all participating mothers, preterm birth, and early-term birth were 3.19, 3.68, and 3.17 μg/g creatinine (Cr), respectively.
	Comparison group(s)	Lowest tertile (≤2.29 μg/g Cr)
Study methods	Water quality measurement used	Not applicable Maternal urinary lead levels: Inductively Coupled Plasma Mass Spectrometry. Urinary creatinine levels: Mindray BS-200 CREA Kit
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Cheng L., Zhang B., Huo W., Cao Z., Liu W., Liao J., Xia W., Xu S. and Li Y. (2017). Fetal exposure to lead during pregnancy and the risk of preterm and early-term deliveries. Int J Hyg Environ Health 220(6): 984-989.

<table>
<tr>
<td rowspan="2"></td>
<td>Method of measurement</td>
<td>

Using Kolmogorov–Smirnov normality test, the distribution of creatinine-adjusted urinary lead concentrations was right-skewed, and therefore natural log-transformation (Ln-lead) was used.
Separate multiple linear regression models were performed to test the relationship between urinary lead levels as a continuous variable or tertile as a categorical variable and gestational age (days) as a continuous variable. Multiple logistic regression models were performed to evaluate the odds ratios (ORs) of preterm (<37 weeks) and early-term (38–39 weeks) deliveries as binary outcomes with tertiles of urinary lead levels, and the lowest tertile was defined as the referent group.
Potential confounding variables were selected based on <i>a priori</i> knowledge of their relationships with lead exposure and preterm and early-term births.
All statistical analyses were conducted with SAS (version 9.4; SAS Institute Inc., Carry, NC). The result was considered to be statistically significant when a two-tailed test value was below the level of 0.05.

</td>
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<tr>
<td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td>
<td>Of the 7299 singleton live births, there were 283 (3.9%) preterm and 2145 (29.4%) early-term births.
Exclusion criteria for this study were missing urine samples or newborns with congenital heart defects (CHDs), cleft lip and cleft palate, anophthalmia and microphthalmia, gastroschisis, etc. For the three women who had two time deliveries during the cohort study, the first delivery was chosen.</td>
</tr>
<tr>
<td rowspan="3">Statistics
(if any)</td>
<td>Statistical method used</td>
<td rowspan="2">The associations between tertiles of urinary lead levels and the risks of preterm and early-term deliveries were assessed using multiple logistic regression models.</td>
</tr>
<tr>
<td>Details on statistical analysis</td>
</tr>
<tr>
<td>Relative risk/odds ratio, confidence interval?</td>
<td>Crude and adjusted odd ratios of early-term and preterm births associated with prenatal exposure to lead.
<table>
<tr><th></th><th>N</th><th>Crude</th><th>Adjusted*</th><th>Adjusted**</th></tr>
<tr><td><i>Preterm births (<37 weeks)</i></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Tertile1</td><td>74</td><td>(reference)</td><td></td><td></td></tr>
<tr><td>Tertile2</td><td>90</td><td>1.21 (0.88, 1.65)</td><td>1.27 (0.93, 1.74)</td><td>1.43 (1.07, 1.89)</td></tr>
<tr><td>Tertile3</td><td>119</td><td>1.64 (1.22, 2.20)</td><td>1.75 (1.30, 2.36)</td><td>1.96 (1.31, 2.44)</td></tr>
<tr><td>p for trend</td><td></td><td><0.01</td><td><0.01</td><td><0.01</td></tr>
<tr><td><i>Early term births (37 – 38 weeks)</i></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Tertile1</td><td>709</td><td>(reference)</td><td></td><td></td></tr>
<tr><td>Tertile2</td><td>708</td><td>1.01 (0.89, 1.14)</td><td>1.01 (0.89, 1.14)</td><td>1.13 (0.89, 1.16)</td></tr>
<tr><td>Tertile3</td><td>728</td><td>1.07 (0.95, 1.22)</td><td>1.07 (0.95, 1.22)</td><td>1.20 (0.98, 2.27)</td></tr>
<tr><td>p for trend</td><td></td><td>0.02</td><td>0.02</td><td><0.01</td></tr>
</table>
*Adjusted model for maternal age, occupation status, pre-pregnancy BMI, parity, passive smoking and pregnancy-induced hypertension.
** Adjusted model for maternal age, occupation status, pre-pregnancy BMI, parity, passive smoking, pregnancy-induced hypertension, and urinary concentrations of cadmium, arsenic, and thallium (μg/g Cr).</td>
</tr>
</table>

Publication Reference: Cheng L., Zhang B., Huo W., Cao Z., Liu W., Liao J., Xia W., Xu S. and Li Y. (2017). Fetal exposure to lead during pregnancy and the risk of preterm and early-term deliveries. Int J Hyg Environ Health 220(6): 984-989.		
Author's conclusions	Interpretation of results	• A significant increase in the risk of preterm births was associated with the highest urinary lead tertile after adjusting for confounders with odds ratio (OR) of 1.96. • The association was more pronounced among 25–36 year old mothers with OR of 2.03. • Though significant p trends were observed between lead exposure (medium and high tertiles) and the risk of early-term births, their ORs were not significant. • Findings indicate that the risk of preterm birth might increase with higher foetal lead exposure, particularly among women between the age of 25 and 36 years.
	Assessment of uncertainty (if any)	Confounders were adjusted for. The models were adjusted for categorised maternal age at delivery (<25, 25–29, ≥30 years), occupation status (employment, unemployment), pre-pregnancy BMI categorised based on the criteria set for Chinese adults body weight (≤18.5, 18.5–23.9, ≥24) (Zhou, 2002), parity (1 or ≥2), passive smoking during pregnancy (yes or no) and pregnancy-induced hypertension (yes or no).
Reviewer comments	Results included/excluded in review (if applicable)	High creatine adjusted urinary Pb level (>4.06 µg/g) was found to be associated with a significant increase in the risk of preterm births. Note blood lead levels were not measured hence a useful dose response data for guideline derivation may be difficult to establish using this study. This study was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Harvey et al. 2016 (Pb leaching study)

Publication Reference: Harvey P. J., Handley H. K. and Taylor M. P. (2016). Widespread copper and lead contamination of household drinking water, New South Wales, Australia. Environ Res 151: 275-285.		
General Information	Date of data extraction	11 July 2023
	Authors	Harvey, P.J., Handley, H.K., Taylor, M.P.
	Publication date	Available online 8 August 2016
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	P. Harvey is funded by a Macquarie University Research Excellence Scholarship (MQRES) (2012195) associated with an Australian Research Council Future Fellowship awarded to H. Handley (FT120100440).
	Possible conflicts of interest	Not stated
Study characteristics	Aim/objectives of study	This study examines arsenic, copper, lead and manganese drinking water contamination at the domestic consumer's kitchen tap in homes of New South Wales, Australia.
	Study type/design	Pb leaching study
	Study duration	Not applicable

Publication Reference: Harvey P. J., Handley H. K. and Taylor M. P. (2016). Widespread copper and lead contamination of household drinking water, New South Wales, Australia. Environ Res 151: 275-285.		
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	212 first draw drinking water samples
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Plumbing fittings
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable. (Taps and plumbing components: Field portable X-ray fluorescence analysis. Metals: Inductively Coupled Plasma Mass Spectrometer (ICP-MS))
	Water sampling methods (monitoring, surrogates)	• For Phase 1, first draw samples (n=212) were collected from each participant's kitchen tap after a 9 h stagnation period. • Ten additional samples were taken as part of the Phase 1 sampling process that involved flushing stagnant water from the internal plumbing for two minutes prior to collection, reflecting the practice recommended by NSW Health.
Results (for each outcome)	Definition of outcome	Not clearly stated. Authors compared heavy metal levels in water from different fittings.
	How outcome was assessed	
	Method of measurement	Measured heavy metal levels in water
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Harvey P. J., Handley H. K. and Taylor M. P. (2016). Widespread copper and lead contamination of household drinking water, New South Wales, Australia. Environ Res 151: 275-285.		
Author's conclusions	Interpretation of results	• Water lead concentrations derived for plumbing components in a laboratory water leaching trial (7-day sampling period) range from 108 µg/L to 1440 µg/L (n=28, mean – 328 µg/L, median – 225 µg/L). Analysis of the lead-free tap fitting showed that <1 µg/L was leached to water samples over the sampling period. • Analysis of 212 first draw drinking water samples shows that almost 100% and 56% of samples contain detectable concentrations of copper and lead, respectively. Lead concentrations were: mean 3.7 µg/L, median 1.3 µg/L. • Samples collected following a 2-minute flush period returned variable lead concentrations (e.g. sample 5 reduced from 10 µg/L to 1.1 µg/L, whereas sample 9 increased from 28 to 150 µg/L). • Analysis of household plumbing fittings (taps and connecting pipework) show that these are a significant source of drinking water lead contamination. • Analysis of kitchen tap fittings demonstrates these are a primary source of drinking water lead contamination (n=9, mean – 63.4 µg/L, median – 59.0 µg/L).The results of this study demonstrate that along with other potential sources of contamination in households, plumbing products that contain detectable lead up to 2.84% are contributing to contamination of household drinking water.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	Plumbing fittings (including taps) that contain detectable lead up to 2.84% are contributing to Pb levels in household drinking water. Mean Pb concentration found in first draw samples of tap water collected from NSW households was 3.7 µg/L (median 1.3 µg/L). Samples collected following a 2-minute flush period returned variable lead concentrations.
	Notes on study quality, e.g. gaps, methods	As this is a leaching study it was not subject to a RoB assessment. 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).

Kim et al. 2017

Publication Reference: Kim Y. S., Ha M., Kwon H. J., Kim H. Y. and Choi Y. H. (2017). Association between Low blood lead levels and increased risk of dental caries in children: a cross-sectional study. BMC Oral Health 17(1): 42.		
General Information	Date of data extraction	13 July 2023
	Authors	Kim, Y., Ha, M., Kwon, H., Kim, H., Choi, Y.
	Publication date	Published online: 13 January 2017
	Publication type	Journal article
	Peer reviewed?	Yes

Publication Reference: Kim Y. S., Ha M., Kwon H. J., Kim H. Y. and Choi Y. H. (2017). Association between Low blood lead levels and increased risk of dental caries in children: a cross-sectional study. BMC Oral Health 17(1): 42.		
	Country of origin	Korea
	Source of funding	This study was financially supported by the National Institute of Environmental Research and Korean Ministry of Environment and by a grant (15162MFDS045) from Ministry of Food and Drug Safety. The funding bodies did not play any role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	The objective of this study was to examine the association between low blood lead levels of <5 µg/dL and the development of dental caries among children.
	Study type/design	Cross-sectional study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	The present study was conducted as a part of the Children's Health and Environment Research (CHEER) study, which was a cohort study conducted from 2005 to 2010 to investigate the association between environmental exposure and health in school-aged children recruited from urban, rural, and industrial areas within Korea.
	Selection criteria for population (if applicable)	
	Subgroups reported	Permanent or deciduous teeth. Further segregated into children with teeth having decayed surfaces (ds or DS), filled surfaces (fs or FS), or the sum of decayed, (missing), and filled surfaces (dfs or DMFS)
	Size of study	A cohort of 7,059 school-aged children from six Korean cities
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	The geometric mean (geometric standard deviation, maximum) blood lead level was 1.53 µg/dL (1.57, 4.89 µg/dL), and 74.4% of children had a level of <2 µg/dL.
	Comparison group(s)	Children in permanent and deciduous teeth groups
Study methods	Water quality measurement used	Not applicable (Blood Pb level: atomic absorption spectrophotometry)
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Compared with the children who did not have dental caries, the risk of having dental caries according to blood lead level was estimated by using the zero-inflated negative binomial model.
	How outcome was assessed	
	Method of measurement	Oral examinations were performed based on the oral examination guidelines for epidemiological investigation established by the World Health Organization

<table>
<tr><th colspan="3"><i>Publication Reference:</i> Kim Y. S., Ha M., Kwon H. J., Kim H. Y. and Choi Y. H. (2017). Association between Low blood lead levels and increased risk of dental caries in children: a cross-sectional study. BMC Oral Health 17(1): 42.</th></tr>
<tr><td></td><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>The final study populations in the permanent and deciduous teeth groups were 1,564 and 1,241 children, respectively, after excluding 4 children with blood lead levels of >5 µg/dL.</td></tr>
<tr><td rowspan="3">Statistics
(if any)</td><td>Statistical method used</td><td rowspan="2">The Kruskal-Wallis or Wilcoxon rank sum tests were applied to assess differences in geometric mean blood lead level according to sociodemographic characteristics. The adjusted mean blood lead levels for dental caries-positive and dental caries-negative statuses were calculated by using the least square mean estimation in the corresponding multiple linear regression model. Based on a previous study, among the Poisson, negative binomial, and zero-inflated Poisson models, the zero-inflated negative binomial model (ZINB) was reported to be the best-fitted model for the dental caries study because of excess zero of caries in children.</td></tr>
<tr><td>Details on statistical analysis</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>Association between blood lead concentration and dental caries in deciduous and permanent teeth
<table>
<tr><th></th><th></th><th colspan="2">Crude Model</th><th colspan="2">Adjusted Model</th></tr>
<tr><th></th><th>N</th><th>PR</th><th>95%CI</th><th>PR</th><th>95%CI</th></tr>
<tr><td><i>Deciduous teeth</i></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>ds</td><td>520</td><td>1.15</td><td>0.96–1.36</td><td>1.16</td><td>0.91–1.49</td></tr>
<tr><td>fs</td><td>903</td><td>1.08</td><td>0.98–1.20</td><td>1.11</td><td>0.98–1.25</td></tr>
<tr><td>dfs</td><td>1,014</td><td>1.09</td><td>1.00–1.19</td><td>1.14</td><td>1.02–1.27</td></tr>
<tr><td><i>Permanent teeth</i></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>ds</td><td>255</td><td>0.77</td><td>0.62–0.97</td><td>0.69</td><td>0.45–1.07</td></tr>
<tr><td>fs</td><td>523</td><td>0.89</td><td>0.81–0.99</td><td>0.87</td><td>0.73–1.04</td></tr>
<tr><td>dfs</td><td>698</td><td>0.86</td><td>0.78–0.95</td><td>0.83</td><td>0.69–0.99</td></tr>
</table>
Notes: ds = decayed surfaces, fs = filled surfaces, dfs = the sum of decayed, (missing), and filled surfaces, PR = prevalence ratio, CI = confidence interval</td></tr>
<tr><td>Author's conclusions</td><td>Interpretation of results</td><td>• Blood lead level was significantly higher in the children with than in those without deciduous dental caries (1.59 vs. 1.51 µg/dL), similarly with permanent dental caries (1.65 vs. 1.51 µg/dL).
• After adjustment for covariates, deciduous teeth surfaces that were decayed and filled increased significantly with increasing blood lead levels in a dose-dependent manner (prevalence ratio, 1.14; 95% confidence interval: 1.02–1.27).
• However, the risk of having dental caries in permanent teeth was not linearly associated with the increase in blood lead level.
• In the sum of decayed and filled surfaces, authors found a significant increase in risk of dental caries of the deciduous teeth with an increase in blood lead levels (<5 µg/dL) but found no statistical significance in the association with decayed and filled surfaces of caries separately.</td></tr>
</table>

Publication Reference: Kim Y. S., Ha M., Kwon H. J., Kim H. Y. and Choi Y. H. (2017). Association between Low blood lead levels and increased risk of dental caries in children: a cross-sectional study. BMC Oral Health 17(1): 42.		
	Assessment of uncertainty (if any)	Potential confounding factors or covariates were considered. These included sex, age, mother's educational level, monthly household income, and cotinine level in urine. Calcium and iron were not included in the multivariate models, as blood lead levels were not associated with calcium and iron concentrations in the subjects of this study. Lead exposure at the time of enamel formation is the mechanism most relevant to a causal lead-caries association. As this was a cross-sectional study, it could not provide evidence that the teeth were influenced by blood lead level during the period of ontogeny or after mineralisation. To identify a causal relationship between blood lead level and dental caries, a cohort study that measures lead exposure in pregnant women and then observes their infants is warranted.
Reviewer comments	Results included/excluded in review (if applicable)	This study found a statistically significant increase in the risk of dental caries in deciduous teeth with an increase in blood lead 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 however this is not discussed or outlined in the conclusions. A RoB assessment was undertaken for this study.
	Notes on study quality, e.g. gaps, methods	

La-Llave-León et al. 2016

Publication Reference: La-Llave-León O., Salas Pacheco J. M., Estrada Martínez S., Esquivel Rodríguez E., Castellanos Juárez F. X., Sandoval Carrillo A., Lechuga Quiñones A. M., Vázquez Alanís F., García Vargas G., Méndez Hernández E. M. and Duarte Sustaita J. (2016). The relationship between blood lead levels and occupational exposure in a pregnant population. BMC Public Health 16(1): 1231.		
General Information	Date of data extraction	11 July 2023
	Authors	La-Llave-León, O., Pacheco, J.M.S., Martínez, S.E., Rodríguez, E.E., Juárez, F.X.C, Carrillo, A.S., Quiñones, A.M.L., Alanís, F.V., Vargas, G.G., Hernández, E.M.M., Sustaita, J.D.
	Publication date	Published Online: 07 December 2016.
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Mexico
	Source of funding	This study was supported by grant no. DGO-2006-C01-4490 from the Council of Science and Technology for the State of Durango (COCYTED), Mexico
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	This study aims to assess the association between blood lead levels and occupational exposure in pregnant women from Durango, Mexico.
	Study type/design	Cross-sectional study
	Study duration	Not applicable

Publication Reference: La-Llave-León O., Salas Pacheco J. M., Estrada Martínez S., Esquivel Rodríguez E., Castellanos Juárez F. X., Sandoval Carrillo A., Lechuga Quiñones A. M., Vázquez Alanís F., García Vargas G., Méndez Hernández E. M. and Duarte Sustaita J. (2016). The relationship between blood lead levels and occupational exposure in a pregnant population. BMC Public Health 16(1): 1231.

	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	From June 2007 to May 2008 a cross-sectional study was conducted to evaluate the association between BLLs and some risk factors in pregnant women who received health attention in the State of Durango, Mexico. The study population consisted of pregnant women who received medical attention in two sanitary jurisdictions pertaining to the Secretary of Health. The inclusion criteria were: being pregnant, living in Durango, able to understand Spanish, and receiving health care paid for by the Secretary of Health.
	Selection criteria for population (if applicable)	
	Subgroups reported	Exposed group and control group
	Size of study	31 women who worked in jobs where lead is used (exposed group) and 268 who did not work in those places (control group).
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Occupational exposure
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Control group
Study methods	Water quality measurement used	Not applicable. Blood lead level: graphite furnace atomic absorption spectrometry
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	A regression with lead levels as outcome allowed to attribute the proportion of risk from occupational and non-occupational exposure. For assessment of the association between blood lead levels and occupational exposure, subjects were classified into two groups: women who worked in places where lead is used (exposed group) and women who did not work in those places (control group). Women who worked in automotive repair shops, mining laboratories, welding workshops, automotive harness factories, hairdressing salons, and road sweepers were included in the exposed group. Unemployed women and those women who had a job where lead- containing materials are not used, were included in the control group.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Among the 299 pregnant women enrolled in the study, 31 (10.4%) worked in places where lead is used, and 268 (89.6%) did not work where lead-containing materials are used.
Statistics (if any)	Statistical method used	Chi-square test was applied to compare exposed and control groups with regard to blood lead levels. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Multivariable regression analysis was applied to determine significant predictors of blood lead concentrations in the exposed group.
	Details on statistical analysis	

<table>
<tr><td colspan="3"><i>Publication Reference:</i> La-Llave-León O., Salas Pacheco J. M., Estrada Martínez S., Esquivel Rodríguez E., Castellanos Juárez F. X., Sandoval Carrillo A., Lechuga Quiñones A. M., Vázquez Alanís F., García Vargas G., Méndez Hernández E. M. and Duarte Sustaita J. (2016). The relationship between blood lead levels and occupational exposure in a pregnant population. BMC Public Health 16(1): 1231.</td></tr>
<tr><td></td><td>Relative risk/odds ratio, confidence interval?</td><td>
Results from the multiple linear regression analysis on the association between blood lead and risk factors
<table>
<tr><th></th><th>ß</th><th>95% CI</th><th>p-value</th></tr>
<tr><td>Washing the workwear together with other clothes</td><td>0.106</td><td>- 0.018 – 0.229</td><td>0.093</td></tr>
<tr><td>Use of lead glazed pottery</td><td>0.033</td><td>- 0.102 – 0.168</td><td>0.634</td></tr>
<tr><td>Dyeing hair</td><td>- 0.016</td><td>- 0.147 – 0.115</td><td>0.813</td></tr>
<tr><td>Living near workplaces where lead is used</td><td>- 0.021</td><td>- 0.197 – 0.156</td><td>0.818</td></tr>
<tr><td>Living near mining zone</td><td>0.237</td><td>0.006 – 0.468</td><td>0.044</td></tr>
<tr><td>Living near battery wshop</td><td>- 0.016</td><td>- 0.209 – 0.177</td><td>0.869</td></tr>
<tr><td>Living near junkyard</td><td>- 0.079</td><td>- 0.284 – 0.127</td><td>0.452</td></tr>
<tr><td>Living near rubbish dump</td><td>0.141</td><td>- 0.060 – 0.342</td><td>0.169</td></tr>
<tr><td>Living near straightening and painting workshop</td><td>0.023</td><td>- 0.172 – 0.218</td><td>0.819</td></tr>
<tr><td>Pica behavior</td><td>0.115</td><td>- 0.032 – 0.261</td><td>0.124</td></tr>
<tr><td>Living with someone who works with lead</td><td>0.056</td><td>- 0.071 – 0.183</td><td>0.387</td></tr>
<tr><td>Living near painting store</td><td>0.081</td><td>- 0.167 – 0.329</td><td>0.521</td></tr>
<tr><td>Living near printing office</td><td>- 0.120</td><td>- 0.441 – 0.201</td><td>0.461</td></tr>
<tr><td>Working in places where lead is used</td><td>0.306</td><td>0.103 – 0.509</td><td>0.003</td></tr>
</table>
Regression analysis for predictors of BLLs in exposed group
<table>
<tr><th></th><th>ß</th><th>95% CI</th><th>p-value</th></tr>
<tr><td>Wearing workwear</td><td>- 0.608</td><td>- 1.115 – -0.102</td><td>0.021</td></tr>
<tr><td>Changing clothes</td><td>- 0.637</td><td>- 1.261 – - 0.013</td><td>0.046</td></tr>
<tr><td>Live near painting store</td><td>3.937</td><td>1.174 – 6.699</td><td>0.008</td></tr>
<tr><td>Living near printing office</td><td>7.418</td><td>.963 – 10.873</td><td>0.001</td></tr>
<tr><td>Living near junkyard</td><td>3.661</td><td>0.691 – 6.632</td><td>0.019</td></tr>
<tr><td>Living near rubbish dump</td><td>3.469</td><td>0.036 – 6.901</td><td>0.048</td></tr>
<tr><td>Washing the workwear together with other clothes</td><td>2.372</td><td>0.267 – 4.477</td><td>0.029</td></tr>
</table>
</td></tr>
</table>

Publication Reference: La-Llave-León O., Salas Pacheco J. M., Estrada Martínez S., Esquivel Rodríguez E., Castellanos Juárez F. X., Sandoval Carrillo A., Lechuga Quiñones A. M., Vázquez Alanís F., García Vargas G., Méndez Hernández E. M. and Duarte Sustaita J. (2016). The relationship between blood lead levels and occupational exposure in a pregnant population. BMC Public Health 16(1): 1231.		
Author's conclusions	Interpretation of results	• Exposed women had higher blood lead levels than those in the control group (4.00 ± 4.08 µg/dL vs 2.65 ± 1.75 µg/dL, p = 0.002). • Furthermore, women in the exposed group had 3.82 times higher probability of having blood lead levels ≥5 µg/dL than those in the control group. • Wearing of special workwear, changing clothes after work, living near a painting store, printing office, junkyard or rubbish dump, and washing the workwear together with other clothes resulted as significant predictors of elevated blood lead levels in the exposed group. • Pregnant working women may be at risk of lead poisoning because of occupational and environmental exposure. The risk increases if they do not improve the use of protective equipment and their personal hygiene.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This study showed that women working within industries with exposure to lead had higher blood lead levels than those not working within these industries; this finding is unsurprising. However, there was no attempt to associate blood lead levels with a health affect thus there is no relevant health related information from these data that could reliably used to derive criteria. Hence, a RoB assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Nkomo et al. 2018

Publication Reference: Nkomo P., Naicker N., Mathee A., Galpin J., Richter L. M. and Norris S. A. (2018). The association between environmental lead exposure with aggressive behavior, and dimensionality of direct and indirect aggression during mid-adolescence: Birth to Twenty Plus cohort. Sci Total Environ 612: 472-479.		
General Information	Date of data extraction	10/07/2023
	Authors	Nkomo, P., Naicker, N ., Mathee, A., Galpin, J., Richter, L.M., Norris, S.A.
	Publication date	Available online 1 September 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	South Africa
	Source of funding	This study is supported by the Medical Research Council (South Africa). The BT20+ cohort is funded by the Wellcome Trust (United Kingdom), the Human Sciences Research Council (South Africa), and the Medical Research Council (South Africa), with support from the University of the Witwatersrand.
	Possible conflicts of interest	Not stated

Publication Reference: Nkomo P., Naicker N., Mathee A., Galpin J., Richter L. M. and Norris S. A. (2018). The association between environmental lead exposure with aggressive behavior, and dimensionality of direct and indirect aggression during mid-adolescence: Birth to Twenty Plus cohort. Sci Total Environ 612: 472-479.		
Study characteristics	Aim/objectives of study	The main aim of this study was to examine the association between lead exposure at 13 years old and dimensions of aggressive behaviour during mid-adolescence.
	Study type/design	Prospective cohort study
	Study duration	Not applicable. Blood samples collected at age 13 years were used to measure blood lead levels. Data on aggressive behaviour was gathered at age 14 to 15.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	The cohort includes all singleton births at public health facilities during a seven-week period from April 23 to June 8, 1990 in Soweto/Johannesburg, South Africa.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	The study sample included 508 males and 578 females in mid-adolescence (age 14 to 15 years) from the Birth to Twenty Plus cohort in Johannesburg, South Africa.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Blood lead levels ranged from 1 to 28.1 µg/dL.
	Comparison group(s)	<5 µg/dL - low – reference category
Study methods	Water quality measurement used	Not applicable Blood Pb levels: atomic absorption spectrometer with a THGA graphite furnace
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Seventeen items characterising aggression from the Youth Self Report questionnaire were used to examine aggressive behaviour.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1086 participants, 508 males and 578 females. Black African and Coloured (mixed race heritage) study participants with blood lead samples at age 13 years and who had completed the Youth Self Report (YSR) during mid-adolescence at ages 14 to 15 were included (n = 1086). White and Indian study participants were excluded due to very low numbers. In addition, to test if study participants exhibiting aggressive behaviour during mid-adolescence have early predisposition to aggressive behaviour, study participants with YSR data for year 11 were included in the study.
Statistics	Statistical method used	

<table>
<tr><th colspan="3">***Publication Reference:*** Nkomo P., Naicker N., Mathee A., Galpin J., Richter L. M. and Norris S. A. (2018). The association between environmental lead exposure with aggressive behavior, and dimensionality of direct and indirect aggression during mid-adolescence: Birth to Twenty Plus cohort. Sci Total Environ 612: 472-479.</th></tr>
<tr><td rowspan="2">(if any)</td><td>Details on statistical analysis</td><td>Principal Component Analysis was used to derive composite variables from the original data for aggressive behaviour; and data were examined for an association between blood lead levels and dimensionality of direct and indirect aggression and disobedience during mid-adolescence. We also examined the dimensions of aggression during mid-adolescence in relation to gender and socio-demographic factors.</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>

Odds Ratios for blood lead levels at age 13 years and aggressive behaviour during mid-adolescence controlling for aggressive behaviour during early adolescence

<table>
<tr><th></th><th>OR</th><th>(95% CI)</th><th>p-value</th></tr>
<tr><td>*Unadjusted*</td><td></td><td></td><td></td></tr>
<tr><td>I argue a lot</td><td>0.68</td><td>(0.47–0.97)</td><td>0.036</td></tr>
<tr><td>I threaten to hurt people</td><td>**3.74**</td><td>**(1.46–9.56)**</td><td>**0.006**</td></tr>
<tr><td>*Adjusted*</td><td></td><td></td><td></td></tr>
<tr><td>I argue a lot</td><td>0.66</td><td>(0.46–0.96)</td><td>0.03</td></tr>
<tr><td>I threaten to hurt people</td><td>**3.75**</td><td>**(1.46–9.59)**</td><td>**0.006**</td></tr>
</table>

Association between blood lead levels and socio-demographic factors and aggressive behaviour: linear regression analysis.

Model 1 (Unadjusted)

<table>
<tr><th></th><th>*β*</th><th>*Std Error*</th><th>*p-Value*</th></tr>
<tr><td>*5–9.99 μg/dL*</td><td></td><td></td><td></td></tr>
<tr><td>Indirect Aggression</td><td>0.004</td><td>0.06</td><td>0.95</td></tr>
<tr><td>Direct Aggression</td><td>−0.10</td><td>0.06</td><td>0.11</td></tr>
<tr><td>Disobedience</td><td>0.08</td><td>0.07</td><td>0.22</td></tr>
<tr><td>*≥10 μg/dL*</td><td></td><td></td><td></td></tr>
<tr><td>Indirect Aggression</td><td>0.26</td><td>0.19</td><td>0.17</td></tr>
<tr><td>Direct Aggression</td><td>**0.37**</td><td>**0.18**</td><td>**0.04**</td></tr>
<tr><td>Disobedience</td><td>−0.26</td><td>0.19</td><td>0.19</td></tr>
</table>

OR for adjusted model not shown.
</td></tr>
</table>

Publication Reference: Nkomo P., Naicker N., Mathee A., Galpin J., Richter L. M. and Norris S. A. (2018). The association between environmental lead exposure with aggressive behavior, and dimensionality of direct and indirect aggression during mid-adolescence: Birth to Twenty Plus cohort. Sci Total Environ 612: 472-479.		
Author's conclusions	Interpretation of results	- Blood lead levels ranged from 1 to 28.1 µg/dL. - Seventy two percent of males and 47.7% of females in the study had blood lead levels ≥5 µg/dL. - The results showed that there is a positive association between elevated blood lead levels (≥ 10 µg/dL) and direct aggression in South African adolescents, even when adjusted for potential confounders. This association was not significant for blood lead levels of 5-9.99 µg/dL. - And there is a positive relationship between adolescent males and direct aggressive behaviour but a negative association with indirect aggressive behaviour. - In contrast, indirect aggressive behaviour was positively associated with the female gender. - As such, the author concludes their findings show how environmental lead exposure potentially contributes to anti-social behaviour patterns among South African youth.
	Assessment of uncertainty (if any)	Confounders were considered in Model 2. Confounders considered included socio-demographic factors such as gender, maternal education at birth, maternal marital status at birth, maternal age at birth, residential area of birth, hospital of birth (public/private), and socio-economic status at birth.
Reviewer comments	Results included/excluded in review (if applicable)	This study found a significant positive association between elevated blood lead levels (*≥10 µg/dL*) and direct aggression in South African adolescents. This study was subject to a RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Reuben et al. 2017

Publication Reference: Reuben A., Caspi A., Belsky D. W., Broadbent J., Harrington H., Sugden K., Houts R. M., Ramrakha S., Poulton R. and Moffitt T. E. (2017). Association of Childhood Blood Lead Levels With Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. Jama 317(12): 1244-1251.		
General Information	Date of data extraction	10 July 2023
	Authors	Reuben, A, Caspi, A., Belsky, D., Broadbent, J., Harrington, H., Sugden, K., Houts, R.M., Ramrakha, S., Poulton, R., Moffitt, T.E.
	Publication date	2017 March 28
	Publication type	Journal Article
	Peer reviewed?	Yes
	Country of origin	New Zealand (with US, NZ and UK researchers)

Publication Reference: Reuben A., Caspi A., Belsky D. W., Broadbent J., Harrington H., Sugden K., Houts R. M., Ramrakha S., Poulton R. and Moffitt T. E. (2017). Association of Childhood Blood Lead Levels With Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. Jama 317(12): 1244-1251.

	Source of funding	The Dunedin Multidisciplinary Health and Development Research Unit is supported by the New Zealand Health Research Council and New Zealand Ministry of Business, Innovation and Employment (MBIE). This research received support from US-National Institute on Aging grants R01AG032282, R01AG049789, R01AG048895, the U.K. Medical Research Council grants MR/K00381X and MR/P005918/1, the Economic and Social Research Council grant ES/M010309/1, and the Jacobs Foundation.
	Possible conflicts of interest	The funders of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript or the decision to submit for publication.
Study characteristics	Aim/objectives of study	To test the hypothesis that childhood lead exposure is associated with cognitive function and socioeconomic status in adulthood and with changes in IQ and socioeconomic mobility between childhood and midlife.
	Study type/design	Prospective cohort study
	Study duration	38 Years
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Population-representative 1972–73 birth cohort from New Zealand, the Dunedin Multidisciplinary Health and Development Study, followed to age 38 years (December, 2012).
	Selection criteria for population (if applicable)	
	Subgroups reported	Lead level was analysed as a continuous measure. However, it is presented in terms of 5 µg/dL units
	Size of study	1037 original participants
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable for water. Childhood lead exposure ascertained as blood lead levels measured at 11 years. High blood lead levels were observed among children from all socioeconomic status levels in this cohort. Childhood blood lead levels ranged from 4 to 31 µg/dL (mean=10.99, SD=4.63).
	Comparison group(s)	Groups sorted into 5 µg/dL units
Study methods	Water quality measurement used	Not applicable Blood lead: graphite furnace atomic absorption spectrophotometry
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Reuben A., Caspi A., Belsky D. W., Broadbent J., Harrington H., Sugden K., Houts R. M., Ramrakha S., Poulton R. and Moffitt T. E. (2017). Association of Childhood Blood Lead Levels With Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. Jama 317(12): 1244-1251.		
	Method of measurement	• The IQ (primary outcome) and indexes of Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed (secondary outcomes) were assessed at 38 years using the Wechsler Adult Intelligence Scale–IV (WAIS-IV; IQ range 40–160). • Socioeconomic status (primary outcome) was assessed at 38 years using the New Zealand Socioeconomic Index-2006, (NZSEI-06; range 10=lowest-90=highest).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Of 1037 original participants, 1007 were alive at 38 years, of whom 565 (56%) had been lead tested at 11 years (54% male; 93% white).
Statistics (if any)	Statistical method used	First, sample descriptive statistics were generated for the sample as a whole and separately for study members with and without blood lead data. Differences between those with and without blood lead data were examined using t-tests or chi-square tests as appropriate. Pearson correlations between all study variables were calculated using standard procedures (i.e. PROC CORR) in SAS v 9.3. Second, the association between childhood blood lead levels and adult outcomes was tested using Ordinary Least Squares multiple regression. The two pre-specified primary outcome variables were adult IQ (measured with the WAIS-IV) and adult socioeconomic status (measured with the NZSEI-06 score), respectively. Each outcome was examined using two models: (1) a “sex adjusted” model in which the outcome was regressed on childhood blood lead levels and sex, and (2) a “fully adjusted” model in which the outcome was regressed on childhood blood lead levels and the following covariates: sex, childhood IQ, maternal IQ (assessed via the Science Research Associates verbal test administered to the Study mothers when the participants were 3 years old) and childhood socioeconomic status. The goal of the fully adjusted model was to evaluate the association between childhood blood lead levels and adult IQ and socioeconomic status using an analysis of covariance model of IQ and socioeconomic status change. Lead level was analysed as a continuous measure. However, it is presented in terms of 5 µg/dL units because the historic “level of concern” during the participant’s childhood was 10 µg/dL and today it is 5 µg/dL, making this unit meaningful to clinicians and policymakers. Moreover, 5 µg/dL represents approximately one standard deviation of blood lead level in this cohort. Analyses were conducted using SAS v9.3. Regression coefficients refer to dose increments of 5 µg/dL in childhood blood-level. The threshold for statistical significance was P<0.05, two-tailed. For sensitivity analyses all statistical analyses were repeated after subjecting the lead measure to a logarithmic transformation and a correction for haematocrit levels, and after incorporating two additional covariates into the fully-adjusted analysis of covariance: maternal smoking during pregnancy (assessed via maternal interview) and child birth weight (from hospital records).
	Details on statistical analysis	

Publication Reference: Reuben A., Caspi A., Belsky D. W., Broadbent J., Harrington H., Sugden K., Houts R. M., Ramrakha S., Poulton R. and Moffitt T. E. (2017). Association of Childhood Blood Lead Levels With Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. Jama 317(12): 1244-1251.

	Relative risk/odds ratio, confidence interval?	**Association between childhood blood lead levels and two primary outcomes at age 38 years: adult IQ and adult socioeconomic status. Secondary outcomes were Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed.** Sex Adjusted b 95% CI P **Full-Scale IQ −1.97 (−3.34, −0.59) 0.005** Verbal Comprehension IQ −1.39 (−3.01, 0.23) 0.09 Perceptual Reasoning IQ **−2.36 (−3.69, −1.03) <0.001** **Working Memory IQ −1.52 (−2.95, −0.08) 0.04** Processing Speed IQ −0.91 (−2.19, 0.37) 0.16 **Socioeconomic status −1.94 (−3.50, −0.37) 0.02** Fully Adjusted b 95% CI P **Full-Scale IQ −1.61 (−2.48, −0.74) <0.001** Verbal Comprehension IQ −1.01 (−2.18, 0.16) 0.09 Perceptual Reasoning IQ **−2.07 (−3.14, −1.01) <0.001** **Working Memory IQ −1.26 (−2.38, −0.14) 0.03** Processing Speed IQ −0.70 (−1.85, 0.45) 0.23 Socioeconomic status **−1.79 (−3.17, −0.40) 0.01** Note: The threshold for statistical significance was P<0.05, two-tailed (**Bolded**).
Author's conclusions	Interpretation of results	• Mean blood lead level at 11 years was 10.99 µg/dL (SD=4.63). Among blood-tested participants included at 38 years, mean WAIS-IV score was 101.16 (SD=14.82) and mean NZSEI-06 score was 49.75 (SD=17.12). • After adjusting for maternal IQ, childhood IQ, and childhood socioeconomic status, each 5 µg/dL higher level of blood lead in childhood was associated with a 1.61-point lower score (95%CI:−2.48, −0.74) in adult IQ, a 2.07-point lower score (95%CI: −3.14, −1.01) in Perceptual Reasoning, and a 1.26-point lower score (95%CI: −2.38, −0.14) in Working Memory. Lead-associated deficits in Verbal Comprehension and Processing Speed were not statistically significant. • After adjusting for confounders, each 5 µg/dL higher level of blood lead in childhood was associated with a 1.79-unit lower score (95%CI: −3.17, −0.40) in socioeconomic status. • An association between greater blood lead levels and a decline in IQ and socioeconomic status from childhood to adulthood was observed, with 40% of the association with downward mobility mediated by cognitive decline from childhood. • In this cohort born in New Zealand in 1972–1973, childhood lead exposure was associated with lower cognitive function and socioeconomic status at age 38 years and with declines in IQ and downward social mobility. Childhood lead exposure may have long-term ramifications.

Publication Reference: Reuben A., Caspi A., Belsky D. W., Broadbent J., Harrington H., Sugden K., Houts R. M., Ramrakha S., Poulton R. and Moffitt T. E. (2017). Association of Childhood Blood Lead Levels With Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. Jama 317(12): 1244-1251.		
	Assessment of uncertainty (if any)	Adjustments for confounders (see earlier text). Although mean blood lead levels in this New Zealand cohort were comparable to other developed-city cohorts born in the early 1970s, the lead level gradient observed in the Dunedin cohort was nearly entirely (94% of participants) above the current blood lead reference value for clinical attention (i.e. 5 µg/dL). This study's results may not, therefore, be informative about the long-term consequences of very low lead exposures (<7.5 µg/dL). This study was observational and correlational, and therefore does not establish a causal relation between lead exposure and outcomes, such as would be the case in a hypothetical experiment with children randomly assigned to lead exposure.
Reviewer comments	Results included/excluded in review (if applicable)	There was a statistically significant association between a 5 µg/dL increase in blood Pb level (BLL) from <5 µg/dL and lower cognitive function and socioeconomic status at age 38 years and with declines in IQ and downward social mobility. A RoB assessment was undertaken for this study.
	Notes on study quality, e.g. gaps, methods	

Vigeh et al. 2014

Publication Reference: Vigeh M., Yokoyama K., Matsukawa T., Shinohara A. and Ohtani K. (2014). Low level prenatal blood lead adversely affects early childhood mental development. J Child Neurol 29(10): 1305-1311.		
General Information	Date of data extraction	11 July 20230
	Authors	Vigeh, M., Yokoyama, K., Matsukawa, T., Shinohara, A., Ohtani, K.
	Publication date	Accepted for publication November 20, 2013
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Iran (Japanese researchers)
	Source of funding	This study was supported in joint collaboration by the Japanese National Institute of Occupational Safety and Health, a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science, and Tehran University of Medical Sciences.
	Possible conflicts of interest	The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Study characteristics	Aim/objectives of study	To estimate prenatal lead exposure effects on early childhood development
	Study type/design	Cohort study
	Study duration	36 months
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: Vigeh M., Yokoyama K., Matsukawa T., Shinohara A. and Ohtani K. (2014). Low level prenatal blood lead adversely affects early childhood mental development. J Child Neurol 29(10): 1305-1311.		
Population characteristics	Selection criteria for population (if applicable)	• A longitudinal study was conducted in 3 teaching hospitals affiliated with the Tehran University of Medical Sciences, Tehran, Iran, from October 2006 to March 2011. • The study originally consisted of 364 pregnant women who attended ambulatory prenatal clinics in the hospital at the first trimester of pregnancy (gestational age of 8-12 weeks). • They were non-smoking women with singleton pregnancies who were aged 16 to 35 years, and who were free from chronic conditions, such as heart disease, hypertension, diabetes, cancer or renal failure. • Authors invited the mothers and their children to participate in the study when children were up to 36 months old.
	Subgroups reported	• Children with developmental scores in normal range • Children with lower scores (less than 20% than expected for children's age and sex).
	Size of study	Maternal blood (n = 364) and umbilical cord blood (n = 224) samples were collected during pregnancy and at delivery.
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Maternal whole blood lead levels in the first trimester were significantly higher in children with developmental scores <20% than in those with normal scores (mean +standard deviation: 6.3 +1.9 vs 4.0 +2.4 µg/dL, respectively, P = 0.01). **Blood lead levels (µg/dL)** N / Mean ± SD / Range First trimester 174 4.15 ± 2.43 1.6-20.5 Second trimester 148 3.44 ± 1.28 1.1-7.5 Third trimester 145 3.78 ± 1.40 1.5-8.0 Umbilical cord 150 2.86 ± 1.09 1.2-6.9
	Comparison group(s)	Trimesters, and range in blood lead levels, and child developmental scores
Study methods	Water quality measurement used	Not applicable (Blood Pb levels: inductively coupled plasma-mass spectrometry (ICP-MS))
	Water sampling methods (monitoring, surrogates)	Not applicable
	Definition of outcome	

Publication Reference: Vigeh M., Yokoyama K., Matsukawa T., Shinohara A. and Ohtani K. (2014). Low level prenatal blood lead adversely affects early childhood mental development. J Child Neurol 29(10): 1305-1311.		
Results (for each outcome)	How outcome was assessed	• Comparison of prenatal blood lead levels in 3 pregnancy trimesters and umbilical cord with percentiles of development scores. • Child developmental score up to 36 months old and maternal whole blood lead (BPb) levels in the first trimester • Mental development was assessed using the Harold Ireton Early Child Development Inventory from 174 children. The cutoff point scores for categorisation as development delay was a developmental score less than 20% of that expected for childrens' age (i.e. 18-19 months, 20-21 months, and so on, with a particular cutoff point score for each age group and sex).
	Method of measurement	-
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• Of the 364 pregnant women, 224 mothers had their deliveries at the research hospitals. • A full follow-up of 174 infants whose mothers had at least valid measurement of blood lead for the first trimester of pregnancy was performed. • The main reason for the attrition of subjects during this period was loss to follow-up with a small percentage of missing data either on outcomes or on relevant covariates.
Statistics (if any)	Statistical method used	Pearson correlation coefficient was calculated to assess the relationship between prenatal blood lead levels and Early Child Development Inventory scores. Differences in characteristics between children with the developmental scores in the normal range and those with lower scores (less than 20% than expected for children's age and sex) were examined by the Student's t test for continuous variables and chi-square test for categorical variables. To examine whether levels of blood lead during pregnancy (first, second, and third trimesters, and in umbilical cord) were independently associated with the risk of lower Early Child Development Inventory scores (as dependent variables of lower [= 1] and normal range [=0]), the authors used a forward stepwise logistic regression analysis.
	Details on statistical analysis	

Publication Reference: Vigeh M., Yokoyama K., Matsukawa T., Shinohara A. and Ohtani K. (2014). Low level prenatal blood lead adversely affects early childhood mental development. J Child Neurol 29(10): 1305-1311.		
	Relative risk/odds ratio, confidence interval?	• Maternal whole blood lead levels in the first trimester were significantly (P = 0.01) higher in children with low development scores (6.31 + 1.95 µg/dL) than in those with scores in the normal range (4.05 + 2.40 µg/dL). • Almost the same result was found when the authors compared prenatal blood lead levels among the development scores percentiles (<25, 25-75, and >75) (Figure 1 in paper). • Maternal whole blood lead levels in the first trimester (original values and after withdrawal outliers) were inversely correlated with Early Child Development Inventory scores (r =<0.150 and –0.173, respectively; P < 0.05) (Figure 2 in paper). • Logistic regression analysis showed significant relationships between increasing maternal whole blood lead levels in the first trimester of pregnancy with a low score of Early Child Development Inventory, adjusting for multiple covariates (odds ratio =1.74, 95% confidence interval = 1.18-2.57, P = 0.005).
Author's conclusions	Interpretation of results	• Maternal blood lead levels in the first trimester were also inversely associated with the development scores (r =–0.155, P = 0.041). • Logistic regression analysis showed a significant relationship between increasing maternal blood lead levels in the first trimester with low development scores (odds ratio =1.74, 95% confidence interval =1.18-2.57, P = 0.005). • The findings of the present study showed a relatively low level of prenatal lead exposure (mean < 6.5 µg/dL) associated with lower developmental scores in early childhood.
	Assessment of uncertainty (if any)	Confounders were adjusted for. The model adjusted for covariates that might contribute to blood lead concentrations, such as haematocrit, and child mental development, such as the maternal educational level, body mass index, family income level, completed gestational age, birth weight, and first born.
Reviewer comments	Results included/excluded in review (if applicable)	Increasing maternal blood lead levels (mean < 6.5 µg/dL) were found to be associated with lower developmental scores in early childhood. It is unlikely that a dose response relationship below 5 µg/dL can be established with these data. Nonetheless, a RoB assessment was undertaken for this study.
	Notes on study quality, e.g. gaps, methods	

Wang et al. 2017

Publication Reference: Wang H., Li J., Hao J. H., Chen Y. H., Liu L., Yu Z., Fu L., Tao F. B. and Xu D. X. (2017). High serum lead concentration in the first trimester is associated with an elevated risk of small-for-gestational-age infants. Toxicol Appl Pharmacol 332: 75-80.		
	Date of data extraction	11 July 2023

Publication Reference: Wang H., Li J., Hao J. H., Chen Y. H., Liu L., Yu Z., Fu L., Tao F. B. and Xu D. X. (2017). High serum lead concentration in the first trimester is associated with an elevated risk of small-for-gestational-age infants. Toxicol Appl Pharmacol 332: 75-80.

General Information	Authors	Wang, H., Li, J., Hao, J., Chen, Y., Liu, L., Yu, Z., Fu, L., Tao, F., Xu, D.
	Publication date	Available online 26 July 2017
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	The present study was supported by the National Natural Science Foundation of China (81473016, 81630084, and 81471467) and the National Key Technology R & D Program (2006BAI05A03 to C-ABCS).
	Possible conflicts of interest	All authors have no conflicts of interest to declare
Study characteristics	Aim/objectives of study	The purpose of this study was to analyse whether gestational Pb exposure elevates risk of small-for-gestational-age (SGA) births in a Chinese population.
	Study type/design	Cohort study
	Study duration	40 weeks
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Total 3125 mother-infant pairs were recruited from the China-Anhui Birth Cohort Study (C-ABCS).
	Selection criteria for population (if applicable)	
	Subgroups reported	All subjects were classified into three groups according to the tertile division of serum Pb concentration: L-Pb (low-Pb, <1.18 µg/dL), M-Pb (medium-Pb, 1.18–1.70 µg/dL), and H-Pb (high-Pb, ≥1.71 µg/dL).
	Size of study	3125 mother-infant pairs
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Serum Pb concentration was analysed among 3125 pregnant women. Mean serum Pb level was 1.50 µg/dL (median: 1.43 µg/dL; minimum: 0.020 µg/dL; maximum: 5.46 µg/dL) among all subjects.
	Comparison group(s)	Low blood lead level tertile (L-Pb, <1.18 µg/dL)
Study methods	Water quality measurement used	Not applicable Blood lead level: Not described (reference to an accompanying study).
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Wang H., Li J., Hao J. H., Chen Y. H., Liu L., Yu Z., Fu L., Tao F. B. and Xu D. X. (2017). High serum lead concentration in the first trimester is associated with an elevated risk of small-for-gestational-age infants. Toxicol Appl Pharmacol 332: 75-80.		
	Method of measurement	In the present study, small for gestational age (SGA) was defined as live-born infants with birth weight below 10th percentile for the babies of the same gestational age according to a global reference. The mean birth weight and standard deviation (SD) at 40 gestational weeks were calculated in the birth cohort.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	3125 mother-infant pairs; L-Pb (n = 1042), M-Pb (n = 1042), and H-Pb (n = 1041)
Statistics (if any)	Statistical method used Details on statistical analysis	In the current study, one-way ANOVA was used for multiple comparisons. Multivariate logistic regression analysis was used to analyse the odds ratio (OR) for correlation of maternal Pb level with risk of SGA infants.
	Relative risk/odds ratio, confidence interval?	• The rate of SGA was 6.2% in subjects with L-Pb, 8.7% in subjects with M-Pb, and 10.1% in subjects with H-Pb, respectively. • The adjusted OR of SGA was 1.45 (95%CI: 1.04, 2.02; P = 0.03) in subjects with M-Pb and 1.69 (95%CI: 1.22, 2.34; P = 0.002) in subjects with H-Pb.
Author's conclusions	Interpretation of results	• There was no difference in birth length, head circumference and chest circumference among different groups. • Interestingly, the rate of SGA infants was elevated only in subjects who had 'H-Pb' in the first trimester (adjusted OR: 2.13; 95%CI: 1.24, 3.38; P = 0.007). • Collectively, high serum Pb level in the first trimester is associated with an elevated risk of SGA infants.
	Assessment of uncertainty (if any)	The study did not analyse the correlation of maternal serum Pb concentration with maternal Pb concentration in whole blood in different trimesters. The study also did not account for potential confounders including exposure to cadmium, arsenic, mercury, zinc and selenium. Although cigarette smokers were excluded from the study, the study did not quantitatively evaluate the influence of environmental tobacco smoke exposure on SGA as a confounder.
Reviewer comments	Results included/excluded in review (if applicable) Notes on study quality, e.g. gaps, methods	High serum Pb level in the first trimester (≥1.71 µg/dL) 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). 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. This study was subject to a RoB assessment.

Wu et al. 2019

Publication Reference: Wu Y., Jansen E. C., Peterson K. E., Foxman B., Goodrich J. M., Hu H., Solano-González M., Cantoral A., Téllez-Rojo M. M. and Martinez-Mier E. A. (2019). The associations between lead exposure at multiple sensitive life periods and dental caries risks in permanent teeth. Sci Total Environ 654: 1048-1055.		
General Information	Date of data extraction	13 July 2023
	Authors	Wua, Y., Jansena, E.C., Petersona, K.E., Foxmanc, B., Goodrichd, J.M., Hue, H., Solano-Gonzálezf, M., Cantoralf, A., Téllez-Rojof, M.M., and Martinez-Mier, E.A.
	Publication date	2019 March 01
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Mexico (Mexican and US researchers)
	Source of funding	The study was supported by the grants R01ES021446, R01ES007821, P42-ES05947 and P30ES017885 from the U.S. National Institute of Environmental Health Sciences (NIEHS), the grant P01ES022844/RD83543601 from NIEHS/U.S. Environmental Protection Agency, by the National Institute of Public Health/Ministry of Health of Mexico, and by a grant from the Binational/Cross-cultural Health Enhancement Center at IUPUI. The American British Cowdray Hospital provided facilities used for this research.
	Possible conflicts of interest	No potential conflict of interest was reported by the authors
Study characteristics	Aim/objectives of study	The primary study aim was to examine the associations between lead exposure at multiple sensitive periods and decayed, missing, filled tooth (DMFT) scores at adolescence. A secondary aim was to evaluate whether there was an interaction between Pb exposure and sugar-sweetened beverage (SSB) intake in relation to caries risk in adolescence.
	Study type/design	Prospective Cohort Study
	Study duration	18 years
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	The study population comprises a subset of participants from the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) project, a longitudinal epidemiological study consisting of three sequentially enrolled birth cohorts: enrolment cohort 1, 2, and 3. The mother/child pairs were recruited between 1997 and 2005 at three maternity hospitals representing a low- to moderate-income population in Mexico City. Authors re-contacted a subset of the offspring (n=250; henceforth referred to as the early-teen visit) from enrolment cohorts 2 and 3 based on availability of prenatal and neonatal biospecimens. One more peri-pubertal visit was completed approximately 5 years later.
	Selection criteria for population (if applicable)	
	Subgroups reported	First trimester (T1), 2nd trimester (T2), 3rd trimester (T3), Early childhood (EC), peri-puberty (PP)
	Size of study	Participants were 386 children living in Mexico City.
	Exposure pathway	Not applicable

<table>
<tr><td colspan="3"><i>Publication Reference:</i> Wu Y., Jansen E. C., Peterson K. E., Foxman B., Goodrich J. M., Hu H., Solano-González M., Cantoral A., Téllez-Rojo M. M. and Martinez-Mier E. A. (2019). The associations between lead exposure at multiple sensitive life periods and dental caries risks in permanent teeth. Sci Total Environ 654: 1048-1055.</td></tr>
<tr><td rowspan="3">Exposure and setting</td><td>Source of chemical/contamination</td><td>Not applicable</td></tr>
<tr><td>Exposure concentrations (if applicable)</td><td>Blood lead (µg/dL, mean ± standard deviation)
<table>
<tr><th></th><th><u>N</u></th><th><u>Male</u></th><th><u>Female</u></th><th><u>p-value</u></th></tr>
<tr><td><i>Rate Ratios</i></td><td></td><td></td><td></td><td></td></tr>
<tr><td>T1</td><td>230</td><td>6.06±3.84</td><td>6.36±5.08</td><td>0.61</td></tr>
<tr><td>T2</td><td>230</td><td>5.24±4.06</td><td>5.25±4.67</td><td>0.98</td></tr>
<tr><td>T3</td><td>230</td><td>5.67±3.48</td><td>5.73±4.46</td><td>0.91</td></tr>
<tr><td>EC</td><td>386</td><td>15.48±7.29</td><td>15.18±6.94</td><td>0.68</td></tr>
<tr><td>PP</td><td>205</td><td>3.60±3.22</td><td>3.34±2.68</td><td>0.53</td></tr>
<tr><td>Patella</td><td>259</td><td>8.64±10.11</td><td>9.68±11.05</td><td>0.43</td></tr>
<tr><td>Tibia</td><td>173</td><td>7.18±10.31</td><td>8.64±9.65</td><td>0.34</td></tr>
</table>
Notes: T1 = first trimester, T2 = 2nd trimester, T3 =- 3rd trimester, EC = Early childhood, PP = peri-puberty</td></tr>
<tr><td>Comparison group(s)</td><td>Not applicable</td></tr>
<tr><td rowspan="2">Study methods</td><td>Water quality measurement used</td><td>Not applicable.
Blood lead levels: graphite-furnace atomic-absorption spectroscopy, Maternal patella and tibia bone Pb levels: K-X-ray fluorescence instrument, and Dental caries presence: DMFT scores</td></tr>
<tr><td>Water sampling methods (monitoring, surrogates)</td><td>Not applicable</td></tr>
<tr><td rowspan="3">Results (for each outcome)</td><td>Definition of outcome</td><td rowspan="3">• Prenatal (trimester 1–3), early-childhood (12, 24, 36, and 48 months of age) and peri-pubertal (10–18 years of age) blood Pb levels were quantified using graphite-furnace atomic-absorption spectroscopy.
• Maternal patella and tibia bone Pb at 1 month postpartum were quantified with K X-ray fluorescence instrument.
• Dental caries presence was evaluated using decayed, missing, and filled teeth (DMFT) scores.</td></tr>
<tr><td>How outcome was assessed</td></tr>
<tr><td>Method of measurement</td></tr>
</table>

<table>
<tr><th colspan="3"><i>Publication Reference:</i> Wu Y., Jansen E. C., Peterson K. E., Foxman B., Goodrich J. M., Hu H., Solano-González M., Cantoral A., Téllez-Rojo M. M. and Martinez-Mier E. A. (2019). The associations between lead exposure at multiple sensitive life periods and dental caries risks in permanent teeth. Sci Total Environ 654: 1048-1055.</th></tr>
<tr><td></td><td>Number of participants (exposed/non-exposed, missing/excluded) (if applicable)</td><td>Mother info: T1, T2, and T3 blood Pb: n=230, Patella Pb: n = 259, Tibia Pb: n = 173.
Child info: Blood Pb: n = 286
Early teen info: Blood lead: n = 205
Of the initial 1,382 mothers who met eligibility criteria, 617 agreed to participate and continued in the study (Figure 1 in study report). Of these, 245 had blood samples collected at all three trimester visits, 349 had patella Pb measured and 249 had tibia Pb measured 1 month postpartum. Their newborns were followed from birth until 4 years of age; blood samples were collected every 12 months. Starting in 2008, the researchers re-contacted a subset of the offspring (n=250; henceforth referred to as the early-teen visit) from enrolment cohorts 2 and 3 based on availability of prenatal and neonatal biospecimens. One more peri-pubertal visit was completed approximately 5 years later (549; henceforth referred to as the peri-pubertal visit), again recruiting children from cohorts 2 and 3, that had prenatal and neonatal biospecimens available. Of those, 497 adolescents had their dental information collected.</td></tr>
<tr><td rowspan="3">Statistics
(if any)</td><td>Statistical method used</td><td rowspan="2">Poisson regression models were used to examine the associations between Pb with D1MFT and D4MFT at adolescence.</td></tr>
<tr><td>Details on statistical analysis</td></tr>
<tr><td>Relative risk/odds ratio, confidence interval?</td><td>Associations between log-transformed lead exposure at specific life stage and D1MFT score
<table>
<tr><th></th><th>N</th><th>Unadjusted</th><th>Adjusted</th></tr>
<tr><td><i>Rate Ratios</i></td><td></td><td></td><td></td></tr>
<tr><td>T1</td><td>230</td><td>1.12 (0.95, 1.31)</td><td>1.07 (0.90, 1.27)</td></tr>
<tr><td>T2</td><td>230</td><td>1.17 (1.00, 1.37)</td><td>1.12 (0.94, 1.32)</td></tr>
<tr><td>T3</td><td>230</td><td>1.20 (1.03, 1.40)</td><td>1.17 (0.99, 1.37)</td></tr>
<tr><td>EC</td><td>386</td><td>1.22 (1.02, 1.48)</td><td>1.14 (0.94, 1.38)</td></tr>
<tr><td>PP</td><td>205</td><td>0.92 (0.77, 1.11)</td><td>0.97 (0.81, 1.16)</td></tr>
<tr><td>Patella</td><td>259</td><td>0.97 (0.89, 1.05)</td><td>0.95 (0.88, 1.03)</td></tr>
<tr><td>Tibia</td><td>173</td><td>1.01 (0.91, 1.12)</td><td>0.98 (0.88, 1.08)</td></tr>
<tr><td><i>Probability of being DMFT score = 0</i></td><td></td><td></td><td></td></tr>
<tr><td>T1</td><td>230</td><td>1.00 (0.59, 1.68)</td><td>1.22 (0.68, 2.21)</td></tr>
<tr><td>T2</td><td>230</td><td>1.20 (0.70, 2.03)</td><td>1.47 (0.82, 2.62)</td></tr>
<tr><td>T3</td><td>230</td><td>0.90 (0.52, 1.53)</td><td>1.02 (0.56, 1.86)</td></tr>
<tr><td>EC</td><td>386</td><td>0.74 (0.38, 1.46)</td><td>0.81 (0.39, 1.65)</td></tr>
<tr><td>PP</td><td>205</td><td>1.13 (0.61, 2.08)</td><td>1.10 (0.59, 2.08)</td></tr>
<tr><td>Patella</td><td>259</td><td>1.05 (0.78, 1.41)</td><td>1.10 (0.81, 1.49)</td></tr>
<tr><td>Tibia</td><td>173</td><td>1.21 (0.77, 1.89)</td><td>1.41 (0.82, 2.43)</td></tr>
</table>
Notes: T1 = first trimester, T2 = 2nd trimester, T3 =- 3rd trimester, EC = Early childhood, PP = peri-puberty</td></tr>
</table>

Publication Reference: Wu Y., Jansen E. C., Peterson K. E., Foxman B., Goodrich J. M., Hu H., Solano-González M., Cantoral A., Téllez-Rojo M. M. and Martinez-Mier E. A. (2019). The associations between lead exposure at multiple sensitive life periods and dental caries risks in permanent teeth. Sci Total Environ 654: 1048-1055.		
Author's conclusions	Interpretation of results	• Maternal second and third trimester and cumulative early childhood Pb exposure were positively associated with peri-pubertal D1MFT scores in unadjusted Zero inflated negative binomial (ZINB) models (2nd trimester: RR=1.17 (1.00, 1.37); 3rd trimester: RR=1.20 (1.03, 1.40); early childhood: RR=1.22 (1.02, 1.48)). • These effect sizes were attenuated and no longer statistically significant after adjusting for covariates. Covariates included in final models were sex, cohort, mother's education and sugar sweetened beverage (SSB) intake during adolescence. • When stratified by high/low sugar-sweetened beverage (SSB) intake, a one unit increase of log-transformed 2nd trimester Pb exposure was associated with a 1.41 times (1.06, 1.86) higher D1MFT count, and 3rd trimester Pb exposure was associated with a 1.50 times (1.18, 1.90) higher D1MFT count among those with higher than median peri-pubertal SSB intake. • Associations among those with lower SSB intake were roughly half those of the higher group and not statistically significant. • Pb exposure during sensitive developmental periods was not statistically significantly associated with caries risk after accounting for confounders among this cohort. • However, evidence from stratified analysis suggested a Pb-caries association among children with high SSB intake.
	Assessment of uncertainty (if any)	Covariates adjusted for and included: Based on *a priori* knowledge and bivariate analysis, covariates included in final models were sex, cohort, mother's education and sugar sweetened beverages (SSB) intake during adolescence. Years of mother's education and interview-administered semi-quantitative food frequency questionnaire (FFQ).
Reviewer comments	Results included/excluded in review (if applicable)	An association between dental caries and Blood Pb levels (ranging from 3.34±2.68 to 15.48±7.29 µg/dL) was not established 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. A RoB assessment was undertaken for this study.
	Notes on study quality, e.g. gaps, methods	

APPENDIX D

Risk of Bias Tables

Cheng et al. 2017

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Cheng et al. 2017 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	Yes	There is insufficient information provided about the comparison group including a different rate of non-response without an explanation (Note: demographic data was reported to have been collected but was not shown).	NR
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, AND there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	--
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about numbers of subjects lost to follow-up (losses to follow up were not discussed).	NR
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure (Note that blood Pb levels were not reported in this study and reference, instead urinary lead levels were reported which are a much less commonly used biomarker of lead exposure).	+
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-

	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Danziger et al. 2021

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-sectional Studies greyed out.

Study ID: Danziger et al. 2021		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Study Type: Cross-sectional (CrSe)				
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	It is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results and it is deemed that the measures used would not appreciably bias results	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	

	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about numbers of subjects lost to follow-up (doesn't discuss lost or excluded participants due to incomplete data etc.)	NR
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure	-
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Danziger et al. 2022

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-sectional Studies greyed out.

Study ID: Danziger et al. 2022 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and	--

			exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	🟩
	Confounding bias			
4.	Confounding (design/analysis)	No	It is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results and it is deemed that the measures used would not appreciably bias results	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about numbers of subjects lost to follow-up (doesn't discuss lost or excluded participants due to incomplete data etc.)	NR
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure	-
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Dave and Yang 2022

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Dave and Yang 2022	**RoB: Yes/No**	**Notes**	**Risk of bias rating**

Study Type: Cohort (Co)		Unknown N/A		(--/-/+/++/NR)
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	-
	Confounding bias			
4.	Confounding (design/analysis)	Yes	There is insufficient information provided about the distribution of known confounders (NR)	NR
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about numbers of subjects lost to follow-up (doesn't discuss lost or excluded participants due to incomplete data etc.)	NR
	Detection Bias			
8.	Exposure characterisation	Yes	There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern (NR)	NR
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	Unusual method of statistical analysis employed which makes it difficult to interpret and confirm significance of results.	+

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

De Almeida Lopes et al. 2017

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: De Almeida Lopes et al. 2017 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, AND there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	--
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure (note that Quartile 4 had BLL >2.76 µg/dL)	+
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results	-
	Selective Reporting Bias			

10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Domeneh et al. 2014

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Domeneh et al. 2014 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/- /+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	Differences between groups would not appreciably bias results (e.g. demographic data not presented but controls recruited from the population near detoxification centres and all men were of similar age).	-
	Confounding bias			
4.	Confounding (design/analysis)	Yes	There is insufficient information provided about the distribution of known confounders (e.g. confounders are not discussed apart from age).	NR
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about why subjects were removed from the study or excluded from analyses.	NR
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure.	-

9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported (Note: the main object of the report is whether opium dependency is correlated with anaemia and although it was discussed in the report it is not stated in the conclusions).	+
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Enehizena and Emokpae 2022

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Case-Control greyed out.

Study ID: Enehizena et al. 2022 **Study Type: Case-Control (CaCo)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is insufficient information provided about the appropriateness of controls including rate of response reported for cases only. Note: minimal demographic data provided in the report.	NR
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching of cases and controls, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified, AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, AND there is direct evidence that	--

			other exposures anticipated to bias results were not present or were appropriately measured and adjusted for	🟩
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is indirect evidence that exclusion of subjects from analyses was not adequately addressed	+
	Detection Bias			
8.	Exposure characterisation	No	Exposure was assessed using less-established methods that directly measure exposure and are validated against well-established methods	-
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed in cases (i.e. case definition) and controls using acceptable methods and subjects had been followed for the same length of time in all study groups. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Fisher et al. 2021

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Fisher et al. 2021 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	

2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made for known confounders (maternal age (continuous), race/ethnicity (categorized as non-Hispanic white, non-Hispanic Black, Hispanic, or Other), and education), and there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements and there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure (note there is a large range in lead concentrations in well water and data was not stratified for lead concentrations).	+
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Hanna-Attisha et al. 2021

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Hanna-Attisha et al. 2021 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	Yes	There is insufficient information provided about the comparison group including a different rate of non-response without an explanation.	NR
	Confounding bias			
4.	Confounding (design/analysis)	No	It is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results.	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study for the Flint group.	--
	Detection Bias			
8.	Exposure characterisation	No	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure.	--
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, subjects had been followed for the same length of time in all study groups, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)			

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Kim et al. 2017

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Kim et al. 2017 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	-
	Confounding bias			
4.	Confounding (design/analysis)	No	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).	++
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure.	-
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a particular outcome).	-

	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	The researchers did not discuss the negative associations (improvements) between blood Pb levels and caries in permanent teeth. This indicates a potential bias in the results.	++

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Macdonald Gibson et al. 2022

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Macdonald Gibson et al. 2022 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	Yes	There is indirect evidence that subjects (both exposed and non-exposed) were not similar. (NB: there was a greater proportion of non-hispanic black people in the community water group than private well, 28.2% vs 20.8%, p=<0.001. There were also differences in when the houses were built and median incomes)	++
	Confounding bias			
4.	Confounding (design/analysis)	Yes	There is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity	+
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	

	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure (a better measure of exposure than Mean BLL could have been to stratify BLL in both groups).	++
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods AND there is indirect evidence that the outcome assessors were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Nkomo et al. 2018

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Nkomo et al. 2018 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and	-

			exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements, and there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for.	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study,	-
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure.	-
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study’s measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Reuben et al. 2017

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Reuben et al. 2017 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	Yes	There is insufficient information provided about the comparison group including a different rate of non-response without an explanation.	NR
	Confounding bias			
4.	Confounding (design/analysis)	No	It is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results and it is deemed that the measures used would not appreciably bias results.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study.	-
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure.	-
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Rodrigues et al. 2016

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Rodrigues et al. 2016 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/- /+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, AND there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements, and there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for.	--
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	It is deemed that the proportion lost to follow-up would not appreciably bias results.	-
	Detection Bias			
8.	Exposure characterisation	No	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure (e.g. measurement of the chemical in blood).	–
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, subjects had been followed for the same length of time in all study groups, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			

10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats identified.	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Sanders et al. 2014

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Ecological studies greyed out.

Study ID: Sanders et al. 2014 **Study Type: Ecological (Ecol)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that cases and controls were similar (e.g. recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome.	--
	Confounding bias			
4.	Confounding (design/analysis)	Yes	There is insufficient information provided about the distribution of known confounders in cases and controls (NR) (e.g. maternal smoking status was unknown)	NR
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			

8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure. Nevertheless, there is a possibility for exposure misclassification due the use of potentially biased samples of tested wells, a large proportion of tracts with limited sampling, and the likelihood of maternal mobility during pregnancy. Attempts were made to address some of these limitations by refining exposure assessment in two sensitivity analyses.	+
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed in cases (i.e. case definition) and controls using acceptable methods and subjects had been followed for the same length of time in all study groups. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)			

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Tort et al. 2018

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-sectional Studies greyed out.

Study ID: Tort et al. 2018 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (in all quartiles) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	--
	Confounding bias			

4.	Confounding (design/analysis)	No	It is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results and it is deemed that the measures used would not appreciably bias results	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	It is deemed that the proportion lost to follow-up (i.e. zero) would not appreciably bias results.	-
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure	-
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study’s measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Vigeh et al. 2014

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Vigeh et al. 2014 **Study Type: Cohort (Co)**		**RoB:** **Yes/No** **Unknown** **N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			

1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, AND there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements, AND there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from the study.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure	-
9.	Outcome assessment	No	There is indirect evidence that the outcome assessment method is an insensitive instrument (because blood lead levels were not stratified).	+
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Wan et al. 2021

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Wan et al. 2021 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/- /+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were not similar. (NB: there was a greater proportion of men and smokers with higher BMI in the higher quartiles). Note: A study will be considered low risk of bias if baseline characteristics of groups differed but these differences were considered as potential confounding or stratification variables (and were corrected for in the statistical analysis).	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified and there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, and there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	--
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			
8.	Exposure characterisation	No	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure (e.g. measurement of the chemical in blood).	--
9.	Outcome assessment	No	It is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that	-

			subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome; lack of blinding is unlikely to bias a particular outcome).	
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Wan et al. 2022

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cross-Sectional Studies greyed out.

Study ID: Wan et al. 2022 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were not similar. (NB: there was a greater proportion of men and smokers with higher BMI and waist circumference in the higher quartiles). Note: A study will be considered low risk of bias if baseline characteristics of groups differed but these differences were considered as potential confounding or stratification variables.	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified and there is direct evidence that primary	--

			covariates and confounders were assessed using valid and reliable measurements, and there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			
8.	Exposure characterisation	No	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure (e.g. measurement of the chemical in blood).	--
9.	Outcome assessment	No	It is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a particular outcome).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Wang et al. 2017

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Wang et al. 2017 **Study Type: Cohort (Co)**	**RoB: Yes/No Unknown**	**Notes**	**Risk of bias rating**

		N/A		(--/-/+/++/NR)
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, AND there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements, AND there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for. However, it is noted the author points out the study was not able to correct for a number of other potential confounders (including other heavy metal exposure).	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern (note that blood Pb levels were not reported in this study; serum Pb levels were reported instead; and reference made to an accompanying study for the measurement technique).	NR
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

Wu et al. 2019

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort Studies greyed out.

Study ID: Wu et al. 2019 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified.	--
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study.	--
	Detection Bias			
8.	Exposure characterisation	No	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure (e.g. measurement of the chemical in air or measurement of the chemical in blood, plasma, urine, etc.).	--
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, and it is deemed that the outcome assessment methods used would not appreciably bias results and it is deemed that lack of	-

			adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study’s measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+) or not reported (NR)	+/NR	Definitely high risk of bias (++)	++

ASIA PACIFIC OFFICES

ADELAIDE
60 Halifax Street
Adelaide SA 5000
Australia
T: +61 431 516 449

BRISBANE
Level 16, 175 Eagle Street
Brisbane QLD 4000
Australia
T: +61 7 3858 4800
F: +61 7 3858 4801

CANBERRA
GPO 410
Canberra ACT 2600
Australia
T: +61 2 6287 0800
F: +61 2 9427 8200

DARWIN
Unit 5, 21 Parap Road
Parap NT 0820
Australia
T: +61 8 8998 0100
F: +61 8 9370 0101

GOLD COAST
Level 2, 194 Varsity Parade
Varsity Lakes QLD 4227
Australia
M: +61 438 763 516

MACKAY
21 River Street
Mackay QLD 4740
Australia
T: +61 7 3181 3300

MELBOURNE
Level 11, 176 Wellington Parade
East Melbourne VIC 3002
Australia
T: +61 3 9249 9400
F: +61 3 9249 9499

NEWCASTLE CBD
Suite 2B, 125 Bull Street
Newcastle West NSW 2302
Australia
T: +61 2 4940 0442

NEWCASTLE
10 Kings Road
New Lambton NSW 2305
Australia
T: +61 2 4037 3200
F: +61 2 4037 3201

PERTH
Grd Floor, 503 Murray Street
Perth WA 6000
Australia
T: +61 8 9422 5900
F: +61 8 9422 5901

SYDNEY
Tenancy 202 Submarine School
Sub Base Platypus
120 High Street
North Sydney NSW 2060
Australia
T: +61 2 9427 8100
F: +61 2 9427 8200

TOWNSVILLE
12 Cannan Street
South Townsville QLD 4810
Australia
T: +61 7 4722 8000
F: +61 7 4722 8001

WOLLONGONG
Level 1, The Central Building
UoW Innovation Campus
North Wollongong NSW 2500
Australia
T: +61 2 4249 1000

AUCKLAND
Level 4, 12 O'Connell Street
Auckland 1010
New Zealand
T: 0800 757 695

NELSON
6/A Cambridge Street
Richmond, Nelson 7020
New Zealand
T: +64 274 898 628

WELLINGTON
12A Waterloo Quay
Wellington 6011
New Zealand
T: +64 2181 7186

SINGAPORE
39b Craig Road
Singapore 089677
T: +65 6822 2203

www.slrconsulting.com