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

Selenium Evaluation Report

Prepared for:

National Health and Medical Research Council

SLR Ref: 640.30609-R06
Version No: -v3.0
November 2023

PREPARED BY

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

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

BASIS OF REPORT

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

This report is for the exclusive use of the Client. No warranties or guarantees are expressed or should be inferred by any third parties. This report may not be relied upon by other parties without written consent from SLR.

SLR disclaims any responsibility to the Client and others in respect of any matters outside the agreed scope of the work.

DOCUMENT CONTROL

Reference	Date	Prepared	Checked	Authorised
640.30609-R06-v3.0 (FINAL)	23 November 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R06-v2.1 (UPDATED DRAFT, Track changes)	23 November 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R06-v2.0 (REVISED DRAFT)	20 July 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R06-v1.1 (REVISED DRAFT, Track changes)	20 July 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R06-v1.1 (DRAFT)	30 June 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen

EXECUTIVE SUMMARY

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

An initial Stage 1 review completed in July 2022 of published guidelines and guidance documents relevant to selenium identified five existing guidance/guideline values from six jurisdictions that were suitable to adopt/adapt based on an assessment of administrative and technical criteria. Potential adaptation of these similar guidance values would result in a health-based drinking water guideline (DWG) of 0.02 mg/L, which is higher than the current Australian DWG of 0.01 mg/L. However, the evidence scan undertaken for the Stage 1 review revealed a number of recently published studies which could potentially impact the conclusions made in the report. As a result, a targeted search and review of relevant primary studies published since 2010 (determined to be the cut-off date for the most recent agency review from Stage 1) was conducted as part of the Stage 2 report.

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

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

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

- High confidence in the evidence for selenium exposure and mild effects of selenosis (i.e. alopecia). A minimal Lowest Observed Adverse Effect Level (LOAEL) for this effect of 200 µg Se/day (as added selenium) is available.
- High confidence for no increase in prostate cancer incidence as a result of selenium exposure, and a possible association with Type 2 Diabetes (T2D). However, the information available is insufficient to inform a No Observed Adverse Effect Level (NOAEL) or LOAEL for T2D.
- Moderate confidence for no increase in mortality from cardiovascular disease, coronary heart disease or stroke as a result of selenium exposure.
- Low or very low confidence for the available evidence for other health outcomes (i.e. mortality from Parkinson's disease, increased cholesterol, amyotrophic lateral sclerosis, melanoma, urinary tract tumours, or multiple myeloma). The evidence is insufficient to derive a NOAEL/LOAEL for these effects.

There is insufficient information to inform the dose response of selenium exposure and T2D (the effect for which there is high confidence in the available evidence), therefore additional studies would be useful to inform this knowledge gap. Additional research is also likely required to clarify the importance of the chemical form of selenium on overall toxicity, and whether different forms are subject to a different dose-response curve.

EXECUTIVE SUMMARY

An adjusted minimal LOAEL of 255 µg Se/d selenium in the diet for mild alopecia in humans was considered relevant to the Australian context for potential adaptation. The candidate selenium DWG derived using this adjusted minimal LOAEL is 0.00425 mg/L (i.e. 4.25 µg/L). The majority of Australian distributed water contains relatively low selenium levels (i.e. typically <2 µg/L) which is lower than the candidate DWG. However, exposure to selenium may also theoretically occur from leaching of selenium from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for selenium from lead replacements in plumbing products be generated for Australian conditions to inform this matter. It is also noted there are some locations around Australia where source waters may contain higher selenium concentrations than measured in the majority of distributed water due to geological origin.

Based on the Stage 1 review results, the concentration of the revised candidate DWG of 0.00425 mg/L appears to be achievable with existing treatment technologies in distributed water and readily measurable with current commercial analytical techniques. Its achievability in waters at the tap is currently unknown due to lack of leachability data from lead replacements in plumbing products.

CONTENTS

DOCUMENT REFERENCES

TABLES

CONTENTS

FIGURES

Abbreviations/Definitions

Acronym	Definition
ACT	Australian Capital Territory
ALS	Amyotrophic Lateral Sclerosis
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
CaCo	Case-control
CaS	Case Study
CI	Confidence Interval
Co	Cohort
CrSe	Cross-sectional Study
CSF	Cerebrospinal Fluid
CVD	Cardiovascular Disease
DWG	Drinking Water Guideline
EFSA	European Food Safety Authority
EU	European Union
FSANZ	Food Standards Australia New Zealand
HCT	Human Controlled Trial
HR	Hazard Ratio
IRR	Incidence Rate Ratio
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg bw	Kilogram of Body Weight
LOAEL	Lowest Observed Adverse Effect Level
LOR	Limit of Reporting
mg/day	Milligrams per Day
NHANES	US National Health and Nutrition Examination Survey
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
NT	Northern Territory
OEHHA	Californian Office of Environmental Health and Hazard Assessment
OHAT	United States Office of Health Assessment and Translation
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QLD	Queensland
RoB	Risk of Bias
RR	Relative Risk

Acronym	Definition
Se	Selenium
SELECT	Selenium and Vitamin E Cancer Trial
SIR	Standardised Incidence Ratio
TAS	Tasmania
T2D	Type 2 Diabetes
The Committee	NHMRC Water Quality Advisory Committee
The Guidelines	NHMRC and NRMMC (2011). Australian Drinking Water Guidelines 6 2011; Version 3.8 updated September 2022, National Health and Medical Research Council and Natural Resource Management Ministerial Council, Commonwealth of Australia, Canberra.
µg/day	Micrograms per Day
US EPA	United States Environmental Protection Agency
VIC	Victoria
WHO	World Health Organization

1 Introduction and Background

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

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

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

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

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

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

The report herein is the Evaluation Report for selenium.

1.1 Objectives

Selenium has been identified as being used to replace lead-based alloys in plumbing. An initial Stage 1 review[1] of published guidelines and guidance documents relevant to selenium identified five existing guidance/guideline values from six jurisdictions that were suitable to adopt/adapt based on an assessment of administrative and technical criteria. Potential adaptation of these similar guidance values would result in a health-based drinking water guideline (DWG) of 0.02 mg/L, which is higher than the current Australian DWG of 0.01 mg/L. However, the evidence scan undertaken for the Stage 1 review revealed a number of recently published studies which could potentially impact the conclusions made in the report. As a result, a targeted search and review of relevant primary studies published since 2010 (determined to be the cut-off date for the most recent agency review from Stage 1) was conducted as part of this Stage 2 report.

The overarching objective of this Stage 2 review is to identify relevant information on the impact of exposure to selenium in drinking water at levels lower than the current health-based guideline value on human health outcomes.

2 Research Questions

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

Table 1 Research Questions for Evidence Evaluation of Selenium

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

[1] Results of this review are summarised in SLR Reports entitled *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Selenium Technical Report* (640.30242-R17-v2.0) and *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Selenium Evaluation Report* (640.30242-R18-v2.0).

[2] This aspect was already covered in SLR Report entitled *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Selenium Technical Report* (640.30242-R17-v2.0) and *Evidence Evaluations for Australian Drinking Water Guideline Chemical Fact Sheets: Selenium Evaluation Report* (640.30242-R18-v2.0).

#	Research Questions
11	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review or further research?

3 Methodology Overview

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

- An update of the targeted literature search of existing health-based guidance/guidelines to capture any new information published since the search undertaken for the Stage 1 investigation (i.e. from 2021-2023). Jurisdictions included in this search were those previously identified by ToxConsult (2019) as providing reliable information and meeting a large proportion of pre-determined technical and administrative criteria. They included the World Health Organization (WHO) including the Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), United States Environmental Protection Agency (US EPA), US Agency for Toxic Substances and Disease Registry (ATSDR), Californian Office of Environmental Health and Hazard Assessment (OEHHA), Food Standards Australia New Zealand (FSANZ), and the Australian Pesticides and Veterinary Medicine Authority (APVMA).
- An additional literature search was undertaken in two scientific databases for published studies relevant to addressing the health-related research questions. A full review of the literature was undertaken (as opposed to simply undertaking an evidence scan for any recent health-based information that could impact the guidance/guideline value).

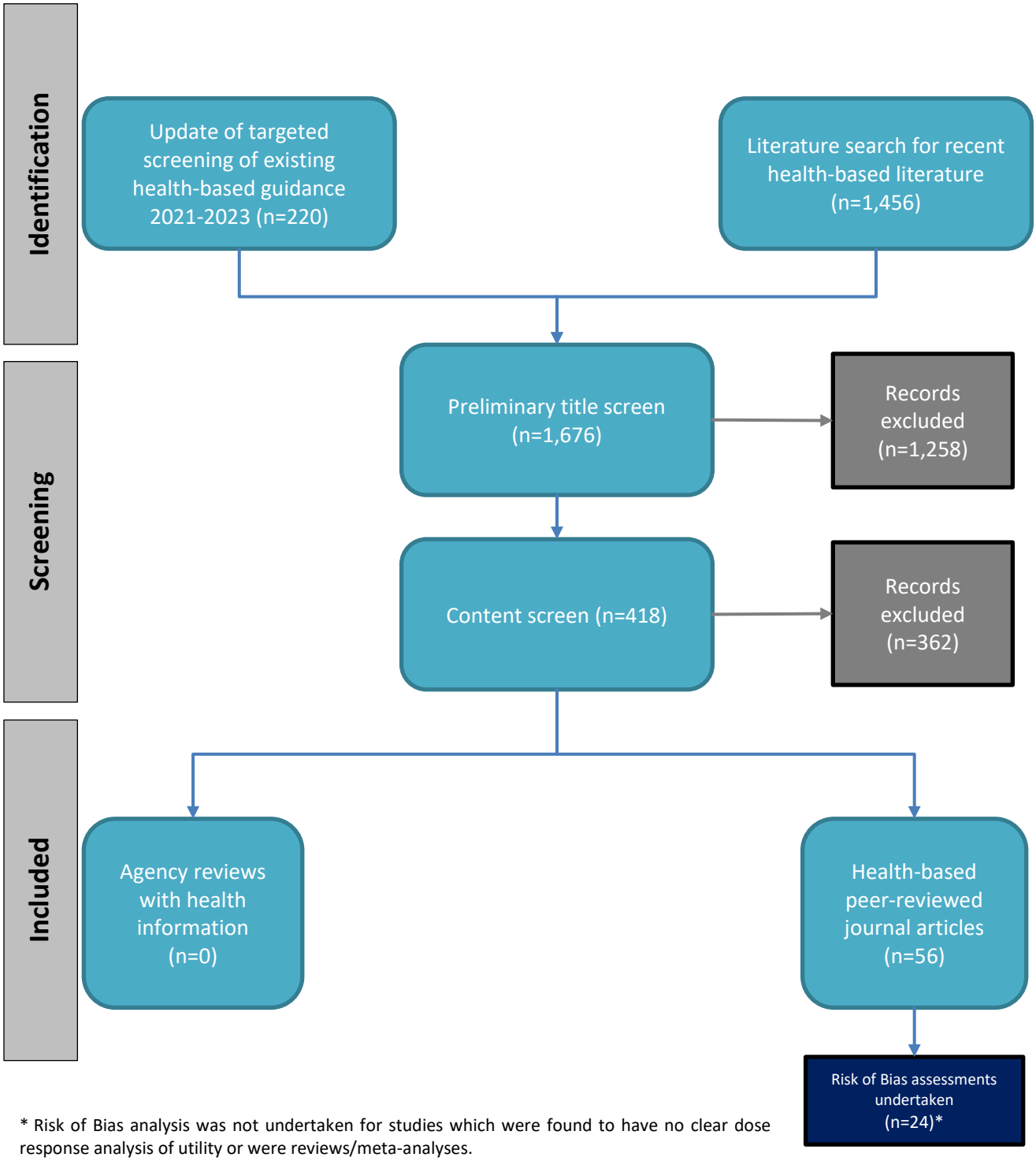
Results were subjected to the following steps in order to identify the most relevant information:

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

Relevant data were extracted by populating various pre-constructed tables which focused on data needed to answer the research questions. Synthesis was conducted by presenting summarised extracted data in tabular format for each individual research question. All critical studies deemed relevant for defining the critical adverse health effects and/or dose response of selenium were subjected to a risk of bias (RoB) assessment with the use of a RoB tool (i.e. modified Office of Health Assessment and Translation, or OHAT, tool). Outcomes of these assessments were provided as a RoB rating. The reader is referred to the accompanying Technical Report for the detailed methodology, records of the literature screening process (including all records that were excluded) and all data extraction and RoB tables. This Evaluation Report also presents summary tables for the following:

- Doses of selenium associated with no adverse effects and potential critical adverse health effects. This was presented along with summaries of study bias/quality for each health endpoint.
- Overall certainty of evidence for different health endpoints / evidence streams where possible. This considered the overall confidence of the body of evidence with regard to RoB, indirectness/applicability, imprecision, inconsistency between studies and publication bias.

Figure 1 shows an overview of the literature search process followed for selenium. 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 have no clear dose response analysis of utility or were reviews/meta-analyses.

Figure 1 Overview of literature search process followed for Selenium

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

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

Guideline value (mg/L) =

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

……**Equation 1**

Note where the dose in the equation in humans was in the form of mg/day, the human weight is not required in the equation.

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

4 Results

The January 2021- January 2023 update of targeted screening of existing health-based guidance identified no existing health-based guidance/guideline values for selenium additional to those already identified in the Stage 1 reports. Responses to research questions were therefore informed by the data extractions conducted for the various cross-sectional (CrSe), cohort (Co), case-control (CaCo), human controlled trial (HCT), and case studies (CaS) found in the literature reviewed.

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

4.1 Health-based aspects

Research Questions 1-7 all cover health-based aspects of the review; this is considered to be the central information in the factsheet. **Table 2** provides a synthesis of the results.

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

#	Research Questions	Response
1	What level of selenium in drinking water causes adverse health effects?	No additional existing health-based guideline values were found for selenium in drinking water. However, Vinceti et al. (2013a), in a review of available information conclude that the European Union (EU) drinking water standard of 10 µg/L (and 2011 WHO guideline of 40 µg/L) are likely too high to protect against chronic adverse health effects of inorganic Se exposure. The authors suggest a value of 1 µg/L would be protective as more research is gathered. The Vinceti et al. (2013a) paper, along with other recently published literature, has been reviewed and considered as part of this Stage 2 report. The value of 1 µg/L suggested by Vinceti et al. (2013a) was considered inappropriate for adoption/adaption due to the very low confidence in the studies underpinning this value and derivation (see also **Section 5.1** and **5.2**). Most studies sourced in the review did not specifically investigate the effects of Se in drinking water, with the exception of an Italian research group (led by Vinceti) which published numerous papers on the same retrospective cohort from Reggio Emilia in Italy where the 'exposed' population were exposed to Se in their drinking water at levels of 8-10 µg/L (due to naturally occurring selenate in the water) compared with the 'unexposed' population from the wider community where Se concentrations were <1 µg/L. The research group investigated associations with a wide variety of endpoints, including motor neuron disease (including amyotrophic lateral sclerosis or ALS), Parkinson's, and various cancers. They found some statistically significantly positive associations, but frequently these were accompanied by wide confidence intervals. An additional small-scale case control study (Bagherzadeh et al. 2022) found no association between Se in drinking water (3 µg/L) and ulcerative colitis. The other studies in the review included several HCTs (e.g. Evans et al. 2019, Mix et al. 2015, Walsh et al. 2021, Stranges 2007, Stranges et al. 2010; Thompson et al. 2016, Lippman et al. 2009, Karp et al. 2013, Klein et al. 2011, Lance et al. 2017) where Se was administered as a supplement (either as selenomethionine or a Se-containing yeast) to people at risk of developing cancer to study its potential protective effect for cancer prevention. The studies investigated various health endpoints, and some found statistically significant associations between certain endpoints and Se exposure at 200 µg/day (typically the only dose tested). This dose has been considered a minimal LOAEL and has been used to derive a candidate guideline value for Se in drinking water in **Section 5.2.2**.

#	Research Questions	Response
2	What is the endpoint that determines this value?	None of the publications consulted apart from Vinceti et al. (2013a) have specifically proposed a new health-based guidance/guideline value for Se in drinking water/diet. Vinceti et al. (2013a) suggest a value of 1µg/L (as selenate) would be protective of recent research on ALS and several site-specific neoplasms in the Italian cohort from Reggio Emilia (uncertainty factor of 10 applied to concentration where effects have been noted at ~8-10 µg/L). According to the other publications, positive statistically significant associations have been found for several adverse effects that have investigated the association with serum Se, Se intake, and/or Se in drinking water. These include the following (see also response to Research Question 1): • Selenosis at ~40.8 mg/day (Aldosary et al. 2012, MacFarquhar et al. 2010) • Mild alopecia and dermatitis (potential effects of selenosis) at 200 µg/day (as selenomethionine) (Rees et al. 2013, Lippman et al. 2009) • Prostate cancer at 200 µg/day (as selenomethionine) (Kristal et al. 2014). • Type 2 Diabetes at 200 µg/day as Se-containing baker's yeast tablet (Vinceti et al. 2018c, Stranges 2007, Stranges et al. 2010). • Amyotrophic lateral sclerosis (ALS) at 8 µg/L in drinking water (or at ≥1 µg/L) (Vinceti et al. 1996, 2010a, 2013b, 2016, 2019). • Melanoma at 8 µg/L in drinking water (Vinceti et al. 2018a) and at higher plasma Se concentrations (Vinceti et al. 2012). • Urinary tract tumours at 8 µg/L in drinking water (Vinceti et al. 2018a). • Multiple myeloma and Parkinson's disease at 8 µg/L in drinking water (Vinceti et al. 2016). • Increased cholesterol (risk factor for cardiovascular disease or CVD) at higher serum Se (Lacaustra et al. 2010).
3	Is the proposed option for a health-based guideline value relevant to the Australian context?	No additional proposed health-based guideline values apart from those in the Stage 1 reports have been found in the Stage 2 searches, with the exception of a suggestion from Vinceti et al. (2013a) that the guideline value should be lowered to 1 µg/L. If this suggested guideline value (or the updated candidate guideline value of 4.25 µg/L derived in **Section 5.2.2** of this report) were adopted in Australia, they are considered relevant to the Australian context.
4	What are the key adverse health hazards from exposure to selenium in Australian drinking water?	As indicated in the response to Research Question 1, adverse health hazards from exposure to inorganic Se in Australian drinking waters may include a few endpoints (i.e. ALS, multiple myeloma, urinary tract tumours, and melanoma) for which positive associations have been observed in a series of cohort studies (studying the same Italian cohort) by a research group at Se concentrations in drinking water ≥ 1 µg/L or 8-10 µg/L. However, this is tempered by the overall confidence in these studies which was found to be VERY LOW (see **Section 5.1** and **5.2.1**). Other potential adverse health hazards associated with ingestion of Se supplements (as selenomethionine or Se-containing baker's yeast at 200 µg/day) in large HCTs include mild signs of selenosis in the form of mild alopecia (and dermatitis), and potential associations with prostate cancer and type 2 diabetes. This is also tempered by the overall confidence in these studies (see **Section 5.1** and **5.2.1**).
5	Are there studies quantifying the health burden (reduction or increase) due to selenium?	Yes. See response to Research Question 1. Some epidemiological information (albeit limited) suggests a potential protective effect of Se in the diet/drinking water in relation to some crude health endpoints (e.g. longevity, congenital heart defects, and others not necessarily subjected to detailed data extraction), whereas other information suggests a potential detrimental effect of Se in diet/drinking water.

#	Research Questions	Response
6	What is the critical human health endpoint for selenium?	See response to Research Question 2. The critical human health endpoint for Se exposure is uncertain due to important HCTs often only including a single dose of Se and crude exposure stratification (i.e. ≥1 vs. <1 µg Se/L in drinking water) in the cohort drinking water studies by the Vinceti research group. The critical human health endpoint of selenosis (as evidenced by mild alopecia in one of the largest HCTs conducted with selenomethionine) may still be appropriate or it may be one of the other endpoints investigated in HCTs and/or cohort studies. The largest confidence exists for the mild selenosis endpoint observed in one of the HCTs as more severe effects of the same type are recognised to occur at higher doses of Se in the diet (see **Section 5.2.1**).
7	What are the justifications for choosing this endpoint?	

4.2 Exposure-related aspects

Another important aspect of the fact sheet covers exposure-related considerations. This is important for consideration of whether exposures by Australians to the chemical evaluated are potentially approaching a health-based guidance value that will be used for deriving a candidate DWG. It is also important for considerations of whether typical levels of the chemical considered in Australian drinking water supplies would adhere to any derived DWG. Research Questions 8-9 cover exposure-related aspects of the review; it is noted the response to Research Question 8 stems from the Stage 1 reports. **Table 3** provides a response to the exposure-related research questions.

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

#	Research Questions	Findings
8	What are the typical selenium levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought? (note this aspect was already covered in previous reports as part of the Stage 1 review)	As per Stage 1 reports: ACT, VIC: <0.001 mg/L (<1 µg/L) QLD: <0.002 mg/L (<2 µg/L) NT: mean range <0.0002 – 0.012 mg/L (<0.2 - 12 µg/L) (high values reported at Kings Canyon and Daly Waters). TAS: mean range <0.0001 – 0.0025 mg/L (<0.1 – 2.5 µg/L) In certain situations (e.g. drought), Se concentrations may be higher (OEHHA 2010).
9	Are there any data for selenium levels leaching into water from in-premise plumbing?	One study (Zietz et al. 2015) was identified in the literature review which investigated in which amount abundant metals were released from different parts of domestic installations (i.e. old lead pipes and valves rather than lead-replacements) into cold tap water. Se was not measured in amounts above the limits of quantification (<0.5 µg/L). However, no relevant data for selenium leachability from low-lead plumbing replacements was found in literature consulted. It is suggested that leachability data for selenium from lead replacements in plumbing products be generated for Australian conditions to provide information on the species of selenium in water and in leachates from lead replacements (as well as form that leaches out) and exposure concentrations.

4.3 Risk-based aspects

Research Questions 10 and 11 are risk-based considerations. The publications subjected to detailed data extraction mentioned at the start of **Section 4** were also consulted to answer these questions. **Table 4** presents a summary of the findings.

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

#	Research Questions	Findings
10	What are the risks to human health from exposure to selenium in Australian drinking water?	The various papers by the Italian research group led by Vinceti express concerns with respect to the human health risks from exposure to Se in drinking water. The review by Frisbie et al. (2015) also expresses concerns and a need to re-evaluate the WHO (2011) drinking water guideline for Se in light of recent studies. Since the publication of the WHO (2011) drinking water guideline for Se, there have been various additional publications in the form of large HCTs, epidemiological investigations (primarily retrospective cohort and cross-sectional studies) and meta-analyses of these studies which have investigated associations between Se intakes (or Se concentration in drinking water in a specific Italian cohort) and various health endpoints. **Section 5.2.1** provides an overall evaluation of the confidence in the data for individual health endpoints. Based on this evaluation, the candidate guideline value for Se presented in the Stage 1 report (i.e. 20 or 3 µg/L, depending on whether the recent information is included) was revised to 4.25 µg/L (see **Section 5.2.2**). Vinceti et al. (2013a) suggest a lower guideline value of 1 µg/L for Se in drinking water should apply. As the majority of drinking water supplies in Australia contain relatively low Se levels (i.e. typically <2 µg/L), the human health risks from exposure to Se in Australian distributed drinking water supplies are likely low even if the suggested candidate guideline of 4.25 µg/L were adopted. It is noted, however, there are some locations around Australia where source waters may contain higher Se concentrations due to geological origin. It is also noted exposure to selenium may also theoretically occur from leaching of selenium from low-lead plumbing materials although no leachability data were found in the literature search undertaken to enable confirmation of potential exposures. Therefore the human health risks from exposure to selenium at the tap are technically unknown. It is suggested that leachability data for selenium from lead replacements in plumbing products be generated for Australian conditions to inform this.

#	Research Questions	Findings
11	Is there evidence of any emerging risks that require review or further research?	There is a suggestion in the various papers published by the Italian research group led by Vinceti (e.g. Vinceti et al. 2010b, 2013a) that inorganic Se (in the form of selenate) may be ~40 times more toxic than the organic forms generally found in the diet, especially with respect to ALS. Contrasting information from MacFarquhar et al. (2010) states that ingestion of organic Se in the form of selenomethionine is associated with much higher serum Se concentrations than ingestion of inorganic forms. Similarly in the study by Mandrioli et al. (2017), relative risk (RR) of ALS was not statistically significant for any form of Se in cerebrospinal fluid (CSF) apart from selenomethionine, again suggesting organic Se may be more potent. In a study by Vinceti et al. (2013b), RR of ALS was not statistically significant for any of the Se species (organic or inorganic) using Se concentrations in CSF, apart from an apparent protective effect of total organic Se. This conflicting information suggests that additional research is likely required to clarify the importance of the chemical form of Se on overall toxicity, and whether different forms are subject to a different dose-response curve.

5 Discussion

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

Individual RoB assessments were summarised in tables for each reported health outcome. Overall RoB ratings for each health outcome were determined using guidance from OHAT (2019) and considered alongside unexplained inconsistency, indirectness, imprecision, publication bias, magnitude of effect, and residual confounding to determine overall confidence ratings.

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

5.1.1 Selenosis

In the Stage 1 reports, it was found that the various jurisdictions which had derived guidance/guideline values for selenium agreed that the critical health endpoint for selenium exposure is selenosis, manifested as brittle hair, nail damage (i.e. loss of fingernails) and in extreme cases, neurological disturbances. The Stage 2 review found additional support for selenosis type effects from the following:

- Two case report summaries (CaS) (Aldosary et al. 2012, MacFarquhar et al. 2010) where symptoms of selenosis were observed in individuals (n=9 and n=227, respectively) after 10-~60 days' consumption of a liquid dietary supplement containing high amounts of selenium due to a formulation error. The daily dose ingested by each individual was 40.8 mg/day (i.e. ~100x the upper safe limit specified by WHO 2011). As the dose of selenium ingested by individuals in these cases was much greater than the dose on which the candidate guidelines were based in Stage 1 (i.e. 0.4 mg/day), these studies would not change any of the outcomes of that report, and therefore were not subjected to RoB assessment.
- A large (n=32,400 men; Se group n=8,752) randomised, double-blind, placebo-controlled HCT referred to as the SELECT trial (Lippman et al. 2009, also included in a subsequent meta-analysis by Rees et al. 2013) which found marginally statistically significant hazard ratios at 200 µg Se/day (from selenomethionine) for two mild adverse events that could potentially be early indications of selenosis:
    - 1.28 for alopecia grade 1-2 (n=265; CI, 1.01–1.62) (not significant for nail changes).
    - 1.17 for dermatitis grade 1-2 (n=605; CI, 1.00-1.35) (not significant for dermatitis grade 3-4).

  The study was concluded to have low RoB (i.e. 'not likely') (see **Table 5** below). Since this study could have a potential impact on the Stage 1 conclusions, the overall confidence rating for this evidence was considered below.

Table 5 RoB summary for Lippman et al. 2009 study

Health outcome:	**Mild effects of selenosis (i.e. alopecia)**
Study ID:	**Lippman et al. 2009**
Selection bias	
Randomization	--
Allocation concealment	NR [3]
Comparison groups appropriate	
Confounding bias	
Confounding (design/analysis)	
Performance Bias	
Identical experimental conditions	
Blinding of researchers during study?	--
Attrition/Exclusion Bias	
Missing outcome data	--
Detection Bias	
Exposure characterisation	NR [1]
Outcome assessment	-
Selective Reporting Bias	
Outcome reporting	--
Other Sources of Bias	
Other threats	
Overall risk of bias across studies (not likely/serious/very serious)	Not likely [2]

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

1. Although there was insufficient information provided about the validity of the exposure assessment method (i.e. no information on purity of the chemical administered), there is no evidence for concern.
2. Based on meeting the criteria of low RoB for most of the key domains. Although information was not reported for a couple domains (i.e. allocation concealment and exposure characterisation), this was not of concern to the study outcomes.
3. This was conservatively assigned 'NR', however due to the study design, lack of adequate allocation concealment may not appreciably bias results. Thus, bias for this domain could potentially be interpreted as 'probably low RoB' instead of 'NR'.

The initial confidence rating for the mild selenosis effects observed in the SELECT HCT is considered high, since there was controlled exposure, exposure occurred prior to measuring the outcome, individual outcome data were assessed, and a comparison (i.e. placebo) group was used. **Table 6** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'high'.

Table 6 Confidence Rating for Lippman et al. 2009 findings in relation to selenosis

Health outcome (number of studies)	**Mild effects of selenosis (i.e. alopecia)** (1)	**Comment** [1]
Initial confidence rating	**HIGH**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence		
Risk of Bias	Not serious.	Confidence not downgraded since RoB is 'not likely' (**Table 5**).
Unexplained inconsistency	Not serious.	There is consistency in the effect in terms of selenosis being the critical health effect on which guidance/guideline values identified in the Stage 1 review are based. This HCT does suggest minimal effects may occur at lower doses than previously thought. The case reports identified in this Stage 2 review also lend support that more severe selenosis effects occur at much higher doses of dietary Se. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	No large standard deviations or large ratios for RR [95% confidence interval (CI) for grade 1-2 alopecia 1.01-1.62; for grade 1-2 dermatitis 1.0-1.35]. Confidence not downgraded.
Publication bias	No.	Although some of the study authors report serving as consultants or expert witnesses to some pharmaceutical companies, the study authors have declared all potential conflicts of interest and come from a wide variety of affiliations as would be expected for such a large HCT. Confidence not downgraded.
Factors Increasing Confidence		
Magnitude	Not large.	Magnitude of effect is not large (RR 1.28 and 1.17), so confidence not upgraded for large magnitude of effect.
Dose response	No.	HCT consisted of only a single dose of Se supplement, therefore no dose response was found, except when considering the case control studies and other studies forming the basis of candidate guidance / guideline values derived in the Stage 1 report where more severe effects of selenosis have been observed at higher doses of Se in the diet. Confidence not upgraded.
Residual confounding	No.	No residual confounding identified. Confidence not upgraded.
Consistency across species	Yes. Cannot be upgraded further.	Selenosis has been reported in case reports where high doses of Se as a supplement were ingested repeatedly, as well as other studies which form the basis of considerations in the Stage 1 report. Confidence of HCT is already **HIGH** and cannot be upgraded further.
Final confidence rating	**HIGH**	

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

5.1.2 Prostate cancer

The studies summarised in **Table 7** investigated the association between selenium administration (as selenomethionine or selenium-containing yeast) or selenium concentration in toenails and the incidence of prostate cancer. The table presents the study findings. Three of the five studies summarised in **Table 7** analysed data from the same HCT (the large SELECT trial) with none finding a statistically significant increase in prostate cancer in the subgroup given a selenium supplement only, whereas one of the three studies (Kristal et al. 2014) found a marginally significant increase in the fifth quintile for 'any selenium vs. placebo' (which includes the selenium + Vitamin E combination group). The remaining studies were for different HCTs which did not find a decrease (nor an increase) of prostate cancer incidence in a small group of patients given selenium supplements.

Table 7 Summary of studies on selenium and risk of prostate cancer

Study	Findings	Dose of selenium (µg/day)
Case-cohort: Kristal et al. 2014 (used HCT data)	SELECT randomised, double-blinded, placebo-controlled HCT of 34,887 men with a risk of getting prostate cancer. Four treatment groups: selenium (n=8,752), vitamin E (n=8,737), both agents (n=8,702), or placebo (n=8,696). Found Se supplementation (at 200 µg Se/day as selenomethionine) significantly (noting statistical significance was marginal) increased risk of high-grade (but not low-grade or total) prostate cancer among men with higher Se status (as measured by toenail Se concentrations). The hazard ratio [95% confidence interval (CI) adjusted for age and race was 1.96 (1.00,3.86) for the fifth quintile (toenail Se of ≥ 1.003 µg/g) for 'any selenium vs. placebo' (sub-cohort n=2,325, case patients n=360][3]. It is noted that none of the hazard ratios for the 'selenium only' group was statistically significantly elevated compared to placebo.	200 (as selenomethionine)
HCT: Klein et al. 2011	SELECT randomised HCT (as per above). No statistically significant increase in prostate cancer in groups taking Se when comparison was made between placebo and the whole group (not with respect to toenail Se, just treatment subgroup). Hazard ratios (99% CI) were 1.09 (0.93, 1.27; n=575) for Se only and 1.05 (0.89, 1.22; n=555) for Se and vitamin E.	200 (as selenomethionine)
HCT: Lippman et al. 2009	SELECT randomised HCT (as per above). No statistically significant differences in the absolute numbers (nor 5-year [median follow-up] incidence rates) of prostate cancer diagnoses between the four treatment arms. There was a statistically non-significant increase (p = 0.06; HR=1.13; 99% CI, 0.95-1.35; 95% CI, 0.99-1.29) in prostate cancer incidence in the vitamin E-alone arm (versus placebo), but not in the combination arm (p=0.52; HR=1.05; 99% CI, 0.88-1.25; 95% CI, 0.91-1.20). The 99.0% CIs around the hazard ratios were 0.87–1.24 for Se, 0.95–1.35 for vitamin E, and 0.88–1.25 for the combination.	200 (as selenomethionine)
HCT: Marshall et al. 2011	Randomised, double-blind, placebo-controlled HCT that investigated the effect of 200 µg/day Se supplementation as selenomethionine on the risk of prostate cancer and high-grade prostate intraepithelial neoplasia (HGPIN) (n=212 Se subgroup, n=211 placebo). The study found no significantly reduced (or increased) prostate cancer risk in the Se vs. placebo patients (95% CI for different serum Se concentration quartiles spanning 0.4-2.78).	200 (as selenomethionine)

[3] 'Any' selenium includes both the 'selenium only' subgroup and the subgroup given selenium + Vitamin E.

Study	Findings	Dose of selenium (µg/day)
HCT: Algotar et al. 2013a	Randomised, double-blind, placebo-controlled HCT (n=232 placebo, n=234 Se 200 µg/day, n=233 Se 400 µg/day) for 3-4 years. The hazard ratios (95% CI) for risk of developing prostate cancer in the Se 200 µg/day or the Se 400 µg/day group were 0.94 (0.52, 1.7) and 0.90 (0.48, 1.7) respectively.	200 or 400 (as Se-containing yeast)
HCT = Human controlled trial. CI = Confidence Interval.		

A RoB summary table for the included studies for the prostate cancer health outcome is presented in **Table 8** below. An overall RoB rating of 'not likely' was determined for the prostate cancer health outcome based on probably low or definitely low RoB across the majority of key domains and across the majority of studies.

Table 8 RoB summary table for studies investigating an association between selenium exposure and prostate cancer

Health outcome:	Prostate cancer				
Study ID:	**Kristal et al. 2014 (Co)**	**Klein et al. 2011 (HCT)**	**Lippman et al. 2009 (HCT)**	**Marshall et al. 2011 (HCT)**	**Algotar et al. 2013a (HCT)**
Selection bias					
Randomization		-	--	-	-
Allocation concealment		--	NR (3)	-	--
Comparison groups appropriate	--				
Confounding bias					
Confounding (design/analysis)	NR				
Performance Bias					
Identical experimental conditions					
Blinding of researchers during study?		--	--	-	--
Attrition/Exclusion Bias					
Missing outcome data	-	NR	--	--	--
Detection Bias					
Exposure characterisation	NR (1)	NR (1)	NR (1)	NR (1)	NR (1)
Outcome assessment	-	-	-	-	-
Selective Reporting Bias					
Outcome reporting	--	-	--	--	-
Other Sources of Bias					
Other threats					
Overall risk of bias across studies (not likely/serious/very serious)	Not likely (2)				

-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB. Co = Cohort. HCT = Human controlled trial.

1. Although there was insufficient information provided about the validity of the exposure assessment method (i.e. no information on purity of the chemical administered), there is no evidence for concern.
2. Based on probably low or definitely low RoB across the majority of key domains and across the majority of studies.
3. This was conservatively assigned 'NR', however due to the study design, lack of adequate allocation concealment may not appreciably bias results. Thus, bias for this domain could potentially be interpreted as 'probably low RoB' instead of 'NR'.

The initial confidence rating for the studies investigating an association between selenium exposure and prostate cancer is considered 'high', since there was controlled exposure, exposure occurred prior to measuring the outcome, individual outcome data were assessed, and a comparison (i.e. placebo) group was used. **Table 9** shows an assessment of the confidence in this body of evidence, with a final confidence rating of 'high'.

Table 9 Confidence Rating for HCT findings in relation to prostate cancer and selenium exposure

Health outcome (number of studies)	**Prostate cancer** (5)	**Comment** [1]
Initial confidence rating	**HIGH**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence		
Risk of Bias	Not serious.	Confidence not downgraded since overall RoB across studies for this endpoint is 'not likely' (see **Table 8**).
Unexplained inconsistency	Not serious.	Inconsistency between the findings of the analysis by Kristal et al. (2014) of the prostate cancer outcomes of the SELECT HCT compared to the other two studies can potentially be explained by the use of toenail Se concentrations, rather than serum/intake. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	No large standard deviations or large ratios for RR [95 or 99% CI for the studies are 1.00-3.86 (Kristal et al. 2004), 0.93-1.27 (Klein et al. 2011), 0.87–1.24 (Lippman et al. 2009), 0.4-2.78 (Marshall et al. 2011), 0.48-1.7 (Algotar et al. 2013a)]. Confidence not downgraded.
Publication bias	Undetected.	Although some of the study authors report serving as consultants or expert witnesses to some pharmaceutical companies, the study authors have declared all potential conflicts of interest and come from a wide variety of affiliations as would be expected for such HCTs. Confidence not downgraded.
Factors Increasing Confidence		
Magnitude	Not large.	Magnitude of effect in Kristal et al. (2004) is not large (RR of ~1.96) (the other studies found no significant effect), so confidence not upgraded for large magnitude of effect.
Dose response	No.	HCTs consisted of only a single dose of Se supplement, therefore no dose response was found. Confidence not upgraded.
Residual confounding	No.	No residual confounding identified. Confidence not upgraded.
Consistency across species	N/A	Only HCTs are available to assess the effect on prostate cancer. Consistency across species, dissimilar populations and/or study types can therefore not be judged. Confidence not upgraded.
Final confidence rating	**HIGH**	-

1. As per guidance provided in OHAT (2019, Table 7)
2. Although Kristal et al. (2014) is a case-cohort study according to the study authors, it uses information obtained in a HCT (the SELECT trial), which also involved controlled exposure, hence a high initial confidence rating has been assigned to all studies investigating the prostate cancer health outcome.

Only one of the five studies (of which three examined the same trial cohort) found a marginally statistically significant (95% CI 1.00-3.86 for the fifth quintile toenail Se of ≥ 1.003 µg/g) association between Se (in toenails) and prostate cancer risk and none of the hazard ratios for the 'selenium only' group was statistically significantly elevated compared to placebo. This is considered insufficient evidence to conclude that exposure to selenium can increase the risk of prostate cancer.

5.1.3 Type 2 diabetes (T2D)

The studies summarised in **Table 10** investigated the association between selenium administration (as selenium-containing baker's yeast) and the incidence of Type 2 diabetes (T2D). The table presents the individual study findings. A visual summary of the findings is also provided in **Table 11**, which clearly shows inconsistent findings with some positive associations and other studies finding no significant association.

Table 10 Summary of studies on selenium and risk of Type 2 diabetes

Study	Findings	Dose of selenium (µg/day)

Meta-analysis: Vinceti et al. 2018c [1]	In this meta-analysis (10 non-experimental cross-sectional and cohort studies and 5 HCTs), the authors found:
	• Increased RR in non-experimental studies with plasma or serum Se concentration when compared to reference (<45 µg/L):
	  ○ 90 µg/L: 1.5 (95% CI 1.2–2.1)
	  ○ 140 µg/L: 3.6 (95% CI 1.4–9.4)
	• A statistically significant increased risk of the disease in HCTs overall (RR 1.11, 95% CI 1.01-1.22) where Se was administered at 200 µg/day. RR for individual HCTs were as follows:
	  ○ Thompson et al. 2016: 1.25 (0.74, 2.09)
	  ○ Lippmann et al. 2009: 1.19 (0.61, 2.35)
	  ○ Algotar et al. 2013b: 1.69 (0.68, 4.21)
	  ○ Karp et al. 2013: 1.08 (0.97, 1.19)
	  ○ Stranges 2007: 1.49 (1.01, 2.20)
	• Conclusion on overall risk seems unusual since Lippman et al. (2009) consists of the largest HCT cohort (SELECT trial) and 4 out of 5 studies cited did not find a significant increase.
	• The authors state they found a higher RR for women than men; however, inspection of the results show they have a similar range (1.01 – 1.69 for men and 1.09 – 1.87 for women). Further, RRs were not statistically significant in three out of three HCTs for women and four out of the five HCTs for men. The overall value for women [RR = 1.43 (0.74, 2.77)] was not statistically significant whereas it was for men [RR = 1.10 (1.00, 1.21)]. This potentially suggests some bias in reporting of results.
		Non-experimental (unknown)
		
		200 (as Se supplement, either Se-containing year or selenomethionine, see details in rows that follow)

HCT: Thompson et al. 2016	Randomised, placebo-controlled HCT investigated whether Se supplementation prevents colorectal adenomas (200 µg/day Se as Se-containing yeast for 6 months) (n=287 placebo, n=284 supplement). Results: • In participants receiving Se, new-onset T2D RR = 1.25 (95% CI 0.74 to 2.11, P =.41). • Statistically significantly increased risk of Se-associated T2D among older participants RR = 2.21; 95% CI 1.04 to 4.67, P =0.03.	200 (as Se-containing yeast)

Study	Findings	Dose of selenium (µg/day)
HCT: Lippman et al. 2009	SELECT HCT (randomised, double-blinded, placebo-controlled) (n=8,696 placebo, n=8,752 Se, n=8,737 vitamin E, n=8,703 combination). A statistically non-significant increase in T2D (diagnosed after randomisation) occurred in the Se-alone arm vs. placebo: 724 (10.0%; 99% CI, 9.1%–11.0%) vs. 669 (9.3%; 99% CI 8.5%–10.2%), respectively (RR=1.07, 99% CI 0.94 – 1.22, p = 0.16). The number (percentage) of cases of T2D was 700 (9.7%; 99% CI 8.8%–10.6%) on vitamin E and 660 (9.1%; 99% CI 8.2%–10.0%) on the combination; p-values of these figures compared with placebo T2D were 0.47 (vitamin E) and 0.61 (combination).	200 (as selenomethionine)
HCT: Algotar et al. 2013b	Randomised, double-blind, placebo-controlled HCT (n=232 placebo, n=234 Se 200 µg/day, n=233 Se 400 µg/day) for 3-4 years. Followed every 6 months for up to 5 years. Changes in serum glucose levels during the course of the trial did not differ significantly between the placebo and selenium 200 µg/day (P = 0.98) and 400 µg/day (P = 0.81) groups. These results do not support a relationship between Se supplementation and risk of diabetes. It is noted the RR for T2D does not seem to be reported in the paper. According to Vinceti et al. (2018c) it was 1.69 (95% CI 0.68, 4.21) (not significant).	200 or 400 (as Se-containing yeast)
HCT: Karp et al. 2013	This double-blinded, randomised, placebo-controlled HCT found no evidence of increased adverse events or diabetes in patients with resected non–small-cell lung cancer (NSCLC) receiving Se supplementation (200 µg/day as selenised yeast for 6-36 months) (n=865 Se group, n=477 placebo). It is noted the RR for T2D does not seem to be reported in the paper. According to Vinceti et al. (2018c) it was 1.08 (95% CI 0.97, 1.19) (not significant).	200 (as Se-containing yeast)
HCT: Stranges 2007	This double-blinded, randomised, placebo-controlled HCT (n=653 in Se group, n=659 in placebo) found a significant increased risk of T2D (HR 1.55, 95% CI 1.03-2.33) associated with Se plasma concentration in participants given 200 µg/d Se (as a Se-containing yeast tablet) for an unknown exposure timeframe, but potentially 7 years. Individuals with plasma Se levels greater than the baseline median value (>113.4ng/mL) exhibited a hazard ratio = 2.50, CI, 1.32 to 4.77, p=0.005.	200 (as Se-containing yeast)

Prospective cohort: Stranges et al. 2010	This study examined the prospective association between dietary Se intake and risk of T2D (n=7,182). Participants were divided in quintiles based on their baseline dietary Se intake. The study found a statistically significant increased risk for T2D (fully adjusted model 2) for the following.
	• Comparison of the highest (>65.9 µg/day) to the lowest quintile (41.7 µg/day) of Se intake: OR = 2.39, 95% CI: 1.32 - 4.32; P = 0.005.
	• OR for other quintiles were:
	  • 1.42 (0.87-2.34) for quintile II (47.1-53 µg/day)
	  • 1.43 (0.86-2.38) for quintile III (53.1-58.5 µg/day)
	  • 1.65 (0.98-2.78) for quintile IV (58.6-65.9 µg/day)
		>65.9 vs. 41.7 in diet

HR = hazard ratio. RR = Relative risk. OR = Odds Ratio. CI = Confidence Interval.

1. No RoB assessment was undertaken for this study, as it is literature review including a meta-analysis.

Table 11 Visual summary of study findings on selenium and risk of Type 2 diabetes

Study	Whole group	Subgroup	Treated group number of participants
Thompson et al. 2010	✗ (intake)	✓ (older population, intake)	284

Study	Whole group	Subgroup	Treated group number of participants
Lippman et al. 2009	✗ (intake)	-	8,752
Algotar et al. 2013b	✗ (intake)	-	234 or 233
Karp et al. 2013	✗ (intake)	-	865
Stranges 2007	✓ (serum)	-	653
Stranges et al. 2010 (cohort)	-	✓ (>65.9 vs. 41.7 µg/day intake)	7,182
✓ = Denotes statistically significant positive association between Se exposure and T2D. ✗ = Denotes no statistically significant association between Se exposure and T2D.			

A RoB summary table for the included studies for the T2D health outcome is presented in **Table 12** below. An overall RoB rating of 'not likely' was determined for the T2D health outcome based on probably low or definitely low RoB across the majority of key domains and across the majority of studies.

Table 12 RoB summary table for epidemiological studies investigating Type 2 Diabetes and selenium exposure

Health outcome:	Type 2 Diabetes					
Study ID:	**Thompson et al. 2016 (HCT)**	**Lippman et al. 2009 (HCT)**	**Algotar et al. 2013b (HCT)**	**Karp et al. 2013 (HCT)**	**Stranges 2007 (HCT)**	**Stranges et al. 2010 (Pro Co)**
Selection bias						
Randomization	--	--	-	--	--	
Allocation concealment	NR (3)	NR (3)	-	--	--	
Comparison groups appropriate						-
Confounding bias						
Confounding (design/analysis)						-
Performance Bias						
Identical experimental conditions						
Blinding of researchers during study?	-	--	-	--	--	
Attrition/Exclusion Bias						
Missing outcome data	--	--	NR	--	--	--
Detection Bias						
Exposure characterisation	NR (1)	NR (1)	NR (1)	NR (1)	NR (1)	NR (1)
Outcome assessment	-	-	-	-	-	-
Selective Reporting Bias						
Outcome reporting	--	--	--	--	--	--
Other Sources of Bias						
Other threats						
Overall risk of bias across studies (not likely/serious/very serious)	Not likely (2)					

Pro Co = Prospective Cohort, HCT = Human Controlled Trial.

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

1. Although there was insufficient information provided about the validity of the exposure assessment method (i.e. no information on purity of the chemical administered), there is no evidence for concern.
2. Based on probably low or definitely low RoB across the majority of key domains and across the majority of studies.
3. This was conservatively assigned 'NR', however due to the study design, lack of adequate allocation concealment may not appreciably bias results. Thus, bias for this domain could potentially be interpreted as 'probably low RoB' instead of 'NR'.

The initial confidence rating for the HCTs is considered high, since there was controlled exposure, exposure occurred prior to measuring the outcome, individual outcome data were assessed, and a comparison (i.e. placebo) group was used. The initial confidence rating for the prospective cohort study (Stranges et al. 2010) is considered moderate since there was no controlled exposure but exposure occurred prior to the outcome (it was a prospective study), individual outcome data were assessed and a comparison (i.e. cohort was divided into quintile dietary Se intake) group was used. Note since all individual HCT studies included in the meta-analysis were examined separately, confidence rating for the meta-analysis itself has not been undertaken. **Table 13** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'high' for the HCTs and 'moderate' for the cohort study.

Table 13 Confidence Rating for HCT and cohort findings in relation to risk of Type 2 diabetes and selenium exposure

Health outcome (number of studies)	**Type 2 Diabetes** (5 x HCTs, 1 x Co)	**Comment** [(1)]
Initial confidence rating	**HIGH** (HCTs) **MODERATE** (Co)	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence		
Risk of Bias	Not serious.	Confidence not downgraded since overall RoB is 'not likely' (see **Table 12**).
Unexplained inconsistency	No (for HCTs). Yes (for Co). Co confidence downgraded to **LOW.**	Inconsistency observed between the findings of the analyses by Stranges (2007) may be potentially explained by different comparators used in the assessment (i.e. serum Se rather than intake), although it is noted Thompson et al. (2016) also found a significant association for T2D and Se intake in the older population in their study (although this is based on a limited sample size). The different findings in the Stranges et al. (2010) study may be due to the different study design (cohort rather than HCT), where intakes were based on dietary surveys, rendering the intake estimates potentially more uncertain. Confidence not downgraded for the HCTs but downgraded for cohort study.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	No large standard deviations or large ratios for RR in HCTs [95 or 99% CI for the studies are 0.74-2.11 (Thompson et al. 2016 – whole population), 1.04-4.67 (Thompson et al. 2016 – older population), 0.94 – 1.22 (Lippman et al. 2009), 0.68-4.21 (Algotar et al. 2013b), 0.97-1.19 (Karp et al. 2013), 1.03-2.33 (Stranges 2007)]. Same for Co study (95% CI = 1.32-4.32 in Stranges et al. 2010). Confidence not downgraded.
Publication bias	Undetected	No downgrade.
Factors Increasing Confidence		
Magnitude	Not large	Magnitude of effect in Thompson et al. (2016) – older population and Stranges (2007), Stranges et al. (2010) is above 2 for two of the three studies (RR of ~2.21, 1.55, 2.39, respectively) (the other studies found no significant effect), however baseline incidence of T2D is large so confidence not upgraded for large magnitude of effect.

Health outcome (number of studies)	**Type 2 Diabetes** (5 x HCTs, 1 x Co)	**Comment** [1]
Dose response	No.	HCTs consisted of only a single dose of Se supplement (except for Algotar et al. 2013b which had two doses but did not observe a dose response). Stranges (2007), Stranges et al. (2010) did find some evidence of a dose-response when dividing exposure into quintiles but it was not a very clear response. Confidence not upgraded.
Residual confounding	No.	No residual confounding identified. Confidence not upgraded.
Consistency across species	N/A	Primarily HCTs available to assess the effect on T2D. The only cohort study had inconsistent results compared to HCTs. Consistency across species and dissimilar populations can therefore not be judged. Confidence not upgraded.
Final confidence rating	**HIGH** (HCTs), **LOW** (Co)	

HCT = Human Controlled Trial. Co = Cohort.

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

As shown above, there are inconsistent results in the findings of T2D associations with Se exposures, with similar confidence between studies (with the exception of the cohort study). Due to the inconsistent findings for T2D, there is high confidence in studies that have associated Se exposure with T2D in humans, but the information is insufficient for deriving a NOAEL for this effect.

5.1.4 Amyotrophic lateral sclerosis (ALS)

The studies summarised in **Table 14** investigated the association between Se exposure in drinking water and the incidence of ALS. It is noted each study is a follow-up by the same research group of the same cohort from Reggio Emilia in Italy where the 'exposed' population in the sub-community of Rivalta were exposed to selenium in their drinking water at levels of 8-10 µg/L (due to naturally occurring selenate in the water) compared with the 'unexposed' population from the wider community where selenium concentrations were <1 µg/L. The table presents the study findings for each individual study.

Table 14 Summary of studies on selenium and risk of ALS

Study	Findings	Concentration of selenium (µg/L)
Cohort: Vinceti et al. 1996	N=5,182 in exposed group (1986-1994). Number of individuals in unexposed group not disclosed. Standardised incidence ratio (SIR): 4.22 (95% CI = 1.15-10.80) Main Cohort — Observed (expected) Case — SIR (95% CI) Males — 1 (0.64) — 1.56 (0.04 – 8.70) Females — 3 (0.31) — 9.77 (2.02 – 28.56) All — 4 (0.95) — 4.22 (1.15-10.8) Long Cohort — Observed (expected) Case — SIR (95% CI) Males — 1 (0.31) — 3.24 (0.08 – 18.3) Females — 3 (0.14) — 21.36 (4.41-62.44) All — 4 (0.45) — 8.90 (2.43-22.79) Note confidence intervals are very large and expected number of cases are below one.	8-10
Case-control: Vinceti et al. 2010a	Updates previous findings in Vinceti et al. (1996) study by extending follow up period to 1995-2006. N=41 newly diagnosed cases, n=82 age- and sex-matched controls. • Consumption of drinking water containing ≥ 1 µg/L of inorganic Se was associated with a RR for ALS of 5.4 (95% confidence interval 1.1-26) after adjustment for confounding factors. • Greater amounts of cumulative inorganic Se intake were associated with progressively increasing effects, with a relative risk of 2.1 (95% confidence interval 0.5-9.1) (not significant) for intermediate levels of cumulative intake and 6.4 (95% confidence interval 1.3-31) for high intake. Study is relatively small and may be subject to exposure misclassification.	8 (compared ≥ 1 µg/L vs. <1 µg/L)
Case-control: Vinceti et al. 2013b	Investigated whether Se in cerebrospinal fluid (CSF) of 38 ALS cases was associated with ALS risk when compared to 38 age- and gender-matched controls. The small study found higher risk ratios for selenite (RR 1.9, 0.8-4.6), human serum bound Se (1.5, 0.9-2.4) and a seemingly protective effect for total organic Se in CSF (0.4, 0.2-0.9) and ALS but elevated RRs were not statistically significant (95% confidence intervals crossed over 1).	Not available (concentration in CSF)
Cohort: Vinceti et al. 2016	Same cohort of 'exposed' residents in Rivalta and residents from the wider Reggio Emilia municipality (the 'unexposed'). N = 5,182 for main cohort, N = 2,065 for 'long-term' exposed cohort (a sub-group of the main cohort) and N = 110,048 for unexposed cohort. Mortality from ALS in 'long-exposed' cohort was significantly elevated: RR 2.79, 95% CI 1.01–7.67.	8-10

Study	Findings	Concentration of selenium (µg/L)
Cohort: Vinceti et al. 2019	Same cohort of 'exposed' residents in Rivalta and residents from the wider Reggio Emilia municipality (the 'unexposed'). N=2,065 exposed, n=95,715 unexposed. • The Incidence Rate Ratio (IRR) comparing exposed with unexposed cohorts was 2.8 (95% CI: 1.3, 6.0) in the crude model and did not change in the fully-adjusted model. • In men and women, the fully-adjusted IRRs were 1.7 (95% CI: 0.5, 5.4) and 5.1 (95% CI: 1.8, 14.3). • When stratified by calendar period of follow-up, fully-adjusted IRRs were 8.2 (95% CI: 2.7, 24.7) during 1986–1994 and 1.5 (95% CI: 0.5, 4.7) during 1995–2015	8-10
HR = hazard ratio. RR = Relative risk. OR = Odds Ratio. CSF = Cerebrospinal fluid. IRR = Incidence Rate Ratio.		

A RoB summary table for the included studies for the ALS health outcome is presented in **Table 15** below. An overall RoB rating of 'very serious' was determined for the ALS health outcome based on definite high detection bias in the majority of studies and inconsistent attrition/exclusion bias as well as definite high bias identified in one study for other threats.

Table 15 RoB summary table for epidemiological studies investigating ALS and selenium exposure

Health outcome:	ALS				
Study ID:	Vinceti et al. 1996 (Co)	Vinceti et al. 2010a (CaCo)	Vinceti et al. 2013b (CaCo)	Vinceti et al. 2016 (Co)	Vinceti et al. 2019 (Co)
Selection bias					
Randomization					
Allocation concealment					
Comparison groups appropriate	+	--	--	-	-
Confounding bias					
Confounding (design/analysis)	-	-	NR	-	-
Performance Bias					
Identical experimental conditions					
Blinding of researchers during study?					
Attrition/Exclusion Bias					
Missing outcome data	+	-	--	NR	NR
Detection Bias					
Exposure characterisation	++	++	NR (1)	++	++
Outcome assessment	-	-	NR	-	-
Selective Reporting Bias					
Outcome reporting	-	-	-	NR	--
Other Sources of Bias					
Other threats			++		
Overall risk of bias across studies (not likely/serious/very serious)	Very serious (2)				

Co = Cohort, CaCo = Case-control.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Although there was insufficient information provided about the validity of the exposure assessment method (i.e. no information on purity of the chemical administered), there is no evidence for concern.
2. Based on definite high detection bias in the majority of studies and inconsistent attrition/exclusion bias as well as definite high bias identified for one study for other threats.

The initial confidence rating for the cohort and case-control studies investigating ALS is considered low, since there was no controlled exposure, exposure may or may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. 'unexposed') group was used. **Table 16** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'very low'. Consequently, based on the available information, there is insufficient information to conclude whether selenium exposure is associated with ALS in humans.

Table 16 Confidence Rating for cohort and case-control findings in relation to risk of ALS

Health outcome (number of studies)	**ALS** (5 – all from same research group)	**Comment** [(1)]
Initial confidence rating	**LOW**	Based on study design as per OHAT (2019, Table 8).
Factors Decreasing Confidence		
Risk of Bias	Very serious. Downgraded to **VERY LOW.**	Confidence downgraded due to definite high detection bias in the majority of studies and inconsistent attrition/exclusion bias as well as definite high bias identified in one study for other threats. Overall RoB was considered 'very serious' (**Table 15**).
Unexplained inconsistency	Not serious.	Not applicable, since all studies are from the same research group investigating the same cohort in Italy, although the study looking at Se in CSF (Vinceti et al. 2013b) did not find a statistically significant association. Confidence not downgraded.
Indirectness	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Serious. Cannot be downgraded further.	All studies found large standard deviations or large ratios for RR (see **Table 14**), which indicates findings could be due to chance. Confidence cannot be downgraded below **VERY LOW.**
Publication bias	Potential bias detected. Cannot be downgraded further.	Upon consultation of some of the research papers and reviews by this research group, it is clear that a new publication (reiterating similar or the same information) appears almost every six months, and authors tend to self-cite frequently. Some publications clearly overstate the statistical significance of the conclusions in the authors' interpretations. This gives the impression of potential publication bias. Confidence cannot be down-graded further than **VERY LOW.**
Factors Increasing Confidence		
Magnitude	Potentially large. Confidence remains **VERY LOW.**	Magnitude of effect in the various studies appears large (i.e. > 2) (RR of ~4.22, 5.4, 2.79, 2.8) so confidence could be potentially upgraded for large magnitude of effect. Nevertheless, confidence remains at **VERY LOW** due to three factors decreasing confidence above.
Dose response	No.	Comparisons were only between two crude exposure classifications (i.e. ≥ 1 µg/L vs. <1 µg/L). Exposure misclassification potential. Confidence not upgraded.
Residual confounding	No.	No residual confounding that could increase confidence identified. Confidence not upgraded.

Health outcome (number of studies)	**ALS** (5 – all from same research group)	**Comment** [(1)]
Consistency across species	N/A	Not applicable, since all studies are from the same research group investigating the same cohort in Italy. Consistency across species and dissimilar populations can therefore not be judged for this health outcome. Confidence not upgraded.
Final confidence rating	**VERY LOW**	

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

5.1.5 Melanoma and urinary tract tumours

A cohort study by Vinceti et al. (2018a), using the same Italian cohort described in **Section 5.1.4**, calculated RR for a large variety of cancers for the overall 'long-term' cohort. The vast majority of cancers[4] investigated returned no statistically significant associations with Se exposure in the 'exposed' cohort. The exceptions were for melanoma in females only (RR 7.11, 95% CI 2.11-23.89) and urinary tract tumours in females only (RR 2.16, 95% CI 1.06-4.39). It is noted there are clear concerns and biases with this study that cannot be understated, as indicated in the overall RoB assessment in **Table 17** below. The authors do not account for smoking and drinking alcohol as a potential confounder for cancer incidence. There are large ranges in most of the confidence intervals that almost all overlap unity (i.e. 1) and therefore most RR are not statistically significant. Neither of these issues are raised by the study authors, instead they claim a low RoB. There also seem to be multiple unnecessary references to the authors' previous works in the paper.

Another cohort study by Vinceti et al. (2016) in the same Italian population in Reggio Emilia discussed previously (n=5,182 in main cohort of 'exposed' group, n=2,065 as sub-group of main cohort for long-term 'exposed' group, both groups exposed to ~8-10 µg/L of selenium in drinking water; n=110,048 in 'unexposed' main cohort group) found no statistically significant increased risk of melanoma (RR 2.3, 95% CI 0.84-6.29) or urinary tract neoplasms (RR 1.54; 95% CI 0.98-2.44).

In another study (case-control) by the same research group (Vinceti et al. 2012), 54 cases of cutaneous melanoma were recruited at the Department of Dermatology of Modena and Reggio Emilia University in Italy following diagnosis from 1999-2002 and selenium exposure (plasma, toenail and estimated dietary exposure) compared with matched controls. The authors found a statistically significant positive association (matched analysis RR 5.86; 95% CI 1.53-22.31) between plasma selenium level and melanoma in the high quartile (≥ 105 µg/L) group compared to the low quartile (< 81 µg/L) group. No statistically significant associations were found for toenail selenium or dietary selenium exposures.

A RoB summary table for the included studies for the two health outcomes (melanoma and urinary tract tumours) is presented in **Table 17** below. An overall RoB rating of 'very serious' was determined for both health outcomes based on definite high detection bias in the majority of studies and potential attrition/exclusion bias.

[4] These included all cancers, buccal cavity and pharynx, stomach, colon-rectum, liver, biliary tract, pancreas, lung, breast, prostate, lymphatic hematopoietic tissue, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, multiple myeloma, and all leukaemia.

Table 17 RoB summary table for epidemiological studies investigating melanoma, urinary tract tumours and selenium exposure

Health outcome:	Melanoma (mixed results)			Urinary tract tumours (mixed results)	
Study ID:	Vinceti et al. 2018a (Co)	Vinceti et al. 2016 (Co)	Vinceti et al. 2012 (CaCo)	Vinceti et al. 2018a (Co)	Vinceti et al. 2016 (Co)
Selection bias					
Randomization					
Allocation concealment					
Comparison groups appropriate	-	-	--	-	-
Confounding bias					
Confounding (design/analysis)	-	-	-	-	-
Performance Bias					
Identical experimental conditions					
Blinding of researchers during study?					
Attrition/Exclusion Bias					
Missing outcome data	NR	NR	+	NR	NR
Detection Bias					
Exposure characterisation	++	++	NR (1)	++	++
Outcome assessment	-	-	-	-	-
Selective Reporting Bias					
Outcome reporting	NR	NR	-	NR	NR
Other Sources of Bias					
Other threats					
Overall risk of bias across studies (not likely/serious/very serious)	Very serious (2)			Very serious (3)	

Co = Cohort, CaCo = Case-control.

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

1. Although there was insufficient information provided about the validity of the exposure assessment method (i.e. no information on purity of the chemical administered), there is no evidence for concern.
2. Based on definite high detection bias in the majority of studies and potential attrition/exclusion bias in all studies.
3. Based on definite high detection bias in both studies and potential attrition/exclusion bias in both studies.

The initial confidence rating for the cohort and case-control studies is considered 'low', since there was no controlled exposure, exposure may or may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. 'unexposed' or control) group was used. **Table 18** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'very low' for both health outcomes. Consequently, based on the available information, there is insufficient information to conclude whether selenium exposure is associated with melanoma or urinary tract tumours in humans.

Table 18 Confidence Rating for cohort and case-control findings in relation to risk of melanoma and urinary tract tumours and selenium exposure

Health outcome (number of studies)	**Melanoma** (3)	**Urinary tract tumours** (2)	**Comment** (1)
Initial confidence rating	**LOW**	**LOW**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence			
Risk of Bias	Very serious. Confidence downgraded to **VERY LOW.**	Very serious. Confidence downgraded to **VERY LOW.**	Confidence downgraded due to definite high detection bias in the majority of studies and attrition/exclusion bias. Overall RoB was considered 'very serious' (**Table 17**).

Health outcome (number of studies)	**Melanoma** (3)	**Urinary tract tumours** (2)	**Comment** [1]
Unexplained inconsistency	Serious. Cannot be downgraded further.	Serious. Cannot be downgraded further.	Findings were inconsistent between the studies. Potential reason for this is unclear. Confidence cannot be downgraded further than **VERY LOW**.
Indirectness	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Serious. Cannot be downgraded further.	Serious. Cannot be downgraded further.	All studies found large standard deviations or large ratios for RR (see text), which indicates findings could be due to chance. Confidence cannot be downgraded further than **VERY LOW**.
Publication bias	Detected in one study. Cannot be downgraded further.		Possible publication bias detected in Vinceti et al. (2018a) investigation (see text). Confidence cannot be downgraded further than **VERY LOW.**
Factors Increasing Confidence			
Magnitude	Potentially large. Confidence remains **VERY LOW.**	Potentially large. Confidence remains **VERY LOW.**	Magnitude of effect in the studies appears large (i.e. > 2) (RR of ~7.11, 2.16, 5.86 where effect was observed) so confidence could be potentially upgraded for large magnitude of effect in two of the studies. Confidence remains at **VERY LOW** due to four factors decreasing confidence above.
Dose response	No.	No.	Comparisons were only between two crude exposure classifications in the Vinceti et al. (2018a, 2016) papers (i.e. ≥ 1 µg/L vs. <1 µg/L). Exposure misclassification potential. Possibility of dose response in terms of serum concentrations in Vinceti et al. (2012) paper, but this was not observed for Se in toenails or dietary intake. Confidence not upgraded.
Residual confounding	No.	No.	No residual confounding that could increase confidence in the results identified. Confidence not upgraded.
Consistency across species	N/A	N/A	Not applicable, since consistency across species and dissimilar populations cannot be judged based on the small number of studies. Confidence not upgraded.
Final confidence rating	**VERY LOW**	**VERY LOW**	-

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

5.1.6 Multiple myeloma and Parkinson's disease

The cohort study by Vinceti et al. (2016) described in the previous section found no statistically significant increased risk of cancers of the buccal cavity and pharynx, colon-rectum, melanoma, or urinary tract. Statistically significant increases were, however, found for multiple myeloma (RR 2.24, 95% CI 1.05-4.78), and mortality from Parkinson's disease (RR 2.47, 95% CI 1.15-5.28).

In contrast, the cohort study by Vinceti et al. (2018a), also described in the previous section, did not find statistically significant associations of selenium exposure in drinking water and multiple myeloma in the same cohort (RR in males 1.56; 95% CI 0.80–3.04; RR in females 2.37; 95% CI 0.57–9.76).

The overall RoB for both studies was previously presented in **Section 5.1.5** for the urinary tract tumour health outcome and would be unchanged from 'very serious' for the outcomes discussed in this section (multiple myeloma and mortality from Parkinson's disease).

The initial confidence rating for the cohort studies is considered low, since there was no controlled exposure, exposure may or may not have occurred prior to the outcome, individual outcome data were assessed, and a comparison (i.e. 'unexposed') group was used. **Table 19** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'very low' (for multiple myeloma) and 'low' (for mortality from Parkinson's disease). Consequently, based on the available information, there is insufficient information to conclude whether selenium exposure is associated with multiple myeloma and low confidence for an association with mortality from Parkinson's disease.

Table 19 Confidence Rating for cohort findings in relation to risk of multiple myeloma and mortality from Parkinson's disease and selenium exposure

Health outcome (number of studies)	**Multiple myeloma** (2)	**Mortality from Parkinson's disease** (1)	**Comment** [(1)]
Initial confidence rating	**LOW**	**LOW**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence			
Risk of Bias	Very serious. Confidence downgraded to **VERY LOW**	Very serious. Confidence downgraded to **VERY LOW**	Confidence downgraded due to definite high detection bias and attrition/exclusion bias. Overall RoB was considered 'very serious' (**Table 17**).
Unexplained inconsistency	Serious. Cannot be downgraded further.	Not serious (single study). Not downgraded.	Findings were inconsistent between the studies for multiple myeloma. Potential reason for this is unclear as it was the same population studied. Only a single study investigated mortality from Parkinson's disease. Confidence cannot be downgraded further than **VERY LOW**.
Indirectness	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Not serious.	No large standard deviations or large ratios for RR (95% CI for multiple myeloma 1.05-4.78; for Parkinson's 1.15-5.28). Confidence not downgraded.
Publication bias	Detected in one study. Cannot downgrade further.	Not detected.	Possible publication bias detected in Vinceti et al. (2018a) investigation (see text in **Section 5.1.5**). Confidence cannot be downgraded further than **VERY LOW.**
Factors Increasing Confidence			
Magnitude	Potentially large. Confidence remains **VERY LOW.**	Potentially large. Confidence upgraded to **LOW.**	Magnitude of effect in the studies appears large (i.e. > 2) (RR of ~2.24, 2.47 where effect was observed) so confidence could be potentially upgraded for large magnitude of effect in Vinceti et al. (2016) study. Confidence remains at **VERY LOW** for multiple myeloma due to three factors decreasing confidence above. Confidence upgraded to **LOW** for mortality from Parkinson's disease.

Health outcome (number of studies)	**Multiple myeloma** (2)	**Mortality from Parkinson's disease** (1)	**Comment** [1]
Dose response	No.	No.	Comparisons were only between two crude exposure classifications (i.e. ≥ 1 µg/L vs. <1 µg/L). Exposure misclassification potential. Confidence not upgraded.
Residual confounding	No.	No.	No residual confounding that could increase study confidence identified. Confidence not upgraded.
Consistency across species	N/A	N/A	Not applicable, since consistency across species and dissimilar populations cannot be judged based on the small number of cohort studies. Confidence not upgraded.
Final confidence rating	**VERY LOW**	**LOW**	-

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

5.1.7 Cardiovascular disease

In a cross-sectional study evaluating the association of serum selenium with fasting serum lipid levels in the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 (n=1,159 adults ≥40 years of age), Lacaustra et al. (2010) found potential risk factors of cardiovascular disease (i.e. total and low-density-lipoprotein or LDL cholesterol) to be associated with selenium levels in serum. The multivariable adjusted average differences (95% CI) comparing the highest (≥147 µg/L) to the lowest (<124 µg/L) serum selenium quartiles were:

- 18.9 (9.9-28.0) for total cholesterol
- 12.7 (3.3-22.2) for LDL cholesterol

The authors noted that the study is limited by its cross-sectional design, and Lacaustra et al. (2010) were unable to determine whether lipid levels rise as a consequence of increased selenium intake or whether a common metabolic pathway or common co-exposures might explain the association between selenium status and lipid levels. Measurement error in dietary data may result in residual confounding.

In a cohort study, also based on NHANES data (n=16,469 adults 20-90 years of age), Bleys et al. (2008) investigated the association between selenium serum levels and all-cause and cause-specific mortality. When serum selenium was divided into tertiles, hazard ratios (HRs) comparing Tertile 3 to Tertile 1 were not statistically significantly increased for any of the parameters investigated (i.e. all-cause mortality, cancer mortality, and mortality from cardiovascular, coronary heart disease and stroke). Indeed, for some (e.g. all-cause mortality and cancer mortality), selenium appeared to have a beneficial effect.

A RoB summary table for the included studies for the cardiovascular disease health outcome is presented in **Table 20** below. An overall RoB rating of 'not likely' was determined for the cardiovascular disease associated health outcomes based on definitely low or probably low bias in the vast majority of key domains.

Table 20 RoB summary table for epidemiological studies investigating cardiovascular disease and selenium exposure

Health outcome:	Increased cholesterol	No increase in mortality from cardiovascular disease, coronary heart disease or stroke
Study ID:	**Lacaustra et al. (2010) (CrSe)**	**Bleys et al. (2008) (Co)**
Selection bias		
Randomization		
Allocation concealment		
Comparison groups appropriate	+	--
Confounding bias		
Confounding (design/analysis)	--	--
Performance Bias		
Identical experimental conditions		
Blinding of researchers during study?		
Attrition/Exclusion Bias		
Missing outcome data	--	--
Detection Bias		
Exposure characterisation	-	NR (1)
Outcome assessment	-	--
Selective Reporting Bias		
Outcome reporting	--	--
Other Sources of Bias		
Other threats		
Overall risk of bias across studies (not likely/serious/very serious)	Not likely (2)	Not likely (2)

Co = Cohort, CaCo = Case-control.
-- = Definitely low RoB, - = Probably low RoB, + or NR = Probably high RoB (+) or not reported (NR), ++ = Definitely high RoB.

1. Although there was insufficient information provided about the validity of the exposure assessment method (i.e. no information on purity of the chemical administered), there is no evidence for concern.
2. Based on definitely low or probably low bias in the vast majority of key domains.

The initial confidence rating for the cohort and cross-sectional studies is considered moderate (cohort for no increase in mortality from CVD) or low (cross-sectional study for increased cholesterol), respectively, since there was no controlled exposure, exposure may or may not have occurred prior to the outcome (although for the cohort study it certainly did since the endpoint was mortality), individual outcome data were assessed, and a comparison (i.e. lower tertile of serum selenium concentrations) group was used. **Table 21** shows an assessment of the confidence in these bodies of evidence, with a final confidence rating of 'moderate' for the cohort study (showing no increase in mortality from CVD) and 'low' for the cross-sectional study (showing increased cholesterol). Consequently, there is moderate confidence that selenium exposure is not associated with mortality from CVD and low confidence for an association between selenium exposure and increased cholesterol.

Table 21 Confidence Rating for cohort and cross-sectional findings in relation to risk of cardiovascular disease (CVD) or mortality from CVD

Health outcome (number of studies)	**Increased cholesterol** (1)	**No increase in mortality from CVD** (1)	**Comment** (1)
Initial confidence rating	**LOW**	**MODERATE**	Based on study design as per OHAT (2019, Table 8)
Factors Decreasing Confidence			

Health outcome (number of studies)	**Increased cholesterol** (1)	**No increase in mortality from CVD** (1)	**Comment** [1]
Risk of Bias	Not serious.	Not serious.	Confidence not downgraded since overall RoB was considered 'not likely' (**Table 20**).
Unexplained inconsistency	Not serious.	Not serious.	Studies looked at different endpoints (one looked at risk factors for CVD, the other at mortality from CVD). Inconsistency in findings is therefore not apparent. Confidence not downgraded.
Indirectness	Not serious.	Not serious.	Human studies generally are not downgraded for indirectness.
Imprecision	Not serious.	Not serious.	Ratios of upper to lower 95% CI is <10 for findings in CrSe study. No large standard deviations or large ratios for RR in Co study (0.73-0.96, 0.72-0.96, 0.57-0.94, 0.53-0.9, 0.78-1.17, 0.77-1.16, 0.71-1.46, 0.67-1.47, 0.41-1.3, 0.66-2.28). Confidence not downgraded.
Publication bias	Undetected.	Undetected.	Confidence not downgraded.
Factors Increasing Confidence			
Magnitude	Not large (risk factor, not disease).	Not large (no adverse effect).	In the CrSe study, effect was to cholesterol, i.e. a potential risk factor of CVD, not the disease itself. Confidence was therefore not increased for magnitude of effect. No adverse effect detected in Co study, so confidence not increased for magnitude.
Dose response	No.	No.	In CrSe study, potential dose response found for increasing serum Se as serum tertile concentration, but only with respect to a risk factor for CVD, not CVD itself. Confidence not upgraded. In Co study, no dose response found, except with respect to potential protective effect (up to a certain threshold), and only for serum tertile concentration. Confidence not upgraded.
Residual confounding	No.	No.	Measurement error may result in residual confounding, but direction of confounding is not known. Confidence not upgraded.
Consistency across species	N/A	N/A	Only two studies available, each investigating a different endpoint with respect to CVD risk. Consistency across species and dissimilar populations cannot be judged based on the small number of studies. Confidence not upgraded.
Final confidence rating	**LOW**	**MODERATE**	-

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

5.2 Overall Evaluation

5.2.1 Hazard identification conclusions

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

In accordance with the OHAT framework for systematic review and evidence integration (OHAT 2019, Figure 2), this indicates the conclusions shown in **Table 22**.

Table 22 Hazard identification conclusions for selenium

Health endpoint [number of studies]	Certainty rating	Conclusion	NOAEL/LOAEL (µg Se/day)?
Mild effects of selenosis (i.e. alopecia) [(1)]			
Human controlled study [1]	**HIGH**	There is high confidence in the body of evidence for an association between exposure to selenium (as selenomethionine) and mild effects of selenosis (i.e. alopecia).	Minimal LOAEL = 200
Prostate cancer			
Human controlled study [4 + 1] [(2)]	**HIGH**	There is high confidence in the body of evidence available for an association between exposure to selenium and prostate cancer in humans. As only one of the five studies (of which three examined the same trial cohort) found a marginally statistically significant association between Se (in toenails) and prostate cancer risk, this is considered insufficient evidence to conclude that exposure to Se can increase the risk of prostate cancer.	Not applicable (evidence of no effect)
Type 2 Diabetes			
Human controlled study [5], Cohort [1]	**HIGH (HCT)** **LOW (Co)**	There are inconsistent results in the findings of T2D associations with selenium exposures, with similar confidence between studies (with the exception of the cohort study). Due to the inconsistent findings for T2D, there is high confidence in studies that have associated Se exposure with T2D in humans, but the information is insufficient for deriving a NOAEL for this effect.	Insufficient
Amyotrophic lateral sclerosis			
Cohort [3], Case-control [2]	**VERY LOW**	There is very low confidence in the body of evidence available for an association between exposure to selenium and ALS.	Insufficient
Melanoma			
Cohort [2], Case-control [1]	**VERY LOW**	There is very low confidence in the body of evidence available for an association between exposure to selenium and melanoma.	Insufficient
Urinary tract tumours			
Cohort [2]	**VERY LOW**	There is very low confidence in the body of evidence available for an association between exposure to selenium and urinary tract tumours.	Insufficient
Multiple myeloma			
Cohort [2]	**VERY LOW**	There is very low confidence in the body of evidence available for an association between exposure to selenium and multiple myeloma.	Insufficient
Mortality from Parkinson's Disease			
Cohort [2]	**LOW**	There is low confidence in the body of evidence available for an association between exposure to selenium and mortality from Parkinson's disease, but the information is insufficient for deriving a NOAEL for this effect.	Insufficient
Increased cholesterol (risk factor for cardiovascular disease)			
Cross-sectional [1]	**LOW**	There is low confidence in the body of evidence available for an association between exposure to selenium and increased cholesterol, but the information is insufficient for deriving a NOAEL for this effect (and the effect is a risk factor for disease, not necessarily an adverse effect *per se*).	Insufficient

Health endpoint [number of studies]	Certainty rating	Conclusion	NOAEL/LOAEL (µg Se/day)?
No increase in mortality from cardiovascular disease, coronary heart disease or stroke			
Cohort [1]	**MODERATE**	There is moderate confidence in the body of evidence available for no association between exposure to selenium and mortality from cardiovascular disease.	Not applicable (evidence of no effect)
(1) Note this is in addition to the studies already underpinning the derivation of existing guidelines reviewed in the Stage 1 reports. (2) Although one study was a 'case-cohort', it used data from a human controlled study.			

In summary, from **Table 22** there is:

- High confidence in the evidence for selenium exposure and mild effects of selenosis (i.e. alopecia). A minimal LOAEL for this effect of 200 µg Se/day for added selenium is available.
- High confidence for no increase in prostate cancer incidence as a result of selenium exposure, and a possible association with T2D. However, the information available is insufficient to inform a NOAEL/LOAEL for T2D.
- Moderate confidence for no increase in mortality from CVD, coronary heart disease or stroke as a result of selenium exposure.
- Low or very low confidence for the available evidence for other health outcomes (i.e. mortality from Parkinson's disease, increased cholesterol, ALS, melanoma, urinary tract tumours, or multiple myeloma). The evidence is insufficient to derive a NOAEL/LOAEL for these effects.

5.2.2 Candidate guidance/guideline values

The Stage 1 evaluation report presented a number of candidate DWGs resulting from adaptation of selenium guidance values from other jurisdictions. This exercise indicated there was very good agreement between the agencies that a DWG of 0.02 mg/L would be defensible based on an upper tolerable daily intake or NOAEL of 400-850 µg/day or ~0.015 mg/kg/day. However, the evidence scan undertaken for the Stage 1 review revealed a number of recently published studies which could potentially impact the conclusions made in the Stage 1 report. As a result, a targeted search and review of relevant primary studies published since 2010 (determined to be the cut-off date for the most recent agency review from Stage 1) was conducted as part of the Stage 2 report.

The detailed review undertaken in this Stage 2 evaluation showed that there is high confidence in the evidence for selenium exposure and mild effects of selenosis (i.e. alopecia), i.e. the endpoint on which the candidate DWGs are based. A minimal LOAEL (i.e. a LOAEL for a mild/minimal effect) for this effect of 200 µg Se/day (as added selenium to that ingested in the diet) is available. There is also high confidence in the evidence for a possible association between selenium exposure and T2D, but the information available is insufficient to inform a NOAEL/LOAEL for this effect.

Although there is very limited information from the available studies to refine the dose response for selenosis and inform a dose response for T2D, the following findings may require reconsideration of the candidate guideline value:

- The large (n=32,400 men; Se group n=8,752) randomised, double-blind, placebo-controlled HCT referred to as the SELECT trial (Lippman et al. 2009, also included in a subsequent meta-analysis by Rees et al. 2013) found a marginally statistically significant HR of 1.28 (n=265; 95% CI 1.01-1.62) for grade 1-2 alopecia[5], a known early indication of selenosis in persons receiving 200 µg Se/day (as selenomethionine). Because the effect just reached statistical significance and the effects were mild (and the confidence in the study is high), the dose of 200 µg Se/day added selenium may be regarded as a minimal LOAEL.
- The cohort study by Stranges et al. (2010) examined the prospective association between dietary selenium intake and risk of T2D (n=7,182). The study found a statistically significant increased risk for T2D (fully adjusted model 2) when comparing the highest (>65.9 µg/day) to the lowest quintile (41.7 µg/day) of selenium intake (OR = 2.39, 95% CI: 1.32 - 4.32; P = 0.005). There is moderate confidence in this study, but it does not inform on the LOAEL or NOAEL of selenium for T2D.

The minimal LOAEL for mild selenosis of 200 µg Se/day as added selenium was first adjusted by adding this to the dietary selenium intake likely to have been ingested by the participants in the study (55 µg Se/day, see below) to provide the point of departure for derivation of a candidate DWG. The potential resulting DWG is summarised in **Table 23**. The calculation assumes the added selenium was administered in addition to a normal recommended amount of selenium in the North American diet (i.e. the country in which the study was conducted) to prevent selenium deficiency. The recommended amount of selenium in the diet for adults is 55 µg/day (NIH 2021), rendering an adjusted minimal LOAEL of 255 µg/day (supplementary + dietary selenium).

The candidate selenium DWG derived by using the adjusted minimal LOAEL of 255 µg/day selenium in the diet is 0.00425 mg/L (i.e. 4.25 µg/L). The majority of Australian distributed drinking water supplies contain relatively low selenium levels (i.e. typically <2 µg/L) (see **Section 4.2**), which are lower than the updated candidate DWG. It is noted, however, there are some locations around Australia where source waters may contain higher selenium concentrations due to geological origin. It is also noted that exposure to selenium may also theoretically occur from leaching of selenium from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for selenium from lead replacements in plumbing products be generated for Australian conditions to inform this matter.

Table 23 Potential drinking water guideline value (mg/L) resulting from use of minimal LOAEL for selenosis from HCT study

Parameter		Lippman et al. 2009
Study population		Humans
Form of selenium studied		Selenomethionine as a supplement
Exposure route		Diet
Study timeframe		7-12 years
Critical Effect		Mild selenosis (grade 1-2 alopecia)
Point of Departure (mg/day)		Minimal LOAEL: 0.255 mg/day (i.e. 255 µg/day) (4)
Uncertainty factors	UF_A	-
	UF_H	1 (2)
	UF_{LOAEL}	3 (3)
	$UF_{database}$	-

[5] The hazard ratio for the grade 1-2 dermatitis also observed in this study had a confidence interval starting at 1.00, therefore there is uncertainty whether the dermatitis finding is due to chance.

Parameter		Lippman et al. 2009
	$UF_{composite}$	3
Health-based guidance value (mg/day)		0.085
Resulting adaptation to a Health Based DWG[(1)] (mg/L)		0.00425 mg/L (i.e. 4.25 µg/L)

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

1. Candidate guideline value has been derived using the default assumptions for derivation of DWGs in Australia using the following equation as outlined in NHMRC (2021):

   DWG (mg/L) = [Guidance value (mg/d) x 0.1] ÷ 2 L/day for adult
2. Uncertainty factor for human variability was not included as the HCT involved controlled exposure to a large population of men >50 years of age (at risk of developing prostate cancer), and there are no indications from the wider literature that females or children are more sensitive to the effects of Se. In addition, the essentiality of Se has to be balanced with the potential for adverse health effects.
3. An uncertainty factor of 3 was applied as the effect was mild and the LOAEL is a minimal LOAEL. It must also be balanced with the essentiality of Se.
4. This minimal LOAEL includes the supplement dose in the HCT of 200 µg/day and the normal recommended amount of Se in the North American diet (i.e. the country in which the study was conducted) to prevent Se deficiency of 55 µg/day (NIH 2021).

6 Conclusions

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

- High confidence in the evidence for selenium exposure and mild effects of selenosis (i.e. alopecia). A minimal LOAEL for this effect of 200 µg Se/day (as added selenium) is available.
- High confidence for no increase in prostate cancer incidence as a result of selenium exposure, and a possible association with T2D. However, the information available is insufficient to inform a NOAEL/LOAEL for T2D.
- Moderate confidence for no increase in mortality from CVD, coronary heart disease or stroke as a result of selenium exposure.
- Low or very low confidence for the available evidence for other health outcomes (i.e. mortality from Parkinson's disease, increased cholesterol, ALS, melanoma, urinary tract tumours, or multiple myeloma). The evidence is insufficient to derive a NOAEL/LOAEL for these effects.

There is insufficient information to inform the dose response of selenium exposure and T2D, therefore additional studies would be useful to inform this knowledge gap. Additional research is also likely required to clarify the importance of the chemical form of selenium on overall toxicity, and whether different forms are subject to a different dose-response curve.

An adjusted minimal LOAEL of 255 µg Se/d selenium for mild alopecia in humans was considered relevant to the Australian context for potential adaptation. The updated candidate selenium DWG derived using this adjusted minimal LOAEL is 0.00425 mg/L (i.e. 4.25 µg/L). The majority of Australian distributed drinking water contain relatively low selenium levels (i.e. typically <2 µg/L), which are lower than the updated candidate DWG. It is noted, however, there are some locations around Australia where source waters may contain higher selenium concentrations due to geological origin. It is also noted that exposure to selenium may also theoretically occur from leaching of selenium from low-lead plumbing materials although no quantitative leachability data were found in the literature search undertaken to confirm potential exposures. It is suggested that leachability data for selenium from lead replacements in plumbing products be generated for Australian conditions to inform this matter.

Based on the Stage 1 review results, the concentration of the revised candidate DWG of 0.00425 mg/L appears to be achievable in distributed water with existing treatment technologies and readily measurable with current commercial analytical techniques. Its achievability in waters at the tap is currently unknown due to lack of leachability data from lead replacements in plumbing products.

7 Review Team

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

8 Declared Interests

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

9 Acknowledgements

The authors acknowledge NHMRC and the members of the Committee for their insightful review comments.

10 References

Aldosary B. M., Sutter M. E., Schwartz M. and Morgan B. W. (2012). Case series of selenium toxicity from a nutritional supplement. Clin Toxicol (Phila) 50(1): 57-64.

Algotar A. M., Stratton M. S., Ahmann F. R., Ranger-Moore J., Nagle R. B., Thompson P. A., Slate E., Hsu C. H., Dalkin B. L., Sindhwani P., Holmes M. A., Tuckey J. A., Graham D. L., Parnes H. L., Clark L. C. and Stratton S. P.

(2013a). Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer. Prostate 73(3): 328-335.

Algotar A. M., Hsu C. H., Singh P. and Stratton S. P. (2013b). Selenium supplementation has no effect on serum glucose levels in men at high risk of prostate cancer. J Diabetes 5(4): 465-470.

Bagherzadeh F., Karami M., Sadeghi M., Ahmadi A., Bahreini R., Fadaei A., Forouzandeh S., Hemati S. and Mohammadi-Moghadam F. (2022). Influence of metal ions concentration in drinking water in the development of ulcerative colitis. International Journal of Environmental Science and Technology 19:3539-3546.

Bleys J., Navas-Acien A. and Guallar E. (2008). Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. Arch Intern Med 168(4): 404-410.

Evans S. O., Jacobson G. M., Goodman H. J. B., Bird S. and Jameson M. B. (2019). Comparative Safety and Pharmacokinetic Evaluation of Three Oral Selenium Compounds in Cancer Patients. Biol Trace Elem Res 189(2): 395-404.

Frisbie S. H., Mitchell E. J. and Sarkar B. (2015). Urgent need to reevaluate the latest World Health Organization guidelines for toxic inorganic substances in drinking water. Environ Health 14: 63.

Karp D. D., Lee S. J., Keller S. M., Wright G. S., Aisner S., Belinsky S. A., Johnson D. H., Johnston M. R., Goodman G., Clamon G., Okawara G., Marks R., Frechette E., McCaskill-Stevens W., Lippman S. M., Ruckdeschel J. and Khuri F. R. (2013). Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597. J Clin Oncol 31(33): 4179-4187.

Kilness A. W. and Hochberg F. H. (1977). Amyotrophic lateral sclerosis in a high selenium environment. Jama 237(26): 2843-2844.

Klein E. A., Thompson I. M., Jr., Tangen C. M., Crowley J. J., Lucia M. S., Goodman P. J., Minasian L. M., Ford L. G., Parnes H. L., Gaziano J. M., Karp D. D., Lieber M. M., Walther P. J., Klotz L., Parsons J. K., Chin J. L., Darke A. K., Lippman S. M., Goodman G. E., Meyskens F. L., Jr. and Baker L. H. (2011). Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama 306(14): 1549-1556.

Kristal A. R., Darke A. K., Morris J. S., Tangen C. M., Goodman P. J., Thompson I. M., Meyskens F. L., Jr., Goodman G. E., Minasian L. M., Parnes H. L., Lippman S. M. and Klein E. A. (2014). Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. J Natl Cancer Inst 106(3): djt456.

Lacaustra M., Stranges S., Navas-Acien A., Ordovas J. M. and Guallar E. (2010). Serum selenium and serum lipids in US adults: National Health and Nutrition Examination Survey (NHANES) 2003-2004. Atherosclerosis 210(2): 643-648.

Lance P., Alberts D. S., Thompson P. A., Fales L., Wang F., San Jose J., Jacobs E. T., Goodman P. J., Darke A. K., Yee M., Minasian L., Thompson I. M. and Roe D. J. (2017). Colorectal Adenomas in Participants of the SELECT Randomized Trial of Selenium and Vitamin E for Prostate Cancer Prevention. Cancer Prev Res (Phila) 10(1): 45-54.

Lippman S. M., Klein E. A., Goodman P. J., Lucia M. S., Thompson I. M., Ford L. G., Parnes H. L., Minasian L. M., Gaziano J. M., Hartline J. A., Parsons J. K., Bearden J. D., 3rd, Crawford E. D., Goodman G. E., Claudio J., Winquist E., Cook E. D., Karp D. D., Walther P., Lieber M. M., Kristal A. R., Darke A. K., Arnold K. B., Ganz P. A., Santella R. M., Albanes D., Taylor P. R., Probstfield J. L., Jagpal T. J., Crowley J. J., Meyskens F. L., Jr., Baker L. H. and Coltman C. A., Jr. (2009). Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama 301(1): 39-51.

MacFarquhar J. K., Broussard D. L., Melstrom P., Hutchinson R., Wolkin A., Martin C., Burk R. F., Dunn J. R., Green A. L., Hammond R., Schaffner W. and Jones T. F. (2010). Acute selenium toxicity associated with a dietary supplement. Arch Intern Med 170(3): 256-261.

Mandrioli J., Michalke B., Solovyev N., Grill P., Violi F., Lunetta C., Conte A., Sansone V. A., Sabatelli M. and Vinceti M. (2017). Elevated Levels of Selenium Species in Cerebrospinal Fluid of Amyotrophic Lateral Sclerosis Patients with Disease-Associated Gene Mutations. Neurodegener Dis 17(4-5): 171-180.

Marshall J. R., Tangen C. M., Sakr W. A., Wood D. P., Jr., Berry D. L., Klein E. A., Lippman S. M., Parnes H. L., Alberts D. S., Jarrard D. F., Lee W. R., Gaziano J. M., Crawford E. D., Ely B., Ray M., Davis W., Minasian L. M. and Thompson I. M., Jr. (2011). Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia: SWOG S9917. Cancer Prev Res (Phila) 4(11): 1761-1769.

Mix M., Ramnath N., Gomez J., de Groot C., Rajan S., Dibaj S., Tan W., Rustum Y., Jameson M. B. and Singh A. K. (2015). Effects of selenomethionine on acute toxicities from concurrent chemoradiation for inoperable stage III non-small cell lung cancer. World J Clin Oncol 6(5): 156-165.

Moher D., Liberati A., Tetzlaff J. and Altman D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339: b2535

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.

NIH (2021). Selenium Fact Sheet for Consumers. National Institutes of Health, US Department of Health & Human Services. [Updated March 22, 2021]. https://ods.od.nih.gov/factsheets/Selenium-Consumer/

OEHHA (2010). Public health goals for chemicals in drinking water – Selenium. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2010.

OHAT (2019). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Toxicology Program, US Department of Health and Human Services, Office of Health Assessment and Translation. March 4, 2019.

Rees K., Hartley L., Day C., Flowers N., Clarke A. and Stranges S. (2013). Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013(1): Cd009671.

Stranges S. (2007). Effects of Long-Term Selenium Supplementation on the Incidence of Type 2 Diabetes. Annals of Internal Medicine 147: 217.

Stranges S., Sieri S., Vinceti M., Grioni S., Guallar E., Laclaustra M., Muti P., Berrino F. and Krogh V. (2010). A prospective study of dietary selenium intake and risk of type 2 diabetes. BMC Public Health 10: 564.

Thompson P. A., Ashbeck E. L., Roe D. J., Fales L., Buckmeier J., Wang F., Bhattacharyya A., Hsu C. H., Chow H. H., Ahnen D. J., Boland C. R., Heigh R. I., Fay D. E., Hamilton S. R., Jacobs E. T., Martinez M. E., Alberts D. S. and Lance P. (2016). Selenium Supplementation for Prevention of Colorectal Adenomas and Risk of Associated Type 2 Diabetes. J Natl Cancer Inst. 108(12).

ToxConsult (2019). Assessment of International and National Agency processes for deriving HBGVs and DWGs. Prepared for National Health and Medical Research Council. ToxConsult document: ToxCR070519-TF, dated 24th December 2019.

Vinceti M., Guidetti D., Pinotti M., Rovesti S., Merlin M., Vescovi L., Bergomi M. and Vivoli G. (1996). Amyotrophic lateral sclerosis after long-term exposure to drinking water with high selenium content. Epidemiology 7(5): 529-532.

Vinceti M., Bonvicini F., Rothman K. J., Vescovi L. and Wang F. (2010a). The relation between amyotrophic lateral sclerosis and inorganic selenium in drinking water: a population-based case-control study. Environ Health 9: 77.

Vinceti M., Bonvicini F., Bergomi M. and Malagoli C. (2010b). Possible involvement of overexposure to environmental selenium in the etiology of amyotrophic lateral sclerosis: a short review. Ann Ist Super Sanita 46(3): 279-283.

Vinceti M., Crespi C. M., Malagoli C., Bottecchi I., Ferrari A., Sieri S., Krogh V., Alber D., Bergomi M., Seidenari S. and Pellacani G. (2012). A case-control study of the risk of cutaneous melanoma associated with three selenium exposure indicators. Tumori 98(3): 287-295.

Vinceti M., Crespi C. M., Bonvicini F., Malagoli C., Ferrante M., Marmiroli S. and Stranges S. (2013a). The need for a reassessment of the safe upper limit of selenium in drinking water. Sci Total Environ 443: 633-642.

Vinceti M., Solovyev N., Mandrioli J., Crespi C. M., Bonvicini F., Arcolin E., Georgoulopoulou E. and Michalke B. (2013b). Cerebrospinal fluid of newly diagnosed amyotrophic lateral sclerosis patients exhibits abnormal levels of selenium species including elevated selenite. Neurotoxicology 38: 25-32.

Vinceti M., Ballotari P., Steinmaus C., Malagoli C., Luberto F., Malavolti M. and Rossi P. G. (2016). Long-term mortality patterns in a residential cohort exposed to inorganic selenium in drinking water. Environmental Research 150: 348-356.

Vinceti M., Vicentini M., Wise L., Sacchettini C., Malagoli C., Ballotari P., Filippini T., Malavolti M. and Giorgi Rossi P. (2018a). Cancer incidence following long-term consumption of drinking water with high inorganic selenium content. The Science of the total environment 635: 390-396.

Vinceti M., Filippini T. and Rothman K. J. (2018c). Selenium exposure and the risk of type 2 diabetes: a systematic review and meta-analysis. Eur J Epidemiol 33(9): 789-810.

Vinceti M., Filippini T., Malagoli C., Violi F., Mandrioli J., Consonni D., Rothman K. J. and Wise L. A. (2019). Amyotrophic lateral sclerosis incidence following exposure to inorganic selenium in drinking water: A long-term follow-up. Environmental Research 179: 108742.

Walsh J., Jacques R., Schomburg L., Hill T., Mathers J., Williams G. and Eastell R. (2021). Effect of selenium supplementation on musculoskeletal health in older women: a randomised, double-blind, placebo-controlled trial. The Lancet Healthy Longevity 2.

WHO (2011). Selenium in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization.

Zietz B. P., Richter K., Laß J., Suchenwirth R. and Huppmann R. (2015). Release of Metals from Different Sections of Domestic Drinking Water Installations. Water Quality, Exposure and Health 7(2): 193-204.

ASIA PACIFIC OFFICES

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

BRISBANE
Level 2, 15 Astor Terrace
Spring Hill QLD 4000
Australia
T: +61 7 3858 4800
F: +61 7 3858 4801

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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