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

Bismuth Technical Report

Prepared for:

National Health and Medical Research Council

SLR Ref: 640.30609-R01
Version No: -v4.0
December 2023

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BASIS OF REPORT

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DOCUMENT CONTROL

Reference	Date	Prepared	Checked	Authorised
640.30609-R01-v4.0 (FINAL)	15 December 2023	Tarah Hagen, MSc, DABT, RACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R01-v3.2 (UPDATED DRAFT, with Track Changes)	15 December 2023	Tarah Hagen, MSc, DABT, RACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R01-v3.1 (UPDATED DRAFT, with Track Changes)	4 October 2023	Tarah Hagen, MSc, DABT, RACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R01-v3.0 (UPDATED DRAFT, no Track Changes)	19 July 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R01-v2.1 (UPDATED DRAFT, with Track Changes)	19 July 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R01-v2.0 (REVISED DRAFT)	26 June 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R01-v1.0 (FIRST DRAFT)	25 May 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen

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Abbreviations/Definitions

Acronym	Definition
AAS	Atomic Absorption Spectrophotometry
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
Bi	Bismuth
BiOCl	Bismuth Oxychloride
BIPP	Bismuth Iodoform Paraffin Paste
CaS	Case Study
CBS	Colloidal Bismuth Subcitrate. De-Nol, TDB and CBS are sometimes used interchangeably depending on the publication.
CSF	Cerebrospinal Fluid
De-Nol	Refers to drug product containing Bismuth Tripotassium Dicitrate. De-Nol, TDB and CBS are sometimes used interchangeably depending on the publication.
EA	Experimental Animal (Study)
EEG	Electroencephalogram
EFSA	European Food Safety Authority
F	Female
FSANZ	Food Standards Australia New Zealand
GI	Gastrointestinal
HCT	Human Controlled Trial
ICP-MS(AES)	Inductively Coupled Plasma Mass Spectrometry (Atomic Emission Spectroscopy)
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg bw	Kilogram of Body Weight
LD_{50}	Median Lethal Dose
LOR	Limit of Reporting
LTQ-MS	Linear Ion Trap Mass Spectrometer
M	Male
MPT	Microwave Plasma Torch
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
OEHHA	Californian Office of Environmental Health and Hazard Assessment
OHAT	United States Office of Health Assessment and Translation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUD	Peptic Ulcer Disease

Acronym	Definition
RoB	Risk of Bias
RQ	Research Question
TDB	Tripotassium Dicitrato Bismuthate. De-Nol, TDB and CBS are sometimes used interchangeably depending on the publication.
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.
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WQAC	NHMRC Water Quality Advisory Committee

1 Introduction and Background

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

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

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

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

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

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

The report herein is the Technical Report for bismuth.

2 Research Questions

Research questions for this review were drafted by SLR and peer reviewed and agreed upon by WQAC and NHMRC prior to conducting the search. They are provided in **Table 1**.

Table 1 Research Questions for Evidence Evaluation of Bismuth

#	Research Questions
Health-based	
1	What level of bismuth in drinking water causes adverse health effects?
2	What is the endpoint that determines this value?

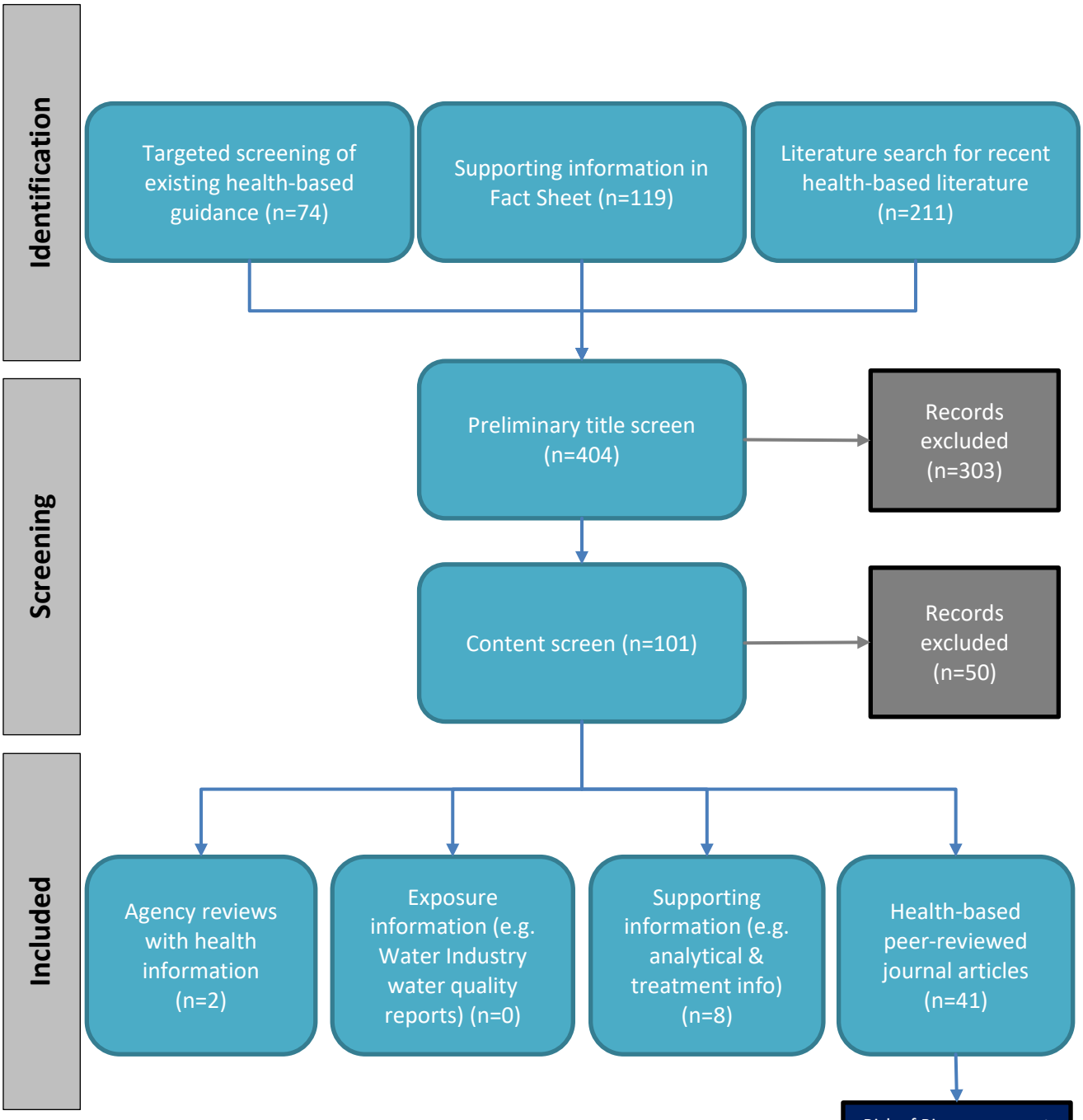
#	Research Questions
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?
4	Is there a knowledge gap from the time at which existing guideline values were developed?
5	Does any recent literature change the proposed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

3 Evidence Evaluation Methods

3.1 Overview

This section summarises the methods followed to undertake the evidence evaluation review for bismuth. 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 bismuth 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 bismuth. This is presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that describes the study selection process and numbers of records at each stage of screening (Moher et al. 2009).



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

Figure 1 Overview of literature search process followed for bismuth

3.2 Targeted screening of existing health-based guidance

Literature search strategy

The literature search strategy for existing health-based guidance documentation for bismuth is summarised in **Table 2** below.

Table 2 Search strategy for Existing Guidance/Guidelines

Parameter	Comments
Search terms	After a few trial runs of various combinations of search terms, it became apparent that the search terms would need to remain relatively broad so as not to miss pivotal references/reviews. Consequently, the selected search term was: • (bismuth)
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) (1): • 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 The following additional sources were searched to provide exposure information in Australian drinking water supplies (to inform responses to Research Questions 10 and 11): • Melbourne Water: https://www.melbournewater.com.au/ • Sydney Water: https://www.sydneywater.com.au/SW/index.htm • TasWater: https://www.taswater.com.au/ • SA Water: https://www.sawater.com.au/ • Water Corporation of Western Australia: https://www.watercorporation.com.au/ • Power and Water Corporation Northern Territory Drinking Water Quality Reports: https://www.powerwater.com.au/about/what-we-do/water-supply/drinking-water-quality/past-drinking-water-quality-reports • Seqwater: https://www.seqwater.com.au/ • Icon Water: https://www.iconwater.com.au/ • Water Research Australia: https://www.waterra.com.au/
Publication Date	No cutoff date (all dates included)
Language	English

Parameter	Comments
Study Type	• Publicly available agency/industry reports and reviews of guidelines or evidence supporting guidelines (near publication drafts are included if available). • Published water quality datasets.

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 bismuth 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.
	• 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	Preliminary searches were undertaken with more specific search terms [(Bismuth) AND (toxicity or health) AND (oral); (Bismuth) AND (health) AND (oral)]. Upon scanning preliminary search results, the reviewer found these search terms to be too specific, as very low or no 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 OHAT (2019).
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.

1. The search within the US EPA general search engine (https://www.epa.gov/) resulted in 2,169 hits, regardless of search term refinement. This number of hits was considered unmanageable to screen with the resources available for this project, especially considering that search results became increasingly less relevant. Consequently, the search was cut off after the first 18 results (subsequent search results were considered irrelevant to answering the research questions).

Data Collection and Quality Assessment

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

- The full text was screened 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 would normally be collected using a specific format. The individual data collection tables are provided in **Appendix B**[1]. It is noted no health-based guidance values were identified in the targeted search undertaken; the only agency documents of relevance found included:
    - A very brief fact sheet from US EPA (1999) which highlights that there were insufficient data (at the time) for calculation of a health-based guidance/guideline value for bismuth.
    - A publication from US FDA (2023) which forms Part 357 of the Code of Federal Regulations (Title 21, Volume 5) providing very brief guidance for products containing bismuth subgallate. In this document, a recommended daily intake for adults and children 12 years of age and over is provided but no further information, or derivation for this value, is given.
    - A UK Poisons Information Document (UK PID) for bismuth that provides a toxicological summary of health effects from exposure to a range of bismuth salts (organic and inorganic) from case studies and studies in humans (WHO 1996). This report outlines toxicokinetics, mechanism of toxicity, clinical features of exposure (acute and chronic), and management (of bismuth poisoning) but does not estimate daily intakes, departure points for toxicity or a health-based guidance/guideline value for bismuth.
- For each health-based guidance review, as per the guidance in the Research Protocol, quality of existing guidance/guidelines would typically be assessed using the Assessment Tool in the Research Protocol. However, as no existing guidance/guideline values for bismuth were identified in the targeted search undertaken, no Assessment Tool tables were completed in this technical report.

Data summary/synthesis

As no relevant health-based guidance/guideline values were identified in the targeted search undertaken, no data summary or synthesis was undertaken in this step.

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. As no relevant existing guidance/guideline values were identified for bismuth from national and international agencies, a full review of the literature was required (as opposed to simply undertaking an evidence scan for any recent health-based information that could impact the guidance/guideline value).

[1] With the exception of the US FDA (2023) publication which is summarised in **Appendix C**, as it was sourced through consulting bibliographies of journal articles sourced as part of the detailed evidence review (see **Section 3.3**).

The literature search strategy for undertaking the full review in scientific databases is summarised in **Table 3** below.

Table 3 Search strategy for full review of health-based studies

Parameter	Comments
Search terms	The selected search terms were: • (Bismuth) AND (toxicity) AND (oral) • (Bismuth) AND (health) AND (oral) • (Bismuth) AND (drinking water) • (Bismuth) AND (plumbing) AND (leaching)
Databases	The following sources were searched: • MEDLINE/PubMed/TOXLINE • SciFinder
Publication Date	As there is no existing fact sheet for bismuth, the search did not have a minimum cutoff date. Dates at which searches were conducted are recorded in individual spreadsheets in **Appendix A**.
Language	English
Study Type	Peer-reviewed published, in press, unpublished (but publicly available) and ongoing studies were included. Study types may include existing systematic reviews or literature reviews, human epidemiological studies, or animal studies (where there was insufficient human information). *In vitro* studies were not included.
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 (bismuth). • Language = Language other than English.
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 full text content 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 collection and analysis step. *Additional search of relevant bibliographies* In addition to the primary search, the bibliographies of critical review papers were consulted 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 OHAT (2019).
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 4.** The format was more applicable to epidemiological studies and was adapted slightly for animal studies and/or reviews. The individual data extraction tables are provided in **Appendix C**.

Table 4 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 date	
	Publication type	
	Peer reviewed?	

Publication Reference: ***Insert full bibliographical reference for report***		
	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	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?	
Author's conclusions	Interpretation of results	
	Assessment of uncertainty (if any)	
Reviewer comments	Results included/excluded in review (if applicable)	

Publication Reference: *Insert full bibliographical reference for report*		
	Notes on study quality, e.g. gaps, methods	

Data analysis

All critical studies deemed relevant for defining the dose response of bismuth were subjected to a risk of bias (RoB) assessment with the use of a RoB tool (i.e. modified OHAT tool, shown in **Table 5**)[2]. 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**.

[2] 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 5 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 **(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	Definitely high risk of bias (++)	++

Relevant data were summarised in tabular format by research question, and by study design. 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 were constructed for the following:

- Threshold doses of bismuth associated with no adverse effects and critical adverse health effects.
- RoB assessments across the body of evidence for each evidence stream and health outcome.
- Overall certainty of evidence for different health endpoints by study design. 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.

3.4 Supporting information in Fact Sheet

In the first instance, the existing guidance/guideline documents identified as per the methods outlined in **Section 3.2** were consulted for supporting information in the Fact Sheet (i.e. general description, uses, measurement techniques and limits of reporting in drinking water, treatment options, etc). However, as no existing guidance/guideline documents were identified, the information collected was limited to published information gathered as part of the full health-related review.

The information was collated into data extraction tables such as the one in **Table 6**. The individual data extraction tables for supporting information are provided in **Appendix E**.

Table 6 Example of data extraction table format for supporting information in Fact Sheet

Agency Report Reference: ***Insert full bibliographical reference for report***		
General Description	Uses	
	Sources in drinking water	
	Other	
Treatment of drinking water	Treatment technology	
	Effectiveness	
	Any special conditions?	
	Other	
Measurement	Analytical method	
	Limit of determination/ Limit of Reporting (LOR)	
	Other	
Additional information	Any additional non-health related information considered important?	

In addition, a literature search of recent publicly available literature was undertaken as per the methodology shown in **Table 7** below.

Table 7 Search strategy for supporting information in Fact Sheet

Parameter	Comments
Search terms	The selected search terms were: • (Bismuth) AND (treatment) AND (drinking water) • (Bismuth) AND (analysis) AND (drinking water) • (Bismuth) AND (testing) AND (drinking water) After a few trial runs of various combinations of search terms in the industry websites, it became apparent that the search capacities varied markedly between different webpages. Consequently, the selected search term (for industry websites) was kept relatively broad: • (Bismuth) As very few relevant papers were identified, the search was supplemented with a generic search in the Google® search engine for 'Bismuth drinking water concentration'.
Databases/Other sources	The following databases were searched: • Medline/Pubmed/Toxline • Scopus • Google® (limited search to supplement lack of apparent information from other sources) The following industry websites were searched: • Water Services Association of Australia: https://www.wsaa.asn.au/ • Standard Methods for the Examination of Water and Wastewater: https://www.standardmethods.org/ • US EPA Drinking Water Treatability Database: https://tdb.epa.gov/tdb/home The following Australian commercial laboratories were contacted directly via e-mail or website form for relevant information: • National Measurement Institute • SGS • ALS • Eurofins
Publication Date	The search was conducted from 2008 to the present date. This covers the last 15 years of information and is considered appropriate for supporting information, as older information may be considered to be outdated (especially in terms of treatment and analytical methods). No date limit was included in the generic Google® search.
Language	English
Study Type	• Peer-reviewed, published or in-press studies. • Unpublished studies (e.g. government reports). • Australian laboratory information sheets or e-mail responses on measurement methods and limits of determination.

Parameter	Comments
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of information: • NR = Not Relevant. Information not directly relevant to answering the research questions. • Research technique (analytical or treatment) = does not appear to be applied commercially. • Language = Language other than English. • NPA = Not publicly available. • NL = Chemical not listed under specific treatment process.
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**).
Screening methods	Results were screened as follows: *Preliminary title and abstract screen* • Titles of results for each search were recorded in an Excel spreadsheet. Each source was on a separate tab of the spreadsheet. These were collated into a single spreadsheet, excluding duplicates. • 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. • The preliminary title and abstract screen was not fully documented for the generic Google® search. Only those papers deemed relevant from the first five (5) pages of search results were recorded. Note there were over 1 million search results in Google®. *Content screen* • The full text content 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 step. Only articles/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 are presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in OHAT (2019).
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.

The following data were extracted from relevant publications and/or obtained from correspondence with Australian laboratories:

- Citation information
- Name of treatment technology (as applicable)

- Name of analytical technique (as applicable)
- Associated Reporting Limit

The individual data extraction tables for supporting information are provided in **Appendix E**.

4 Results

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

No existing health-based guidance/guideline values were found in the literature retrieved. Thus responses to research questions are based on the data extractions conducted for the various human case study (CaS) reports, experimental animal (EA) studies and human controlled trials (HCT) found in the literature reviewed.

4.1 Health-based research question analysis

Table 8 Synthesis of extracted data for health-based research questions

#	Research Questions	Publications	Response to Research Questions
1	What level of bismuth in drinking water causes adverse health effects?	Not applicable	No existing health-based guideline values were found in the literature reviewed. No studies investigating the adverse health effects of bismuth in drinking water to humans were found in the literature consulted. Numerous experimental animals investigating the toxicity of bismuth to rodents in the diet (and one in drinking water, Tubafard and Fatemi 2008) were found. Findings from these studies are summarised in more detail below. It is noted the US FDA (2023) sets a recommended daily intake for adults and children 12 years of age and over for bismuth subgallate as an oral dose of 200-400 mg up to 4 times daily (i.e. 848 mg bismuth/day). At an adult body weight of 78 kg, this equates to 10.9 mg/kg/d (or 12.1 mg/kg/d at 70 kg bw). However, no further information, or derivation for this value, is provided.
2	What is the endpoint that determines this value?	Not applicable	See response to Research Question 1.
3	If there are existing guidance/guideline values, is the proposed option for a health-based guideline value relevant to the Australian context?	Not applicable	See response to Research Question 1.

#	Research Questions	Publications	Response to Research Questions
4	Is there a knowledge gap from the time at which existing guideline values were developed?	Not applicable	See response to Research Question 1.
5	Does any recent literature change the proposed guideline value (e.g. demonstrating a new critical endpoint or changed level of effect that should be considered)?	Not applicable	See response to Research Question 1.
6	What are the key adverse health hazards from exposure to bismuth in Australian drinking water?	**CaS: Atwal and Cousin 2016, Bridgeman and Smith 1994, Jones 1990, Morgan and Billings 1974, Ovaska et al. 2008, Buge et al. 1981, Burns et al. 1974, Weller 1988**	No data for bismuth in drinking water. However, various case reports have been published which have found signs of neurotoxicity (i.e. encephalopathy) after exposure to bismuth via bismuth iodoform paraffin paste (BIPP) gauze, or oral exposure to bismuth subgallate, tripotassium dicitrato bismuthate, bismuth subnitrate, or other bismuth salts. For a summary of doses at which these effects occurred (where this information was available), refer to **Section 5.1.1** of the Evaluation Report or the individual case study data extraction tables in **Appendix C** of this report.
		CaS: Akpolat et al. 1996, Urizar and Vernier 1966, Huwez et al. 1992	No data for bismuth in drinking water. However, several case reports have been published which have found signs of acute renal failure or acute tubular necrosis after ingestion of large amounts of bismuth in the form of bismuth sodium triglycollamate, tripotassium dicitrato bismuthate, and bismuth subcitrate.
		Clinical trial: Hollanders 1986	No data for bismuth in drinking water. However, in this single-blind clinical trial (designed as an efficacy study), no self-reported overt adverse events were noted after administration of 480 mg/day of TDB (equivalent to 142 mg Bi/day) to 46 patients with duodenal ulceration.

#	Research Questions	Publications	Response to Research Questions
		HCT: Koch et al. 1996	No data for bismuth in drinking water. However, in this human placebo-controlled trial (double-blinded) no adverse events or drug-related changes in biochemical parameters were seen in any of the males studied after oral administration of ranitidine bismuth citrate twice per day for 28 days (limited health outcomes were assessed). The dose of bismuth administered per day was ~512 mg Bi/person.
		EA: Tubafard and Fatemi 2008	This is the only drinking water study found for bismuth. Bismuth orally administered to rats in drinking water or food for 55 days (as bismuth nitrate), presumably at 20 or 40 mg/kg bw/day (although doses are unclear), reduced body weights and food consumption in the food (but not drinking water) group and resulted in clinical signs and decreased iron levels. Paper reporting lacks quality (see **Table 12** in Evaluation Report).
		EA: Laval et al. 2018, Abbrachio et al. 1985, Canena et al. 1998	Oral administration of various bismuth compounds to rodents for up to 60 days via gavage (various doses) did not result in overt adverse effects. Timeframes and dose combinations were as follows. • 141 mg Bi^{3+}/kg bw/d for 60 days • 100 or 250 mg/kg Bi_2O_3 for 4 days • bismuth subcitrate: 13.7 mg/kg/d, ranitidine hydrochloride: 8.6 mg/kg/d, ranitidine bismuth citrate: 22.8 mg/kg/d for 15 days
		EA: Leussink et al. 2000, 2001	Bismuth orally administered as a single dose to rats at 627 mg/kg bw (as colloidal bismuth subcitrate (CBS)) caused nephrotoxicity in all rats and mortality in some (5/33) (Leussink et al. 2000). Bismuth orally administered to rats at 313 or 627 mg/kg bw in a single oral dose (as CBS) caused dose-dependent nephrotoxicity and mortality in some. Acute NOAEL in this study was 157 mg Bi/kg bw (Leussink et al. 2001).
		EA: Preussman and Ivankovic 1975	This is a 2-year chronic toxicity / carcinogenicity assay for BiOCl in the diet of rats. The descriptions provided in the study report are small; although from the information available, the study methods followed appear to be in line with standardised methods for conducting such experiments, there are discrepancies with respect to the doses reported which could not be reconciled. No effects observed [NOAEL in the study was the highest dose tested (assumed to be 1534/1918 g Bi/kg bw/d in female/male rats, respectively)]. However, there is large uncertainty with respect to the doses reported in the paper (see detailed description in **Appendix C**).
		EA: Sano et al. 2005	This is an acute and repeat dose oral (by gavage) toxicity study using bismuth metal (pure metal powder, mean particle diameter 10 µm) in rats (likely most relevant in terms of bismuth exposure in alloys). LD_{50} was >2,000 mg/kg (no adverse findings in acute study). The study was well conducted and included all standardised endpoints which are typically investigated in such studies. It establishes a 28-day NOAEL as the highest dose tested (i.e. 1,000 mg Bi/kg bw/d in female/male rats).

#	Research Questions	Publications	Response to Research Questions
7	Are there studies quantifying the health burden (reduction or increase) due to bismuth?	**Reviews: Poddalogoda et al. 2020, Slikkerveer and de Wolff 1989, Bader 1987, Crossland and Bath 2011**	No studies have quantified this in humans *per se*. However the studies described in response to Question 6 above have investigated adverse effects from bismuth exposure in medications and the diet. Reviews have also summarised bismuth health-based information. These reviews indicate the following: • Numerous bismuth salts and complexes have been used medicinally for over two centuries for a range of clinical conditions. • In the mid-1970s, concerns over bismuth toxicity were raised when an outbreak of neurotoxicity in France and Australia was associated with bismuth intake of inorganic and organic bismuth salts (e.g. bismuth subnitrate, subcarbonate and subgallate) for treatment of gastrointestinal (GI) disorders. Some researchers have suggested that the outbreak was due to an increase in the prevalence of an otherwise benign group of gastro-intestinal microbes that promoted the methylation of bismuth, producing a more easily absorbed form. • Some researchers have suggested that maintaining blood bismuth concentration below a certain level (e.g. 100 µg/L) may prevent the occurrence of neurological effects, although the threshold concentration is debated among the scientific community. In the prodromal phase patients developed problems in walking, standing or writing, deterioration of memory, changes in behaviour, insomnia and muscle cramps, together with several psychiatric symptoms. The manifest phase started abruptly and was characterised by changes in awareness, myoclonia, astasia and/or abasia and dysarthria. Patients recovered spontaneously after discontinuation of bismuth. • The bismuth encephalopathy occurred only in France and the surrounding countries, despite extensive use of bismuth elsewhere. A small outbreak of poisoning was also seen in Australian patients who had undergone a colostomy or an ileostomy and taken oral bismuth subgallate. A so far unidentified additional factor besides bismuth was held responsible for these intoxications. Despite many theories on enhanced intestinal absorption, the exact aetiology of bismuth encephalopathy remains a mystery. • One reviewer concluded that the uncontrolled and uninhibited ingestion of bismuth salts constituted misuse on such a scale that it would seem the factor most likely to have brought about the cases of neurotoxicity in the epidemic in France. • To confirm the diagnosis of bismuth encephalopathy, it is essential to find elevated bismuth concentrations in blood, plasma, serum or cerebrospinal fluid (CSF). A safety level of 50 µg/L and an alarm level of 100 µg/L have been suggested in the past, but no proof is available to support the choice of these levels. • The neurotoxic effects of bismuth were caused by the so-called insoluble inorganic bismuth compounds, whereas the compounds used in the treatment of syphilis caused kidney and bone disease, but not neurotoxicity. It appears unlikely that bismuth is hepatotoxic in humans.

#	Research Questions	Publications	Response to Research Questions
8	What is the critical human health endpoint for bismuth?	**CaS and Reviews**	From the case studies of very high human intakes of soluble bismuth salts and reviews available (see response to Research Question 6), the critical human health endpoints for bismuth exposure appear to be neurotoxicity (i.e. encephalopathy) and nephrotoxicity (renal disease).
		EA	From the experimental animal studies available (see response to Research Question 6), no adverse effects have been identified from chronic exposure at the doses (and compounds) tested albeit only one chronic study was found in the literature consulted. Acute exposures to high doses appear to potentially result in nephrotoxicity.
9	What are the justifications for choosing this endpoint?	As above	Neurotoxicity and nephrotoxicity appear to be the two ailments potentially causally associated with high medicinal bismuth exposures in case study reports in humans. No adverse effects have been observed in human controlled trials (albeit doses administered and bismuth form likely differ from those in case studies). Two experimental animal studies conducted in line with methods typically employed in standardised toxicity experiments have not identified critical adverse effects at the following doses: • Bismuth oxychloride (BiOCl) administered in diet of rats for 2 years did not result in adverse effects (NOAEL was highest dose tested = assumed to be 1534/1918 mg Bi/kg bw/day in female/male rats) (Preussman and Ivankovic 1975). However, there is uncertainty with respect to the doses administered as the units reported in this study (g/kg bw) are nonsensical. • Bismuth metal (pure metal powder, mean particle diameter 10 µm) administered orally via gavage to rats for 28 days did not result in adverse effects (NOAEL was highest dose tested = 1,000 mg Bi/kg bw/d) (Sano et al. 2005).

4.2 Exposure-related research question analysis

Table 9 Synthesis of extracted data for exposure-related research questions

#	Research Questions	Publications	Response to Research Questions
10	What are the typical bismuth levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought?	Water corporations	No relevant information for bismuth was found in the search conducted of water supplier websites to inform a response to this Research Question.
		Hinwood et al. 2015	This paper describes a cross-sectional study of persistent substance exposure in non-smoking pregnant women >18 yrs in Western Australia. Pregnant women were recruited between 2008-2011. 172 women provided a drinking water sample. Each sample was analysed for numerous elements including bismuth. Concentrations of bismuth in drinking water: Median <0.005 µg/L, 100% of samples were lower than the LOR (0.005 µg/L in drinking water).
		Malassa et al. 2014	Although this study measured heavy metals (including bismuth) in harvested rainwater used for drinking, it was conducted in Hebron, Palestine (there is water scarcity in this area). It is unknown how applicable these data would be to the Australian situation. Sampling was carried out in November 2012 where 44 water samples were collected from 44 house cisterns. Bismuth was detected in all samples with a concentration range of 1.33-96.52 µg/L. Study suggests bismuth in drinking water could be present at high concentrations if sourced from the roof (although roofing material was not specified). The authors speculated the source of heavy metals in harvested water used for drinking may have been due to uncontrolled burning of solid wastes in illegal waste dumping sites, where it is expected ashes and dust of these wastes are transported via wind to house roofs.
		Al-Khatib et al. 2019	An additional study of heavy metals in harvested water was undertaken for water samples collected from the Yatta area of Palestine in January and February 2016. This study was a health risk assessment used to calculate intakes and health risk indices for most heavy metals from adults and children drinking this water. Bismuth concentrations in four rural areas ranged from 0.01 to 0.05 µg/L and in the fifth area (Khallet Salih) it was 0.75 µg/L.
		UK COT 2008	Limited information provided except that drinking water in the USA contains on average of 0.01 mg/L bismuth (with no supporting information provided).

#	Research Questions	Publications	Response to Research Questions
		Poursharifi and Moghimi 2011	Bismuth was measured in a rainwater sample (0.399±0.01 µg/L) and a tap water sample (0.165±0.01 µg/L) collected from locations in Iran using a mean of three experiments. The samples were tested as a means to validate a novel analytical method (Electrothermal Atomic Absorption Spectrometry (ET-AAS) After Cloud Point Extraction) with a low detection limit (0.04 µg/L) and small sample size (10 mL).
		Jaiswal et al. 2019	In this review it was stated that in "*natural water, concentrations of Bismuth are found to be very low, usually less than 0.2 µg/L*". Presumably, this would apply to raw water from which drinking water may be supplied, however no further details on this statement were provided.
11	Are there any data for bismuth levels leaching into water from in-premise plumbing?	No data found for bismuth. It is suggested that leachability data for bismuth from lead replacement alloys in plumbing products be generated for Australian conditions to inform the form of bismuth in lead replacements (and chemical form leaching from lead replacements) as well as exposure concentrations.	

4.3 Risk-based research question analysis

Table 10 Synthesis of extracted data for risk-associated research questions

#	Research Questions	Publication	Response to Research Questions
12	What are the risks to human health from exposure to bismuth in Australian drinking water?		No risks to human health from exposure to bismuth in drinking water have been identified in any of the publications reviewed. This may be due to the fact that no regulatory agency reviews could be found on the subject. The case studies and human controlled trials focused on oral intakes of bismuth from medicinal use. In these studies, the most important potential adverse health effects from bismuth exposure appear to be neurotoxicity (i.e. encephalopathy) and nephrotoxicity. Experimental animal studies with oral bismuth exposures have identified nephrotoxicity after acute administration of tripotassium dicitrato bismuthate, but otherwise no adverse effects have been found (see response to Research Question 6).
13	Is there evidence of any emerging risks that require review or further research?		None identified, however the toxicological database for bismuth is limited.

4.4 Supporting Fact Sheet information research question analysis

Supporting information in fact sheets for chemicals in the Guidelines typically consists of the following (NHMRC and NRMMC 2011):

- **General Description**
- **Typical values in Australian drinking water**
- **Treatment of drinking water**
- **Measurement**

The table below presents the limited information identified in the literature search conducted which could be used to inform supporting information for a bismuth fact sheet. Available information on typical values in Australian drinking water supplies was addressed in **Table 9** as part of an analysis for exposure-related research questions.

Table 11 Synthesis of extracted data for research questions relevant to supporting Fact Sheet information

#	Research Questions	Publication	Response to Research Questions
14	What is bismuth used for and how might people be exposed?	**Hinwood et al. 2015**	Bismuth has been used in pharmaceuticals and cosmetics and has been found in low concentrations in biological and environmental samples including blood, urine, food and water.
		Xiong et al. 2017	Bismuth is a rare and important element, widely used in several fields such as in metallurgy and in the cosmetics industry as an additive to creams and hair dyes. It also has specific properties in pharmaceutical preparations and can be used as an antiulcer, antibacterial, anti-HIV, and radiotherapeutic agent.
		Crossland and Bath 2011	Bismuth compounds have been used to treat a variety of ailments for hundreds of years. They have been used topically as astringents and antiseptics, orally to treat gastrointestinal complaints, and parenterally to treat syphilis.
		Poddalogoda et al. 2020	Numerous bismuth salts and complexes have been used medicinally for over two centuries for a range of clinical conditions, including oral and upper respiratory tract infections, syphilis, diarrhoea, heartburn (pyrosis), dyspepsia (indigestion), gastroesophageal reflux, and peptic ulcer disease (PUD). Bismuth substances also have broad anti-microbial, anti-leishmanial and anti-cancer properties. The most commonly used bismuth forms include bismuth subsalicylate (Pepto Bismol®, Maalox®) and bismuth subcitrate, for the treatment of diarrhoea and peptic ulcer disease. These medicinal products contain high concentrations of bismuth. For instance, one form of Pepto Bismol®, pepto bismol ultra (bismuth subsalicylate) contains approximately 303 mg Bi/tablet, with a maximum suggested dose of 8 tablets a day for adults. Similarly, bismuth subcitrate contains 108 mg Bi/tablet.
		WHO 1996	• Bismuth exists in trivalent and pentavalent oxidation states (the trivalent being more abundant and stable) and forms soluble and insoluble, organic and inorganic salts. Soluble bismuth salts include tripotassium dicitrato bismuthate (TDB), bismuth sodium tartrate and bismuth sodium tri(thio)glycollamate. Insoluble bismuth salts include bismuth oxide, bismuth (sub)carbonate, bismuth (sub)gallate, bismuth hydroxide, bismuth oxychloride, bismuth (sub)salicylate, bismuth iodide, and bismuth subnitrate. • Exposure to bismuth in people generally occurs through bismuth-containing drugs.
15	How does the specific chemical end up in drinking water and in what form?	No information was found to answer this Research Question. Most of the studies available in the literature have focused on the medicinal exposures to bismuth from purposeful administration.	

#	Research Questions	Publication	Response to Research Questions
16	How is the concentration of bismuth measured in drinking water?	**Australian Commercial Laboratory Correspondence**	Bismuth concentration in water can be determined by inductively coupled plasma-mass-spectrometry (ICP-MS) according to USEPA 6010/6020.
		Hinwood et al. 2015, Malassa et al. 2014	ICP-MS
		Vetrivel et al. 2017	Inductively coupled plasma-atomic emission-spectrometry (ICP-AES)
		Xiong et al. 2017	Novel method using microwave plasma torch (MPT) ion source coupled with linear ion trap mass spectrometer (LTQ-MS).
		Poursharifi and Moghimi 2011	Novel method using Electrothermal Atomic Absorption Spectrometry (ET-AAS)
		Al-Khatib et al. 2019	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)
		Jaiswal et al. 2019	Multiple methods listed: UV-Visible Spectroscopy; Atomic Absorption Spectrophotometry (AAS); Ion Chromatography; Voltammetry/ Polarography; Inductively Coupled Plasma Optical Emission Spectroscopy/ (ICE-OES); ICP Mass Spectrometry (ICP-MS); and Neutron Activation and Analysis (NAA).
17	What are the indicators of the risks? How can we measure exposure?	No studies were found specifically evaluating human exposure to bismuth in drinking water. However, exposure concentrations in drinking water could be monitored using existing commercial analytical techniques (ICP-MS).	
		CaS and Reviews	In case studies, exposure to bismuth from medicinal use of various bismuth salts and compounds has been ascertained by measuring bismuth in blood, serum, plasma, urine and cerebrospinal fluid (CSF). A safety level of 50 µg/L bismuth in blood and an alarm level of 100 µg/L have been suggested in the past (French papers cited by Slikkerveer and Wolff 1989), but no proof is available to support the choice of these levels.
18	What are the limits of quantification or limit of reporting for bismuth in drinking water?	**Australian Commercial Laboratory Correspondence**	Standard LOR: 0.001-0.01 µg/L, depending on the laboratory. Trace LOR (only offered by one commercial laboratory): 0.0001 µg/L
		Hinwood et al. 2015	0.005 µg/L
		Xiong et al. 2017	0.028 µg/L

#	Research Questions	Publication	Response to Research Questions
		Poursharifi and Moghimi 2011	0.04 µg/L (from a 10 mL sample)
19	How is drinking water treated to minimise bismuth concentrations?	No data were found to answer this Research Question.	
20	What are the current practices to minimise or manage the risks identified?	No data were found to answer this Research Question.	

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WHO (1996). UK PID Monograph. Bismuth. 16/7/1996. International Programme on Chemical Safety (IPCS). INCHEM. World Health Organisation (WHO)

Xiong X., Chen G., Zhu M., Li Y., Yang C., Xie K. and Zhu Z. (2018). The study of bismuth ions in drinking water at ultratrace levels by a microwave plasma torch coupled with linear ion trap mass spectrometry. Analytical Methods 10(11): 1346-1352.

Zhang L., Liu J., Meng F., Guan Y., Wang Y., Zhu S., Liu Y., Xie Q., Yu J. and Zhang S. (2020). Pharmacokinetics of Bismuth following Oral Administration of Wei Bi Mei in Healthy Chinese Volunteers. Evid Based Complement Alternat Med 2020: 2679034.

APPENDIX A

Literature search screening outcome spreadsheets

Appendix A contents here

APPENDIX B

Data extraction tables – Health-based guidance/guidelines

Existing Health-Based Guidance for Bismuth

US EPA 1999

Agency Report Reference: US EPA (1999). Human Health Fact Sheet for Bismuth (Human Health - fish ingestion only), Ohio Environmental Protection Agency, U.S Environmental Protection Agency.		
General Information	Date of data extraction	02/03/2023
	Authors	Developed by Bob Heitzman
	Publication date	28/01/1999
	Publication type	Very brief agency fact sheet.
	Description	No guidance value was derived in this document; the fact sheet indicates there is insufficient data to derive a value.
	Findings	• Acceptable daily exposure (ADE): Not available • Carcinogen assessment: Not available. • No drinking water criteria available.

WHO 1996

Agency Report Reference: WHO (1996). UK PID Monograph. Bismuth. 16/7/1996. International Programme on Chemical Safety (IPCS). INCHEM. World Health Organisation (WHO)		
General Information	Date of data extraction	24/05/2023
	Authors	Developed by Bradberry, S.M., Beer, S.T., and Vale, J.A.
	Publication date	1996
	Literature search timeframe	Latest publication referenced from 1996
	Publication type	UK Poison Information Document (UK PID): Toxicological summary of human health effects for Bismuth from the National Poisons Information Service Centre in the United Kingdom.
	Peer reviewed?	Yes (Directors of the UK National Poisons Information Service.).
	Country of origin	United Kingdom (UK)
	Source of funding	UK Departments of Health
	Possible conflicts of interest	None stated

Agency Report Reference: WHO (1996). UK PID Monograph. Bismuth. 16/7/1996. International Programme on Chemical Safety (IPCS). INCHEM. World Health Organisation (WHO)		
	Findings	• Outlines the chemical properties, uses, mechanism of toxicity, toxicokinetics and human health effects from case studies / studies. • Bismuth exists in trivalent and pentavalent oxidation states (the trivalent being more abundant and stable) and forms soluble and insoluble, organic and inorganic salts. Soluble bismuth salts include tripotassium dicitrato bismuthate (TDB), bismuth sodium tartrate and bismuth sodium tri(thio)glycollamate. Insoluble bismuth salts include bismuth oxide, bismuth (sub)carbonate, bismuth (sub)gallate, bismuth hydroxide, bismuth oxychloride, bismuth (sub)salicylate, bismuth iodide, and bismuth subnitrate. • Exposure to bismuth in people generally occurs through bismuth-containing drugs. • In general, insoluble salts, such as bismuth subcarbonate, are of low toxicity while lipid soluble organic salts (e.g. bismuth subgallate) are associated predominantly with neurotoxicity, and water soluble organic compounds (e.g. bismuth sodium triglycollamate) more usually cause renal damage. • Bismuth (and iodoform) contact sensitivity has followed the topical application of bismuth and iodoform paste dressing (>99.2% purity of iodoform, 75% bismuth in bismuth subnitrate) in a patient following a radical mastoidectomy after the dressing was left *in situ* for four weeks (Goh and Ng 1987). • "*Although occupational exposure to bismuth may occur in the manufacture of cosmetics, industrial chemicals and pharmaceuticals, most cases of poisoning occur following accidental or deliberate overdosage with bismuth-containing drugs. In general, insoluble salts, such as bismuth subcarbonate, are of low toxicity while lipid soluble organic salts (e.g. bismuth subgallate) are associated predominantly with neurotoxicity, and water soluble organic compounds (e.g. bismuth sodium triglycollamate) more usually cause renal damage (Winship 1983)*". • No guidance value was derived in this document. References: Goh CL and Ng SK. Contact allergy to iodoform and bismuth subnitrate. Contact Dermatitis 1987; 16: 109-10. Winship KA. Toxicity of bismuth salts. Adverse Drug React Acute Poisoning Rev 1983; 2: 103-21. As cited by WHO 1996.

APPENDIX C

Data extraction tables – Full Review for Health-based Studies

Akpolat et al. 1996

Publication Reference: Akpolat I., Kahraman H., Arik N., Akpolat T., Kandemir B. and Cengiz K. (1996). Acute renal failure due to overdose of colloidal bismuth. Nephrol Dial Transplant 11(9): 1890-1891.		
General Information	Date of data extraction	03/04/2023
	Authors	Akpolat I, Kahraman H, Arik N, Akpolat T, Kandemir B, Cengiz K
	Publication date	1996
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	Turkey
	Source of funding	Not stated (authors are from a School of Medicine at a University)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of a patient complaining of nausea, vomiting, and dizziness and oliguria after taking 10-15 tablets of tripotassium dicitrato bismuthate (3-4.5 g) a week earlier.
	Study type/design	Case report
	Study duration	Single overdose (3-4.5 g tripotassium dicitrato bismuthate, i.e. 0.89-1.33 g Bi).
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report) 16-year old female patient
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of tripotassium dicitrato bismuthate tablets (10-15 tablets)
	Exposure concentrations (if applicable)	Single overdose (3-4.5 g tripotassium dicitrato bismuthate, i.e. 0.89-1.33 g Bi).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Patient admitted to hospital with complaints of nausea, vomiting and dizziness for 4-5 days and oliguria for 2 days.

Publication Reference: Akpolat I., Kahraman H., Arik N., Akpolat T., Kandemir B. and Cengiz K. (1996). Acute renal failure due to overdose of colloidal bismuth. Nephrol Dial Transplant 11(9): 1890-1891.		
	How outcome was assessed	• On admission, physical examination was unremarkable except minimal right costovertebral tenderness. Abnormal blood findings were: blood urea nitrogen 146 mg/dl, serum creatinine 17.9 mg/dl. Urinary examination showed pH 6.0, density 1020, protein 100 mg/dl, glucose negative, bilirubin negative, with abundant erythrocytes and leukocytes. Kidney size was normal. • Renal biopsy revealed acute tubular necrosis. • Patient was managed with haemodialysis, protein restriction, metoclopramide, and aluminium hydroxide. Her condition was reversible.
	Method of measurement	Not applicable (method of measurement for blood bismuth not reported).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Acute tubular necrosis is a rare and reversible complication of an overdose of colloidal bismuth.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Large ingested dose of bismuth (i.e. 890 – 1,330 mg Bi) caused acute tubular necrosis. • No bismuth monitoring conducted in blood; it is unclear whether bismuth in Bi alloys would have the same effect as tripotassium dicitrato bismuthate which was responsible for the nephrotoxicity observed. • As the study provided a dose of bismuth associated with health effects, it was included in risk of bias analysis.
	Notes on study quality, e.g. gaps, methods	

Atwal and Cousin 2016

Publication Reference: Atwal A. and Cousin G. C. S. (2016). Bismuth toxicity in patients treated with bismuth iodoform paraffin packs. British Journal of Oral and Maxillofacial Surgery 54(1): 111-112.		
General Information	Date of data extraction	02/03/2023
	Authors	Atwal A and Cousin GCS
	Publication date	2016
	Publication type	Case report

Publication Reference: Atwal A. and Cousin G. C. S. (2016). Bismuth toxicity in patients treated with bismuth iodoform paraffin packs. British Journal of Oral and Maxillofacial Surgery 54(1): 111-112.		
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not stated.
	Possible conflicts of interest	The authors report no conflicts of interest.
Study characteristics	Aim/objectives of study	Case report of two cases experiencing neurotoxicity after use of bismuth iodoform paraffin paste (BIPP) antiseptic dressings in operations on the jaws.
	Study type/design	Case report
	Study duration	Case 1: Exposure duration not stated. *Initial treatment of keratocystic odontogenic tumour involved marsupialisation and packing with BIPP-impregnated gauze, followed by sequential replacement dressings with decompression and packing to allow healing over a long period of time.* Case 2: BIPP pack placed in oral cavity and left in for 9 days after it was removed due to symptoms being observed.
	Type of water source (if applicable)	Not applicable (exposure to bismuth was via BIPP antiseptic dressings)
Population characteristics	Population/s studied	Two case studies. Case 1: 59-yr old man, admitted to hospital with infective swelling of his mandible.
	Selection criteria for population (if applicable)	Case 2: 92-yr old woman, with a well-differentiated squamous cell carcinoma in right upper buccal sulcus.
	Subgroups reported	Not applicable (case reports)
	Size of study	2 cases
Exposure and setting	Exposure pathway	Absorption through buccal cavity (exposure to bismuth was via BIPP antiseptic dressings applied to buccal cavity).
	Source of chemical/contamination	Not applicable (intentional application of bismuth-containing dressing for therapeutic purposes)
	Exposure concentrations (if applicable)	External exposure concentrations not provided. Blood bismuth concentrations (internal exposure) was: Case 1: 109.9 nmol/L (reference <0.48 nmol/L, ~200x > reference) (23 ng/mL) Case 2: 144 nmol/L (300x reference) (30 ng/mL).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Signs of neurotoxicity

Publication Reference: Atwal A. and Cousin G. C. S. (2016). Bismuth toxicity in patients treated with bismuth iodoform paraffin packs. British Journal of Oral and Maxillofacial Surgery 54(1): 111-112.		
	How outcome was assessed	Case 1: *Patient became progressively more fatigued, confused, apathetic and forgetful, and was convinced that the lesion was malignant and that he was going to die.* Also described spasms in his quadriceps. He became clinically depressed and required admission to a psychiatric ward because of suicidal thoughts. Treated with antidepressants and BIPP was removed. His mood gradually improved, and 18 months after original operation, his blood bismuth was 0.02 nmol/L. Case 2: Became progressively confused. No evidence that another condition could have caused her confusion, imaging of brain showed no intracranial disease. Four months after operation and removal of pack, bismuth blood concentration was 8.9 nmol/L.
	Method of measurement	Not applicable (method of measurement for blood bismuth not reported).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	2 cases (both exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	The rarest reaction to BIPP packs is encephalopathy, which is presumably caused by bismuth toxicity, but the mechanisms are not fully understood. Bismuth is used in a wide variety of applications including common over-the-counter medications that are generally considered safe. As it is only poorly absorbed from the mucosa of the gastrointestinal tract, compounds that contain it can be used as anti-diarrhoeal medication. Although bismuth could have leached into saliva that was swallowed, poor absorption from the gut suggested that it had been absorbed haematogenously over the wide area of raw cancellous bone that was exposed within the cystic cavity. Although neurotoxicity caused by the absorption of bismuth from BIPP is rare, it can be fatal if not recognised, and its presentation may be atypical as it was in the first patient who had suicidal thoughts.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (2 case reports). • Applied dose of bismuth unknown.

Publication Reference: Atwal A. and Cousin G. C. S. (2016). Bismuth toxicity in patients treated with bismuth iodoform paraffin packs. British Journal of Oral and Maxillofacial Surgery 54(1): 111-112.		
	Notes on study quality, e.g. gaps, methods	• Although bismuth concentration in blood was very high, it is unclear whether bismuth (or some other component of BIPP) was responsible for neurotoxicity observed. • Although dose of bismuth is unknown, the case report was included in risk of bias analysis as evidence of neurotoxicity was observed.

Abbracchio et al. 1985

Publication Reference: Abbracchio M. P., Balduini W., Cavallaro A., Adamoli P., Fittipaldi M., Muzio F., Malandrino S. and Cattabeni F. (1985). Brain and blood levels of bismuth after oral or parenteral administration of tripotassium-dicitrato bismuthate to rats. Neurotoxicology 6(3): 139-143.		
General Information	Date of data extraction	23/03/2023
	Authors	Abbrachio MP, Balduini W, Cavallaro A, Adamoli P, Fittipaldi M, Muzio F, Malandrino S, Cattabeni F
	Publication date	1985
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Italy
	Source of funding	Not specified (authors from university, laboratory and government hygiene department).
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To conduct a series of bismuth determinations on blood and brain in rats after oral or parenteral administration of tripotassium dicitrato bismuthate (a colloidal bismuth compound, TDB).
	Study type/design	Experimental animal study
	Study duration	Acute study: 12 or 24 hours after a single dose Repeat dose study: 4 days of treatment, sacrifice on 5th day
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Male Sprague-Dawley rats (150-200 g, Charles River, Italy). 3 rats/group
	Selection criteria for population (if applicable)	Not applicable (animal study)
	Subgroups reported	Administration by gavage (820 mg/kg or 250 mg/kg Bi_2O_3) or intraperitoneal injection (25 mg/kg Bi_2O_3) (3 rats/group); control group received saline or water administered intraperitoneally or by gavage, respectively.
	Size of study	3 rats/ exposure group
Exposure and setting	Exposure pathway	Oral or intraperitoneal injection
	Source of chemical/contamination	Not applicable (Treatment with TDB was intentional in experimental animals)

Publication Reference: Abbracchio M. P., Balduini W., Cavallaro A., Adamoli P., Fittipaldi M., Muzio F., Malandrino S. and Cattabeni F. (1985). Brain and blood levels of bismuth after oral or parenteral administration of tripotassium-dicitrato bismuthate to rats. Neurotoxicology 6(3): 139-143.		
	Exposure concentrations (if applicable)	Gavage: 328 or 820 mg/kg TDB; or 100 or 250 mg/kg Bi_2O_3 Intraperitoneal: 82 mg/kg TDB or 25 mg/kg Bi_2O_3
	Comparison group(s)	Controls receiving saline or water.
Study methods	Water quality measurement used	Not applicable. Measurement of bismuth levels by AAS in blood (at different time periods) & brain (at end of study)
	Water sampling methods (monitoring, surrogates)	Not applicable. **Acute study:** Blood was sampled 30 minutes, 1, 2, 4, 6, 8, 12 and 24 hours after administration. Brain at end of experiment. **Repeat dose study:** Blood and brain were sampled at end of exposure period.
Results (for each outcome)	Definition of outcome	**I.p. treatment:** • In acute exposure, Bi in blood of treated rats reached highest value (~2.5 µg/g) within 30 mins & quickly declined to a plateau maintained until 6th hour (12-hr average = 1.22 ± 0.2 µg/g). Bi crossed blood-brain barrier with lower brain concentrations compared to blood (12-hr: 0.24 ± 0.03 µg/g). • After 4 daily treatments, Bi in blood was 0.68 ± 0.13 µg/g and in brain was 0.27 ± 0.09 µg/g. **Oral treatment:** • In acute exposure, much lower Bi concentrations were detected in blood of rats. Bi in brain was lower than LoR (<0.04 µg/g). • After 4 daily treatments, Bi in blood at higher dose was 0.32 ± 0.04 µg/g and in brain was 0.053 ± 0.002 µg/g. At lower dose they were 0.07 ± 0.01 µg/g and <0.04 µg/g, respectively.
	How outcome was assessed	
	Method of measurement	No obvious signs of neurotoxicity were observed by clinical observation.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.
Author's conclusions	Interpretation of results	The ability of Bi to cross the blood-brain barrier depends on the route of administration of TDB, being much higher after intraperitoneal injection with respect to oral treatment. The fact that no Bi seems to be present in brain after oral administration of TDB apparently indicates minimal risk of neurotoxicity following treatment with the Bi derivative.

Publication Reference: Abbracchio M. P., Balduini W., Cavallaro A., Adamoli P., Fittipaldi M., Muzio F., Malandrino S. and Cattabeni F. (1985). Brain and blood levels of bismuth after oral or parenteral administration of tripotassium-dicitrato bismuthate to rats. Neurotoxicology 6(3): 139-143.		
	Assessment of uncertainty (if any)	Since Bi compounds are administered for long periods, the conclusion is tempered by the fact the animal model was not tested in a chronic exposure situation.
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on Bi toxicokinetics. However, this study assessed limited health outcomes (and methods for assessment of those outcomes were not reported), so provides limited information with respect to defining a health-based guidance value for Bi (single dose administration). As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Bader 1987

Publication Reference: Bader J. P. (1987). The safety profile of De-Nol. Digestion 37 Suppl 2: 53-59.		
General Information	Date of data extraction	03/04/2023
	Authors	Bader JP
	Publication date	1987
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	France
	Source of funding	Not specified (author affiliation is a Hospital)
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	Review of safety profile of colloidal bismuth subcitrate (CBS, De-Nol®)
	Study type/design	Review/commentary (methods of literature review not specified, does not appear to be systematic).
	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)	Not applicable
	Exclusion criteria	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)	Not applicable

Publication Reference: Bader J. P. (1987). The safety profile of De-Nol. Digestion 37 Suppl 2: 53-59.		
Study methods	Water quality measurement used	Not applicable
	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	• CBS was not available in France in the early 70's and therefore played no role in the cases of neurotoxicity. • CBS, given in a standard dose of 480 mg (as bismuth trioxide) in four daily divided doses has been employed from the beginning of the clinical research program and has been given mostly for 4, and also up to but not exceeding 8 weeks, results in only a slight rise of Bi in blood (~7 µg/L). • Around 60 days are necessary for urine levels to return to pre-treatment values. • During the clinical research program with CBS, no serious adverse reactions were ever observed. Mild effects such as headache and gastrointestinal tract disturbances were few and insignificant. The reactions which can be said to have been caused by CBS were: 1 case of headache, 1 of stomach pain, 1 of diarrhoea and 2 of allergy mainly in the form of skin rashes.
	Assessment of uncertainty (if any)	It cannot be stated with absolute certainty that no serious adverse reaction will ever occur, however the safety profile of the drug appears to be high. Other as yet unidentified factors, perhaps genetically or environmentally determined, may cause a reaction in a patient somewhere, sometime.
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on bismuth in CBS. However, this study was a limited review / commentary so provides limited information with respect to defining a health-based guidance value for Bi. As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.

Benet 1991

Publication Reference: Benet L. Z. (1991). Safety and pharmacokinetics: colloidal bismuth subcitrate. Scand J Gastroenterol Suppl 185: 29-35.		
General Information	Date of data extraction	23/03/2023
	Authors	Benet LZ
	Publication date	1991
	Publication type	Commentary
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	Not specified (author affiliation is a University)
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	Discussion of pharmacokinetic factors of bismuth.
	Study type/design	Commentary/literature review (methods of literature review not specified, does not appear to be systematic).
	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)	Not applicable
	Exclusion criteria	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)	Not applicable
Study methods	Water quality measurement used	Not applicable
	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	

Publication Reference: Benet L. Z. (1991). Safety and pharmacokinetics: colloidal bismuth subcitrate. Scand J Gastroenterol Suppl 185: 29-35.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Clearance of colloidal bismuth subcitrate from the human body averages 50-95 mL/min (the higher value assumed biliary clearance is a significant portion of elimination). • Bioavailability of bismuth averages 0.16-0.28% (the higher value depends on degree of biliary elimination). • The Hillemand proposal of steady-state blood concentrations of >50 ng/mL and >100 ng/mL as 'safety' and 'alarm' levels for bismuth toxicity are probably overly cautious, and there is little likelihood of bismuth neurotoxicity occurring with steady state concentrations between 50 and 100 ng/mL. • There is no evidence to suggest that the transient, high peak concentrations seen after oral doses of a particular colloidal bismuth subcitrate formulation are in any way related to toxicity measures. No observation of bismuth neurotoxicity has been made for transient concentrations higher than 50-100 ng/mL (in fact, only reversible renal toxicity occurs after acute, massive overdoses of bismuth). Also pharmacokinetic theory suggests that high peak concentrations after an oral dose (even if consistently seen after multiple doses) would result in only negligible increases in predicted steady-state blood-plasma concentrations and steady-state amounts of bismuth in the body.
	Assessment of uncertainty (if any)	No assessment of uncertainty undertaken.
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on bismuth toxicokinetics. However, this study was a limited review/commentary so provides limited information with respect to defining a health-based guidance value for Bi.
	Notes on study quality, e.g. gaps, methods	As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.

Bridgeman and Smith 1994

Publication Reference: Bridgeman A. M. and Smith A. C. (1994). Iatrogenic bismuth poisoning. Case report. Aust Dent J 39(5): 279-281.		
General Information	Date of data extraction	24/03/2023
	Authors	Bridgeman AM and Smith AC
	Publication date	1994
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	Not stated.

Publication Reference: Bridgeman A. M. and Smith A. C. (1994). Iatrogenic bismuth poisoning. Case report. Aust Dent J 39(5): 279-281.		
	Possible conflicts of interest	The authors report no conflicts of interest.
Study characteristics	Aim/objectives of study	Case report of a 71-year old man experiencing neurotoxicity after use of bismuth iodoform paraffin paste (BIPP) impregnated half-inch ribbon gauze in operations on the jaws.
	Study type/design	Case report
	Study duration	BIPP packs renewed post-operatively, first symptoms arose 3 weeks post-operation.
	Type of water source (if applicable)	Not applicable (BIPP impregnated gauze in buccal cavity)
Population characteristics	Population/s studied	71-year old Sri Lankan male
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	Not applicable
	Size of study	Case report (n=1)
Exposure and setting	Exposure pathway	Buccal mucosal absorption from applied BIPP gauze
	Source of chemical/contamination	BIPP (50% iodoform, 25% liquid paraffin, 25% bismuth subnitrate powder).
	Exposure concentrations (if applicable)	Not reported
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable. Serum bismuth was measured (result 41 µg/L, elevated above reference range of 1-15 µg/L).
	Water sampling methods (monitoring, surrogates)	Serum bismuth sampling & analysis method not reported.
Results (for each outcome)	Definition of outcome	Self-reported outcome (patient reported unusual difficulty sleeping and irritability and lack of energy; wife reported changes were dramatic and out of character). 6 weeks after removal of BIPP packs, patient reported cessation of effects. Serum bismuth had decreased to 13 µg/L.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable (one case report)
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Bridgeman A. M. and Smith A. C. (1994). Iatrogenic bismuth poisoning. Case report. Aust Dent J 39(5): 279-281.		
Author's conclusions	Interpretation of results	In the reported case, a serum bismuth level of 41 µg/L, three times the normal levels, accompanied by recognised mild symptoms of bismuth encephalopathy supported the diagnosis of bismuth poisoning. This diagnosis was further supported by cessation of symptoms and normalisation of serum bismuth levels following the removal of the BIPP packs. The most likely mechanism of absorption of the bismuth subnitrate in BIPP would be from the gastrointestinal tract following ingestion of bismuth-laden saliva. However, it has been suggested that absorption may occur across the large surface area of the raw cancellous bone against which the BIPP is packed.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Applied dose of bismuth unknown. Although bismuth concentration in blood was three-fold higher than reference range, it is unclear whether bismuth (or some other component of BIPP) was responsible for neurotoxicity observed. Although dose of bismuth is unknown, the case report was included in risk of bias analysis as evidence of neurotoxicity was observed.
	Notes on study quality, e.g. gaps, methods	

Buge et al. 1981

Publication Reference: Buge A, Supino-Viterbo V, Rancurel G, and Pontes C (1981). Epileptic phenomena in bismuth toxic encephalopathy. Journal of Neurology, Neurosurgery, and Psychiatry. 44: 62-67.		
General Information	Date of data extraction	24/03/2023
	Authors	Buge A, Supino-Viterbo V, Rancurel G, and Pontes C
	Publication date	1981
	Publication type	Case report summary
	Peer reviewed?	Yes
	Country of origin	France
	Source of funding	Not stated.
	Possible conflicts of interest	No conflict of interest statement included.
Study characteristics	Aim/objectives of study	Examining and describing the clinical manifestations (i.e. presence or absence of seizures) in 70 patients with bismuth encephalopathy.
	Study type/design	Summary of 70 cases (case report).
	Study duration	4 weeks to 30 years exposure
	Type of water source (if applicable)	Not applicable

Publication Reference: Buge A, Supino-Viterbo V, Rancurel G, and Pontes C (1981). Epileptic phenomena in bismuth toxic encephalopathy. Journal of Neurology, Neurosurgery, and Psychiatry. 44: 62-67.		
Population characteristics	Population/s studied	70 patients admitted to hospital with bismuth encephalopathy who had repeated clinical and electroencephalogram (EEG) examinations.
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	Not applicable
	Size of study	Case report (n=70)
Exposure and setting	Exposure pathway	Oral daily dose of bismuth subnitrate (5-20 g daily over a period of 4 weeks to 30 years) for complaints related to the digestive tract.
	Source of chemical/contamination	Bismuth subnitrate
	Exposure concentrations (if applicable)	5-20 g daily of bismuth subnitrate (i.e. 3.6-14.6 g bismuth).
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable. Serum bismuth was measured (150-2,200 µg/L).
	Water sampling methods (monitoring, surrogates)	Serum bismuth sampling & analysis method not reported.
Results (for each outcome)	Definition of outcome	All patients exhibited myoclonic jerks but no paroxysmal features ever appeared on EEG. Computed tomography showed cortical hyperdensities. Seizures were observed in 22 patients, but epileptic EEG patterns appeared only when bismuth was below 1,500 µg/L. Clinical manifestations were reversible after cessation of bismuth therapy.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	70 cases
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	Authors suggested that a high cortical intracellular bismuth concentration induces a "cortical inhibition" which causes suppression of physiological electrical brain activity, the absence of EEG paroxysmal phenomena during myoclonic jerks, and explains the rarity of epileptic seizures.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• 70 patients

Publication Reference: Buge A, Supino-Viterbo V, Rancurel G, and Pontes C (1981). Epileptic phenomena in bismuth toxic encephalopathy. Journal of Neurology, Neurosurgery, and Psychiatry. 44: 62-67.		
	Notes on study quality, e.g. gaps, methods	• Patients ingested large doses of Bi (i.e. 3.6-14.6 g Bi), seemingly as a daily dose for 4 weeks to 30 years. • This resulted in high serum Bi measurements (150-2,200 µg/L) • Clinical manifestations were reversible after cessation of bismuth therapy. • Confounders not discussed. • Dose of bismuth was reported, therefore the case report was included in risk of bias analysis.

Burns et al. 1974

Publication Reference: Burns R., Thomas D. W. and Barron V. J. (1974). Reversible encephalopathy possibly associated with bismuth subgallate ingestion. Br Med J 1(5901): 220-223.		
General Information	Date of data extraction	03/04/2023
	Authors	Burns R, Thomas DW, Barron VJ
	Publication date	1974
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	Not stated (authors are from a Hospital)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on four patients who developed a very similar recurrent and reversible neurological syndrome consisting of confusion, tremulousness, clumsiness, myoclonic jerks, and an inability to walk, possibly associated with bismuth subgallate ingestion.
	Study type/design	Case report (n=4)
	Study duration	
	Type of water source (if applicable)	Not applicable
	Population/s studied	4 cases:

Publication Reference: Burns R., Thomas D. W. and Barron V. J. (1974). Reversible encephalopathy possibly associated with bismuth subgallate ingestion. Br Med J 1(5901): 220-223.		
Population characteristics	Selection criteria for population (if applicable)	• Case 1: 43-yr old farmer who had an abdominoperineal resection for a carcinoma of the colon in 1966, after which he took charcoal by mouth together with a third of a teaspoon of Bi subgallate 3 times/day for 4 years. • Case 2: 55-year old businessman who had an abdominoperineal resection for carcinoma of the colon in June 1971. Was given Bi subgallate and told to take a third of a teaspoon twice a day, but he probably took one level teaspoon twice a day. • Case 3: 52-year old housewife who underwent an abdominoperineal resection in August 1971 for carcinoma of the colon. Was then advised to take a third of a teaspoon of Bi subgallate by mouth twice daily. • Case 4: 70-year old retired male clerk who had an abdominoperineal resection for carcinoma of the rectum in 1965. He had been taking charcoal by mouth together with one third of a teaspoon of Bi subgallate regularly since the operation.
	Subgroups reported	Not applicable (case reports)
	Size of study	N=4 cases
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful ingestion of bismuth subgallate.
	Exposure concentrations (if applicable)	Not provided (given in measures of teaspoons).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

	How outcome was assessed	• Case 1: Drowsy for about a week, after which he was unable to work on his farm because of tremulousness, clumsiness and poor memory. Symptoms seemed to fluctuate but in 1970 (4 years after starting on Bi) his tremulousness and confusion became such that he was admitted to hospital. Numerous myoclonic jerking movements evident. Numerous admissions over several years; during his last admission he became delirious, had several grand mal epileptic attacks and finally died. At necropsy, terminal pulmonary oedema was found. His brain and spinal cord were extensively examined. There was no evidence of metastases in the nervous system or elsewhere. There was no evidence of inflammation, demyelination, or inclusion bodies in the brain, and the only abnormal finding was a paucity of Purkinje cells in the cerebellum. • Case 2: 10 months after operation, patient became irritable and antisocial, and had lapses in memory. His gait became ataxic and he was generally clumsy. One grand mal epileptic attack occurred. He was admitted to hospital where he was noted to be confused and demented, and unable to understand or co-operate. There was tremulous shaking of both legs, and he was unable to walk. No focal neurological signs were found. After three weeks his condition had improved greatly and it was noted then that he performed his intellectual tests well and that the tremulousness had disappeared. He was discharged from hospital, but two months later he was readmitted with a recurrence of his confusion and ataxia. After three weeks he had again recovered and was discharged. However, within nine days he was readmitted in a confused and ataxic state, and on this occasion bismuth subgallate was continued while in hospital in a dose of one teaspoon three times a day. His condition did not improve so he was transferred to a nursing home for terminal care. Within three weeks he had recovered and was sent home. In November 1972 (~1.5 years) his bismuth subgallate was finally stopped, and 10 months later there had been no further episodes of confusion or ataxia. • Case 3: 6 months after operation she became shaky & tremulous. Recovered spontaneously in 10 days. In May 1972 she again became unsteady & confused along with gait disturbance. After 2 weeks, she recovered. In July 1972 she again became confused and agitated, with jerky involuntary movements and an inability to walk. She recovered within a few weeks and was discharged from hospital. Over the next few months she had further episodes of a minor nature consisting of shaking and loss of balance. In June 1973 she had a further episode of confusion and tremulousness again related to the onset of her menses and to the ingestion of bismuth subgallate, which she had stopped several months before. This was one of the worst attacks, but after six weeks she had almost fully recovered. She had ceased to take bismuth subgallate shortly after the attack began. • Case 4: 6 years after surgery patient had an episode of confusion and loss of memory, together with jerking spasms of the arms and difficulty walking which lasted for 3 weeks. He was investigated in a country hospital and his symptoms

Publication Reference: Burns R., Thomas D. W. and Barron V. J. (1974). Reversible encephalopathy possibly associated with bismuth subgallate ingestion. Br Med J 1(5901): 220-223.		
		cleared without any cause being found. In June 1973 he again developed difficulty in walking, poor concentration, and tremulousness over a period of several days. For two weeks before this his colostomy had been working less often. He had continued to take his bismuth subgallate. Examination at that time showed confusion and disorientation. Limb movements were clumsy and ataxic and occasional myoclonic jerking movements of the arms and to a less extent of the legs were seen. He was unable to walk or even stand unsupported. His bismuth subgallate was withdrawn, and over a period of seven days his condition improved remarkably to the extent that he was able to walk, his involuntary movements almost ceased, and he was able to think clearly enough to do crossword puzzles. While he was still in hospital and under careful observation it was decided to reintroduce bismuth subgallate together with codeine to constipate his motions. Over the next 10 days he became tremulous and ataxic and he claimed that he was unable to think clearly. While his neurological condition was not florid it was decided to stop the bismuth subgallate, and within three days his condition had again returned to normal.
	Method of measurement	See above description
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=4 cases
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	• While there is not a clear history of excessive ingestion of Bi subgallate immediately before the onset of the neurological symptoms, the authors believe that the substance may well be the toxic agent responsible. • Though it has not been possible to obtain an accurate chronological drug history, it would seem that in all patients bismuth subgallate was stopped while they were in hospital, resulting in clinical improvement. When they returned home it was recommenced, resulting in an exacerbation or relapse of their condition.
	Assessment of uncertainty (if any)	Not done.

Publication Reference: Burns R., Thomas D. W. and Barron V. J. (1974). Reversible encephalopathy possibly associated with bismuth subgallate ingestion. Br Med J 1(5901): 220-223.		
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (4 case reports). • Applied dose of bismuth unknown. • Bismuth concentration in blood not determined. • However, results suggest that bismuth subgallate administration was responsible for the neurotoxicity observed. • Although dose of bismuth is unknown, the case report was included in risk of bias analysis as evidence of neurotoxicity was observed.

Canena et al. 1998

Publication Reference: Canena J., Reis J., Pinto A. S., Santos A. M., Leitão J., Pinheiro T. and Quina M. G. (1998). Distribution of bismuth in the rat after oral dosing with ranitidine bismuth citrate and bismuth subcitrate. J Pharm Pharmacol 50(3): 279-283.		
General Information	Date of data extraction	24/03/2023
	Authors	Canena J, Reis J, Pinto AS, Santos AM, Leitao J, Pinheiro T and Quina G
	Publication date	1998
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Portugal
	Source of funding	Not specified (authors from university and government department).
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To examine bismuth levels in selected organs (brain, liver, kidney, lung), blood, urine and faeces of the rat after oral dosing with ranitidine bismuth citrate. In addition, to determine any influence of an increase in gastric pH, the study has compared the results with bismuth deposition results obtained after dosing with bismuth subcitrate alone and with bismuth subcitrate plus ranitidine hydrochloride.
	Study type/design	Experimental animal study
	Study duration	15 days oral dosing, bismuth content of organs measured 30 days later.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Male Wistar rats (220 g). Caged individually. 6-8 rats/group
	Selection criteria for population (if applicable)	Not applicable (animal study)

Publication Reference: Canena J., Reis J., Pinto A. S., Santos A. M., Leitão J., Pinheiro T. and Quina M. G. (1998). Distribution of bismuth in the rat after oral dosing with ranitidine bismuth citrate and bismuth subcitrate. J Pharm Pharmacol 50(3): 279-283.		
	Subgroups reported	Study 1: Oral gavage twice daily for 15 days of 0.9% NaCl (n=8), bismuth subcitrate (13.7 mg/kg/d, n=8), bismuth subcitrate (13.7 mg/kg/d) plus ranitidine hydrochloride (8.6 mg/kg/d, n=8), or ranitidine bismuth citrate (22.8 mg/kg/d, n=6). Gastric pH measured on day 10, samples of liver, brain, blood, kidney, lung faeces & urine taken on day 15. Study 2: Oral gavage twice daily for 15 days of 0.9% NaCl (n=6), bismuth subcitrate (13.7 mg/kg/d, n=6) or ranitidine bismuth citrate (22.8 mg/kg/d, n=6). After 30 days, samples of liver, brain, blood, kidney, lung, faeces and urine were collected.
	Size of study	6-8 rats/group
Exposure and setting	Exposure pathway	Oral gavage
	Source of chemical/contamination	Not applicable (Treatment with bismuth compounds was intentional in experimental animals)
	Exposure concentrations (if applicable)	Bismuth subcitrate: 13.7 mg/kg/d Ranitidine hydrochloride: 8.6 mg/kg/d Ranitidine bismuth citrate: 22.8 mg/kg/d
	Comparison group(s)	Controls receiving saline (0.9% NaCl).
Study methods	Water quality measurement used	Not applicable. Measurement of bismuth levels in tissues was by particle-induced X-ray emission (PIXE) in blood (at different time periods) & brain (at end of study)
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	• During both series of experiments there was no evidence of encephalopathy in any of the 48 rats studied. • Immediately after 15 days of oral dosing with either bismuth subcitrate 13.7 mg/kg/d or with bismuth subcitrate 13.7 mg/kg/d plus ranitidine hydrochloride 8.6 mg/kg/d, bismuth was present in kidney, blood, brain, lung and liver (in descending order). There were no differences between organ concentrations after the two treatments, suggesting that bismuth deposition after oral bismuth subcitrate is not influenced by a concurrent elevation of gastric pH. • A differing pattern of bismuth deposition was observed after the same duration of dosing with ranitidine bismuth citrate 22.8 mg/kg/day. Significantly lower concentrations of bismuth were found in the kidney and bismuth was not detectable in the brain. • In the second study, performed 30 days after acute oral dosing with either bismuth subcitrate or ranitidine bismuth citrate, although bismuth could be found in the urine, none could be detected in the kidney, blood, brain, lung, liver or faeces.
	How outcome was assessed	

Publication Reference: Canena J., Reis J., Pinto A. S., Santos A. M., Leitão J., Pinheiro T. and Quina M. G. (1998). Distribution of bismuth in the rat after oral dosing with ranitidine bismuth citrate and bismuth subcitrate. J Pharm Pharmacol 50(3): 279-283.		
	Method of measurement	During both studies, animals were tested twice daily for signs of encephalopathy: rats that did not move outside a 30 cm^2 area were considered to show loss of activity; animals unable to right themselves after being placed on their back were considered to have lost righting ability, and immobile rats with loss of corneal reflex were considered comatose.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Data presented as means ± Standard Error of Mean of concentrations of bismuth in those tissues for which bismuth content was above LoR. Statistical analysis performed by Student's t-test.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.
Author's conclusions	Interpretation of results	Bismuth was deposited in the kidney, brain, lung and liver of the rat after oral dosing with bismuth subcitrate. When rats were dosed orally with an equivalent amount of bismuth in the form of ranitidine bismuth citrate, significantly lower concentrations of bismuth were deposited in the kidney and bismuth was not detectable in the brain. In both series of studies reported here there was no evidence of encephalopathy among any of the experimental animals.
	Assessment of uncertainty (if any)	No comment made on limitations or uncertainties.
Reviewer comments	Results included/excluded in review (if applicable)	This study assessed single doses of different bismuth compounds and limited health outcomes but provides some information with respect to defining a health-based guidance value for Bi. Risk of bias assessment was undertaken.

Chaleil et al. 1981

Publication Reference: Chaleil D., Lefevre F., Allain P. and Martin G. J. (1981). Enhanced bismuth digestive absorption in rats by some sulfhydryl compounds: nmr study of complexes formed. Journal of Inorganic Biochemistry 15(3): 213-221.		
General Information	Date of data extraction	27/03/2023
	Authors	Chaleil D, Lefevre F, Allain P and Martin GJ
	Publication date	1981
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	France
	Source of funding	Not specified (authors from university laboratories).

Publication Reference: Chaleil D., Lefevre F., Allain P. and Martin G. J. (1981). Enhanced bismuth digestive absorption in rats by some sulfhydryl compounds: nmr study of complexes formed. Journal of Inorganic Biochemistry 15(3): 213-221.		
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To investigate the biological interactions between bismuth and some thiol compounds as well as the nmr properties of complexed and uncomplexed thiol derivatives. Nmr study not summarised here.
	Study type/design	Experimental animal study
	Study duration	Study 1 (metabolism study): 24-hour follow-up after single administration. Study 2 (toxicological study bismuth-cysteine complex): single dose, 8-day follow-up
	Type of water source (if applicable)	Not applicable.
Population characteristics	Population/s studied	Male Wistar rats (~200 g)
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	Study 1: Bismuth subnitrate (followed by demineralised water) (n=23), or followed by 1 mmol/kg in 0.2 mL demineralised water of L-cysteine HCl H_2O, DL-homocysteine, 3-mercaptopropionic acid, 2-mercaptoethane, 2-mercaptoethylamine HCl, D-penicillamine, L-methionine, L-serine, or L-alanine (n=5/group except homocysteine where n=7 and cysteine where n=9) Study 2: Bismuth-cysteine complex given to 36 rats (66.7, 100, 150 or 225 mg/kg bismuth) (n=9/group).
	Size of study	
Exposure and setting	Exposure pathway	Intragastric administration (i.e. gavage)
	Source of chemical/contamination	Merck of Sigma (purchased chemicals)
	Exposure concentrations (if applicable)	Study 1: 0.5 mmol/kg bismuth subnitrate followed immediately by 0 or 1 mmol/kg of various sulfhydryl compounds or amino acids. Study 2: 66.7, 100, 150 or 225 mg/kg bismuth given as a bismuth-cysteine complex (cysteine chlorohydrate monohydrate and bismuth chloride)
	Comparison group(s)	Reference group (for Study 1): Bismuth subnitrate only followed by demineralised water.
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	Study 1: Blood for bismuth determination at 0.5, 1, 2, 4 and 8 hours after exposure. 24-hour urinary excretion of bismuth collected. Study 2: Observations during 8 days, brain & kidney bismuth concentration of each dead rat analysed.
	How outcome was assessed	
	Method of measurement	Study 1 & 2: Bismuth analysed by AAS.

Publication Reference: Chaleil D., Lefevre F., Allain P. and Martin G. J. (1981). Enhanced bismuth digestive absorption in rats by some sulfhydryl compounds: nmr study of complexes formed. Journal of Inorganic Biochemistry 15(3): 213-221.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	See above.
Statistics (if any)	Statistical method used	Not applicable. No statistical analysis undertaken.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.
Author's conclusions	Interpretation of results	Study 1: • Most potent enhancers of Bi in blood: 3-mercaptopropionic acid > cysteine > homocysteine > penicillamine >> 2-mercaptoethane ~ 2-mercaptoethylamine > control • Non-thiol compounds alanine, serine and methionine do not increase, and perhaps decrease Bi blood levels. • Urinary elimination confirms the increase of absorption since each thiol compound significantly enhances metal excretion. Study 2: • Survival (out of 9): 66.7 mg/kg (9), 100 mg/kg (8), 150 mg/kg (4), 225 mg/kg (1). Gait troubles and myoclonic responses to hand flicking were observed in some rats before death (reminiscent of human encephalopathies). • Acute oral LD_{50} = 156 ± 20 mg/kg. Authors conclude the results confirm that bismuth absorption (and toxicity) increases with cysteine.
	Assessment of uncertainty (if any)	None provided.
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on Bi toxicokinetics and increased absorption if administered with cysteine. However, this study assessed limited health outcomes (i.e. mortality only), so provides limited information with respect to defining a health-based guidance value for Bi (single dose administration, in combination with cysteine only). As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Chowdhury et al. 2001

Publication Reference: Chowdhury H., Yunus M., Zaman K., Rahman A., Faruque S., Lescano A. and Sack R. B. (2001). The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea. Acta Pædiatrica 90.		
General Information	Date of data extraction	27/03/2023
	Authors	Chowdhury HR, Yunus M, Zaman K, Rahman A, Faruque SM, Lescano AG, and Sack RB

Publication Reference: Chowdhury H., Yunus M., Zaman K., Rahman A., Faruque S., Lescano A. and Sack R. B. (2001). The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea. Acta Pædiatrica 90.		
	Publication date	2001
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Bangladesh and USA
	Source of funding	Funded by ICDDR, B: Centre for Health and Population Research, via the International Child Health Foundation, which received a grant from the Procter & Gamble company. The centre is funded by countries and agencies that share its concern for the health problems of the developing countries. Current donors providing unrestricted support include: the aid agencies of the Government of Australia, Bangladesh, Belgium, Canada, Japan, The Netherlands, Sweden, Sri Lanka, Switzerland, the United Kingdom and the United States of America and international organisations including the United Nations Children's Fund.
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To undertake a controlled, randomised, double-blind study in Bangladeshi children with acute diarrhoea to determine whether bismuth subsalicylate (BSS) would prevent the development of persistent diarrhoea (PD) in young children.
	Study type/design	Randomised, double-blind study
	Study duration	Administration for 5 days
	Type of water source (if applicable)	Not applicable.
Population characteristics	Population/s studied	Children ages 4-36 months
	Selection criteria for population (if applicable)	Children of either sex, ages 4–36 mo, who resided in the demographic surveillance area of Matlab, (in rural Bangladesh, 45 km southeast of Dhaka) and were admitted to the Diarrhoea Hospital of the Matlab Health Research Programme and had a history of acute watery diarrhoea of less than 72 h duration, with three or more watery stools in the last 24 h, were considered eligible for inclusion in the study. Exclusion criteria included: use of antimicrobials within the previous 48 h, presence of gross blood in the stool, severe malnutrition (weight for age less than the 5th percentile (National Center for Health Statistics), any other systemic illness, known intake of salicylates in the previous 24 h, allergy to salicylates, an attack of varicella or measles in the past 3 mo, or previously having been a study patient.
	Subgroups reported	BSS group: n=226 given liquid oral BSS (as Pepto-Bismol), 100 mg/kg for 5 d Placebo group: n=225 given placebo of identical appearance.
	Size of study	
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Pepto Bismol (Procter & Gamble; purchased in the US) was the active test material containing BSS. The placebo was made in Bangladesh by Ganoshastha Pharmaceuticals using the same formula of Pepto-Bismol (provided by Procter and Gamble) but without BSS. Each 5 mL Pepto-Bismol contains 175 mg BSS.

Publication Reference: Chowdhury H., Yunus M., Zaman K., Rahman A., Faruque S., Lescano A. and Sack R. B. (2001). The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea. Acta Pædiatrica 90.		
	Exposure concentrations (if applicable)	0 or 100 mg/kg/d for 5 days
	Comparison group(s)	Placebo group (see above)
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	Patient's diarrhoeal status (definitions provided in paper). The paper examined efficacy of the medication; this information is not reported here in detail as this summary focuses on the adverse effect reporting. Weight gain from admission to day 5 in BSS group was significantly greater (2.3%) than in placebo (0.5%) (p=<0.001). No adverse reactions were observed during the study. Two children were noted to have 'black tongue' during treatment, indicating this known side effect of BSS. BSS did not prevent the development of persistent diarrhoea, based on this sample size.
	How outcome was assessed	
	Method of measurement	Not applicable.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=226 (study group) N= 225 (placebo)
Statistics (if any)	Statistical method used	Analysis was done using SPSS 6.1 in triple-blinded fashion. Treatment group codes were broken only after finishing the analysis. Categorical data were analysed using Pearson's chi squared, applying Fisher's exact test when required. All continuous variables were compared using Student's t-tests. Duration of diarrhoeal episodes was compared using the Kaplan–Meier method and statistical significance was evaluated with the log-rank test.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.
Author's conclusions	Interpretation of results	There were no side effects of BSS at the dosage used, thus confirming the previous studies on its safety. BSS did not prevent the development of persistent diarrhoea in children with acute diarrhoeal disease, but it had a mild, beneficial therapeutic effect in decreasing the severity and duration of the acute episode, and resulted in significantly increased weight gain during the period of hospitalisation, which has not been noted previously and for which there is no obvious explanation.
	Assessment of uncertainty (if any)	Not stated.

Publication Reference: Chowdhury H., Yunus M., Zaman K., Rahman A., Faruque S., Lescano A. and Sack R. B. (2001). The efficacy of bismuth subsalicylate in the treatment of acute diarrhoea and the prevention of persistent diarrhoea. Acta Pædiatrica 90.		
Reviewer comments	Results included/excluded in review (if applicable)	The primary objective of this study was to test the efficacy of a bismuth-containing drug. Although the study provides supporting information that there were no adverse reactions from the drug, it assessed limited health outcomes, so provides limited information with respect to defining a health-based guidance value for Bi (efficacy study, bismuth containing drug, not a simple Bi salt). As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Coffey and Graham 1974

Publication Reference: Coffey G. L. and Graham J. W. (1974). Letter: Mental illness or metal illness? Bismuth subgallate. Med J Aust 2(24): 885.		
General Information	Date of data extraction	05/04/2023
	Authors	Coffey GL and Graham JW
	Publication date	1974
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	Not stated (authors are from a Hospital)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of reversible dementia occurring in a colostomy patient consuming bismuth subgallate.
	Study type/design	Case report
	Study duration	Not stated
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report) 49-year old accountant, who had had an abdominoperineal resection 4 years previously for carcinoma of the rectum. He has been well since his operation until a few months before his admission to hospital. He then developed short episodes of tremulousness and unsteadiness, which improved. However, 1 month before admission he had become unsteady and tremulous again and this persisted. He was also confused and vague and had difficulty comprehending commands. He was ataxic on heel-toe walking. Also had marked impairment of short term memory.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
	Exposure pathway	Presumably oral but not stated

Publication Reference: Coffey G. L. and Graham J. W. (1974). Letter: Mental illness or metal illness? Bismuth subgallate. Med J Aust 2(24): 885.		
Exposure and setting	Source of chemical/contamination	Not stated (bismuth subgallate, presumably oral)
	Exposure concentrations (if applicable)	Not available
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Bi subgallate was suspended on admission to hospital and he showed a progressive improvement during his period of hospitalisation. This improvement continued since leaving hospital and at his last review, some 6 months after his illness, he was completely normal both psychologically and neurologically and returned to work. • No Bi measurements in blood or serum reported.
	How outcome was assessed	
	Method of measurement	Results of EEG and cerebral scan were normal. Right carotid angiogram gave normal results.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Authors conclude it is possible bismuth subgallate administration is responsible for effects observed.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Administered dose and timeframe unknown. • Serum Bi was not measured. • The information was considered too limited to provide any useful considerations for dose-response assessment, therefore the study was not included in risk of bias analysis.

Crossland and Bath 2011

Publication Reference: Crossland G. J. and Bath A. P. (2011). Bismuth iodoform paraffin paste: a review. J Laryngol Otol 125(9): 891-895.		
General Information	Date of data extraction	03/04/2023
	Authors	Crossland GJ and Bath AP

Publication Reference: Crossland G. J. and Bath A. P. (2011). Bismuth iodoform paraffin paste: a review. J Laryngol Otol 125(9): 891-895.		
	Publication date	2011
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not specified (authors are affiliated with hospitals)
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	Review of literature pertaining to Bi iodoform paraffin paste (BIPP), i.e. history, properties & side effects.
	Study type/design	Review/commentary (methods of literature review not specified, does not appear to be systematic).
	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)	Not applicable
	Exclusion criteria	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)	Not applicable
Study methods	Water quality measurement used	Not applicable
	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

Publication Reference: Crossland G. J. and Bath A. P. (2011). Bismuth iodoform paraffin paste: a review. J Laryngol Otol 125(9): 891-895.		
Author's conclusions	Interpretation of results	• BIPP is one part bismuth subnitrate, two parts iodoform and one part sterilised liquid paraffin by weight. • Bismuth compounds have been used to treat a variety of ailments for hundreds of years. They have been used topically as astringents and antiseptics, orally to treat gastrointestinal complaints, and parenterally to treat syphilis. • Neurotoxicity due to the absorption of bismuth from BIPP is rare but may be fatal if it is not recognised. Bismuth is thought to interfere with oxidative metabolism in the brain by binding the thiol groups of essential enzymes and by reducing cerebral blood flow. Symptoms of toxicity include headache, nausea and stomatitis. Blue-black deposits in the gingiva may be seen, the so-called 'bismuth line'. • Toxicity from BIPP usage is possible, even from the relatively modest quantities used in modern surgical practice.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on bismuth in BIPP. However, this study was a limited review / commentary so provides limited information with respect to defining a health-based guidance value for Bi. As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.

Dunk et al. 1990

Publication Reference: Dunk AA, Prabhu U, Tobin A, O'Morain C, Mowat NAG (1990). The safety and efficacy of tripotassium dicitrato bismuthate (De-Nol) maintenance therapy in patients with duodenal ulceration. Alimentary Pharmacology & Therapeutics. 4(2): 157-162.		
General Information	Date of data extraction	19/07/2023
	Authors	Dunk AA, Prabhu U, Tobin A, O'Morain C, Mowat NAG
	Publication date	1990
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	UK and Ireland
	Source of funding	Not stated (authors are from hospitals)
	Possible conflicts of interest	No conflict-of-interest statement is included in the paper.
Study characteristics	Aim/objectives of study	Double-blind placebo-controlled study to evaluate safety and efficacy of TDB in long-term management of patients with duodenal ulceration.
	Study type/design	HCT
	Study duration	12 months following an initial 4-week treatment period.

Publication Reference: Dunk AA, Prabhu U, Tobin A, O'Morain C, Mowat NAG (1990). The safety and efficacy of tripotassium dicitrato bismuthate (De-Nol) maintenance therapy in patients with duodenal ulceration. Alimentary Pharmacology & Therapeutics. 4(2): 157-162.		
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	71 patients whose duodenal ulcers had healed after an initial 4-week treatment period. Randomly allocated to receive maintenance treatment with either one TDB swallow tablet nocte (equivalent to 120 mg Bi_2O_3 or 108 mg Bi per day) or an identical placebo. 60 patients were recruited from Aberdeen Teaching Hospitals group and 30 from Meath and Adelaide hospitals in Dublin. Exclusion criteria were: age over 75 years, non-steroidal anti-inflammatory drug-related ulceration, previous peptic ulcer surgery, impaired renal function, symptoms and signs of neurological diseases, and concurrent administration of benzo-diazepines or thiol-containing drugs. Patients who presented with gastrointestinal haemorrhage were studied, provided that their ulcers showed no stigmata of recent haemorrhage. Four tablets, equivalent to 480 mg Bi_2O_3 were taken daily for 4 weeks. Those patients with documented ulcer healing were then entered into the double-blind placebo-controlled maintenance phase of the study, where one tablet or an identical looking placebo, was taken nightly at bedtime for up to 12 months. The two groups did not differ significantly with respect to age, sex, cigarette or alcohol consumption.
	Selection criteria for population (if applicable)	
	Subgroups reported	TDB group = (n=34) Placebo group = (n=37)
	Size of study	71 patients
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of TDB or placebo in tablet form.
	Exposure concentrations (if applicable)	Each tablet contained 120 mg Bi_2O_3 (i.e. maintenance dose = 108 mg Bi/day)
	Comparison group(s)	Placebo group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Patients were withdrawn from the study upon ulcer relapse, if whole-blood bismuth levels rose above 50 µg/L in the first 6 months or above 100 µg/L in the second 6 months, or if any neurological signs developed.
	How outcome was assessed	

Publication Reference: Dunk AA, Prabhu U, Tobin A, O'Morain C, Mowat NAG (1990). The safety and efficacy of tripotassium dicitrato bismuthate (De-Nol) maintenance therapy in patients with duodenal ulceration. Alimentary Pharmacology & Therapeutics. 4(2): 157-162.		
	Method of measurement	• Neurological examination of cranial nerves and motor and sensory function of arms and legs was done monthly. • Blood also removed monthly and examined for full blood count, urea and electrolytes, serum creatinine, serum liver function, and whole blood bismuth levels. • Endoscopy repeated after 3, 6 and 12 months and whenever symptoms recurred.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	71 (34 exposed, 37 non-exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable. Relevant results as follows: • Maintenance TDB therapy was well tolerated. No patient in this group was withdrawn because of the development of treatment-related side-effects or because of adverse changes in haematological or biochemical indices (data not shown). • No patient who received TDB was withdrawn because of bismuth accumulation. One asymptomatic placebo-treated patient, however, developed a whole-blood bismuth concentration of 220 µg/L after the first month of maintenance treatment; this returned to base-line concentrations when repeated 2 weeks after withdrawal from the study. This isolated elevation of bismuth concentration is unexplained, and the patient denied the consumption of known bismuth-containing medications. Abnormal neurological signs were not detected in this or any other patient studied. • Patients who received maintenance TDB therapy had significantly less duodenal ulcer relapses over the 12-month study period than did those who received placebo ($P < 0.025$).
Author's conclusions	Interpretation of results	• Authors concluded that maintenance TDB, in the dose used in this study, appears to be safe when taken up to 12 months. No signs or symptoms suggestive of bismuth neurotoxicity developed during the 13-month study period. • Maintenance TDB therapy is statistically significantly better than placebo in the prevention of duodenal ulcer relapse over a 12-month period.
	Assessment of uncertainty (if any)	As detailed neuropsychological and neurophysiological testing was not performed, authors cannot exclude the development, if such a condition exists, of subclinical neurotoxicity. Electroencephalographs were not performed, as the authors' experience of this investigation in acute bismuth self-poisoning suggests that the EEG is likely to be of little or no value in the detection of a state of subclinical encephalopathy. Authors stress results are for a relatively small study population.

Publication Reference: Dunk AA, Prabhu U, Tobin A, O'Morain C, Mowat NAG (1990). The safety and efficacy of tripotassium dicitrato bismuthate (De-Nol) maintenance therapy in patients with duodenal ulceration. Alimentary Pharmacology & Therapeutics. 4(2): 157-162.		
Reviewer comments	Results included/excluded in review (if applicable)	• Double-blind HCT of 71 patients (34 exposed) found no adverse effects on neurotoxicity, biochemical or haematological indicators after oral administration of 108 mg Bi/day (i.e. at 78 kg body weight this is 1.4 mg Bi/kg/day) as TDB for up to 12 months. • Subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Figueroa-Quintanilla et al. 1993

Publication Reference: Figueroa-Quintanilla D., Salazar-Lindo E., Sack R. B., León-Barúa R., Sarabia-Arce S., Campos-Sánchez M. and Eyzaguirre-Maccan E. (1993). A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. N Engl J Med 328(23): 1653-1658.		
General Information	Date of data extraction	27/03/2023
	Authors	Figueroa-Quintanilla D, Salazar-Lindo E, Sack RB, Leon-Barua R, Sarabia-Arce S, Campos-Sanchez M, Eyzaguirre-Maccan E
	Publication date	1993
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Peru and USA
	Source of funding	Supported by a grant from the International Child Health Foundation (a 501(C) non-profit organisation supported by gifts and grants from individuals, foundations and corporations) and by funds from the Procter & Gamble Company.
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To undertake a placebo-controlled, randomised trial to evaluate the effect of bismuth subsalicylate on the duration and volume of acute watery diarrhoea (as an adjunct to oral rehydration therapy in infants with acute watery diarrhoea).
	Study type/design	Randomised, placebo-controlled, double-blind study
	Study duration	Doses given every four hours for 5 days or until diarrhoea stopped, which ever occurred first.
	Type of water source (if applicable)	Not applicable.
	Population/s studied	Male children mean age 13.5 months

Publication Reference: Figueroa-Quintanilla D., Salazar-Lindo E., Sack R. B., León-Barúa R., Sarabia-Arce S., Campos-Sánchez M. and Eyzaguirre-Maccan E. (1993). A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. N Engl J Med 328(23): 1653-1658.		
Population characteristics	Selection criteria for population (if applicable)	Boys brought to an oral rehydration unit in Peru for treatment of acute diarrhoea between January 1990 and March 1991 were eligible for this study if they were 3-59 months old and has passed three or more watery stools in preceding 24 hours. Patients were excluded if they had blood in their stools (at admission or within the next 24 hours), had had diarrhoea for more than 5 days, had received antibiotics or antidiarrheal medication or any treatment with acetylsalicylic acid in 72 hours before admission, had clinical evidence of another illness requiring antibiotic therapy (at admission or within the next 24 hours), had severe malnutrition (<60% of value for 50th percentile for weight for age), had a history of allergy to salicylate or bismuth, or had been exclusively breast-fed.
	Subgroups reported	Group 1: Placebo Group 2: 100 mg bismuth subsalicylate/kg/day Group 3: 150 mg bismuth subsalicylate/kg/day
	Size of study	
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Source of bismuth subsalicylate not provided.
	Exposure concentrations (if applicable)	0, 100, or 150 mg bismuth subsalicylate/kg/d for 5 days
	Comparison group(s)	Placebo group (see above)
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	• Diarrhoea stopped within 120 hours of admission in 74% of placebo, 89% of 100 mg group (p=0.009), 88% of 150 mg group (p=0.019). • Duration of hospitalisation and total stool output were significantly reduced in both bismuth groups. • Total intake of oral rehydration solution was significantly less (~25% lower) in both bismuth groups. • No significant differences were found among the three groups in total caloric intake, mean percentage of weight change or volume of vomitus. • There were no serum samples with Bi levels of 100 ng/mL or more. • Two patients (one in placebo group, the other in 150 mg group) had a rash during the study. They were given an antihistamine in syrup and the rash cleared rapidly. Neither patient had to be withdrawn from the study.
	How outcome was assessed	
	Method of measurement	Not applicable.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=84 (placebo) N=85 (100 mg/kg/d group) N=83 (150 mg/kg/d group)

Publication Reference: Figueroa-Quintanilla D., Salazar-Lindo E., Sack R. B., León-Barúa R., Sarabia-Arce S., Campos-Sánchez M. and Eyzaguirre-Maccan E. (1993). A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. N Engl J Med 328(23): 1653-1658.		
Statistics (if any)	Statistical method used	Two-way comparisons of baseline and outcome data were made between the three study groups, and three-way comparisons (with time since start of treatment as third variable) were made of variables measured several times during follow-up. Chi-square tests were used to compare discrete variables and one-way analysis of variance with two degrees of freedom used to compare continuous variables. Statistical analysis included all patients who completed the study. If patients were withdrawn before completion of study because of treatment failure or at their parents' request, the data on these patients up to the time of withdrawal were included in the analysis.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.
Author's conclusions	Interpretation of results	There were no treatment-related side effects of bismuth subsalicylate at the dosage used. The results show effectiveness of bismuth subsalicylate as adjunctive therapy to oral rehydration and early continued feeding of children with acute diarrhoea.
	Assessment of uncertainty (if any)	There is a need to determine the effectiveness of lower doses of bismuth.
Reviewer comments	Results included/excluded in review (if applicable)	The primary objective of this study was to test the efficacy of a bismuth-containing drug. Although the study provides supporting information that there were no adverse reactions from the drug, it assessed limited health outcomes, so provides limited information with respect to defining a health-based guidance value for Bi (efficacy study, bismuth containing drug, not a simple Bi salt). As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Garrett and Chambers 1917

Publication Reference: Garrett L. and Chambers H. (1917). The treatment of septic wounds with bismuth-iodoform-paraffin paste. The Lancet 189: 331-333.		
General Information	Date of data extraction	28/03/2023
	Authors	Garrett Anderson L and Chambers H
	Publication date	1917
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	England
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in article.

Publication Reference: Garrett L. and Chambers H. (1917). The treatment of septic wounds with bismuth-iodoform-paraffin paste. The Lancet 189: 331-333.		
Study characteristics	Aim/objectives of study	Reporting on experiences with treatment of septic wounds with bismuth-iodoform paraffin paste (BIPP) in the World War I military hospital in Endell-Street, London.
	Study type/design	Observational study
	Study duration	Cases treated with BIPP wounded during July, August and September 1916.
	Type of water source (if applicable)	Not applicable.
Population characteristics	Population/s studied	Military personnel wounded in combat suffering from septic wounds admitted to military hospital in 1916.
	Selection criteria for population (if applicable)	As above.
	Subgroups reported	400 cases treated with BIPP. Results of 62 cases presented in paper.
	Size of study	
Exposure and setting	Exposure pathway	Dermal (application of BIPP paste to septic wounds)
	Source of chemical/contamination	Purposeful application of BIPP (2 ounces iodoform, 1 ounce bismuth subnitrate, and liquid paraffin)
	Exposure concentrations (if applicable)	Not reported.
	Comparison group(s)	None
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	• Report focused on effectiveness of treatment with BIPP. • In terms of adverse events, one case of iodoform poisoning occurred when treatment was first begun and when larger quantities (not reported) of paste were used; it was characterised by fever, emaciation, and delirium. Symptoms subsided when treatment was discontinued. • Several cases of 'blue gum' were observed, but the authors were not satisfied that these are attributable to bismuth absorption.
	How outcome was assessed	
	Method of measurement	Not applicable.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	400 cases exposed to BIPP
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	Authors indicate that BIPP is a promising new treatment for septic wounds.

Publication Reference: Garrett L. and Chambers H. (1917). The treatment of septic wounds with bismuth-iodoform-paraffin paste. The Lancet 189: 331-333.		
	Assessment of uncertainty (if any)	Not provided.
Reviewer comments	Results included/excluded in review (if applicable)	The primary objective of this study was to test the efficacy of a bismuth-containing drug (BIPP). Although the study provides supporting information that there were no clear adverse reactions from absorption of bismuth through the skin of these cases, it is an observational study and provides limited information with respect to defining a health-based guidance value for Bi (dose of Bi applied to skin not provided, limited health outcomes monitored). As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Gurnani et al. 1993

Publication Reference: Gurnani N., Sharma A. and Talukder G. (1993). Comparison of clastogenic effects of antimony and bismuth as trioxides on mice in vivo. Biol Trace Elem Res 37(2-3): 281-292.		
General Information	Date of data extraction	28/03/2023
	Authors	Gurnani N, Sharma A, Talukder G
	Publication date	1993
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	India
	Source of funding	Financial assistance provided by Council of Scientific and Industrial Research, New Delhi
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To compare the relative clastogenicity of antimony and bismuth trioxides, given the same concentrations orally to mice.
	Study type/design	Experimental animal study
	Study duration	21 days exposure, killed on days 7, 14, and 21 of treatment.
	Type of water source (if applicable)	Not applicable (*ad libitum*)
Population characteristics	Population/s studied	Swiss albino male mice (8 wk old, 25-30 g).
	Selection criteria for population (if applicable)	Not applicable.
	Subgroups reported	5 animals/group
	Size of study	
Exposure and setting	Exposure pathway	Gavage
	Source of chemical/contamination	Aqueous suspensions of antimony trioxide (Sb_2O_3) (E. Merck/India) and bismuth trioxide (Bi_2O_3) (E. Merck/India).

Publication Reference: Gurnani N., Sharma A. and Talukder G. (1993). Comparison of clastogenic effects of antimony and bismuth as trioxides on mice in vivo. Biol Trace Elem Res 37(2-3): 281-292.		
	Exposure concentrations (if applicable)	Sb_2O_3 : 400, 666.67, 1000 mg/kg bw (corresponding to 1/50, 1/30 and 1/20 of LD_{50}). Bi_2O_3 : Same amounts as antimony trioxide for comparison.
	Comparison group(s)	Control (distilled water only)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Scoring done for: • Chromosomal aberrations in bone marrow • Dividing cells (200 cells/animal) were scored for cellular proliferation. • Sperm heads (500/animal) were scored for sperm abnormalities. Results: • Frequency of aberrations (with and without gaps) by antimony increased to significance (p≤0.001) proportionately with dose for first 14 days. Both highest & longest exposure were lethal. Same effect with bismuth, but highest dose was not lethal. The degree of clastogenicity of antimony trioxide was higher than that of bismuth trioxide for the same dose and duration of exposure. • Neither salt increased frequency of sperm head abnormalities.
	How outcome was assessed	
	Method of measurement	Scoring after staining under microscope
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	5 animals/group
Statistics (if any)	Statistical method used	The results of exposure to Sb_2O_3 and Bi_2O_3 were analysed individually by one-tailed trend test. The data obtained from the two chemicals were compared by Student's t-test and analysis of variance (ANOVA), followed by Duncan's multiple range test, in order to determine any significant differences between the effects of the two compounds for the different doses and durations. The data on divisional frequency for each of the doses and durations were compared by t-test as well. Sperm head abnormalities were compared by t-test with the control.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	The frequencies of chromosomal aberrations induced by both chemicals were directly proportional to the dose used and the duration of exposure. The highest dose of antimony, given for the longest period was, however, lethal. Effects on germ cells, as shown by screening for sperm head abnormalities, were not significant.
	Assessment of uncertainty (if any)	Not done.

Publication Reference: Gurnani N., Sharma A. and Talukder G. (1993). Comparison of clastogenic effects of antimony and bismuth as trioxides on mice in vivo. Biol Trace Elem Res 37(2-3): 281-292.		
Reviewer comments	Results included/excluded in review (if applicable)	Study provides dose response for clastogenicity but at relatively high doses of bismuth. Risk of bias assessment was nevertheless undertaken.

Hanzlik et al. 1938

Publication Reference: Hanzlik P. J., Lehman A. J. and Richardson A. P. (1938). Sobisminol: toxicity, tolerance and irritation according to different channels of administration. Journal of Pharmacology and Experimental Therapeutics 62(3): 372-388.		
General Information	Date of data extraction	28/03/2023
	Authors	Hanzlik PJ, Lehman AJ, and Richardson AP
	Publication date	1938
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	No details provided on source of funding, but authors are from a University.
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To report on pharmacological and clinical actions of sobisminol, a soluble bismuth product prepared from sodium bismuthate (3%), triisopropanolamine (8%), propylene glycol (50%) and water (balance) intended for oral and intramuscular uses in the treatment of syphilis. Although the study included administration via the intravenous, intramuscular and oral route, only the data for the oral route was considered relevant to extract here.
	Study type/design	Experimental animal study
	Study duration	Oral study: Single dose, 7-day observation.
	Type of water source (if applicable)	Not applicable.
Population characteristics	Population/s studied	113 white rats 21 rabbits 10 cats 10 dogs
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	See above cells for numbers of organisms. Numbers of animals per group varied.
	Size of study	
Exposure and setting	Exposure pathway	Gavage (gastric administration); cats and dogs vomited as they did not tolerate the large volumes of sobisminol used in determining fatal doses. Therefore, small doses of morphine (10 mg/kg) were injected subcutaneously in dogs and pentobarbital (0.02 g/kg) injected intraperitoneally in cats, as anti-emetics, before administration of sobisminol.

Publication Reference: Hanzlik P. J., Lehman A. J. and Richardson A. P. (1938). Sobisminol: toxicity, tolerance and irritation according to different channels of administration. Journal of Pharmacology and Experimental Therapeutics 62(3): 372-388.		
	Source of chemical/contamination	Not applicable (purposeful administration of chemicals to experimental animals).
	Exposure concentrations (if applicable)	White rats: 84, 168, 252, 294, 336, 420, 504, 588 mg Bi/kg bw Rabbits: 84, 168, 252, 294, 310.8, 326, 357, 420 mg Bi/kg bw Cats: 140, 210, 280, 350 mg Bi/kg bw Dogs: 17.5, 35, 70, 87.5, 105, 140, 210, 280, 350 mg Bi/kg bw
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Mortality (observation)
	How outcome was assessed	
	Method of measurement	Observation
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Rats: 5-25 animals/dose Rabbits: 3 animals/dose Cats: 1-3 animals/dose Dogs: 1-2 animals/dose
Statistics (if any)	Statistical method used	Not described (no statistics used).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• No mortality observed at 84 mg Bi/kg (rats), 252 mg Bi/kg (rabbits). • 50% mortality observed at 294 mg Bi/kg (rats) and 310.8 mg Bi/kg (rabbits). • Number of cats and dogs used was too small and contributory effects of CNS depressants too uncertain to stress exactness of lower fatal doses. • The results indicate definite gastrointestinal absorption of sobisminol in different animals. However, the doses necessary for fatal outcome were large and far exceeded clinical therapeutic doses, suggesting ample margin of safety in clinical oral administration with respect to serious systemic toxicity. • Pathological tissue changes in important viscera are minor, negligible or non-existent after acute toxic and sometimes fatal doses in animals, except for damage to renal tubules after fatal doses.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	Study provides dose response for acute oral toxicity of bismuth. Risk of bias assessment was undertaken.

Hollanders 1986

Publication Reference: Hollanders D (1986). Twice daily tripotassium dicitrato bismuthate in the treatment of duodenal ulceration. Postgraduate Medical Journal. 62: 19-21.		
General Information	Date of data extraction	19/07/2023
	Authors	Hollanders D
	Publication date	1986
	Publication type	Journal article
	Peer reviewed?	Unclear
	Country of origin	UK
	Source of funding	Not stated (author is from a Hospital)
	Possible conflicts of interest	No conflict-of-interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To compare the efficacy of giving tripotassium dicitrato bismuthate (TDB) tables four times daily with twice daily regime for healing of duodenal ulcer.
	Study type/design	Single-blind human clinical trial
	Study duration	4 week treatment initially & additional 4 weeks if healing had not taken place.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	53 patients enrolled in trial and assigned randomly to receive TDB chewable tables one four times daily (QDS group) or two twice daily (BD group). All patients had endoscopically proven duodenal ulceration and had used no ulcer healing grugs the preceding 2 weeks. 7 withdrawals leaving 46 patients at end of study. Groups were well matched for age, duration of ulcer disease, length of current relapse, smoking and drinking habits. Antacids of their choice were allowed as required and patients were asked not to change their drinking or smoking habits for the duration of the study. Patients specifically excluded were any who had previously undergone upper gastrointestinal surgery or who suffered from debilitating conditions likely to interfere with tissue healing.
	Selection criteria for population (if applicable)	
	Subgroups reported	QDS group = 1 tablet x 4 times daily (n=21) BD group = 2 tablets x 2 times daily (n=25)
	Size of study	53 patients
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of TDB in chewable tablet form.
	Exposure concentrations (if applicable)	Each tablet contained 120 mg TDB (i.e. dose = 480 mg TDB per day, equivalent to ~142 mg Bi/day).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable

Publication Reference: Hollanders D (1986). Twice daily tripotassium dicitrato bismuthate in the treatment of duodenal ulceration. Postgraduate Medical Journal. 62: 19-21.		
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Information on side effects was requested at each visit for repeat endoscopy. • Blood for the estimation of bismuth levels was obtained at entry and repeated at 4 weeks. In those cases still on treatment a further sample was taken at 8 weeks.
	How outcome was assessed	
	Method of measurement	Not specified
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	46 patients included (7 excluded) Non-compliance with dosage requirements resulted in five withdrawals (four from the QDS and one from the BD group) while a further two cases (one from each group) needed urgent surgery, one for bleeding and the other for pyloric stenosis.
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable. Relevant results as follows: • No statistically significant difference found between ulcer healing in two groups at 4 weeks or at 8 weeks. • Mean bismuth levels at 4 and 8 weeks were 10 µg/L and 10 µg/L respectively for the group receiving TDB four times daily and 13 µg/L and 12 µg/L for those given TDB twice daily. • No clinically significant side effects were encountered. The commonest complaint was of a mild and temporary blackish discolouration of the tongue which occurred in 8 cases in the QDS group and 9 cases in BD group. No patient considered this an unacceptable problem and in no case was discontinuation of the medication required because of it. Other side effects reported were of an unpleasant lingering taste after chewing the tablets (one complaint from each group) and one instance of flatulent dyspepsia after the tablets in the BD group.
Author's conclusions	Interpretation of results	• Authors concluded twice daily TDB maintains the effectiveness of the drug and has advantages for patient compliance.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small single-blinded study focusing on efficacy of TDB administration 2 vs 4 times daily (but same dose). • No adverse events noted, although this was self-reported information. • As the study does not provide useful dose response information for bismuth and adverse health effects, it was not subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Hudson et al. 1989

Publication Reference: Hudson M. and Mowat N. A. (1989). Reversible toxicity in poisoning with colloidal bismuth subcitrate. Bmj 299(6692): 159.		
General Information	Date of data extraction	03/04/2023
	Authors	Hudson M, Ashley N, Mowat G
	Publication date	1989
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not stated (authors are from an Infirmary)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of a patient with various adverse findings due to an overdose of colloidal bismuth.
	Study type/design	Case report
	Study duration	Single overdose, admitted to hospital 4 hours later
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report) 27-year old man, admitted four hours after overdose of 100 De-Nol (colloidal bismuth) tablets (12 g), paracetamol (blood concentration 30 mg/L) and alcohol (blood concentration 162 mg/L).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of 100 De-Nol (colloidal bismuth) tablets (12 g), paracetamol (blood concentration 30 mg/L) and alcohol (blood concentration 162 mg/L).
	Exposure concentrations (if applicable)	Single overdose (12 g colloidal bismuth).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: Hudson M. and Mowat N. A. (1989). Reversible toxicity in poisoning with colloidal bismuth subcitrate. Bmj 299(6692): 159.		
	How outcome was assessed	• After admission, patient felt well and was discharged. 10 days later he was admitted again complaining of anorexia, nausea, vomiting, general malaise, weakness of his legs, blurring of vision, thirst, and poor urinary output. • He was dehydrated and unwell but had no fever or tachycardia. He had proximal leg muscle weakness with hyperreflexia and ankle clonus. He was lucid with no signs of encephalopathy. • Blood Bi was 260 µg/L, urine 120 µg/L and stool 26.9 mg/g. Not detectable in CSF. • Renal failure and neurotoxicity induced by bismuth were diagnosed. After purgation with magnesium sulphate and rehydration, haemodialysis was started. 5 days later renal function had returned to normal and neurological issues resolved. • 96 days after ingestion, blood Bi reduced to 8 µg/L.
	Method of measurement	Blood Bi concentration was not measured at first admission, but it was measured 10 days later (method not provided).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Absence of Bi in CSF may explain why patient was not encephalopathic, and his transient neurological signs may have reflected his uraemia, itself a result of Bi toxicity.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Large ingested dose of colloidal bismuth (i.e. 12 g) caused renal failure (nephrotoxicity) and neurotoxicity, the latter being potentially related to the kidney effects. • Blood Bi 10 days after overdosing was 260 µg/L, reducing to 8 µg/L 96 days after overdosing. • The overdose occurred concomitantly with other agents (paracetamol and alcohol), which may confound the effects observed. Nevertheless, the large ingested dose of Bi is in line with other case reports that have found nephrotoxicity or neurotoxicity after high ingested doses of Bi. • RoB analysis was undertaken.
	Notes on study quality, e.g. gaps, methods	

Huwez et al. 1992

Publication Reference: Huwez F., Pall A., Lyons D. and Stewart M. J. (1992). Acute renal failure after overdose of colloidal bismuth subcitrate. Lancet 340(8830): 1298.		
General Information	Date of data extraction	04/04/2023
	Authors	Huwez F, Pall A, Lyons D, Stewart MJ
	Publication date	1992
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not stated (authors are from an Infirmary)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of a patient with acute renal failure after ingesting an overdose of bismuth subcitrate.
	Study type/design	Case report
	Study duration	Single overdose, admitted to hospital 3 hours later
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report) 21-year old man, admitted 3 hours after overdose of 39 tablets (4.68 g) of bismuth subcitrate (i.e. 1.4 g bismuth).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of 39 tablets of bismuth subcitrate (1.4 g bismuth).
	Exposure concentrations (if applicable)	Single overdose (~1.4g bismuth in the form of bismuth subcitrate).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: Huwez F., Pall A., Lyons D. and Stewart M. J. (1992). Acute renal failure after overdose of colloidal bismuth subcitrate. Lancet 340(8830): 1298.		
	How outcome was assessed	• After admission, emesis was induced within 2 hours. On admission, patient showed no encephalopathy, was not clinically dehydrated, pulse was 80 per min, blood pressure 118/75 mmHg and he had epigastric pain. Biochemistry was normal but he had neutrophil leukocytosis. Was prescribed intravenous crystalloid infusion but over the next 48 hrs urinary output fell and renal function deteriorated. 3 days later he was transferred to renal unit. • Renal biopsy at 4 days revealed moderate acute tubular necrosis with focally prominent regenerative atypia; no Bi was detected in biopsy specimen. After treatment he was discharged well on day 120. • Serum bismuth on admission was ~1500 µg/L and decreased rapidly (to ~400 µg/L) in the first few hours due to distribution, then over time gradually to ~10 µg/L at day 14.
	Method of measurement	Serum Bi was measured by ICP-MS.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Mechanism by which high concentrations of Bi cause nephrotoxicity is not clear and management of Bi overdose is still being developed.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Large ingested dose of bismuth subcitrate (i.e. 4.68 g, i.e. ~1.4g Bi) caused acute renal failure (nephrotoxicity). • Serum Bi immediately after overdosing was ~1,500 µg/L, reducing rapidly to ~400 µg/L in the first few hours and then to 10 µg/L 14 days after overdosing. • The large ingested dose of Bi is in line with other case reports that have found nephrotoxicity after high ingested doses of Bi. • RoB analysis was undertaken.

Jones 1990

Publication Reference: Jones J. A. (1990). Bipp: a case of toxicity? Oral Surg Oral Med Oral Pathol 69(6): 668-671.		
	Date of data extraction	29/03/2023

Publication Reference: Jones J. A. (1990). Bipp: a case of toxicity? Oral Surg Oral Med Oral Pathol 69(6): 668-671.		
General Information	Authors	Jones JAH
	Publication date	1990
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not stated (author is from University hospital).
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	Case report of a 79-year old man experiencing neurotoxicity after use of bismuth iodoform paraffin paste (BIPP) impregnated ribbon gauze (two yards) in operations on the jaws.
	Study type/design	Case report
	Study duration	BIPP packs renewed post-operatively every 2 weeks, first symptoms arose 7 weeks post-operation.
	Type of water source (if applicable)	Not applicable (BIPP impregnated gauze in buccal cavity)
Population characteristics	Population/s studied	79-year old male
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	Not applicable
	Size of study	Case report (n=1)
Exposure and setting	Exposure pathway	Buccal mucosal absorption from applied BIPP gauze
	Source of chemical/contamination	BIPP (50% iodoform, 25% liquid paraffin, 25% bismuth subnitrate powder).
	Exposure concentrations (if applicable)	Not reported
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable. Serum bismuth was measured (result >30 µg/L).
	Water sampling methods (monitoring, surrogates)	Serum bismuth sampling & analysis method not reported.
Results (for each outcome)	Definition of outcome	Self-reported outcome (patient reported a feeling of general malaise for several days, difficulty sleeping, cold & shakiness; confirmed by patient's family). No evidence of infection found to account for his symptoms. Medical examination suggested a mild Parkinson tremor with 'cogwheel rigidity' of the arms. After removal of BIPP packs and replacement with Vaseline gauze, patient reported cessation of effects a few months later.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable (one case report)
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	

Publication Reference: Jones J. A. (1990). Bipp: a case of toxicity? Oral Surg Oral Med Oral Pathol 69(6): 668-671.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	In the reported case, a serum bismuth level of 30 µg/L, accompanied by potentially mild symptoms of bismuth encephalopathy which created the suspicion of early neurotoxicity caused by BIPP.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Applied dose of bismuth unknown. Although bismuth concentration in blood was slightly higher than reference range (<20 µg/L as noted in paper), it is unclear whether bismuth (or some other component of BIPP) was responsible for neurotoxicity observed. A differential diagnosis of Parkinson's disease was also made in the case and medication for this disease prescribed. Only later did the patient report not having taken any of the medication, although his neurotoxicity symptoms improved (presumably due to removal of the BIPP pack). The study was subjected to RoB analysis.
	Notes on study quality, e.g. gaps, methods	

Koch et al. 1996

Publication Reference: Koch K. M., Kerr B. M., Gooding A. E. and Davis I. M. (1996). Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. Br J Clin Pharmacol 42(2): 207-211.		
General Information	Date of data extraction	29/03/2023
	Authors	Koch KM, Kerr BM, Gooding AE, Davis IM
	Publication date	1996
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	Not specified (authors from Glaxo Wellcome Inc, i.e. drug manufacturer).
	Possible conflicts of interest	No conflict of interest statement included in article, although it is noted the authors are affiliated with Glaxo Wellcome Inc (the drug manufacturer).
Study characteristics	Aim/objectives of study	To examine the pharmacokinetics of bismuth and ranitidine derived from oral doses of ranitidine bismuth citrate 800 mg given twice daily for 28 days in a double-blind, placebo-controlled, parallel-group study in 27 healthy subjects.
	Study type/design	Double-blind placebo controlled human controlled trial
	Study duration	28 days
	Type of water source (if applicable)	Not applicable
	Population/s studied	27 healthy male subjects aged 20-49 years

Publication Reference: Koch K. M., Kerr B. M., Gooding A. E. and Davis I. M. (1996). Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. Br J Clin Pharmacol 42(2): 207-211.		
Population characteristics	Selection criteria for population (if applicable)	Restricted from using other medications during study.
	Subgroups reported	Randomly assigned to receive: • 800 mg ranitidine bismuth citrate (n=18) twice daily for 28 days or • Placebo (n=9)
	Size of study	N=26 (one subject withdrew from participation due to adverse events that were not typical of Bi toxicity).
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not applicable. Purposeful administration of drug being trialled for use. All subjects monitored for 7 days (days 29-35) after dosing was completed. Subjects receiving ranitidine bismuth citrate also participated in an unblinded post-dosing pharmacokinetic sampling period, beginning day 36 and lasting approximately 6 months.
	Exposure concentrations (if applicable)	Ranitidine bismuth citrate = 1,600 mg/day (i.e. ~512 mg Bi/day, ~256 mg Bi per dose)
	Comparison group(s)	Placebo group (n=9)
Study methods	Water quality measurement used	Not applicable. Ranitidine plasma concentrations were determined by High Performance Liquid Chromatography with UV absorbance detection. Bi plasma and urine concentrations were determined by ICP-MS.
	Water sampling methods (monitoring, surrogates)	Not applicable. Blood samples for determination of plasma Bi and ranitidine and urine samples for determination of urinary Bi were collected at various time points throughout the study and post-study period.
Results (for each outcome)	Definition of outcome	

Publication Reference: Koch K. M., Kerr B. M., Gooding A. E. and Davis I. M. (1996). Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. Br J Clin Pharmacol 42(2): 207-211.		
	How outcome was assessed	• Ranitidine displayed very little accumulation with repeated dosing of ranitidine bismuth citrate, consistent with administration of ranitidine alone. • Bismuth accumulated in plasma over 28 days of repeated twice-daily dosing with ranitidine bismuth citrate in a multi-compartmental fashion. Steady state was achieved by day 28 of dosing. Bismuth was measurable at low concentrations in plasma for up to 5 months after the last dose on day 28. The half-lives observed for the three plasma elimination / distribution phases, averaging 20 minutes, 11.1 hours, and 20.7 days, were comparable with values reported elsewhere for bismuth. • Urinary excretion is presumed to be the primary route of Bi elimination. Assuming steady-state urinary recovery accounts for the majority of absorbed Bi, it appears that 0.05% of the amount administered (~256 mg Bi) is bioavailable. • Bismuth clearance was unaltered by time or concentration during repeated dosing. • No serious adverse events or clinically significant drug related biochemical abnormalities were observed during the study (data not shown).
	Method of measurement	As per blood and urine analysis methods summarised above.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Exposed = 17 (one subject withdrew) Non-exposed = 9
Statistics (if any)	Statistical method used	Various pharmacokinetic parameters were estimated by fitting data to various equations and models. Analysis of variance (ANOVA) was used to assess temporal differences in ranitidine C_{max}, C_{min}, and AUC_t, as well as log-transformed values of bismuth C_{max}, C_{min}, and AUC_t, $A_{ut,}$ and CL_r. These bismuth parameters were log-transformed to satisfy the assumption of equal variances on each day. The Wilcoxon Signed-Rank test was used to assess temporal differences in t_{max} for both ranitidine and bismuth.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Koch K. M., Kerr B. M., Gooding A. E. and Davis I. M. (1996). Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. Br J Clin Pharmacol 42(2): 207-211.		
Author's conclusions	Interpretation of results	• Bi accumulation in plasma reflected its multi-compartmental disposition, achieving the majority of predicted steady state within 14-28 days. • Bi absorption from ranitidine bismuth citrate is limited (<0.5% of the dose) and Bi elimination is predominantly renal secretion. • Peak plasma concentration did not exceed 19 ng/mL. • Bismuth was measurable at low concentrations in plasma and urine for up to 5 months after the last dose. • The pharmacokinetics of ranitidine derived from ranitidine bismuth citrate were similar to those of ranitidine administered alone. Ranitidine did not appreciably accumulate in plasma. • Ranitidine bismuth citrate was well-tolerated during 28 days of repeated dosing.
	Assessment of uncertainty (if any)	No comment made on limitations or uncertainties.
Reviewer comments	Results included/excluded in review (if applicable)	This study was a well-controlled oral repeat-exposure study in humans but consisted of a small sample size (n=17 exposed individuals) and exposure was to a bismuth-containing drug. The principal aim of the study was to describe the pharmacokinetics of Bi and ranitidine, therefore the level of reporting on health endpoints (i.e. adverse events) was limited. Risk of bias assessment was undertaken.

Laval et al. 2018

Publication Reference: Laval M., Dumesny C., Eutick M., Baldwin G. S. and Marshall K. M. (2018). Oral trivalent bismuth ions decrease, and trivalent indium or ruthenium ions increase, intestinal tumor burden in ApcΔ14/+ mice†. Metallomics 10(1): 194-200.		
General Information	Date of data extraction	29/03/2023
	Authors	Laval M, Dumesny C, Eutick M, Baldwin GS, Marshall KM
	Publication date	2018
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	The work was supported by the National Health and Medical Research Council [grant number 1020983 to GSB].
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	The aim of the study was to determine the effect of blocking Fe^{3+} ion binding to glycine-extended gastrin (Ggly) using Bi^{3+}, In^{3+} or Ru^{3+} ions, on the development of intestinal tumours in $APC^{\Delta 14/+}$ mice. The results reported in this extract focus on the results for Bi^{3+}.

Publication Reference: Laval M., Dumesny C., Eutick M., Baldwin G. S. and Marshall K. M. (2018). Oral trivalent bismuth ions decrease, and trivalent indium or ruthenium ions increase, intestinal tumor burden in ApcΔ14/+ mice†. Metallomics 10(1): 194-200.		
	Study type/design	Experimental animal study
	Study duration	Oral study: ~60 days (3 times/week, up to 20 weeks of age)
	Type of water source (if applicable)	Not applicable.
Population characteristics	Population/s studied	$APC^{\Delta 14/+}$ mice (deletion of exon 14 engineered into one allele of their APC tumour suppressor gene) – providing a model of spontaneous intestinal cancers *in vivo* without the use of carcinogens. 8-10 weeks old.
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	Four treatment groups: • Phosphate-buffered saline (control) (16 female, 17 male mice) • Bismuth citrate (9 female and 8 male mice, 141 mg Bi^{3+}/kg bw/d) • Indium citrate (7 female and 8 male mice, 141 mg In^{3+}/kg bw/d) • Ruthenium citrate (7 female and 8 male mice, 6.5 mg Ru^{3+}/kg bw/d)
	Size of study	
Exposure and setting	Exposure pathway	Oral gavage
	Source of chemical/contamination	Deliberate experimental administration
	Exposure concentrations (if applicable)	Bismuth citrate: 141 mg Bi^{3+}/kg bw/d once per day (for other substances, see above), 3 times/week, up to 20 weeks of age.
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Full blood examination (haematology) was performed on mice.
	How outcome was assessed	• All metals were absorbed as serum concentrations increased significantly in treated animals at the end of the experiment compared to controls. However the ratio of Bi3+ absorbed to the amount given orally was low (i.e. ~0.1%). • Bi3+ did not affect mouse survival. • Haematological parameters in Bi3+ treated group were not significantly different from controls. • Bi3+ treatment significantly decreased number of tumours larger than 3 mm in male mice.
	Method of measurement	Haematological parameters via Advia 120 automated haematological analyser. Serum trace metals analysed by ICP-MS.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Exposed (bismuth group): 9 females, 8 males Non-exposed (control group): 16 females, 17 males

Publication Reference: Laval M., Dumesny C., Eutick M., Baldwin G. S. and Marshall K. M. (2018). Oral trivalent bismuth ions decrease, and trivalent indium or ruthenium ions increase, intestinal tumor burden in ApcΔ14/+ mice†. Metallomics 10(1): 194-200.		
Statistics (if any)	Statistical method used	Survival statistics were performed using log-rank and cox-regression (SPSS version 22.0, IBM, Armonk, NY, USA). All other statistics were analysed using either student's t-test or one-way ANOVA (SigmaStat, Jandel Scientific, San Rafael, CA, USA). P< 0.05 was considered significant.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Bi3+ treatment significantly decreased number of tumours larger than 3 mm in male $APC^{\Delta 14/+}$ mice. • Inhibitory effect is unlikely to be gastrin-dependent. However, further testing of higher doses of Bi3+ ions for longer periods as an oral treatment for intestinal tumours is warranted.
	Assessment of uncertainty (if any)	See above (further testing warranted).
Reviewer comments	Results included/excluded in review (if applicable)	This study was undertaken for a very specific therapeutic objective. However, it does provide some information on limited health outcomes (e.g. mortality, haematological parameters) indicating Bi^{3+} orally administered to mice at 141 mg Bi^{3+}/kg bw/d for 60 days did not cause overt toxicity. Risk of bias analysis undertaken.

Le Quesne 1981

Publication Reference: Le Quesne P. M. (1981). Toxic substances and the nervous system: the role of clinical observation. J Neurol Neurosurg Psychiatry 44(1): 1-8.		
General Information	Date of data extraction	04/04/2023
	Authors	Le Quesne PM
	Publication date	1981
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not specified (author affiliation is a Hospital)
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	Review of several substances that cause toxicity to the nervous system (bismuth is included as one of the examples)
	Study type/design	Review/commentary (methods of literature review not specified, does not appear to be systematic).
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable

Publication Reference: Le Quesne P. M. (1981). Toxic substances and the nervous system: the role of clinical observation. J Neurol Neurosurg Psychiatry 44(1): 1-8.		
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	Not applicable
	Exclusion criteria	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)	Not applicable
Study methods	Water quality measurement used	Not applicable
	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

Publication Reference: Le Quesne P. M. (1981). Toxic substances and the nervous system: the role of clinical observation. J Neurol Neurosurg Psychiatry 44(1): 1-8.		
Author's conclusions	Interpretation of results	• New neurological disease was first reported in Australia where patients had been treated with oral Bi subgallate to control colostomy, and who became confused, unable to walk, and developed myoclonus. All improved when Bi was stopped. • At the same time, in 1973 and 1974, the disease reached epidemic proportions in France where relatively large quantities of Bi were consumed in the treatment of a variety of chronic colon disorders. 942 cases of bismuth encephalopathy were recorded with 72 deaths. There is a prodromal phase lasting weeks or months of depression, anxiety, irritability and possibly mild incoordination. Deterioration then occurs rapidly over 24-48 hours with confusion, myoclonic jerks and dysarthria. Inability to stand or walk is a striking feature and partly due to apraxia. Coma may ensue. Recovery may be complete, or there may be mild residual memory loss. • One theory is that an intestinal microorganism can convert the bismuth salt into an absorbable form, perhaps by methylation, and that spread of this organism determined the spread of the disease.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on bismuth encephalopathy. However, this study was a limited review / commentary so provides limited information with respect to defining a health-based guidance value for Bi. As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.

Leussink et al. 2000

Publication Reference: Leussink B. T., Slikkerveer A., Krauwinkel W. J., van der Voet G. B., de Heer E., de Wolff F. A. and Bruijn J. A. (2000). Bismuth biokinetics and kidney histopathology after bismuth overdose in rats. Arch Toxicol 74(7): 349-355.		
General Information	Date of data extraction	30/03/2023
	Authors	Leussink BT, Slikkerveer A, Krauwinkel WJJ, van der Voet GB, de Heer E, de Wolff FA, Bruijn JA
	Publication date	2000
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	The Netherlands
	Source of funding	Source of funding not provided. Authors are from a University Medical Centre and a Research Laboratory.
	Possible conflicts of interest	No conflict of interest statement included in article.

Publication Reference: Leussink B. T., Slikkerveer A., Krauwinkel W. J., van der Voet G. B., de Heer E., de Wolff F. A. and Bruijn J. A. (2000). Bismuth biokinetics and kidney histopathology after bismuth overdose in rats. Arch Toxicol 74(7): 349-355.		
Study characteristics	Aim/objectives of study	To study the development of bismuth induced nephropathy and bismuth biokinetics in rats (since bismuth induced nephrotoxicity has been reported to occur after acute overdoses of Bi-containing therapeutic drugs).
	Study type/design	Experimental animal study
	Study duration	Single oral overdose of colloidal bismuth subcitrate, animals sacrificed after 1-48 hours.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Inbred young adult (11-12 weeks) female Wistar rats (177±13.3 g)
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	• Exposed group: 3 mmol Bi/kg (i.e. 627 mg/kg) as bismuth subcitrate (n=33) • Control: Vehicle only (n=7)
	Size of study	
Exposure and setting	Exposure pathway	Oral gavage
	Source of chemical/contamination	Colloidal bismuth subcitrate (CBS) containing 35.4% (w/w) of bismuth donated by Yamanouchi Europe.
	Exposure concentrations (if applicable)	0 or 627 mg Bi/kg bw
	Comparison group(s)	Vehicle control group (saline only)
Study methods	Water quality measurement used	Not applicable. Urine and blood samples were collected just before sacrifice. Kidneys examined after sacrifice.
	Water sampling methods (monitoring, surrogates)	Not applicable. Bismuth contents of whole blood and kidneys was determined by electrothermal furnace atomic absorption spectrometry. Urinary bismuth was determined by flow injection atomic absorption spectrometry.
Results (for each outcome)	Definition of outcome	• 5/33 animals in experimental group died before they could be sacrificed. 3 animals died within 1 hour of CBS administration, during the narcosis needed for collection of the first blood sample. The two other animals died approximately 24 and 48 hours after administration of the dose. • Some animals in experimental group became anuric after CBS administration.

Publication Reference: Leussink B. T., Slikkerveer A., Krauwinkel W. J., van der Voet G. B., de Heer E., de Wolff F. A. and Bruijn J. A. (2000). Bismuth biokinetics and kidney histopathology after bismuth overdose in rats. Arch Toxicol 74(7): 349-355.		
	How outcome was assessed	• Histological examination of kidneys revealed cytoplasmic vacuolation of tubular cells at the corticomedullary boundary 1 hour after CBS administration. After 3 hours tubular necrosis had developed, and after 6 hours cytoplasmic vacuolation occurred in tubular cells in the cortex. After 12 hours necrotic tubules appeared in both cortex & corticomedullary boundary zone. • Biokinetics of Bi in blood could best be described with a one-compartment model characterised by an absorption half-life of 0.32 hours and an elimination half-life of 16 hours. • The peak concentration of about 7 mg Bi/L was reached after 2 hours.
	Method of measurement	See previous cells
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=33 exposed (n=5 excluded due to premature death) N=7 controls (non-exposed)
Statistics (if any)	Statistical method used	Statistical analysis was carried out using SPSS 7.5.2. Data obtained from animals that died not according to the schedule (i.e. from five animals in the experimental group) were excluded from the statistical analysis. All values below the detection limit were replaced with the detection limit itself for analysis. Means of parameters with a normal distribution were compared by paired or unpaired Student's t test. The Kruskal-Wallis one-way analysis of variance and Mann-Whitney U test were used for those parameters lacking a normal distribution. $P<0.05$ considered statistically significant.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	Wistar rats develop tubular necrosis in the S3 segment of the proximal tubule between 1 and 3 hours after administration of an oral CBS overdose containing 627 mg Bi/kg bw. After 12 hours necrotic cells are also present in the S1/S2 segment. The calculated curve for bismuth in the blood among the general population is characterised by a peak of 7 mg Bi/L 2 hours after administration and an elimination half-life of Bi from blood of 16 hours. Thus, if conclusions can be extrapolated to humans, treatment of bismuth-induced nephropathy aimed at preventing renal damage must be performed within 3 hours after the intake of the CBS overdose.
	Assessment of uncertainty (if any)	Not stated.

Publication Reference: Leussink B. T., Slikkerveer A., Krauwinkel W. J., van der Voet G. B., de Heer E., de Wolff F. A. and Bruijn J. A. (2000). Bismuth biokinetics and kidney histopathology after bismuth overdose in rats. Arch Toxicol 74(7): 349-355.		
Reviewer comments	Results included/excluded in review (if applicable)	This study was undertaken for a very specific objective, i.e. to determine the development of renal injury over time and the biokinetics of bismuth after a large single CBS overdose. It does provide some information on limited health outcomes (e.g. mortality, nephropathy) indicating Bi orally administered to rats at 627 mg/kg bw in a single oral dose causes nephrotoxicity and mortality in some. Risk of bias analysis undertaken.

Leussink et al. 2001

Publication Reference: Leussink B. T., Slikkerveer A., Engelbrecht M. R., van der Voet G. B., Nouwen E. J., de Heer E., de Broe M. E., de Wolff F. A. and Bruijn J. A. (2001). Bismuth overdosing-induced reversible nephropathy in rats. Arch Toxicol 74(12): 745-754.		
General Information	Date of data extraction	30/03/2023
	Authors	Leussink BT, Slikkerveer A, Engelbrecht MRW, van der Voet GB, Nouwen EJ, de Heer E, de Broe ME, de Wolff FA, Bruijn JA
	Publication date	2001
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	The Netherlands
	Source of funding	Source of funding not provided. Authors are from a University Medical Centre and a Research Laboratory.
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To characterise the renal lesions and to determine whether the nephrotoxic effect of an acute colloidal bismuth subcitrate (CBS) overdose is reversible in rats, as reported in humans. In addition, authors sought to determine whether Bi whole blood and urine concentrations at various time points correlate with the extent of kidney damage.
	Study type/design	Experimental animal study
	Study duration	Single oral dose by gavage of colloidal bismuth subcitrate in saline, animals observed for a maximum of 14 days.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Inbred young adult (11-12 weeks) female Wistar rats (163.3±10.6 g)
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	

Publication Reference: Leussink B. T., Slikkerveer A., Engelbrecht M. R., van der Voet G. B., Nouwen E. J., de Heer E., de Broe M. E., de Wolff F. A. and Bruijn J. A. (2001). Bismuth overdosing-induced reversible nephropathy in rats. Arch Toxicol 74(12): 745-754.		
	Size of study	• Exposed groups: 0.75, 1.5 or 3 mmol Bi/kg (i.e. 157, 313, or 627 mg/kg)[3] as bismuth subcitrate (n=20/group) • Control: Vehicle (saline) only (n=20)
Exposure and setting	Exposure pathway	Oral gavage
	Source of chemical/contamination	Tripotassium dicitratobismuthate (CBS) containing 35.4% (w/w) of bismuth donated by Yamanouchi Europe.
	Exposure concentrations (if applicable)	0, 157, 313 or 627 mg Bi/kg bw
	Comparison group(s)	Vehicle control group (saline only)
Study methods	Water quality measurement used	Not applicable. Urine and blood samples were collected just before sacrifice. Kidneys and liver examined after sacrifice.
	Water sampling methods (monitoring, surrogates)	Not applicable. Bismuth contents of whole blood, liver and kidneys was determined by electrothermal furnace atomic absorption spectrometry. Urinary bismuth was determined by flow injection atomic absorption spectrometry.
Results (for each outcome)	Definition of outcome	• No adverse effects observed in lowest dose group, including mortality, kidney function parameters, or morphological changes. • In intermediate dose group, functional kidney damage was greatest after 24 hours with full recovery after 48 hours. Tubular necrosis was only observed in 2/4 animals sacrificed on day 2 in this group. This correlated with the highest Bi blood levels within this group (665 and 742 nmol Bi/L, i.e. 139 and 155 µg/L).
	How outcome was assessed	• Clinical signs of acute Bi intoxication were only observed in the highest dose group and consisted of erect hairs and hunched posture. A swollen caecum filled with gas and black fluid was noted after 48 hours in these animals. In some rats in the highest dose group, kidneys were covered with white speckles, an observation indicative of ascites and severe kidney damage. Functional kidney damage was greatest at 48 hours. Extensive tubular necrosis was present in corticomedullary transition zone and in cortex in all animals sacrificed on day 2, with 1/3 animals on day 4, and none on day 7, 10 or 14. These animals had histological signs of repair.
	Method of measurement	See previous cells
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	20/group (3 exposed groups, 1 control)

[3] Calculated by SLR using the molecular weight of bismuth of 208.98 g/mol. For example: 0.75 mmol/kg x 208.98 mg/mmol = 157 mg/kg (rounded).

Publication Reference: Leussink B. T., Slikkerveer A., Engelbrecht M. R., van der Voet G. B., Nouwen E. J., de Heer E., de Broe M. E., de Wolff F. A. and Bruijn J. A. (2001). Bismuth overdosing-induced reversible nephropathy in rats. Arch Toxicol 74(12): 745-754.		
Statistics (if any)	Statistical method used	Statistical analysis was carried out using SPSS 7.5.2. Data obtained from animals that died not according to the schedule (i.e. from two animals in the highest dose group) were excluded from the statistical analysis. All values below the detection limit were replaced with the detection limit itself for analysis. Due to non-normal distribution of most parameters, the non-parametric Kruskal-Wallis one-way ANOVA was used to establish the significance of differences between all experimental groups at one time point. If a significant difference was present, each of the three dose groups was compared with the control using Mann-Whitney U test. The Wilcoxon signed-ranks test was used to detect significant changed over time within one experimental group. Pearson's correlation coefficient was used to express the linear associations between two variable. P<0.05 considered statistically significant except in Kruskal-Wallis one-way ANOVA where p<0.01 was considered significant to correct for multiple testing.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The functional kidney damage observed in this study was dose-related and reversible. Kidney function recovers fully within 10 days. • The absorbed Bi expressed as a percentage of the oral CBS load is <0.5%. • In Wistar rats, a large single oral overdose of CBS initially damages the S3 segment of the nephron. As more Bi is excreted the S1/S2 segment also becomes affected.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	This study was undertaken for a specific objective. It does provide some information on limited health outcomes (e.g. mortality, nephropathy) indicating Bi orally administered to rats at 313 or 627 mg/kg bw in a single oral dose causes dose-dependent nephrotoxicity and mortality in some. The acute NOAEL in this study was 157 mg Bi/kg bw. Risk of bias analysis undertaken.

Morgan and Billings 1974

Publication Reference: Morgan F. P. and Billings J. J. (1974). Is this subgallate poisoning? Med J Aust 2(18): 662-663.		
General Information	Date of data extraction	04/04/2023
	Authors	Morgan FP and Billings JJ
	Publication date	1974
	Publication type	Case report

Publication Reference: Morgan F. P. and Billings J. J. (1974). Is this subgallate poisoning? Med J Aust 2(18): 662-663.		
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	Not stated (authors are from a Hospital)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of a patient with severe chronic reversible encephalopathy likely due to Bi subgallate given orally.
	Study type/design	Case report
	Study duration	Repeated chronic oral intake (daily ingestion over 8 years)
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report) 51-year old man sent to medical due to lack of energy for 3 years prior, then tremor and unsteadiness of lower limbs for 2 months. Additional symptoms were lack of confidence, impaired memory for names and mental confusion. 8 years earlier he had had a colostomy performer for cancer of the bowel and thus he had been taking 2 heaped teaspoons of Bi subgallate every morning for 8 years.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of 2 heaped teaspoons of Bi subgallate every morning for 8 years.
	Exposure concentrations (if applicable)	Not available (2 heaped teaspoons daily for 8 yrs)
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Examination of patient revealed a gross but variable tremor and a degree of mental confusion. Disordered gait and intellectual impairment. • Temporary improvement followed discharge from hospital, where he had taken a reduced dose of Bi subgallate. On his reverting to the original dose, gradual deterioration set in. • In May 1972, patient stopped taking Bi subgallate. By this time his condition had severely deteriorated with pronounced tremor, ataxia, dyscalculia, dysgraphia, disorientation in place, and impaired memory and more severe intellectual impairment. • In August 1972, patient reported marked improvement and 'felt like his old self again'. All his old symptoms had disappeared.
	How outcome was assessed	
	Method of measurement	Not applicable

Publication Reference: Morgan F. P. and Billings J. J. (1974). Is this subgallate poisoning? Med J Aust 2(18): 662-663.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Authors conclude the strong probability that Bi subgallate intoxication was responsible for encephalopathy observed.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Repeat chronic administration of Bi subgallate (2 heaped teaspoons daily) likely was cause of observed encephalopathy. • Serum Bi was not measured. • Risk of bias analysis undertaken.

Ong et al. 2018

Publication Reference: Ong Y. C., Kedzierski L. and Andrews P. C. (2018). Do bismuth complexes hold promise as antileishmanial drugs? Future Med Chem 10(14): 1721-1733.		
General Information	Date of data extraction	30/03/2023
	Authors	Ong YC, Kedzierski L, Andrews PC
	Publication date	2018
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	Australia
	Source of funding	Monash University and the Australian Research Council (SP110103812) provided financial support.
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	To describe recent efforts into developing antileishmanial Bi(III) and Bi(V) drugs, which may resemble Sb analogues in effect and mode of action while providing lower mammalian cell toxicity and opportunities for oral delivery. The description herein has focused on health and safety related considerations of Bi discussed in the review.
	Study type/design	Commentary/literature review (methods of literature review not specified, does not appear to be systematic).
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable

Publication Reference: Ong Y. C., Kedzierski L. and Andrews P. C. (2018). Do bismuth complexes hold promise as antileishmanial drugs? Future Med Chem 10(14): 1721-1733.		
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	Not applicable
	Exclusion criteria	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)	Not applicable
Study methods	Water quality measurement used	Not applicable
	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	• Bi is described as the most non-toxic heavy element, this has been proven in its application as simple inorganic compounds. Oral formulations of bismuth subsalicylate are used to treat gastrointestinal ailments, and both bismuth subsalicylate and bismuth citrate can be consumed daily in the treatment of *Helicobacter pylori*. The apparent low toxicity of bismuth in humans means that toxic effects are not normally observed unless there is deliberate overdosage. Furthermore, any toxic effects can be reversible upon the removal of bismuth from the system.
	Assessment of uncertainty (if any)	No assessment of uncertainty undertaken.
Reviewer comments	Results included/excluded in review (if applicable)	Results included in review in terms of general knowledge on bismuth toxicology. However, this study was a limited review so provides limited information with respect to defining a health-based guidance value for Bi. As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.
	Notes on study quality, e.g. gaps, methods	

Ovaska et al. 2008

Publication Reference: Ovaska H., Wood D. M., House I., Dargan P. I., Jones A. L. and Murray S. (2008). Severe iatrogenic bismuth poisoning with bismuth iodoform paraffin paste treated with DMPS chelation. Clin Toxicol (Phila) 46(9): 855-857.		
General Information	Date of data extraction	30/03/2023
	Authors	Ovaska H, Wood DM, House I, Dargan PI, Jones AL, Murray S
	Publication date	2008
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	UK and Australia
	Source of funding	Not stated (authors are from Poisons Unit and Hospital)
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	Case report of a 67-year old man experiencing neurotoxicity after use of bismuth iodoform paraffin paste (BIPP) soaked gauze in pelvic/sacral area. Removal of BIPP packing and 2,3-dimercaptopropane-1-sulphonate (DMPS) chelation therapy resulted in improvement in his symptoms.
	Study type/design	Case report
	Study duration	First symptoms arose 5 days post-operation.
	Type of water source (if applicable)	Not applicable (BIPP impregnated gauze in sacral/pelvic area)
Population characteristics	Population/s studied	67-year old male
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	Not applicable
	Size of study	Case report (n=1)
Exposure and setting	Exposure pathway	Systemic absorption from applied BIPP gauze to pelvic/sacral area
	Source of chemical/contamination	BIPP (50% iodoform, 25% liquid paraffin, 25% bismuth subnitrate powder) (OxBipp™; Oxford Pharmaceuticals).
	Exposure concentrations (if applicable)	Not reported
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable. Serum and urine bismuth was measured (result 340 µg/L and 2,800 µg/L respectively).
	Water sampling methods (monitoring, surrogates)	Serum and urine bismuth sampling & analysis method not reported.
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Ovaska H., Wood D. M., House I., Dargan P. I., Jones A. L. and Murray S. (2008). Severe iatrogenic bismuth poisoning with bismuth iodoform paraffin paste treated with DMPS chelation. Clin Toxicol (Phila) 46(9): 855-857.		
	Method of measurement	• Self-reported outcome (patient reported acute confusion, disorientation, delusion, was verbally aggressive to medical and nursing staff; also had abdominal discomfort, nausea and tremor). Apical hospital-acquired pneumonia was diagnosed. His confusion failed to resolve over the next 5 days, despite appropriate therapy for his sepsis. By now, patient's condition had deteriorated, and he had developed myoclonic jerks with intermittent episodes of drowsiness and worsening confusion. • Blood and urine bismuth concentrations were determined and were 340 µg/L and 2,800 µg/L, respectively. • BIPP packaging was removed and replaced with alginate dressing. Intravenous chelation therapy with DMPS was commenced (5 mg/kg four times daily for 5 days, 5 mg/kg three times daily for 5 days followed by 5 mg/kg twice a day for 17 days); subsequently followed by oral DMPS 200 mg three times a day for 10 days, then 200 mg twice a day for 14 days. • His abdominal symptoms settled within 5 days of initiation of DMPS, and the confusion and tremor improved gradually over the next month. The patient's general condition improved; wound healing was satisfactory and repeated blood and urine bismuth levels declined to levels <LOR (<0.21 µg/L) 6 months following discharge.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable (one case report)
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 characteristic symptoms reported in bismuth-related neurotoxicity are myoclonia, unsteady gait, ataxia, dysarthria, disorientation, delirium, and coma. Due to the proximity of the BIPP packing to the sacral nerves and spinal cord in this patient, there was the potential for greater neuronal uptake of bismuth with subsequent retrograde axonal transport leading to more prominent neurological toxicity. • In the reported case, who had a serum bismuth level of 340 µg/L, overt neurological symptoms (confusion, disorientation, delusion, aggression, tremor, myoclonic jerks) were observed.

Publication Reference: Ovaska H., Wood D. M., House I., Dargan P. I., Jones A. L. and Murray S. (2008). Severe iatrogenic bismuth poisoning with bismuth iodoform paraffin paste treated with DMPS chelation. Clin Toxicol (Phila) 46(9): 855-857.		
	Assessment of uncertainty (if any)	As well as bismuth, BIPP contains iodoform, which along with its metabolite di-iodomethane is highly lipophilic and known to cause neurotoxicity even in the absence of bismuth. It is possible that some of the neurological features seen in the patient were related to iodoform in addition to bismuth. However, none of the other features of iodoform toxicity were present. It is not possible to determine from this single case to what extent the clinical improvement and fall in bismuth blood concentrations seen was due to removal of the BIPP packing and to what extent the DMPS chelation contributed.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Applied dose of bismuth unknown. Bismuth concentration in blood was very high therefore it seems likely Bi contributed to the effects observed, however it is unclear whether some other component of BIPP also contributed to the neurotoxicity observed. Risk of bias analysis was undertaken.

Poddalgoda et al. 2020

Publication Reference: Poddalgoda D., Hays S. M. and Nong A. (2020). Derivation of biomonitoring equivalents (BE values) for bismuth. Regul Toxicol Pharmacol 114: 104672.		
General Information	Date of data extraction	30/03/2023
	Authors	Poddalgoda D, Hays SM, Nong A
	Publication date	2020
	Publication type	Review/opinion piece
	Peer reviewed?	Yes
	Country of origin	Canada and USA
	Source of funding	Summit Toxicology received funding to prepare the analysis and manuscript from Health Canada (Contract No. 4500323309).
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	Derive Biomonitoring Equivalent (BE) values for the interpretation of population biomonitoring data for Bi. BE values are estimates of the concentration of a chemical or its metabolite in blood or urine that are consistent with the defined exposure guidance values such as RfDs or TDIs.
	Study type/design	Review/report/opinion piece
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
	Population/s studied	Not applicable

Publication Reference: Poddalgoda D., Hays S. M. and Nong A. (2020). Derivation of biomonitoring equivalents (BE values) for bismuth. Regul Toxicol Pharmacol 114: 104672.		
Population characteristics	Selection criteria for population (if applicable)	Not 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)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	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	• Toxicity database for Bi is fairly limited, which may be due to the fact that Bi is considered a relatively low toxic metal, especially resulting from low bioavailability (and thus systemic absorption) following oral dosing. However, acute or chronic administration of therapeutic compounds with significantly high concentrations of Bi have attributed to a number of toxic effects, including nephropathy, encephalopathy, osteoarthropathy, gingivitis, stomatitis, colitis and hepatitis. Most of the available data are based on case studies on Bi-induced encephalopathy and nephrotoxicity. In general, the available database for Bi-induced toxicity is relatively old (e.g. encephalopathy data are from 1970's). Conversely, some recent publications have also reported encephalopathy or nephrotoxicity in certain individuals, who consumed large doses of over-the-counter Bi-containing medications. • Bismuth-induced encephalopathy is often associated with chronic overexposure, whereas nephrotoxicity is generally reported for acute overdosing. In addition, different therapeutic compounds appeared to be responsible for different Bi-related toxic effects. In most cases, Bi-induced toxicity effects are reversible after discontinuation of exposure. It should be noted that these toxic effects are rarely seen with normal use of Bi compounds because systemic absorption of Bi through the GI tract is low. • No risk assessments have been conducted to establish exposure guidance values for bismuth. US FDA (2019) has recommended daily intake (RDI) of 200–400 mg up to 4 times daily of bismuth subgallate, which is a deodorant drug product for internal use as an aid to reduce odour from a colostomy or an ileostomy (Bismuth subgallate (C7H5BiO6, mw = 394 g/mol - 53% bismuth, by mass). Therefore, the US FDA's recommended intake of 400 mg up to 4 times daily equates to a daily intake of 848 mg of bismuth. Assuming a standard adult body weight of 70 kg, this equates to 12.1 mg bismuth/kg-d (i.e. RDI). The US FDA's RDI for bismuth subgallate can be used as a surrogate for the screening health risk of bismuth exposure, as there is an absence of health-based guidance values for the general population. • In a chronic 2-yr study, rats were given bismuth oxychloride (BiOCl, mw = 261.44) at 1, 2 or 5% in diet, which is equivalent to 224, 448 and 1120 mg bismuth/kg-d for females and 280, 560 and 1400 mg/kg-d for males (with an average daily food intake of 40 and 50 g, respectively). The No Observed Adverse Effect Level (NOAEL) for males and females were reported as 1120–1400 mg bismuth/kg-d, respectively. If default values of 10 are used for uncertainty factors for both inter- and intra-species variation, the value becomes 11.2–14 mg Bi/kg-d, which is also in agreement with the US FDA (2019) guidance value. • The study authors used data from two published studies in humans to conduct a linear regression between oral Bi intake and plasma Bi concentration in order to derive BE values. This yielded the following relationships: ○ BP (µg/L) = 0.66 × BDD (mg/kg-d) ○ BB (µg/L) = 0.6 × BP

Publication Reference: Poddalgoda D., Hays S. M. and Nong A. (2020). Derivation of biomonitoring equivalents (BE values) for bismuth. Regul Toxicol Pharmacol 114: 104672.		
		Where BP is bismuth plasma concentration, BDD is bismuth daily dose and BB is bismuth concentration in whole blood. • The BEs associated with US FDA's (2019) RDI of bismuth subgallate (i.e. daily doses of 12.1 mg/kg-d of bismuth) would be: i) Plasma – 8.0 µg/L, ii) Whole blood – 4.8 µg/L, iii) Urine 0.18 µg/L, µg/g cr
	Assessment of uncertainty (if any)	The BEs developed in this study are based on the pharmacokinetics of bismuth in ranitidine bismuth citrate, thus are expected to be lowered than those developed based on the pharmacokinetics of bismuth from TDB or other more bioavailable preparations of bismuth. There is a medium to high confidence in the derived BEs in the current study. If different exposure guidance values are developed for environmental exposures to bismuth in the future, the unit dose based BEs derived in this study can be easily adapted to convert exposure guidance values into internal concentrations. The BE derivation approach is based on robust kinetic studies in healthy volunteers and therefore, there is a medium to high confidence in the derived BE values for whole blood, plasma and urine. The derived BE values can be used as a tool in interpreting population-level biomonitoring data in health risk context and thereby prioritising screening-level health risk assessments of a population. The BE values do not represent medical diagnostic criteria and cannot be used in evaluation of the likelihood of adverse health effects of bismuth exposure in an individual. The BE values should only be used for interpreting exposure in the general population and should not be used in interpreting occupational exposure.
Reviewer comments	Results included/excluded in review (if applicable)	The study is a review which provides some useful general information and toxicokinetic information for Bi. It also references two potential critical papers/reports as potential information for deriving a health-based guidance value (US FDA 2019 which is the same as US FDA 2023, Preussmann and Ivankovic 1975) which have been examined separately in this report. As the article is a review paper, risk of bias assessment was not undertaken.

Preussman and Ivankovic 1975

Publication Reference: Preussmann R. and Ivankovic S. (1975). Absence of carcinogenic activity in BD rats after oral administration of high doses of bismuth oxychloride. Food Cosmet Toxicol 13(5): 543-544.		
General Information	Date of data extraction	30/03/2023
	Authors	Preussmann R and Ivankovic S
	Publication date	1975
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes

Publication Reference: Preussmann R. and Ivankovic S. (1975). Absence of carcinogenic activity in BD rats after oral administration of high doses of bismuth oxychloride. Food Cosmet Toxicol 13(5): 543-544.		
	Country of origin	Germany
	Source of funding	Work was supported financially by the Industrieverband Körperpflege- und Waschmittel e.V. Frankfurt (i.e. Industry body of cosmetics and washing products).
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To determine the carcinogenicity and toxicity of bismuth oxychloride, a colouring agent for decorative cosmetics, in BD rats after administration in the diet for 2 years.
	Study type/design	Experimental animal study
	Study duration	2 years
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Inbred BD rats (100 days old at start of test)
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	• Exposed groups: 1, 2, or 5% BiOCl (i.e. M: 383, 767, or 1918 g Bi/kg bw/d; F: 307, 614, or 1534 g Bi/kg bw/d)[4] converting BiOCl to Bi (n=20/sex/group) but there is uncertainty with respect to the true doses that were administered. • Untreated Control: (n=30/sex)
	Size of study	
Exposure and setting	Exposure pathway	Oral in diet (7 days/week for 2 years)
	Source of chemical/contamination	Bismuth oxychloride (BiOCl; CI (1956) no. 77,163; Schultz no. 1415) purposefully fed to rats in an experimental study. Purity conformed to criteria of the Deutsche Forschungsgemeinschaft, Farbstoff-Kommission (1968).
	Exposure concentrations (if applicable)	1, 2, or 5% BiOCl in homogenous diet prepared every day in the form of solid mash containing Altromin® animal feed in powder form, sugar, and Livio oil.
	Comparison group(s)	Control group (fed diet only without BiOCl)
Study methods	Water quality measurement used	Not applicable. Body weight recorded monthly. At autopsy, all important organs (including brain and nervous system) were examined and tissues fixed for histological investigation.

[4] Doses in paper were provided as BiOCl reported in Table 1 of paper as 'g/kg'. However, the text of the paper indicates daily feed intakes by male and female rats were 50 and 40 g/day, respectively and the concentration of BiOCl in feed was 1, 2 or 5% in the treated groups (i.e. 10, 20, or 50 g/kg feed). No body weights are provided for the BD rats (apparently 100 days of age at the start of the experiment). Back-calculation of the rat body weights from the doses provided in Table 1 of the paper suggests rats weighed only 1.4 g [i.e. X kg bw = (10 g/kg feed x 0.05 kg feed) ÷ 350 g/kg bw = 0.0014 kg bw or 1.4g], which is not possible (for example, 84 day old Sprague Dawley rats weigh between 219 and 492 g, https://www.arc.wa.gov.au/?page_id=125). If the dose units of 'g/kg' were incorrectly reported in the paper and actually corresponded to 'mg/kg' then back-calculation of rat body weight gives 1.4 kg body weight which is, again, non-sensical. For this reason, the correct doses provided in the paper could not be reconciled with the other information in the paper and there is uncertainty with respect to the true doses that were administered. Nevertheless, it is noted that other authors (e.g. Poddalgoda et al. 2020) have cited this study and reported doses in units of mg/kg bw/d.

Publication Reference: Preussmann R. and Ivankovic S. (1975). Absence of carcinogenic activity in BD rats after oral administration of high doses of bismuth oxychloride. Food Cosmet Toxicol 13(5): 543-544.		
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	• Oral administration of BiOCl was well tolerated. Mean body weights of the test group did not differ significantly from those of controls. • The mean survival times for the groups of treated animals also corresponded approximately to those of the controls, but with much larger deviations around the mean value. • No macroscopic or histological findings could be attributed to the BiOCl treatment, and the types and incidence of tumours observed were closely comparable in the test and control groups. The mammary fibroadenomas and hypophyseal adenomas seen are spontaneous tumours characteristic of this strain.
	How outcome was assessed	
	Method of measurement	See previous cells
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	20/sex/group (treated) 30/sex (controls)
Statistics (if any)	Statistical method used	Statistical method not reported.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• BiOCl was not carcinogenic in rats after oral administration even at high doses. These results are in agreement with earlier investigations of the carcinogenic effect of other bismuth compounds.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	This study provides results of a 2-year chronic toxicity / carcinogenicity assay for BiOCl in the diet of rats. The descriptions provided in the study report are small. Although from the information available, the study appears to have been conducted in line with standardised methods for conducting such experiments, there is a discrepancy with the reported doses in the paper that could not be reconciled. The NOAEL in the study was the highest dose tested (i.e. 1534/1918 g Bi/kg bw/d in female/male rats, respectively, according to the authors). However back-calculation of rat body weight (not given in paper) based on doses and feed intake per day results in non-sensical values for rat body weight. Risk of bias analysis was undertaken.

Sano et al. 2005

Publication Reference: Sano Y., Satoh H., Chiba M., Okamoto M., Serizawa K., Nakashima H. and Omae K. (2005). Oral toxicity of bismuth in rat: single and 28-day repeated administration studies. J Occup Health 47(4): 293-298.		
General Information	Date of data extraction	30/03/2023
	Authors	Sano Y, Satoh H, Chiba M, Okamoto M, Serizawa K, Nakashima H, Omae K
	Publication date	2005
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Japan
	Source of funding	Not reported (authors are from University Schools of Medicine and a Research Laboratory for Hitachi Ltd).
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To characterise the potential toxic effects of pure bismuth through acute and repeat oral administration in SPF rats.
	Study type/design	Experimental animal study
	Study duration	Single dose, 14 days observation OR Repeat dose for 28 days
	Type of water source (if applicable)	Not applicable (Tap water irradiated by UV rays after passing through a 5 µm filter provided *ad libitum*).
Population characteristics	Population/s studied	Crj:CD(SD)IGS rats (SPF) from Charles River Japan Inc (n=5/sex for acute study, 36/sex for repeat dose toxicity study) (5 weeks of age at start of study; weights 128-176 g males, 113-147 g females).
	Selection criteria for population (if applicable)	Animals were assigned to experimental groups to provide homogenous distribution of body weights between the acute and repeat dose study.
	Subgroups reported	• Acute study: 2,000 mg/kg in corn oil or vehicle control alone • Repeat dose study: 0, 40, 200 or 1,000 mg/kg/d (6 rats/sex in the two lower doses; 12 rats/sex in control and high dose group)
	Size of study	
Exposure and setting	Exposure pathway	Oral via gavage
	Source of chemical/contamination	Pure metal bismuth particles of ≤10 µm average particle diameter (bismuth, purity 99.9% purchased from Kojundo Chemical Laboratory Co., Ltd) purposefully administered to rats
	Exposure concentrations (if applicable)	• Acute study: 2,000 mg/kg in corn oil or vehicle control alone • Repeat dose study: 0, 40, 200 or 1,000 mg/kg/d
	Comparison group(s)	Vehicle control (corn oil)

Publication Reference: Sano Y., Satoh H., Chiba M., Okamoto M., Serizawa K., Nakashima H. and Omae K. (2005). Oral toxicity of bismuth in rat: single and 28-day repeated administration studies. J Occup Health 47(4): 293-298.		
Study methods	Water quality measurement used	Not applicable. Acute oral toxicity study conducted in accordance with OECD TG 401. Body weight, pathological examination & clinical signs performed. Repeat dose study: Clinical signs, body weight, food consumption, haematology, blood chemistry, urinalysis, organ weights, gross and histopathology (the latter conducted in control and high dose groups only).
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	• Acute study: No abnormal clinical signs, no significant differences in body weight and no treatment-related histopathological abnormalities. • Repeat-dose study: No abnormal clinical signs, no significant body weight or food consumption differences between control and any treatment group during dosing or recovery period, no treatment-related significant haematological changes during dosing, urinalysis, and no treatment-related statistically significant pathological findings.
	How outcome was assessed	• Repeat dose study: After the recovery period, a significantly higher value of the ratio of monocytes versus leukocytes (%) was observed in males of the 1,000 mg/kg/d group and a significantly lower value of leukocyte count was observed in females of the 1,000 mg/kg/d group, as compared with the control group (likely unrelated to treatment since they did not occur during dosing). A significantly higher value of potassium in males of the 40 mg/kg/d group (not treatment-related) and a significantly higher value of total protein in females of the 1,000 mg/kg/d group was also observed after the dosing period (likely unrelated to treatment as there were no changes in other parameters of protein nor changes in liver involved in protein synthesis). After the recovery period, a significantly lower value of urea nitrogen was observed in males at 1,000 mg/kg/d (not treatment-related).
	Method of measurement	See previous cells
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Repeat dose study: 6 rats/sex in the two lower doses; 12 rats/sex in control and high dose group.
Statistics	Statistical method used	

Publication Reference: Sano Y., Satoh H., Chiba M., Okamoto M., Serizawa K., Nakashima H. and Omae K. (2005). Oral toxicity of bismuth in rat: single and 28-day repeated administration studies. J Occup Health 47(4): 293-298.		
(if any)	Details on statistical analysis	Multiple comparison test to analyse statistical significance in the numerical data (body weight, food consumption, hematology, blood chemistry, and organ weights). If there was statistical significance in the data between groups, Dunnett's test or a Dunnett-type rank-sum test was conducted. Statistical significance in graded categorical data (urinalysis, necropsy findings and histopathological findings) was analysed by a × b chi-square test. If statistically significant data were found, data were compared from the control group with those obtained from each dose group using Armitage's chi-square test. A significance level of 5% and 1% was set for all statistical analysis.
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Found no changes attributable to Bi in the acute oral toxicity study with rats. LD50 > 2,000 mg/kg for both sexes. • In repeat dosing study, there were no treatment-related changes in clinical signs, body weights, food consumption, haematology, urinalysis, organ weights, necropsy or histopathological findings after oral administration of bismuth to rat for 28 days up to the dose of 1,000 mg/kg/d (NOAEL = 1,000 mg/kg/d in both sexes). • The authors concluded the adverse toxic effects of Bi as a simple metal substance are predicted to be low compared with the adverse effects of lead under the conditions of this study.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	This study provides results of a 28-day repeat dose toxicity assay for bismuth metal (pure bismuth) in rats. The study was well conducted and included all standardised endpoints which are typically investigated in such studies. It establishes a 28-day NOAEL as the highest dose tested (i.e. 1,000 mg Bi/kg bw/d in female/male rats). This is likely a critical study for potential health-based guideline derivation; risk of bias analysis was undertaken.

Slikkerveer and de Wolff 1989

Publication Reference: Slikkerveer A. and de Wolff F. A. (1989). Pharmacokinetics and toxicity of bismuth compounds. Med Toxicol Adverse Drug Exp 4(5): 303-323.		
General Information	Date of data extraction	31/03/2023
	Authors	Slikkerveer A and de Wolff FA
	Publication date	1989
	Publication type	Review
	Peer reviewed?	Yes
	Country of origin	Netherlands

Publication Reference: Slikkerveer A. and de Wolff F. A. (1989). Pharmacokinetics and toxicity of bismuth compounds. Med Toxicol Adverse Drug Exp 4(5): 303-323.		
	Source of funding	Not stated (authors are from a University Hospital)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To review (then) current information on Bi toxicity (particularly in medicinal use) in order to make it more accessible to the clinician.
	Study type/design	Review
	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)	Not 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)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	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: Slikkerveer A. and de Wolff F. A. (1989). Pharmacokinetics and toxicity of bismuth compounds. Med Toxicol Adverse Drug Exp 4(5): 303-323.		
Author's conclusions	Interpretation of results	• Inorganic bismuth salts are poorly soluble in water: solubility is influenced by the acidity of the medium and the presence of certain compounds with (hydr)oxy or sulfhydryl groups. The analysis of bismuth in biological material is not standardised and is subject to large variation; it is difficult to compare data from different studies and older data should be approached with caution. • The normal concentration of Bi in blood is between 1 and 15 µg/L, but absorption from oral preparations produces a significant rise. Distribution of Bi in the organs is largely independent of the compound administered or the route of administration: the concentration in kidney is always highest and the substance is also retained there for a long time. Elimination from the body takes place by the urinary and faecal routes. • A number of toxic effects have been attributed to bismuth compounds in humans: nephropathy, encephalopathy, osteoarthropathy, gingivitis, stomatitis and colitis. Whether hepatitis is a side effect, however, is open to dispute. Each of these adverse effects is associated with certain bismuth compounds. Bismuth encephalopathy occurred in France as an epidemic of toxicity and was associated with the intake of inorganic salts including bismuth subnitrate, subcarbonate, and subgallate. • A safety level of 50 µg/L and an alarm level of 100 ug/L have been suggested in the past (Hillemand et al. 1977, Hillemand and Cottet 1976), but no proof is available to support the choice of these levels. • The bismuth encephalopathy occurred only in France and the surrounding countries, despite extensive use of bismuth elsewhere. A small outbreak of poisoning was also seen in Australian patients who had undergone a colostomy or an ileostomy and taken oral bismuth subgallate. A so far unidentified additional factor besides bismuth was held responsible for these intoxications. Despite many theories on enhanced intestinal absorption, the exact aetiology of bismuth encephalopathy remains a mystery. References: Hillemand P, Cottet J. A propos de la toxicite du sous-nitrate de bismuth et des regles de son emploi en therapeutique digestive. Bulletin de l'Academie Nationale de Medecine 160: 274-278, 1976. As cited in Slikkerveer and Wolff 1989. Hillemand P, Palliere M, Laquais B, Bouvet P. Traitement bismuthique et bismuthemie, Semaine des Hopitaux de Paris 53: 1663-1669, 197. As cited in Slikkerveer and Wolff 1989.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	The study is a review which provides some useful general information for Bi. As the article is a review paper, risk of bias assessment was not undertaken.

Taylor and Klenerman 1990

Publication Reference: Taylor E. G. and Klenerman P. (1990). Acute renal failure after colloidal bismuth subcitrate overdose. Lancet 335(8690): 670-671.		
General Information	Date of data extraction	05/04/2023
	Authors	Taylor EG and Klenerman P
	Publication date	1990
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not stated (authors are from a Hospital)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of acute renal failure after an overdose of colloidal bismuth subcitrate.
	Study type/design	Case report
	Study duration	4 weeks daily administration, followed by single overdose
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report)
	Selection criteria for population (if applicable)	76-year old man who had been taking bismuth tripotassium dicitrate ('De-Nol') for 4 weeks for haemorrhagic gastritis and duodenitis was admitted to hospital after having taken an overdose of 6 'Deteclo' (tetracycline hydrochloride 115.4mg, chlortetracycline hydrochloride 115.4 mg and demeclocycline hydrochloride 69.2 mg per tablet) and 80 De-Nol tablets 4 hours earlier. The only other prescribed drug ingested in the month before admission was fluoxetine.
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	6 'Deteclo' tablets (tetracycline hydrochloride 115.4 mg, chlortetracycline hydrochloride 115.4mg and demeclocycline hydrochloride 69.2mg per tablet) and 80 De-Nol (bismuth tripotassium dicitrate, dose of Bi not reported) tablets 4 hours earlier.
	Exposure concentrations (if applicable)	Not available
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable

Publication Reference: Taylor E. G. and Klenerman P. (1990). Acute renal failure after colloidal bismuth subcitrate overdose. Lancet 335(8690): 670-671.		
Results (for each outcome)	Definition of outcome	• Bi was detectable in the blood (1,600 µg/L). • An abdominal X-ray film showed opacification of the colon by ingested Bi and a chest X-ray film showed no evidence of free gas under diaphragm. • Patient had vomited profusely at home and in emergency department. After admission, he was noted to be oliguric and 4 hours later began passing bloody stools but no source was seen at sigmoidoscopy. • He was started on ranitidine and regular antacid, and magnesium sulphate enemas were prescribed to purge his colon of bismuth. After 48 h of oliguria plasma creatinine was 516 µmol/L and serum potassium was 8.1 mmol/L and he was dialysed for 3 days, during which time he continued to pass bloody stools and needed further transfusion. • Acute abdominal pain then developed with absent bowel sounds but he was judged unfit for surgery and died 4 days later. • Necropsy revealed a perforated duodenal ulcer and "pale kidneys" which proved to contain bismuth (11 mg/g and 16 mg/g).
	How outcome was assessed	
	Method of measurement	See above.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Authors conclude patient has toxic serum Bi concentrations 4 hours after ingestion of 80 De-Nol tables and Bi was shown to have accumulated in his renal tissue. Bismuth nephropathy probably contributed to acute renal failure, although there was the additional insult of gastrointestinal bleeding.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Very high dose of Bi administered as Bi subcitrate (80 De-Nol tablets) concurrently with a few other medications which resulted in acute renal failure. • Serum Bi was very high (1,600 µg/L). • Risk of bias analysis was undertaken.

Tubafard and Fatemi 2008

Publication Reference: Tubafard S. and Fatemi S. J. (2008). Chelation of bismuth by combining desferrioxamine and deferiprone in rats. Toxicol Ind Health 24(4): 235-240.		
General Information	Date of data extraction	31/03/2023
	Authors	Tubafard S and Fatemi SJ
	Publication date	2008
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Iran
	Source of funding	The authors thank the head and director of International Center of Science, High Technology and Environmental Science and Shahid Bahonar University of Kerman Faculty Research Funds for their support of these investigations.
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To test the chelation potency of DFO and L1 in combination given to rats after bismuth loading. Testing was performed by using an acute experimental model on rats with individual or combined chelators given shortly after bismuth application. The summary herein focuses on the results of bismuth administration, rather than the chelators.
	Study type/design	Experimental animal study
	Study duration	55 days
	Type of water source (if applicable)	First and third group were given distilled water to drink. Second group (drinking group) was given water containing 20 µg/L (presumably this is Bi, but it is not stated in paper).
Population characteristics	Population/s studied	Male Wistar rats (Razi Institute of Karaj).
	Selection criteria for population (if applicable)	Not applicable
	Subgroups reported	• Group 1 (control): Given normal food & distilled water to drink • Group 2 (drinking group): Given water containing 20 µg/L (presumably Bi but this is not stated in paper) • Group 3 (food group): Given food incorporating 40 mg Bi(III) nitrate into 1 kg of food.
	Size of study	
Exposure and setting	Exposure pathway	Oral administration was performed once a day (unclear how this could have occurred with the drinking water and food groups).
	Source of chemical/contamination	Bismuth nitrate (purity 99.9%) (Sigma Chemicals Co., USA) purposely administered to rats
	Exposure concentrations (if applicable)	• See subgroups cells above. • It is unclear from the paper what the doses administered were. Food and water consumption data were not provided. There is conflicting information in the abstract of the paper and the paper itself on dose levels.
	Comparison group(s)	Control group (given normal food and distilled water)

Publication Reference: Tubafard S. and Fatemi S. J. (2008). Chelation of bismuth by combining desferrioxamine and deferiprone in rats. Toxicol Ind Health 24(4): 235-240.		
Study methods	Water quality measurement used	Not stated
	Water sampling methods (monitoring, surrogates)	Not stated
Results (for each outcome)	Definition of outcome	• After 55 days, the Bi in food group weighed significantly less than controls and had reduced food consumption (statistical analysis not presented). • Clinical signs in Bi administered groups included appearance of black line on gums, loss of appetite and weight, loss of hair, skin reactions, decrease in food consumption and organ weights. • As Bi concentrations increased in blood serum, iron levels decreased.
	How outcome was assessed	
	Method of measurement	Methods not reported in detail.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	9 rats/group
Statistics (if any)	Statistical method used	Authors mention t-test was used for comparison between groups (chelation vs. no chelation), but it is unclear what statistical analysis was used for effects on body weight and food consumption. Organ weight data is mentioned but not presented in paper.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• See definition of outcome.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	The quality of reporting in this paper leaves something to be desired. It is unclear from the paper what the doses administered were. Food and water consumption data were not provided. There is conflicting information in the abstract of the paper and the paper itself on dose levels. Only limited outcomes were reported in the paper. The confidence in the findings with respect to informing a health-based guidance level for Bi is considered low. Risk of bias analysis was undertaken.

Urizar and Vernier 1966

Publication Reference: Urizar R. and Vernier R. L. (1966). Bismuth nephropathy. Jama 198(2): 187-189.		
General Information	Date of data extraction	05/04/2023
	Authors	Urizar R and Vernier RL
	Publication date	1966

Publication Reference: Urizar R. and Vernier R. L. (1966). Bismuth nephropathy. Jama 198(2): 187-189.		
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	The investigation was supported by Public Health Service grant AI-06797.
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of acute renal failure in a child 8 years of age who had been taking an oral Bi preparation for multiple warts.
	Study type/design	Case report
	Study duration	3 months of Bi administration from Jan-Mar 1962, followed by 5 additional weeks during May-June.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report) 8-year old girl admitted to the University of Minnesota Hospitals on Aug 10, 1962, following the discovery that she had not urinated during the past two days. Five days prior to admission she had complained of not feeling well and had seemed less active than normal. Two days prior to admission she vomited repeatedly, developed a low grade fever, had severe abdominal pain and was oliguric.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	On Aug 17 (7 days after admission) a history of ingestion of Bi was obtained. The patient had taken bismuth sodium triglycollamate as therapy for multiple warts over the hands (2 x 75 mg Bi twice daily for period of 3 months, and then again for another 5 weeks). Mother was unaware that child was ingesting the medication (which was prescribed to older sister) therefore precise dates that medication was ingested remains unknown.
	Exposure concentrations (if applicable)	Not available (estimated to be 18 g Bi over 5 months)
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Bi was detectable in plasma (300-400 µg/L) and urine (220 µg / 24 hr).

Publication Reference: Urizar R. and Vernier R. L. (1966). Bismuth nephropathy. Jama 198(2): 187-189.		
	How outcome was assessed	• Oliguria and vomiting. Physical examination on admission revealed a well developed and well nourished child who was lethargic & complained of abdominal pain. Only abnormalities were abdominal tenderness, slight periorbital oedema, and a minimally enlarged liver. • Diagnosed with acute renal insufficiency, but cystoscopy demonstrated normal bladder, ureter and collecting system. • Haemodialysis was associated with improvement. A urine culture obtained 5 days after admission grew greater than 100,000 colonies of *Escherichia coli*. • Recovery was complete after treatment.
	Method of measurement	Dithizone colorimetric technique
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Authors conclude the clinical and laboratory findings in this child, and the presence of detectable Bi in both blood and urine suggest the renal injury was caused by Bi.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report of a child). • High repeat dose of Bi administered as bismuth sodium triglycollamate (likely 18 g Bi over 5 months but exact amount unknown) resulted in acute renal failure. • Plasma Bi measured 12 days after hospitalisation was high (300-400 µg/L). • Risk of bias analysis was undertaken.

US FDA 2023

Publication Reference: US FDA (2023). CRF - Code of Federal Regulations Title 21, U.S Food and Drug Administration.		
General Information	Date of data extraction	30/03/2023
	Authors	United States Food and Drug Administration
	Publication date	Unclear, but last updated Jan 17, 2023
	Publication type	Brief Code of Federal Regulations Excerpt
	Peer reviewed?	Unknown
	Country of origin	USA
	Source of funding	Not applicable

Publication Reference: US FDA (2023). CRF - Code of Federal Regulations Title 21, U.S Food and Drug Administration.		
	Possible conflicts of interest	Not applicable (agency publication)
Study characteristics	Aim/objectives of study	Part 357 of the Code of Federal Regulations (Title 21, Volume 5) provides very brief guidance for products containing bismuth subgallate. Recommended daily intake for adults and children 12 years of age and over is oral dose of 200-400 mg up to 4 times daily. No further information, or derivation for this value, is provided.
	Study type/design	Not applicable
	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)	Not 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)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	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	Part 357 of the Code of Federal Regulations (Title 21, Volume 5) provides very brief guidance for products containing bismuth subgallate. Recommended daily intake for adults and children 12 years of age and over is oral dose of 200-400 mg up to 4 times daily. No further information, or derivation for this value, is provided.

Publication Reference: US FDA (2023). CRF - Code of Federal Regulations Title 21, U.S Food and Drug Administration.		
	Assessment of uncertainty (if any)	Not provided
Reviewer comments	Results included/excluded in review (if applicable)	Recommended daily intake for adults and children 12 years of age and over for bismuth subgallate is oral dose of 200-400 mg up to 4 times daily. No further information, or derivation for this value, is provided. As the excerpt is a single-page mention with no further information, risk of bias assessment could not be undertaken.

Wang et al. 2012

Publication Reference: Wang Y., Tang N., Meng L., Zhang P., Xu K., Jiang N., Zhang H., Ou N., Wu D., Chen A., Zhang X. and Shi R. (2012). Safety and tolerability of bismuthyl ecabet suspension, a novel anti-ulcer agent, following single and multiple oral dose administration in healthy Chinese subjects. Clin Drug Investig 32(4): 247-252.		
General Information	Date of data extraction	03/04/2023
	Authors	Wang Y, Tang N, Meng L, Zhang P, Xu K, Jiang N, Zhang H, Ou N, Wu D, Chen A, Zhang X, Shi R
	Publication date	2012
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	The study was supported by Cinmed Pharmaceuticals Co. Ltd., Shanghai, China
	Possible conflicts of interest	No conflict of interest statement included in article.
Study characteristics	Aim/objectives of study	To assess the safety and tolerability of bismuthyl exabet suspension, a combination of sulfodehydroabietic acid and bismuth forming a new type of salt useful for treating peptic ulcers and gastritis, in healthy Chinese subjects.
	Study type/design	Randomised, open-label, dose-escalating study
	Study duration	Single dose studies: Single dose, 72-hour observation Multiple dose study: Twice daily dose for 7 days, monitored for 10 days after first dosing
	Type of water source (if applicable)	Not applicable.
	Population/s studied	77 healthy subjects (39 males and 38 females)

Publication Reference: Wang Y., Tang N., Meng L., Zhang P., Xu K., Jiang N., Zhang H., Ou N., Wu D., Chen A., Zhang X. and Shi R. (2012). Safety and tolerability of bismuthyl ecabet suspension, a novel anti-ulcer agent, following single and multiple oral dose administration in healthy Chinese subjects. Clin Drug Investig 32(4): 247-252.		
Population characteristics	Selection criteria for population (if applicable)	Good general health based on medical history, physical examination, electrocardiogram, electroencephalogram, type-B ultrasound, chest x-ray, routine blood investigation, urine and faeces tests, as well as serum biochemistry (the latter conducted before and at end of study). Subjects were excluded if they (a) had a history of clinical manifestations of significant metabolic, haematological, pulmonary, cardiovascular, gastrointestinal, hepatic, renal or psychiatric disorders; (b) had a history or presence of an abnormal electrocardiogram or electroencephalogram; (c) had a history of alcoholism or drug addiction within 6 months prior to study entry; (d) had participated in a clinical trial or received an investigational drug within 3 months prior to the start of the study; (e) had donated blood within the preceding 30 days; and (f) had taken prescription or over-the-counter drugs within 1 week prior to study entry or during the study.
	Subgroups reported	77 subjects: i) Single-dose studies (7-18/group), ii) Repeat-dose study (8 participants)
	Size of study	
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of bismuthyl ecabet suspension (provided by Cinmed Pharmaceuticals Co. Ltd, Shanghai, China).
	Exposure concentrations (if applicable)	Single dose studies: 200, 400, 800, 1200 or 1600 mg (7-18 subjects/group balanced by sex & body mass index) Multiple dose study: 1200 mg twice daily for 7 consecutive days (8 subjects, 4 males and 4 females)
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	

Publication Reference: Wang Y., Tang N., Meng L., Zhang P., Xu K., Jiang N., Zhang H., Ou N., Wu D., Chen A., Zhang X. and Shi R. (2012). Safety and tolerability of bismuthyl ecabet suspension, a novel anti-ulcer agent, following single and multiple oral dose administration in healthy Chinese subjects. Clin Drug Investig 32(4): 247-252.		
	Method of measurement	• Details of any symptoms were recorded. Safety assessments such as physical examinations, vital signs including body temperature, pulse rate, respiratory rate and blood pressure were assessed pre-dose and at 1, 4, 12, and 24 hours after each dose. Adverse events were monitored and recorded throughout the study. The relationship between the study drug and an adverse event was described as 'certain', 'probable', 'possible', 'suspected' or 'not related'. • No severe adverse events occurred during the study and all subjects showed good compliance, with no symptoms or signs of adverse events observed. • In the single-dose study, high GGT concentrations were found in one subject from the 400 mg dose group and in one subject from the 800 mg group. In the 800 mg dose group, another subject was found to have high BUN concentrations and in the 1200 mg dose group one subject was found to have high ALT concentrations. Another subject from the 400 mg group was found to have a skin rash after a single administration. All the above adverse events were judged to have a possible relationship to the drug. There was a slight increase in TBIL in two of the subjects (one each in the 400 mg and 1600 mg groups), which were judged to have a suspected link to the drug. • In the multiple-dose study, increases in ALT and AST concentrations were found in one subject. • All laboratory abnormalities that were judged to be possibly related to the drug were mild and tolerable, and did not lead to discontinuation of the study. All serum biochemistry returned to normal levels and skin rash resolved after 7 days without any special treatment.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Single dose studies: 7-18 subjects/group balanced by sex & body mass index Multiple dose study: 8 subjects, 4 males and 4 females
Statistics (if any)	Statistical method used	The statistical software SPSS 11.5 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis, and a p-value of <0.05 was considered significant. Analysis of safety included descriptive summaries of baseline characteristics and all the other safety variables, including adverse events, vital signs, and clinical laboratory results. The values obtained before and after administration in single- and multiple-dose studies were analysed by paired t-testing and the variances in single-dose groups were measured by analysis of variance (ANOVA). Any adverse events were summarised by the use of frequencies and percentages.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.
Author's conclusions	Interpretation of results	• Bismuthyl ecabet suspension was well tolerated at doses up to 1600 mg administered once daily and at doses of up to 1200 mg administered twice daily for 7 days.

Publication Reference: Wang Y., Tang N., Meng L., Zhang P., Xu K., Jiang N., Zhang H., Ou N., Wu D., Chen A., Zhang X. and Shi R. (2012). Safety and tolerability of bismuthyl ecabet suspension, a novel anti-ulcer agent, following single and multiple oral dose administration in healthy Chinese subjects. Clin Drug Investig 32(4): 247-252.		
	Assessment of uncertainty (if any)	The agent merits further clinical development to evaluate and confirm its preliminary safety.
Reviewer comments	Results included/excluded in review (if applicable)	The primary objective of this study was to test the safety of a bismuth-containing organic drug. Although the study provides supporting information that the drug was well tolerated, the applicability to inorganic bismuth such as that present in bismuth alloys for lead-replacements in plumbing is likely limited due to potential confounding from the organic drug component. In addition, the percentage of bismuth in the drug is not reported in the paper. Limited health outcomes were assessed, so the study provides limited information with respect to defining a health-based guidance value for Bi. As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.

Weller 1988

Publication Reference: Weller M. P. (1988). Neuropsychiatric symptoms following bismuth intoxication. Postgrad Med J 64(750): 308-310.		
General Information	Date of data extraction	27/04/2023
	Authors	Weller MPI
	Publication date	1988
	Publication type	Case report
	Peer reviewed?	Yes
	Country of origin	UK
	Source of funding	Not stated (author is from a Hospital)
	Possible conflicts of interest	No conflict of interest statement is included in the paper.
Study characteristics	Aim/objectives of study	To report on a case of seemingly neurotic symptoms, similar to those reported in bismuth intoxication, after taking bismuth tripotassium dicitrate (De-Nol) for over 2 years.
	Study type/design	Case report
	Study duration	2 years
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (single case report)
	Selection criteria for population (if applicable)	41-year old professional man with previously healed duodenal ulcer who took the bismuth preparation De-Nol for 2 years, intermittently as and when dyspeptic symptoms were troubling him.

Publication Reference: Weller M. P. (1988). Neuropsychiatric symptoms following bismuth intoxication. Postgrad Med J 64(750): 308-310.		
	Subgroups reported	Not applicable (case report)
	Size of study	1 case
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Purposeful administration of De-Nol (2x28-day course of 600 mg four times/day, then continued with 240 mg/day).
	Exposure concentrations (if applicable)	Not available (240-2,400 mg De-Nol/day for ~2 years).
	Comparison group(s)	None (not applicable)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• In the last 4 months of the 2-year treatment, patient began to experience numbness and paraesthesia in both hands, particularly at night. Also felt unusually irritable and fatigued, with poor concentrations and impaired short term memory. Blue line could be seen in a small area of gum surrounding a crown. Radiological examination of epicondyle region and wrist failed to reveal any abnormality. • All symptoms gradually disappeared after Bi preparation was stopped and replaced with calcium and magnesium salts. • No Bi measurements made in blood or other bodily fluids/tissues.
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1 case report (exposed)
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (case study report)
Author's conclusions	Interpretation of results	Authors conclude the case illustrates the apparent cause for the neurotic complaints was the prolonged use of oral bismuth preparation.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Small study (1 case report). • Repeat dose of Bi unknown, but the objective and subjective neurotoxic symptoms appeared to be related to 2-year repeat dose of bismuth preparation bismuth tripotassium dicitrate (De-Nol). • Risk of bias analysis was undertaken.

Zhang et al. 2020

Publication Reference: Zhang L., Liu J., Meng F., Guan Y., Wang Y., Zhu S., Liu Y., Xie Q., Yu J. and Zhang S. (2020). Pharmacokinetics of Bismuth following Oral Administration of Wei Bi Mei in Healthy Chinese Volunteers. Evid Based Complement Alternat Med 2020: 2679034.		
General Information	Date of data extraction	03/04/2023
	Authors	Zhang L, Liu J, Meng F, Guan Y, Wang Y, Zhu S, Liu Y, Xie Q, Yu J, Zhang S
	Publication date	2020
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	None stated
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	To determine the pharmacokinetics of bismuth to evaluate the safety and use of Wei Bi Mei, a new drug containing a combination of chemicals and Chinese medicine components. It contains heavy magnesium carbonate and sodium bicarbonate, as well as multiple Chinese herbal medicinal ingredients including licorice extract, cortex frangulae, aloe, fructus foeniculi and *Acorus gramineus*.
	Study type/design	Pharmacokinetic investigation in humans (clinical trial)
	Study duration	Single dose: One bag of Wei Bi Mei granules (containing 200 mg Bi) Multiple dose: One bag of Wei Bi Mei granules after meal 3 times/day on days 2-9 (7 days).
	Type of water source (if applicable)	Not applicable.
Population characteristics	Population/s studied	7 healthy Chinese adults (mean age 25.4 ± 2.2 yrs)
	Selection criteria for population (if applicable)	Non-smokers who did not use medications. Use of tobacco, caffeine, or any medications was also prohibited during the study.
	Subgroups reported	7 subjects
	Size of study	
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Wei Bi Mei granules (20150406) manufactured by Holwray Pharmaceutical (China) Co. Ltd.
	Exposure concentrations (if applicable)	Single dose: 200 mg Bi Multiple doses: 200 mg Bi 3 times/day (600 mg Bi/day) for 7 days
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.

Publication Reference: Zhang L., Liu J., Meng F., Guan Y., Wang Y., Zhu S., Liu Y., Xie Q., Yu J. and Zhang S. (2020). Pharmacokinetics of Bismuth following Oral Administration of Wei Bi Mei in Healthy Chinese Volunteers. Evid Based Complement Alternat Med 2020: 2679034.		
Results (for each outcome)	Definition of outcome	• Clinical parameters were monitored to evaluate the health of the subjects during the trial, which mainly included alanine aminotransferase activity, alkaline phosphatase activity, total protein, albumin, total bilirubin, direct bilirubin, glucose, creatinine, blood urea nitrogen, aspartate aminotransferase activity, potassium ions, sodium ions, and chloride ions. • In single dose study, blood samples (brachial vein blood) were collected at 10 min, 30 min, 60 min, 90 min, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, and 24 h after ingestion. • In multiple dose study, blood samples were collected on day 8 and day 9 at 30 min before and 30 min after the first daily administration. The drug was stopped on day 10 after the oral administration of one bag of Wei Bi Mei granules. Then, blood samples were collected on days 12, 13, 16, 20, 26, 33, 40, 55, and 70. Urine samples were collected on days 12, 13, 16, 20, 26, 33, 40, 55, and 70 over a period of 12 h to record the volume after blending. • One subject withdrew from participation due to diarrhoea on the second day of the oral administration of Wei Bi Mei granules and had dark green watery stools about 3-4 times/day, without abdominal pain and tenesmus. The diarrhoea stopped on the second day after withdrawal of the medication. No similar or other adverse events appeared in the remaining subjects. All clinical parameters tested with the blood samples of subjects remained within normal ranges. • For single dose Wei Bi Mei granules administration, the mean time to peak concentration (t_{max}) of bismuth was 2.29±0.76 h, and the mean peak concentration (C_{max}) of bismuth was 0.85±0.55 ng/mL. • For multiple-dose Wei Bi Mei granules administration, the C_{max} was 2.25±1.18 ng/mL at day two, and the volume of distribution (Vd) was (22.97±9.82)× 10^3 L. The urinary excretion of bismuth was the fastest during the first two days, with a mean excretion rate of 3.84±1.23 ng/h. The bismuth concentration in urine was significantly reduced at day 16.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N=7
Statistics (if any)	Statistical method used	The pharmacokinetics of Wei Bi Mei were evaluated using DAS 2.2 (Mathematical Pharmacology Professional Committee of China, Shanghai, China). Pharmacokinetic analysis included determination of the following parameters: maximum concentration (C_{max}); time of maximum concentration (t_{max}); apparent elimination rate constant (K_{el}); AUC, the area under the plasma concentration-time curve (AUC_{0-t}), calculated by the linear trapezoidal rule; mean residence time (MRT); Vd, volume of distribution; elimination half-life ($t_{1/2}$).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable.

Publication Reference: Zhang L., Liu J., Meng F., Guan Y., Wang Y., Zhu S., Liu Y., Xie Q., Yu J. and Zhang S. (2020). Pharmacokinetics of Bismuth following Oral Administration of Wei Bi Mei in Healthy Chinese Volunteers. Evid Based Complement Alternat Med 2020: 2679034.		
Author's conclusions	Interpretation of results	• Bi was excreted slowly in plasma and even more slowly in urine, with most Bi eliminated within 60 days indicating consecutive courses of treatment should be paused after this time period in clinical practice. • The concentration of Bi in blood after drug administration was far less than the 'safe level' and thus Wei Bi Mei is safe in clinical practice. Wei Bi Mei could be recommended for wide use in bismuth-containing quadruple therapy.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	The primary objective of this study was to test the pharmacokinetics of bismuth in healthy human subjects after administration of a bismuth-containing drug, containing numerous other ingredients including various Chinese medicines. Although the study provides supporting information that the drug was well tolerated (with the exception of diarrhoea in one individual), the applicability to inorganic bismuth such as that present in bismuth alloys for lead-replacements in plumbing is likely limited due to potential confounding from the other drug components. Limited health outcomes were assessed, so the study provides limited information with respect to defining a health-based guidance value for Bi. As the study was not deemed to be a critical study, risk of bias assessment was not undertaken.

APPENDIX D

Risk of Bias Assessment Tables

Akpolat et al. 1996

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 studies greyed out.

Study ID: Akpolat et al. 1996 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	Yes	There is insufficient information provided about the exposure assessment (i.e. exposure was not assessed) (NR).	NR
9.	Outcome assessment	No	Indirect evidence that outcome was assessed using acceptable methods and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (i.e. outcomes were objective measures, including kidney histopathology and urine output).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Atwal and Cousin 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 Case studies greyed out.

Study ID: Atwal and Cousin 2016 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured in blood.	--
9.	Outcome assessment	Yes	Indirect evidence that outcome assessment method is an insensitive instrument, i.e. relying on self-reported subjective outcomes with respect to behaviour (e.g. fatigue, confusion, etc).	+
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Bridgeman and Smith 1994

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 studies greyed out.

Study ID: Bridgeman and Smith 1994 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured in blood. A pathology laboratory was used providing indirect evidence the result was likely part of routine commercial laboratory analysis which typically is validated against well-established methods.	--
9.	Outcome assessment	Yes	Indirect evidence that outcome assessment method is an insensitive instrument, i.e. relying on self-reported subjective outcomes with respect to behaviour (e.g. insomnia, irritability). With respect to measurement of exposure, a pathology laboratory was used to measure bismuth in blood thereby providing indirect evidence the result was not appreciably biased by the assessor. There was no quality control sample or field duplicate sent in for analysis hence the reporting laboratory may have known to expect elevated bismuth in blood.	+
	Selective Reporting Bias			
10.	Outcome reporting	Yes	Only results for bismuth were reported even though the authors were considering heavy metal poisoning in general. It is not clear whether other metals were analysed and what the results of such analysis was.	++
	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 (++)	++

Buge et al. 1981

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 studies greyed out.

Study ID: Buge et al. 1981 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured in blood, urine and CSF.	--
9.	Outcome assessment	No	Indirect evidence that outcome was assessed using acceptable methods and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (i.e. outcomes were objective measures, including clinical manifestations such as myoclonic seizures).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Burns et al. 1974

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 studies greyed out.

Study ID: Burns et al. 1974 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	Yes	Exposure of bismuth was not measured directly, relied on patient history.	+
9.	Outcome assessment	No	Indirect evidence that outcome was assessed using acceptable methods and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (i.e. outcomes were objective measures, including clinical manifestations such as grand mal seizures). Other outcomes were self-reported and somewhat subjective.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Canena et al. 1998

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 Experimental Animal Studies greyed out.

Study ID: Canena et al. 1998 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	The randomisation method was not stated (i.e. there is indirect evidence that animals were allocated randomly to study group) AND one group received saline only (i.e. there is direct evidence that a concurrent control group was used). Paper states: *Rats were randomly allocated to….groups*	-
2.	Allocation concealment	Unknown	It is not stated whether group treatment was concealed (i.e. there is indirect evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to). However, lack of adequate allocation concealment is unlikely to appreciably bias results, as results were based on measured bismuth concentrations in blood and tissues and no clinical signs of encephalopathy (e.g. ataxia, seizures etc) were observed in any group.	-
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	Experimental conditions were identical between groups in Study 1 or Study 2.	--
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	+
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR (i.e. there is insufficient information provided about loss of animals)	NR
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	No	Outcome assessment unlikely to appreciably bias results, as results were based on measured bismuth concentrations in blood and tissues and no encephalopathy was observed in any group (i.e. the expected positive bias for treated groups was not reported).	-
	Selective Reporting Bias			

10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Coffey and Graham 1974

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 studies greyed out.

Study ID: Coffey and Graham 1974 **Study Type: Case study (CaS)**		**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)	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**	**N/A**	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	Yes	Exposure of Bi was an indirect measure, not confirmed by serum or blood measurements. Also no information provided on length of exposure or even a rough dose taken per day.	++
9.	Outcome assessment	No	It is unknown if outcome was assessed using acceptable methods; however clinical signs are evident and it is deemed the lack of adequate blinding of outcome assessors would not appreciably bias results.	-

	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Dunk et al. 1990

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 Human Controlled Trials (HCT) greyed out.

Study ID: Dunk et al. 1990 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	Paper states that subjects were randomly assigned to study groups.	--
2.	Allocation concealment	No	The paper states that the study was double-blinded.	--
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	The paper states that the study was double-blinded.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	No subjects appear to have withdrawn from the maintenance therapy component of the study.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is insufficient information provided about the validity of the exposure assessment method (i.e. purity and stability of test material), but there is no evidence for concern (NR).	NR

9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. reporting of adverse events and monitoring of biochemical changes) however details are not reported. There is also indication (a statement in the paper) that the outcome assessors were adequately blinded throughout the study.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	Indirect evidence that all of the study's measured outcomes have not been reported (e.g. results of biochemical data and details of adverse events not provided; only a statement to the effect).	+
	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 (++)	++

Gurnani et al. 1993

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 Experimental Animal Studies greyed out.

Study ID: Gurnani et al. 1993 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	There is insufficient information provided about how animals were allocated to study groups (NR)	NR
2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	Experimental conditions were identical between groups.	--
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	No missing outcome data	--
	Detection Bias			

8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	Unknown	It is not specified in the paper whether outcome assessors were blinded to treatment level (NR).	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	Direct evidence that all of the study's measured outcomes 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 (++)	++

Hanzlik et al. 1938

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 Experimental Animal Studies greyed out.

Study ID: Hanzlik et al. 1938 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	There is insufficient information provided about how animals were allocated to study groups (NR)	NR
2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	Yes	There is direct evidence that non-treatment related experimental conditions were not comparable between study groups. Dogs and cats were given an anti-emetic which authors note could reduce confidence in mortality results.	++
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			

7.	Missing outcome data	No	No missing outcome data	--
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	Unknown	It is not specified in the paper whether outcome assessors were blinded to treatment level (NR).	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes 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 (++)	++

Hudson et al. 1989

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 studies greyed out.

Study ID: Hudson et al. 1989 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured directly, but with delay (i.e. 10 days after overdose occurred).	-
9.	Outcome assessment	Yes	Limited information on outcomes assessed. Single sentence indicates nephrotoxicity and neurotoxicity was diagnosed but no detail provided. (NR)	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Huwez et al. 1992

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 studies greyed out.

Study ID: Huwez et al. 1992 **Study Type: Case study (CaS)**	**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured directly, i.e. in serum by ICP-MS.	--
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed the lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Jones 1990

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 studies greyed out.

Study ID: Jones 1990 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	Unknown	Exposure of bismuth was measured in blood, but exposures to other substances in BIPP are unknown.	+
9.	Outcome assessment	Yes	Indirect evidence that outcome assessment method is an insensitive instrument, i.e. relying on self-reported subjective outcomes with respect to behaviour (e.g. insomnia).	+
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Koch et al. 1996

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 Human Controlled Trials (HCT) greyed out.

Study ID: Koch et al. 1996 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	Paper states that subjects were randomly assigned to study groups.	--
2.	Allocation concealment	No	The paper states that the study was double-blinded, except for the post-dosing pharmacokinetic component in which subjects were unblinded.	--
3.	Comparison groups appropriate	N/A	Comparison groups: not applicable	
	Confounding bias			
4.	Confounding (design/analysis)	N/A	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	

6.	Blinding of researchers during study?	No	The paper states that the study was double-blinded, except for the post-dosing pharmacokinetic component in which subjects were unblinded.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that the one subject who was withdrawn from the study did so due to adverse events that were not typical of bismuth toxicity (detail of adverse events not reported).	-
	Detection Bias			
8.	Exposure characterisation	Unknown	There is insufficient information provided about the validity of the exposure assessment method (i.e. purity and stability of test material), but there is no evidence for concern (NR).	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. reporting of adverse events and monitoring of biochemical changes) however details are not reported. There is also evidence that the outcome assessors were adequately blinded throughout the study.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	Indirect evidence that all of the study's measured outcomes have not been reported (e.g. results of biochemical data and details of adverse events experienced by the one person who withdrew from study).	+
	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 (++)	++

Laval 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 Experimental Animal Studies greyed out.

Study ID: Laval et al. 2018 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	There is insufficient information provided about how animals were allocated to study groups (NR)	NR
2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	Comparison groups appropriate	N/A	Comparison groups: not applicable	

	Confounding bias			
4.	Confounding (design/analysis)	N/A	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and identical non-treatment-related experimental conditions are assumed as authors did not report differences in housing or husbandry.	-
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	+
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	No missing outcome data	--
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	Unknown	It is not specified in the paper whether outcome assessors were blinded to treatment level (NR).	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes 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 (++)	++

Leussink et al. 2000

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 Experimental Animal Studies greyed out.

Study ID: Lessink et al. 2000 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that animals were allocated to any study group including controls using a method with a random component (used a randomisation table).	--

2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and there is direct evidence that non-treatment-related experimental conditions were identical across study groups.	--
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	No missing outcome data	--
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	Unknown	It is not specified in the paper whether outcome assessors were blinded to treatment level (NR).	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes 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 (++)	++

Leussink et al. 2001

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 Experimental Animal Studies greyed out.

Study ID: Lessink et al. 2001 **Study Type: Experimental Animal (EA)**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q			
	Selection bias		

1.	Randomization	No	There is direct evidence that animals were allocated to any study group including controls using a method with a random component (likely a randomisation table as per previous publication by same authors, although this is not explicitly stated).	--
2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and there is direct evidence that non-treatment-related experimental conditions were identical across study groups.	--
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Missing outcome data unlikely to impact on study conclusions. The proportion of animals lost is unlikely to appreciably bias results.	-
	Detection Bias			
8.	Exposure characterisation	Unknown	NR: There is insufficient information provided about the validity of the exposure assessment method (i.e. purity of substances used).	NR
9.	Outcome assessment	Unknown	It is not specified in the paper whether outcome assessors were blinded to treatment level (NR).	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes have been reported or selective reporting would not appreciably bias results.	-
	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 (++)	++

Morgan and Billings 1974

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 studies greyed out.

Study ID: Morgan and Billings 1974	**RoB: Yes/No**	**Notes**	**Risk of bias rating**

Study Type: Case study (CaS)		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	N/A	Comparison groups: not applicable	
	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	Yes	Exposure of Bi was indirectly measured, not confirmed by serum or blood measurements.	+
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed the lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Ovaska et al. 2008

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 studies greyed out.

Study ID: Ovaska et al. 2008	**RoB: Yes/No**	**Notes**	**Risk of bias rating**

Study Type: Case study (CaS)		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	N/A	Comparison groups: not applicable	
	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured in blood.	--
9.	Outcome assessment	No	Indirect evidence that outcome assessment method is an insensitive instrument, i.e. relying on self-reported outcomes with respect to behaviour (e.g. confusion), however some of the outcomes (e.g. tremor, myoclonic convulsions) are objective outcomes and readily observable. Hence considered to be probably low risk of bias.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-
	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 (++)	++

Preussman and Ivankovic 1975

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 Experimental Animal Studies greyed out.

Study ID: Preussman and Ivankovic 1975 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	There is insufficient information provided about how subjects were allocated to study groups (NR)	NR
2.	Allocation concealment	Yes	There is insufficient information provided about allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and identical non-treatment-related experimental conditions are assumed since authors did not report differences in housing or husbandry.	-
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Missing outcome data unlikely to impact on study conclusions. Limited reporting of pathological findings in short publication, but no mention in publication of any adverse findings. Unlikely to appreciably bias results.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is indirect evidence that the exposure (including purity and stability of the test substance) was independently characterised and purity confirmed as conforming to standards and there is indirect evidence that exposure was consistently administered (i.e. with the same method and timeframe) across treatment groups. However, the doses reported in the paper (in g/kg bw) are non-sensical when converting the doses and the reported feed intakes to rat body weight (see Appendix C for detail).	++
9.	Outcome assessment	Unknown	It is not specified in the paper whether outcome assessors were blinded to treatment level (NR).	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes have been reported, although not to markedly high detail.	-
	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 (++)	++

Sano et al. 2005

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 Experimental Animal Studies greyed out.

Study ID: Sano et al. 2005 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	The study followed standardised protocols for testing but does not state the method of randomisation in the paper. Direct evidence is provided in the paper that stratified randomisation (i.e. minimising imbalances between groups with respect to body weights) was undertaken.	-
2.	Allocation concealment	Yes	There is insufficient information provided about blinding of allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	No	There is direct evidence that the same vehicle was used in control and experimental animals and there is direct evidence that non-treatment-related experimental conditions were identical across study groups.	--
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence of no missing data.	--
	Detection Bias			
8.	Exposure characterisation	No	There is indirect evidence that the exposure (including purity and stability of the test substance) was independently characterised and purity confirmed as ≥99%. Additionally, there is direct evidence that exposure was consistently administered (i.e. with the same method and timeframe) across treatment groups.	-
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. the gold standard, such as OECD standard protocols) and assessed at the same length of time after initial exposure in all study groups. Although it is not stated whether outcome assessors were blinded, the lack of adequate blinding would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes 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 (++)	++

Taylor and Klenerman 1990

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 studies greyed out.

Study ID: Taylor and Klenerman 1990 **Study Type: Case study (CaS)**		**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)	Yes	Confounders may include other drugs that were taken simultaneously.	++
	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	Yes	Exposure of Bi was a direct measure, confirmed by blood measurement. Information also provided on number of tablets containing Bi subgallate given, but bismuth content not reported.	-
9.	Outcome assessment	No	It is unknown if outcome was assessed using acceptable methods; however outcomes are objective measures and it is deemed the lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported; selective reporting would not appreciably bias results.	-

	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 (++)	++

Tubafard and Fatemi 2008

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 Experimental Animal Studies greyed out.

Study ID: Tubarfard and Fatemi 2008 **Study Type: Experimental Animal (EA)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	There is insufficient information provided about how subjects were allocated to study groups (NR).	NR
2.	Allocation concealment	Yes	There is insufficient information provided about blinding of allocation to study groups (NR)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	Yes	The authors did not report the vehicle used, and there is indirect evidence that non-treatment related experimental conditions were not comparable between study groups.	+
6.	Blinding of researchers during study?	Unknown	There is insufficient information provided about blinding to study groups during the study	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about loss of animals (NR)	NR
	Detection Bias			
8.	Exposure characterisation	Yes	There is insufficient information provided about the validity of the exposure assessment (NR). There is some evidence of concern, due to no water or food consumption rates provided in the paper and differences in dose reporting in abstract vs. body of paper.	+
9.	Outcome assessment	Yes	There is insufficient information provided about blinding of outcome assessors (NR)	NR
	Selective Reporting Bias			

10.	Outcome reporting	Yes	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 not been reported. Missing data on organ weights, for example, although they are mentioned in the text.	+
	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 (++)	++

Urizar and Vernier 1966

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 studies greyed out.

Study ID: Urizar and Vernier 1966 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	No	Exposure of bismuth was measured in plasma and urine. A pathology laboratory was used providing indirect evidence the result was likely part of routine commercial laboratory analysis which typically is validated against well-established methods.	--

9.	Outcome assessment	No	Outcome assessment was likely assessed using acceptable methods and is unlikely to have been biased as it was based on objective measures of kidney function and was diagnosed prior to knowing of the child's potential bismuth exposure. With respect to measurement of exposure, a pathology laboratory was used to measure bismuth in blood thereby providing indirect evidence the result was not appreciably biased by the assessor. There was no quality control sample or field duplicate sent in for analysis hence the reporting laboratory may have known to expect elevated bismuth in blood/urine.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	Only results for bismuth were reported. It is not clear whether other metals were analysed and what the results of such analysis was.	++
	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 (++)	++

Weller 1988

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 studies greyed out.

Study ID: Weller 1988 **Study Type: Case study (CaS)**		**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)	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	N/A	Missing outcome data: not applicable	
	Detection Bias			
8.	Exposure characterisation	Yes	Exposure of bismuth was not measured in biological fluids. Exposure reliant on self-reported administration of a Bi preparation. Insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used since ceasing the exposure resolved the symptoms.	+
9.	Outcome assessment	No	It is deemed that the outcome assessment methods used would not appreciably bias results, as the patient sought help from his doctor due to his symptoms and appeared unaware of the links between the medication he was taking and his symptoms. It is therefore deemed that lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	There is insufficient information provided about selective outcome reporting (NR)	NR
	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 (++)	++

APPENDIX E

Data extraction tables – Supporting Information for Fact Sheet

Supporting Information for Bismuth Fact Sheet

Hinwood et al. 2015

Reference: Hinwood A. L., Stasinska A., Callan A. C., Heyworth J., Ramalingam M., Boyce M., McCafferty P. and Odland J. (2015). Maternal exposure to alkali, alkali earth, transition and other metals: Concentrations and predictors of exposure. Environ Pollut 204: 256-263.		
General Description	Uses	Bismuth has been used in pharmaceuticals and cosmetics and has been found in low concentrations in biological and environmental samples including blood, urine, food and water.
	Sources in drinking water	Pharmaceuticals and cosmetics
	Other	This paper describes a cross-sectional study of persistent substance exposure in non-smoking pregnant women >18 yrs in Western Australia. Pregnant women were recruited between 2008-2011. 173 women provided a first morning void urine, 172 a whole blood sample and a drinking water sample. Each sample was analysed for numerous elements including bismuth. Concentrations: • Blood: Median <0.05 µg/L (<0.05-1.54 µg/L) – 91.9% <LOR • Urine: Median <0.005 µg/L (<0.005-0.321 µg/L) – 66.5% <LOR • Drinking water: Median <0.005 µg/L– 100% <LOR
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	ICP-MS (Agilent 7500cs-Octopole Reaction Cell, Agilent Technologies, USA)
	Limit of determination/ Limit of Reporting (LOR)	0.005 µg/L (in drinking water)
	Other	-
Additional information	Any additional non-health related information considered important?	-

Malassa et al. 2014

Reference: Malassa H., Al-Rimawi F., Al-Khatib M. and Al-Qutob M. (2014). Determination of trace heavy metals in harvested rainwater used for drinking in Hebron (south West Bank, Palestine) by ICP-MS. Environ Monit Assess 186(10): 6985-6992.		
General Description	Uses	-
	Sources in drinking water	Speculated sources in harvested water used for drinking: Uncontrolled burning of solid wastes in illegal waste dumping sites, where it is expected ashes and dust of these wastes is transported via wind to house roofs.
	Other	Study was conducted to measure heavy metals (including Bi) in harvested rainwater used for drinking in Hebron, Palestine (there is water scarcity in this area). Sampling was carried out in November 2012 where 44 water samples were collected from 44 house cisterns.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	ICP-MS (Agilent Technologies 7500 Series)
	Limit of determination/ Limit of Reporting (LOR)	LOR for Bi not provided.
	Other	Bi was detected in all samples with a concentration range of 1.33-96.52 µg/L.
Additional information	Any additional non-health related information considered important?	-

Vetrivel et al. 2017

Reference: Vetrivel S., Diptanghu M., Masto R., Sydavalli S., Nehru G. and Tiger K. (2017). Green algae of the genus Spirogyra: A potential absorbent for heavy metal from coal mine water. Remediation 27: 81-90.		
General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	Investigated treatment of coal mine water containing various heavy metals with the use of absorption with *Spirogyra.*

Reference: Vetrivel S., Diptanghu M., Masto R., Sydavalli S., Nehru G. and Tiger K. (2017). Green algae of the genus Spirogyra: A potential absorbent for heavy metal from coal mine water. Remediation 27: 81-90.		
	Effectiveness	Biosorption equilibrium study revealed Bi (amongst other metals) was maximally absorbed by algal biomass at 100% concentration from mine water. Bhowra Mine Water contained 0.1301 ppm Bi prior to treatment. This reduced to 0.044 ppm after treatment (i.e. ~76% reduction).
	Any special conditions?	-
	Other	-
Measurement	Analytical method	ICP-AES (Thermo Scientific iCAP 6000 series ICP-AES spectrometer [Cambridge, UK])
	Limit of determination/ Limit of Reporting (LOR)	LOR for Bi not provided.
	Other	-
Additional information	Any additional non-health related information considered important?	-

Xiong et al. 2017

Reference: Xiong X., Chen G., Zhu M., Li Y., Yang C., Xie K. and Zhu Z. (2018). The study of bismuth ions in drinking water at ultratrace levels by a microwave plasma torch coupled with linear ion trap mass spectrometry. Analytical Methods 10(11): 1346-1352.		
General Description	Uses	Bismuth is a rare and important element, widely used in several fields such as in metallurgy and in the cosmetics industry as an additive to creams and hair dyes. It also has specific properties in pharmaceutical preparations and can be used as an antiulcer, antibacterial, anti-HIV, and radiotherapeutic agent.
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Novel method using microwave plasma torch (MPT) ion source coupled with linear ion trap mass spectrometer (LTQ-MS).
	Limit of determination/ Limit of Reporting (LOR)	0.028 µg/L (i.e. ultratrace levels).
	Other	-

Reference: Xiong X., Chen G., Zhu M., Li Y., Yang C., Xie K. and Zhu Z. (2018). The study of bismuth ions in drinking water at ultratrace levels by a microwave plasma torch coupled with linear ion trap mass spectrometry. Analytical Methods 10(11): 1346-1352.		
Additional information	Any additional non-health related information considered important?	-

UK COT 2008

Reference:. UK COT (2008). The Al-Zn of element toxicity: A summary of the toxicological information on 24 elements. Tox/2008/29 Annex B. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). United Kingdom (UK COT).		
General Description	Uses	Bismuth has a long history of pharmaceutical use in Europe and North America as both the inorganic and organic salts.
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	*"In the USA, drinking water contains on average 0.01 mg/L [bismuth]"*
Additional information	Any additional non-health related information considered important?	-

Poursharifi and Moghimi 2011

Reference:. Poursharifi, M.J. and Moghimi, A. (2011). Determination of Ultratrace Amounts of Bismuth in Water Samples by Electrothermal Atomic Absorption Spectrometry (ET-AAS) After Cloud Point Extraction. Asian Journal of Chemistry; Vol. 23, No. 4 (2011), 1424-1428		
General Description	Uses	*"bismuth is used in the cosmetics industry for the preparation of creams and hair dyes, while some of its colloidal salts (subcitrate and subgallate), due to their antiseptic, astringent and diuretic properties, have important applications in pharmaceutical preparations and are employed as antiulcer, antibacterial, anti HIV and radiotherapeutic agents"*
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Electrothermal Atomic Absorption Spectrometry (ET-AAS)
	Limit of determination/ Limit of Reporting (LOR)	0.04 µg/L (from a 10 mL sample)
	Other	Bismuth levels in samples were as follows: • Tap water: 0.165±0.01 µg/L (from Saveh, Iran) • Rainwater: 0.399±0.01 µg/L (from Varamin, Iran)
Additional information	Any additional non-health related information considered important?	-

Al-Khatib et al. 2019

Reference:. Al-Khatib, I.A., Arafeh, G.A., Al-Qutob, M., Jodeh, S., Hasan, A.R., Jodeh, D., van der Valk, M. (2019). Health Risk Associated with Some Trace and Some Heavy Metals Content of Harvested Rainwater in Yatta Area, Palestine. Water 2019, 11, 238; doi:10.3390/w11020238.		
General Description	Uses	-
	Sources in drinking water	Naturally occurring through the weathering of rocks and soil erosion and anthropogenic sources (agricultural, mining and melting of minerals)
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-

Reference:. Al-Khatib, I.A., Arafeh, G.A., Al-Qutob, M., Jodeh, S., Hasan, A.R., Jodeh, D., van der Valk, M. (2019). Health Risk Associated with Some Trace and Some Heavy Metals Content of Harvested Rainwater in Yatta Area, Palestine. Water 2019, 11, 238; doi:10.3390/w11020238.		
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)
	Limit of determination/ Limit of Reporting (LOR)	Not stated (potentially 0.01 µg/L)
	Other	Concentrations reported in selected rainwater harvesting cisterns from five regions in rural areas of Palestine were as follows: • Al-Hadidya: 0.05 ± 0.07 µg/L • Al-Hila (n = 13): 0.05 ± 0.11 µg/L • Yatta Center (n = 21): 0.01 ± 0.02 µg/L • Khallet Salih (n = 13): 0.75 ± 1.8 µg/L • Khallet El Mayya (n = 15): 0.04 ± 0.08 µg/L (Refer to Table S1).
Additional information	Any additional non-health related information considered important?	No health-based guidance was available for Bismuth hence risk indices were not calculated. In Khallet Salih, intake from drinking water was 0.02 µg/kg/d for both adults and children (and an order of magnitude lower in other areas).

Jaiswal et al. 2019

Reference: Jaiswal, A.K., Solanki, S., Priya, A., Sehrawat, S., Kumar, R., Kumar, R. (2019). Bismuth Poisoning: With Analytical Aspects and its Management. International Journal of Medical Laboratory Research, Vol. 4 Issue 1, April 2019.		
General Description	Uses	"*Its alloys with tin or cadmium have low melting points and are used in fire detectors, electric fuses, solders and extinguishers*". "*It is used in the manufacture of cosmetics and pharmaceuticals, ceramic glazes, pearlescent pigments, permanent magnets and safety devices in fire detection and extinguishing systems*".
	Sources in drinking water	-
	Other	"Anthropogenic sources of bismuth include copper, lead, silver and gold smelting, wastewater and sewage sludge". "*The most common mineral ores are Bismuthinite (Bi2S3) and Bismite (α-Bi2O3)*".
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-

Reference: Jaiswal, A.K., Solanki, S., Priya, A., Sehrawat, S., Kumar, R., Kumar, R. (2019). Bismuth Poisoning: With Analytical Aspects and its Management. International Journal of Medical Laboratory Research, Vol. 4 Issue 1, April 2019.		
Measurement	Analytical method	UV-Visible Spectroscopy method, Atomic Absorption Spectrophotometry method (AAS), Ion Chromatography, Voltammetry/ Polarography method, Inductively Coupled Plasma Optical Emission Spectroscopy/ (ICE-OES), ICP Mass Spectrometry (ICP-MS) and Neutron Activation and Analysis (NAA)
	Limit of determination/ Limit of Reporting (LOR)	-
	Other	In natural water, concentrations of bismuth are found to be very low, usually less than 0.2 µg/L. No further details are provided for this statement, including region, type of water, or a reference for this statement.
Additional information	Any additional non-health related information considered important?	"*Over exposure to bismuth can lead to the formation of a black deposit on the gingiva. This is known as a bismuth line. Bismuth and its salts lead to kidney damage, although generally to a mild degree. However, large doses can be fatal, although industrially it is considered one of the less toxic heavy metals*".

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