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

Selenium Technical Report

Prepared for:

National Health and Medical Research Council

SLR Ref: 640.30609-R05
Version No: -v4.0
December 2023

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BASIS OF REPORT

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DOCUMENT CONTROL

Reference	Date	Prepared	Checked	Authorised
640.30609-R05-v4.0 (FINAL, with minor updates)	15 December 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R05-v3.1 (FINAL, with minor updates, Track changes)	15 December 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R05-v3.0 (FINAL)	23 November 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R05-v2.1 (UPDATED DRAFT, Track changes)	23 November 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R05-v2.0 (REVISED DRAFT)	19 July 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R05-v1.1 (REVISED DRAFT, Track changes)	19 July 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen
640.30609-R05-v1.0 (DRAFT)	30 June 2023	Tarah Hagen, MSc, DABT, FACTRA	Giorgio De Nola, MSc, RACTRA	Tarah Hagen

CONTENTS

DOCUMENT REFERENCES

TABLES

FIGURES

APPENDICES

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
CHD	Congenital Heart Defect
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
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IPCS	International Programme on Chemical Safety
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
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
NPCT	Nutritional Prevention of Cancer Trial
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

Acronym	Definition
RoB	Risk of Bias
RR	Relative Risk
Se	Selenium
SELECT	Selenium and Vitamin E Cancer Trial
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 / bismuth brasses and silicon / silicon brasses (if available).
2. Review all primary studies and other relevant data.
3. Collate and review any useful supporting information for a potential chemical factsheet.

For the other two substances (lead and selenium), requirements 1 and 3 were completed in July 2022 (referred to as 'Stage 1' in this report).

The report herein is the Technical Report for selenium.

2 Research Questions

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

Table 1 Research Questions for Evidence Evaluation of Selenium

#	Research Questions
Health-based	
1	What level of selenium in drinking water causes adverse health effects?

#	Research Questions
2	What is the endpoint that determines this value?
3	Is the proposed option for a health-based guideline value relevant to the Australian context?
4	What are the key adverse health hazards from exposure to 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)[1]
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?
11	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review or further research?

3 Evidence Evaluation Methods

3.1 Overview

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

It was evident that some flexibility was required in adapting the methodology recorded in the final Research Protocol for selenium to maximise efficiency in sourcing relevant information. Deviations from the final Research Protocol methodology have been recorded in this report. **Figure 1** shows an overview of the literature search process followed for 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).

[1] 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).

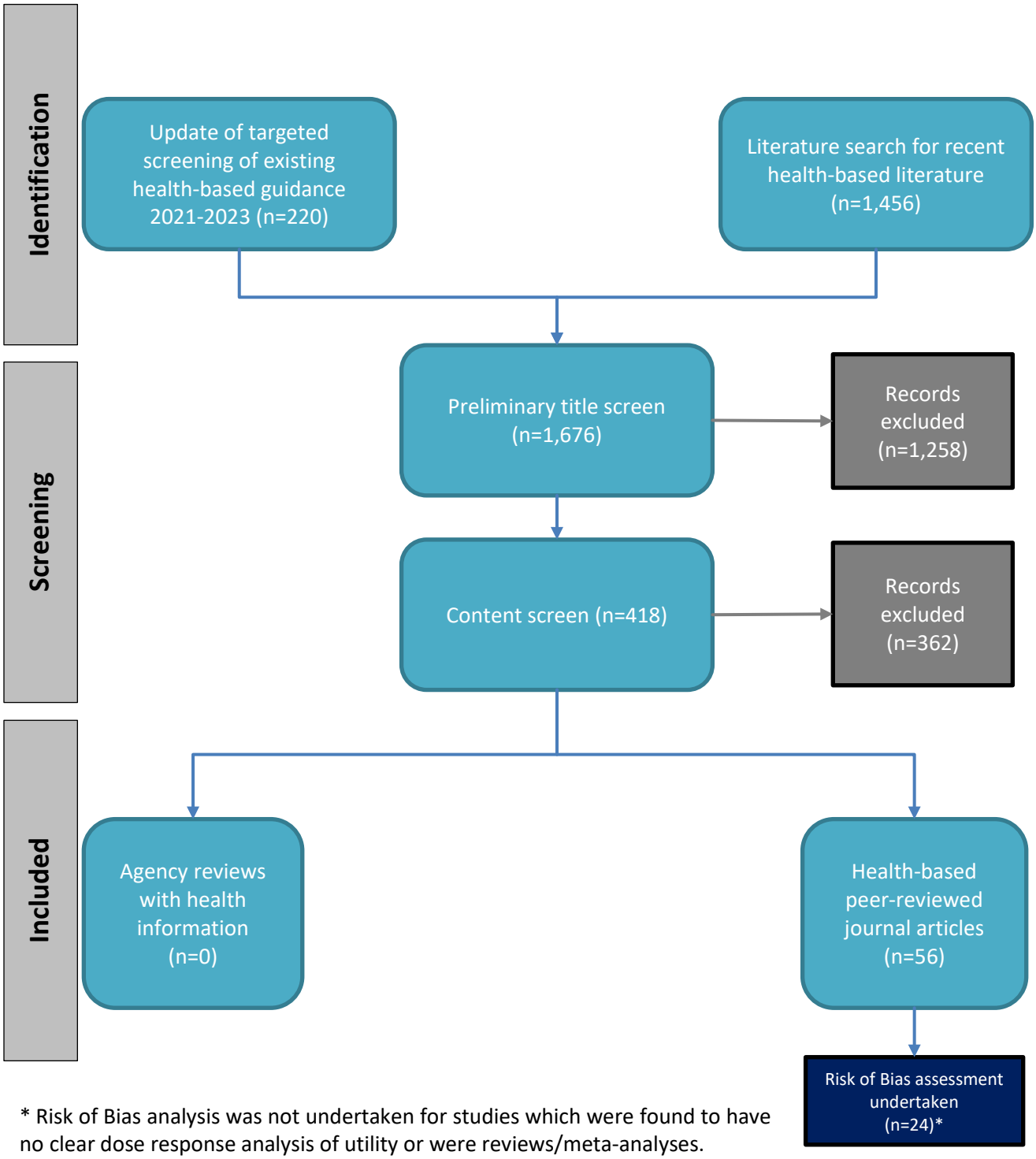

Figure 1 Overview of literature search process followed for selenium

3.2 Update of targeted screening of existing health-based guidance

Literature search strategy

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

Table 2 Search strategy for Existing Guidance/Guidelines

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

Parameter	Comments

Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of agency reports/reviews:
	• NR = Not Relevant. Information not directly relevant to answering research questions. Rationale for non-relevance was provided for transparency. E.g.
	  ○ Not HH related = Not human health related (e.g. criteria are for protection of aquatic life).
	  ○ Not a relevant exposure pathway = Since selenium is not volatile, guidelines for non-oral and non-dermal routes of exposure are not considered relevant (e.g. inhalation).
	  ○ Not relevant to substance of interest.
	• DB = Dated before 2021
	• AR = Already reviewed (in Stage 1 reports)
	• NPA = Basis of guideline value or information underpinning review conclusions are Not Publicly Available, e.g. health-based guideline value has used unpublished proprietary information which could not be verified.
	• L = Language other than English.

Validation methods used	As per the Stage 1 reports, preliminary searches were previously undertaken with more specific search terms [(Selenium) AND (toxicity or health) AND (oral); (Selenium) AND (health) AND (oral)]. Upon scanning preliminary search results for the Stage 1 reports, the reviewer found these search terms to be too specific, as very low or no agency reports appeared in the results. The search terms were consequently refined (see **Appendix A**).
Screening methods	Results were screened as follows: *Preliminary title screen* • Titles of results for each search were recorded in an Excel spreadsheet. • The researcher scanned the titles. In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The full text content of reports/reviews selected to be included from the preliminary title screen were reviewed by a subject expert to determine which reports/reviews to include in the data extraction step. Only reports/reviews which provided information relevant to answering the research questions were taken through to the data extraction step.
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in OHAT (2019).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

Data Collection and Quality Assessment

As no additional or new existing health-based guidance/guidelines were identified in the updated literature search, no data collection or quality assessment was undertaken on this information.

Data summary/synthesis

As no additional or new existing health-based guidance/guidelines were identified in the updated literature search, no data summary/synthesis was required for this information.

3.3 Detailed full evidence review of health-related studies

Literature search strategy

An additional literature search was undertaken in two scientific databases for published studies relevant to addressing the health-related research questions. A full review of the literature was undertaken as recommended in the Stage 1 reports for literature published from 2010 to March 2023.

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

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

Parameter	Comments
Search terms	The selected search terms were: • (Selenium) AND (toxicity) AND (oral) • (Selenium) AND (health) AND (oral) • (Selenium) AND (toxicity) AND (drinking water) • (Selenium) AND (health) AND (drinking water) • (Selenium) AND (plumbing) AND (leaching)
Databases	The following sources were searched: • MEDLINE/PubMed/TOXLINE • SciFinder
Publication Date	The search was conducted from 2010 to the March 2023. This is to coincide with the approximate literature searching cutoff date from the second most recent agency review identified in Stage 1. This date was estimated by consulting the bibliographies of the various agency reviews identified in Stage 1. Although one of the reviews is dated 2014 (by EFSA), the review does not appear to contain any updated information on selenium excess compared to the 2006 review by the same agency. The 2011 review by WHO is the next most-recent review which contained cited literature up to 2010.
Language	English
Study Type	Peer-reviewed published, in press, unpublished (but publicly available) and ongoing studies were included. In addition, publicly available documents of guidelines or evidence supporting guidelines (including near publication drafts) were included (see also **Section 3.2**). Study types may include existing systematic reviews or literature reviews not considered in Stage 1, human epidemiological studies, or animal studies (where there was insufficient human information). *In vitro* studies were not included.

Parameter	Comments
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of information: • NR = Not Relevant. Information not directly relevant to answering research questions. • Provides little or no useful information about substance of interest (selenium). • Language = Language other than English. • Animal studies = Animal studies were excluded since sufficient human information was available (the evidence evaluation conducted as part of the Stage 1 investigation already provided candidate guideline values based on human information, therefore experimental animal studies were considered unlikely to alter the conclusions from the Stage 1 reports).
Validation methods used	Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened (see **Appendix A**).
Screening methods	Results were screened as follows: *Preliminary title and abstract screen* • Titles of results for each search were recorded in an Excel spreadsheet. The results for each combination of search terms were exported into a separate tab of the spreadsheet. To readily eliminate duplicate records, results from all search term combinations were subsequently collated into one spreadsheet. • The researcher scanned the titles (and abstracts, if required). In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required. • Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included. *Content screen* • The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data collection and analysis step. *Additional search of relevant bibliographies* In addition to the primary search, the bibliographies of critical review papers were consulted to source additional papers of potential relevance. The latter papers were only subjected to the content screen.
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.** Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in OHAT (2019).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.

Data Collection

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

- Where deemed to be relevant to the research questions, relevant data were extracted using the example format shown in **Table 4.** The format was more applicable to epidemiological studies and was adapted slightly for reviews (note no experimental animal studies were included, as there was sufficient information in humans). The individual data extraction tables are provided in **Appendix B**.

Table 4 Example of data collection table format for full review of health-based studies

Publication Reference: ***Insert full bibliographical reference for report***		
General Information	Date of data extraction	
	Authors	
	Publication date	
	Publication type	
	Peer reviewed?	
	Country of origin	
	Source of funding	
	Possible conflicts of interest	
Study characteristics	Aim/objectives of study	
	Study type/design	
	Study duration	
	Type of water source (if applicable)	
Population characteristics	Population/s studied	
	Selection criteria for population (if applicable)	
	Subgroups reported	
	Size of study	
Exposure and setting	Type of water source (if applicable)	
	Exposure pathway	
	Source of chemical/contamination	
	Exposure concentrations (if applicable)	
	Comparison group(s)	
Study methods	Water quality measurement used	
	Water sampling methods (monitoring, surrogates)	
Results (for each outcome)	Definition of outcome	
	How outcome was assessed	
	Method of measurement	

Publication Reference: *Insert full bibliographical reference for report*		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	
Statistics (if any)	Statistical method used	
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	
Author's conclusions	Interpretation of results	
	Assessment of uncertainty (if any)	
Reviewer comments	Results included/excluded in review (if applicable)	
	Notes on study quality, e.g. gaps, methods	

Data analysis

All critical studies deemed relevant for defining the dose response of selenium were subjected to a risk of bias (RoB) assessment with the use of a RoB tool (i.e. modified OHAT tool, shown in **Table 5**)[2]. The justification for excluding some studies from RoB assessments can be found in the individual data extraction summary tables in **Appendix B.** Outcomes of the RoB assessments are provided as a rating for each parameter; individual assessments are provided in **Appendix C**.

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

Table 5 Modified OHAT risk of bias tool (example: case study report) adapted from OHAT, 2019

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

Risk of bias rating:

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

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

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

- Doses of selenium associated with no adverse effects and critical adverse health effects (where possible).
- RoB assessments across the body of evidence for each health outcome.
- Overall certainty of evidence for different health endpoints. This considered the overall confidence of the body of evidence with regard to risk of bias, indirectness/applicability, imprecision, inconsistency between studies and publication bias, with information provided as a certainty rating where possible using guidance from OHAT (2019). Note hazard identification conclusions were not developed.

These aspects are presented in the Evidence Evaluation Report.

4 Results

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

No additional existing health-based guidance/guideline values were found in the updated literature search of agency reviews. Responses to research questions are based on 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. Also included was information from various meta-analysis/reviews consulted.

4.1 Health-based research question analysis

Table 6 Synthesis of extracted data for health-based research questions

#	Research Questions	Publications	Response to Research Questions
1	What level of selenium in drinking water causes adverse health effects?	**Frisbie et al. 2015 (review)**	Raises questions with regards to the reliability of the revised WHO (2011) drinking water guideline of 40 µg/L identified in the Stage 1 review. The references identified to be critical references by this review were sourced and included individually in this Stage 2 review.
		Hadrup and Ravn-Haren 2020 (review)	Although not in drinking water, this review of case studies in the published literature on acute toxicity of oral Se found ingested doses associated with mortality are in the range of 1-100 mg Se/kg bw, i.e. ~200-2,000 times higher than the health-based guidance values used for derivation of candidate guideline values in the Stage 1 reports. The information in this review does not change the conclusions in the Stage 1 report.
		Li et al. 2012 (review) (selenosis)	Provides limited information on endemic selenosis occurrences in Chinese villages but indicates dietary intakes of Se in these areas were very high (3.2–6.8 mg/day). These intakes are 8-17x higher than the upper tolerable intake of 0.4 mg/day referenced by WHO (2011) and others in the derivation of the candidate guideline values in the Stage 1 report. Information would not change the outcomes of the Stage 1 report.
		Pan et al. 2022 (review) (congenital heart defects)	Did not investigate Se in drinking water. Meta-analysis of observational studies finding a potential relationship between low maternal Se exposure (in blood) and an increased risk of congenital heart defects (CHDs) in offspring suggesting a protective effect of Se for this effect.

#	Research Questions	Publications	Response to Research Questions
		Vinceti et al. 2001, 2009a (review)	These reviews summarise the health effects of chronic low-dose Se over-exposure in humans, with emphasis on the latest epidemiological studies and biochemical findings. The authors give general summaries for each organ system/endpoint and indicate suggestive associations between most health effects (e.g. cancer, neurotoxic effects, endocrine system effects, immune system effects, hepatotoxicity, dental caries, dermatologic effects, diabetes, amyotrophic lateral sclerosis) and Se exposure. They indicate further research is needed and suggest that adverse effects are observed at much lower doses than previously thought.
		Vinceti et al. 2013a (review)	Conclude that the 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.
		Vinceti et al. 2014 (review) (type 2 diabetes, alopecia and dermatitis)	Did not investigate Se in drinking water. Nutritional Prevention of Cancer Trial (NPCT) and the Selenium and Vitamin E Cancer Trial (SELECT) raise concerns about a possible increased risk of type 2 diabetes (T2D), alopecia and dermatitis due to Se supplements.
		Vinceti et al. 2017, 2018b (review) (alopecia and dermatitis)	At Se intake of around 250-300 µg/day there is an increased risk of type-2 diabetes. Overall, Se intake in the supplemented group of one of the largest trials averaged 300 µg/day and was associated with 'minor' adverse effects such as dermatitis and alopecia. These effects indicate the Se LOAEL is much lower than previously considered by regulatory agencies, calling for an update of the risk assessment of this element.
		Fairweather-Tait et al. 2011 (review)	Review of doses of dietary Se that have been associated with selenosis overseas (475-4,990 µg/day) as well as a summary of studies examining associations between different health endpoints. Concluded more research needed to refine upper safe levels of intake. Data do not lend themselves to defining dose response for these effects for potential revision of a guidance value.
		Rees et al. 2013 (review) (alopecia and dermatitis)	Did not investigate Se in drinking water. Systematic review of HCTs found no statistically significant effects of Se supplementation (36.4-800 µg/day) on all-cause mortality, cardiovascular disease or CVD (including CVD mortality, non-fatal CVD events, all CVD events), type 2 diabetes or total cholesterol. Relative Risks (RR) that did reach statistical significance in SELECT trial (reported by Lippman et al. 2009) found for mild alopecia and dermatitis.
		Vinceti et al. 2018c (review) (type 2 diabetes)	Did not investigate Se in drinking water. Meta-analysis of HCTs (Se at 200 µg/day) found an increased statistically significant risk of type 2 diabetes. Further inspection of relative risks potentially suggests some bias in reporting of results.

#	Research Questions	Publications	Response to Research Questions
		Zhang et al. 2016 (review) (no CVD)	Did not investigate Se in drinking water. Meta-analysis found majority of RR for Se exposure and CVD were not statistically significant. This includes for CVD from both observational studies and HCTs.
		Evans et al. 2019, Mix et al. 2015, Walsh et al. 2021 (HCT) (no effects)	Did not investigate Se in drinking water. Although limited endpoints were examined in relatively small populations, the findings support the notion that 400 µg/day of Se (upper tolerable intake in Stage 1 report) in different forms can be tolerated safely.
		Stranges et al. 2007, Thompson et al. 2016 (HCT) (type 2 diabetes)	Did not investigate Se in drinking water. In Stranges et al. (2007), administration of high-selenium baker's yeast tablet at 200 µg/day was associated with statistically significant increase in risk of T2D (all individuals = 1.55, 95% CI, 1.03 to 2.33, p=0.03). Thompson et al. (2016) found increased risk among older participants (RR = 2.21; 95% CI 1.04 to 4.67, P =0.03).
		Lippman et al. 2009 (HCT) (alopecia and dermatitis)	Did not investigate Se in drinking water. This reference has been cited in various reviews (see above) for the finding of two mild adverse events in a large HCT where adult male patients were given 200 µg Se/d as selenomethionine. These were: • 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). (Found no statistical significance for type 2 diabetes).
		Karp et al. 2013, Klein et al. 2011, Lance et al. 2017 (HCT) (no effects)	Did not investigate Se in drinking water. Found no evidence of increased adverse events of diabetes in cancer patients receiving 200 µg/day as selenised yeast or selenomethionine, nor for prostate cancer, T2D, lung, colorectal, and total other cancers, deaths and grade 4 cardiovascular events.
		Bagherzadeh et al. 2022 (CaCo) (no ulcerative colitis)	This small-scale study found no association between Se in drinking water at low concentrations (3 µg/L) and ulcerative colitis.
		Bao et al. 2020, Wang et al. 2022 (CaCo) (no oral cancer)	Did not investigate Se in drinking water. Suggests inverse association between serum Se levels and oral cancer risk (no dose response information reported for adverse effects).

#	Research Questions	Publications	Response to Research Questions
		Vinceti et al. 2010a (CaCo) (ALS)	Small study found exposure to inorganic Se in drinking water (≥1 µg/L vs. <1 µg/L) was found to be associated with development of amyotrophic lateral sclerosis (ALS) (RR 5.4, 95% CI 1.1-26).
		Mandrioli et al. 2017 (CaCo) (ALS)	Did not investigate Se in drinking water. Very small study in ALS patients with specific genetic mutations found no statistically significant odds ratio (OR) of ALS for various Se species in patient cerebrospinal fluid (CSF), with the exception of selenomethionine where 95% CI were very large.
		Vinceti et al. 2013b (CaCo) (no ALS)	Did not investigate Se in drinking water. Risk ratios (RR) for ALS and selenite, human serum bound Se and total organic Se in CSF were not statistically significant.
		Vinceti et al. 2012 (CaCo) (melanoma)	Did not investigate Se in drinking water. Small study found a statistically significant positive association between plasma Se (but not toenail or dietary Se) and melanoma in the high quartile group (RR = 5.86 (1.53 – 22.31), p = 0.010) compared to the low quartile group.
		Hao et al. 2016, Liu et al. 2018 (CrSe) (longevity)	Potential beneficial effect of Se on longevity. Estimated intakes of Se from drinking water (and rice) were relatively low (i.e. mean drinking water ranged from 0.33 to 2.88 µg/L in Hao et al. 2016; concentration difference of Se in drinking water in Liu et al. 2018 study was very minimal, ~0.95 vs ~2.0 µg/L); no information reported for dose response of adverse effects of Se.
		Yang et al. 2022 (CrSe) (glycaemic indices)	Did not investigate Se in drinking water. Positive associations were found between blood Se concentration and glycaemic biomarkers in US adults with normoglycaemia.
		Lacaustra et al. 2010 (CrSe) (CVD)	Did not investigate Se in drinking water. Found potential risk factors of CVD (i.e. increased cholesterol) to be associated with Se levels in serum of US population.
		Stranges et al. 2010 (Co) (T2D)	Did not investigate Se in drinking water. Comparison of highest (75.1 µg/day) to the lowest quintile (41.7 µg/day) of Se intake was associated with higher risk of T2D (OR = 2.39, 95% CI: 1.32 – 4.32; P = 0.005). Most other associations for T2D and dietary Se intake were not statistically significant.
		Vinceti et al. 2016 (Co) (ALS, Parkinson's, cancer)	Comparison of exposed group (drinking water containing inorganic Se at 8 µg/L) to 'unexposed' group (0.6 µg/L) for a large number of health endpoints found majority of results not statistically significant except lymphohematopoietic cancers (mainly multiple myeloma, RR 2.24, 95% CI 1.05–4.78), Parkinson's disease (RR 2.47, 95% CI 1.15–5.28) and ALS (RR 2.79, 95% CI 1.01–7.67).

#	Research Questions	Publications	Response to Research Questions
		Vinceti et al. 2018a (Co) (cancer)	Same cohort as Vinceti et al. (2016) and other Vinceti papers. Exposed (8-10 µg/L) vs. unexposed (<1 µg/L) groups compared for a large variety of cancer incidence. There was a statistically significant result for melanoma (RR = 7.11, 2.11–23.89) and urinary tract tumours (RR = 2.16, 1.06–4.39). All others were not statistically significant with large Cis.
		Vinceti et al. 1996, 2019 (Co) (ALS)	Same cohort as other Vinceti papers. Vinceti et al. (1996) found exposure to Se in drinking water may be associated with ALS. Later paper found exposed (≥ 1 µg Se/L) incidence rate ratios (IRR) for ALS were statistically significantly higher (IRR 2.8, 95% CI 1.3, 6.0) compared to unexposed (<1 µg/L).
		Kristal et al. 2014 (Co) (prostate cancer)	Did not investigate Se in drinking water. Found an association between increased risk of high-grade prostate cancer among men in the SELECT trial and toenail Se concentrations (in patients receiving 200µg Se/day) (Quartile 5, any Se: 1.96, 95% CI 1.00-3.86).
		Aldosary et al. 2012, MacFarquhar et al. 2010 (CaS) (selenosis)	Case series provides evidence of classic selenosis symptoms (e.g. alopecia, diarrhoea, memory difficulties, myalgia, joint pain, nail brittleness, nausea) in individuals after 10-~60 days' consumption of a liquid dietary supplement containing high amounts of Se due to a formulation error. Daily dose ingested by each individual was ~40.8 mg/day (i.e. ~100x the upper safe limit specified by WHO). Does not alter conclusions of Stage 1 reports.
		Kilness and Hochberg 1977 (CaS) (ALS)	Four cases of unrelated farmer-ranchers (without family history of ALS) diagnosed with ALS between 1964-1975 living in sparsely populated county in South Dakota (living <3km apart); cases occurred in a region where naturally occurring Se intoxication was endemic in farm animals. No intakes of drinking water concentrations provided.

#	Research Questions	Publications	Response to Research Questions
2	What is the endpoint that determines this value?	**All papers summarised in RQ 1**	None of the publications consulted apart from Vinceti et al. (2013) have proposed a new health-based guidance/guideline value for Se in drinking water/diet. Vinceti et al. (2013) suggest a value of 1 µg/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 • Mild alopecia and dermatitis (potential effects of selenosis) at 200 µg/day (as selenomethionine) • Prostate cancer at 200 µg/day (as selenomethionine). • Type 2 Diabetes at 200 µg/day as Se-containing baker's yeast tablet. • ALS at 8 µg/L in drinking water (or at ≥1 µg/L). • Multiple myeloma at 8 µg/L in drinking water. • Urinary tract tumours at 8 µg/L in drinking water. • Melanoma at higher plasma Se and at 8 µg/L in drinking water. • Increased cholesterol (risk factor for CVD) at higher serum Se.
3	Is the proposed option for a health-based guideline value relevant to the Australian context?	**Various**	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. (2013) that the guideline value should be lowered to 1 µg/L. If this guideline value (or the other candidate guideline value of 3 µg/L summarised in the Stage 1 reports) 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?	**Various**	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 different 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 investigating exposure to Se concentrations in drinking water ≥ 1 µg/L or 8-10 µg/L. However, this is tempered by the overall confidence in these studies (to be assessed in the evaluation report). 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 (to be assessed in the evaluation report).

#	Research Questions	Publications	Response to Research Questions
5	Are there studies quantifying the health burden (reduction or increase) due to selenium?	**Various**	Yes. See response to Research Question 1. Some epidemiological information (albeit limited) suggests a potential protective effect of selenium in the diet/drinking water in relation to some 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 selenium in diet/drinking water.
6	What is the critical human health endpoint for selenium?	**Various**	See response to Research Question 2. The critical human health endpoint for selenium exposure is uncertain due to important HCTs often only including a single dose of selenium 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. Nevertheless, the critical health endpoint may still be selenosis (as evidenced by mild alopecia and dermatitis in one of the largest HCTs conducted with selenomethionine) or it may be one of the other endpoints investigated in HCTs and/or cohort studies.
7	What are the justifications for choosing this endpoint?	As above	As above.

4.2 Exposure-related research question analysis

Table 7 Synthesis of extracted data for exposure-related research questions

#	Research Questions	Publications	Response to Research Questions
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)	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?	**Zietz et al. 2015**	This study 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).
		No studies were found investigating the leachability of Se from lead replacement alloys in plumbing. It is suggested that leachability data for Se from lead replacements in plumbing products be generated for Australian conditions to provide information on the species of Se in water and in leachates from lead replacements as well as exposure concentrations.	

4.3 Risk-based research question analysis

Table 8 Synthesis of extracted data for risk-associated research questions

#	Research Questions	Publication	Response to Research Questions
10	What are the risks to human health from exposure to 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 selenium 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. These concerns were expressed in journal articles that were available at the time that the WHO (2011) drinking water guideline (DWG) was derived (e.g. Lacaustra et al. 2010, Stranges et al. 2007, 2010; Vinceti et. al. 1996, 2001, 2009a, 2009b, 2010). 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. The evaluation report provides an overall evaluation of the confidence in the data for individual health endpoints. Based on this evaluation, candidate guideline values for Se are consistent with those presented in the Stage 1 report (i.e. 20 or 3 µg/L, depending on whether the recent information is included). Vinceti et al. (2013a) suggest a lower guideline value of 1 µg/L for Se in drinking water. 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 selenium in Australian drinking water are likely low even if the lower candidate guideline of 3 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 (up to 12 µg/L in parts of NT, see Research Question 8). In addition, it is reiterated that no data were found for leachability of Se from lead replacements in plumbing, thus exposure concentrations (and therefore risks to human health) of Se at the tap are unknown.

#	Research Questions	Publication	Response to Research Questions
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 selenium (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. The Se urinary levels in farmer Case 1 in the report by Kilness and Hochberg (1977) of 0.45 mg/L (as opposed to 0.03 mg/L expected for people in non-seleniferous areas) may lend some support to this theory, i.e. for the difference in uptake/toxicity of inorganic vs. organic selenium. Contrasting information from MacFarquhar et al. (2010) states that ingestion of organic selenium in the form of selenomethionine is associated with much higher serum selenium concentrations than ingestion of inorganic forms. Similarly in the study by Mandrioli et al. (2017), RR with ALS were not statistically significant for any form of Se in CSF apart from selenomethionine, again suggesting organic Se may be more potent. In a study by Vinceti et al. (2013b), RR of ALS were 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 selenium. This conflicting information suggests that additional research is likely required to clarify the importance of the chemical form of selenium on overall toxicity.

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APPENDIX A

Literature search screening outcome spreadsheets

Appendix A contents here

APPENDIX B

Data extraction tables – Full Review for Health-based Studies

Aldosary et al. 2012

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Aldosary BM, Sutter ME, Schwartz M, Morgan BW
	Publication date	2012
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Saudi Arabia and USA
	Source of funding	Funding sources not described (authors are from hospitals and a university).
	Possible conflicts of interest	The authors declare no conflicts of interest.
Study characteristics	Aim/objectives of study	To describe the clinical features, biomonitoring data of selenium levels, and the estimated total dose of selenium ingestions of nine patients with selenium toxicity who presented after use of a liquid dietary supplement with a formulation error.
	Study type/design	Case series
	Study duration	Exposures occurred between January 2008 and April 2008. • Patient 1: 38-year old male (24 days) • Patient 2: 37-year old female (24 days) • Patient 3: 15-year old male (24 days) • Patient 4: 57-year old male (47 days) • Patient 5: 56-year old female, spouse of Patient 4 (47 days) • Patient 6: 43-year old female (uncontaminated product for 10 years, then contaminated product for 46 days) • Patient 7: 49-year old male (non-contaminated product for years without effects, contaminated product for 18 days intermittently in a 56-day period) • Patient 8: 46-year old female (10 days) • Patient 9: 57-year old male (uncontaminated product for 6 years, then contaminated product likely for <60 days)
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Between March and May 2008, 9 individuals were evaluated in the authors' medical toxicology clinics with a history of ingesting a liquid nutritional supplement implicated in selenosis. • Two patients presented with symptoms but no diagnosis. • Four patients presented after the FDA warning but had no biological testing performed. • Three patients were referred after having confirmatory biological testing performed on them by their physician.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable

Publication Reference: 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.		
	Size of study	9 case reports
Exposure and setting	Exposure pathway	Oral (ingestion of liquid nutritional supplement containing selenium and possibly chromium)
	Source of chemical/contamination	Not stated
	Exposure concentrations (if applicable)	FDA analysis of this product found the selenium concentration to be 1360 µg/ml, approximately 200 times the claimed concentration of 6.6 µg/ml and more than 700 times the US recommended dietary allowance (RDA) per serving of 30 ml per day. Additional testing of this product showed a modestly elevated trivalent chromium concentration, which was 17 times the concentration of 6.6 µg/ml reported on the label. After the formulation error was identified, the manufacturer voluntarily removed the product from the market. **Estimated cumulative amount of Se ingested ranged from 408 to 2448 mg (i.e. 40.8 mg/day).**
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
	Definition of outcome	

Publication Reference: 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.		
Results (for each outcome)	How outcome was assessed	• Patient 1: Severe myalgia in lower extremities made worse with exiting vehicle and muscle massage; scalp alopecia and brittle fingernails; memory difficulties, lower limb tingling sensations, tinnitus by third week • Patient 2: Hair loss; then after two weeks nail changes, memory difficulties, ongoing hair loss; after three weeks, numbness and tingling in lower limbs, tinnitus • Patient 3: Nail changes (weak and brittle); within second week, decreased memory and ability to focus; end of second week, hair loss and myalgia • Patient 4: Diarrhoea; three weeks later, onset of hair loss, memory difficulty and fingernail abnormalities. • Patient 5: Diarrhoea; two weeks later, hair loss of scalp progressing to entire body except eyebrows; difficulty concentration, arthralgias, discolouration of fingernails. • Patient 6: Alopecia, pain in knee, hip and shoulders; progression to severe tenderness over entire body; by end of second week, nail discolouring, constipation, and nausea; progression to blisters on tongue and gums, metallic taste in mouth, garlic odour breath, desquamation of soles and palms. • Patient 7: Malaise progressing to cough, arthralgia and myalgia; diarrhoea and abdominal pain; by second week, hair loss, nail changes and memory difficulty; diarrhea lasted 1 month. • Patient 8: Hair loss, painful rash with bullae over scalp, metallic taste and garlic odour breath, memory difficulty, myalgia, fatigue. • Patient 9: Hair loss; progressively developed myalgia, memory difficulty, tinnitus, symptoms of sinusitis • No patient suffered from major co-morbid illness that would have contributed to their presentation. Neurologic and cardiovascular examinations were normal. • After 4 weeks of abstinence of the implicated product, most patients had significant resolution of their symptoms.
	Method of measurement	• Evaluated by two different medical toxicologists who determine what additional testing to obtain. • Standardised medical questionnaire completed by all patients, including past medical history, family history, social history, occupational history, exposure history and a review of symptoms.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• Selenium is an essential nutrient at minute amounts and can result in adverse effects and toxicity in large amounts. Selenosis symptoms may initially present within the first week of exposure. Alopecia, mental alertness changes, fingernail changes, and gastrointestinal symptoms were the most common findings seen in our case series. The dietary supplement industry can expose the public to the risk of adverse events.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• This case series of 9 case reports provides evidence of classic selenosis symptoms (e.g. alopecia, diarrhoea, memory difficulties, myalgia) in individuals aged 15-57 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). • As the dose of selenium ingested by individuals in this case series was much greater than the dose on which the candidate guidelines are based in Stage 1, this study would not change any of the outcomes of that report, and therefore was not subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Algotar et al. 2013a

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Algotar AM, Stratton MS, Ahmann FR, Ranger-Moore J, Nagle RB, Thompson PA, Slate E, Hsu CH, Dalkin BL, Sindhwani P, Holmes MA, Tuckey JA, Graham DL, Parnes HL, Clark LC, Stratton SP
	Publication date	2013
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA and New Zealand
	Source of funding	This work was supported by grants from the National Cancer Institute (PHS CA077789 and PHS 023074).
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	To investigate the effect of Se supplementation on prostate cancer incidence in men at high risk for prostate cancer.
	Study type/design	Human controlled trial (HCT) – Phase 3, randomised, double-blinded, placebo-controlled

Publication Reference: 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.		
	Study duration	Daily for 3-5 years Followed up every six months. Median months of follow-up were 36.8, 35.4, and 35 in each group.
	Type of water source (if applicable)	Not applicable (Se given via pill of high-selenium yeast)
Population characteristics	Population/s studied	Subjects had to be < 80 years of age with one or more of the following: prostate specific antigen (PSA) >4ng/ml, digital rectal exam (DRE) suspicious for prostate cancer, or PSA velocity >0.75ng/ml/year. All subjects had a prostate biopsy negative for cancer.
	Selection criteria for population (if applicable)	Subjects were recruited from urology offices at 20 sites in the United States and New Zealand. Participants with adequate adherence to the protocol (80% or more pills taken during a 30 day run-in period) were randomised to receive placebo (N = 232), selenium 200 µg/day (N =234), or selenium 400 µg/day (N=233). Treatment group assignments were stratified based on study clinic and ethnicity. Subjects were followed every six months for up to up to five years. For subjects in the US, participation was complete at five years, whereas subjects in New Zealand received intervention for no more than three years.
	Subgroups reported	Placebo, Selenium 200 µg/day, Selenium 400 µg/day
	Size of study	Placebo, n=232 Selenium 200 µg/day, n=234 Selenium 400 µg/day, n=233
Exposure and setting	Exposure pathway	Oral (via pills containing high-selenium yeast)
	Source of chemical/contamination	Purposeful administration of high-selenium containing yeast in capsule/pill form. High-selenium yeast was provided by Cypress Systems (Fresno, CA). The study agent (two doses) and matched placebo caplets were coated with titanium oxide to ensure identical appearance, weight, taste and smell.
	Exposure concentrations (if applicable)	0, 200 or 400 µg Se/day
	Comparison group(s)	Placebo group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: 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.		
	How outcome was assessed	• The primary endpoint was the incidence of biopsy-proven prostate cancer over the course of the study. The secondary endpoint was the rate of change of PSA over time (i.e. PSA velocity) using biannual PSA measurements. • Neither treatment group was significantly different from placebo in terms of study completion or withdrawal. • Twenty-six (11.3%), 24 (10.3%) and 23 (10%) subjects reached the study endpoint (biopsy proven prostate cancer) in the placebo, Se 200 µg/day and Se 400 µg/day treatment groups, respectively (p=0.88). • Time to study endpoint was not statistically significantly different in the two selenium groups versus placebo after adjusting for age, plasma selenium concentration, and serum PSA at baseline. The PSA velocities for the 200 and 400 µg/day treatment groups did not differ significantly from placebo. Of the 699 randomized participants, there were five deaths (2.2%) in the placebo group, three deaths (1.3%) in the 200 µg/day selenium treatment group, and two deaths (0.9%) in the 400 µg/day selenium treatment group (p = 0.45, Table 3). None were related to study treatment. • With respect to grade 3 or 4 adverse events, there were 43 (18.6%) in the placebo group, 45 (19.2%) in the 200 µg/day group, and 39 (16.8%) in the 400 µg/day group (p = 0.78). Time to onset of the first grade 3 or 4 adverse event was the same in all treatment groups (p = 0.79). No significant differences were seen in the incidences of cataract/glaucoma or in hair/nail changes in the three treatment groups.
	Method of measurement	Blood was drawn at baseline and at each subsequent visit to analyse complete blood count, plasma selenium concentration and PSA. At each visit, questionnaires were administered to obtain demographic characteristics, medical history, selenium toxicity information, and urological symptoms to verify eligibility. Tissue samples from the subject's qualifying biopsy were requested from the subject's physician and compiled in a biospecimen repository. Total selenium concentration was measured by automated electrothermal atomic absorption spectrophotometry. Expected adverse events included brittle nails, brittle hair, garlic breath, and liver/kidney function test abnormalities. Based on prior observations, additional potential expected adverse events included cataracts, glaucoma, and non-melanoma skin cancers. Collection of adverse event data occurred at each study visit.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	875 recruited, 699 (79.9%) randomised to receive placebo (n=232), 200 µg/day Se (n=234) or 400 µg/day Se (n=233). 292 (41.8%) completed the trial, 74 (10.6%) reached the study endpoint (diagnosis of biopsy proven prostate cancer) and 61 (8.7%) were still receiving study agent when trial was stopped by a Data and Safety Monitoring Committee (DSMC) (see below).
Statistics	Statistical method used	

Publication Reference: 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.		
(if any)	Details on statistical analysis	The statistical analyses for this trial used the intention-to-treat principle. The sample size estimate for this trial was based on a three-arm design. It was estimated that 700 participants would allow for detection of at least a 50% treatment effect with 90% power, significance level of 0.05 with a dropout rate approximately 5% per year. Standard survival analysis techniques were used for analysis of the primary end-point. Cox proportional hazards regression was used to determine if the incidence of prostate cancer in the selenium arms was statistically significantly different as compared to placebo after adjusting for potential confounders such as age at baseline, baseline PSA, and baseline selenium concentrations. A mixed effects model with patient-level random effects was used to assess the effect of selenium on PSA velocity in the three treatment groups. Models were adjusted for race, baseline selenium, baseline age, duration of subject on study, and type of assay used to estimate PSA. Analyses stratified by tertiles of baseline selenium were also performed to determine whether the effect of selenium supplementation differed by baseline selenium level. Proportions of adverse events were compared across groups using Fisher's exact and log-rank test. An external DSMC was established before study initiation. This committee was responsible for reviewing protocol amendments, consent forms, accrual and retention rates, adverse events, and data analysis reports. Based on recommendation from the DSMC, an interim analysis for futility was carried out by an external statistician using a conditional power approach. The focus of these analyses was to determine the probability of finding a statistically significant difference in time to occurrence of prostate cancer between placebo and the combined selenium arms if the study was continued as specified in the protocol. These analyses indicated that the probability (conditional power) that the trial would eventually reach the conclusion that the selenium treatment arms are significantly better than the placebo arm was very low. Hence the DSMC recommended that the trial be stopped before all participants completed the full intervention duration. The interim analysis for futility was based on a conditional probability approach, whereas the data analysis plan for the full study utilized the Cox proportional hazards model.
	Relative risk/odds ratio, confidence interval?	The hazard ratios [95% confidence intervals] for risk of developing prostate cancer in the selenium 200 µg/day or the selenium 400 µg/day group were 0.94 [0.52, 1.7] and 0.90 [0.48, 1.7] respectively.
Author's conclusions	Interpretation of results	• Selenium supplementation appeared to have no effect on the incidence of prostate cancer in men at high risk.
	Assessment of uncertainty (if any)	Not done.

Publication Reference: 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.		
Reviewer comments	Results included/excluded in review (if applicable)	• This long-term Phase 3, randomised, double-blinded, placebo-controlled HCT found no effect of Se supplementation (at 200 or 400 µg/day) on incidence of prostate cancer in met at high risk. There were also no significant differences in the incidence and frequency of adverse events between the treated and placebo groups. • Although limited health endpoints were investigated in this study, it does provide an indication that a dose of 400 µg/day supplemental selenium as yeast (containing both organic and inorganic selenium) to males over a period of 3-5 years did not result in selenosis or an increase in prostate cancer incidence. • As the study provides some information on the dose-response of selenium at doses similar to those on which candidate guidelines are based, it was subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Algotar et. al. 2013b

Publication Reference: 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.		
General Information	Date of data extraction	20/06/2023
	Authors	Algotar, A.M., Hsu, C.H., Singh, P., Stratton, S.P.
	Publication date	Accepted 6 March 2013
	Publication type	Journal Article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This project was supported by grants from the National Cancer Institute (PHS CA079080 and CA023074).
	Possible conflicts of interest	The authors declare no conflict of interests.
Study characteristics	Aim/objectives of study	A longitudinal study was conducted to investigate the effect of selenium supplementation on serum glucose levels in elderly men.
	Study type/design	Human Controlled Trial (HCT). A randomised double-blind placebo-controlled Phase 3 clinical trial
	Study duration	Up to 5 years (average duration 3 years)
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: 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.		
Population characteristics	Selection criteria for population (if applicable)	Men enrolled in the Negative Biopsy Trial (NBT) at high risk of prostate cancer, as evidenced by PSA >4 ng/mL and/or suspicious digital rectal examination and/or PSA velocity (rate of PSA change over time) >0.75 ng/mL per year. In addition, subjects were required to have undergone a prostate biopsy negative for cancer within 12 months of enrolment.
	Subgroups reported	Not applicable
	Size of study	A total of 699 subjects were randomised to receive Placebo, 200 µg/day selenium, or 400 µg/day selenium
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplement
	Exposure concentrations (if applicable)	Placebo, 200 µg/day selenium, or 400 µg/day selenium
	Comparison group(s)	Placebo group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Whether the rate of change of serum glucose levels was significantly different in the selenium-supplemented groups compared with placebo.
	How outcome was assessed	Serum glucose levels were measured at baseline and at alternate follow-up visits by Sonora Quest Laboratories (Tucson, AZ, USA). Plasma selenium was measured at baseline and at every follow-up visit using electrothermal atomic absorption spectrophotometry. Glucose values were transformed using the logarithmic function to correct for skewed distribution. Questionnaires at baseline and at every follow-up visit recorded diabetes status.
	Method of measurement	Selenium: electrothermal atomic absorption spectrophotometry Serum glucose: Pathology lab
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Placebo (n = 232), 200 µg/day selenium (n = 234), or 400 µg/day selenium (n = 233).
Statistics (if any)	Statistical method used	Mixed-effects regression models were used to assess whether the rate of change of serum glucose levels was significantly different in the selenium-supplemented groups compared with placebo. Sensitivity analyses were performed to assess the robustness of findings and to minimise the possibility of residual bias due to fasting status.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	• 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.

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• These results do not support a relationship between selenium supplementation and risk of diabetes. • Hence, recommendations regarding selenium supplementation based on increased risk of diabetes seem premature.
	Assessment of uncertainty (if any)	• Sensitivity analyses demonstrated comparable results for models using the total population and models restricted to subjects with only fasting glucose data.
Reviewer comments	Results included/excluded in review (if applicable)	This study was done as current literature regarding the effect of selenium supplementation on the risk of diabetes is inconclusive. This article was subject to a RoB assessment as it is a HCT.

Bagherzadeh et al. 2022

Publication Reference: 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.		
General Information	Date of data extraction	08/06/2023
	Authors	Bagherzadeh F, Horestani MK, Ahmadi A, Bahreini R, Fadaei A, Forouzandeh S, Hemati S, Mohammadi-Moghadam F
	Publication date	2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Iran
	Source of funding	This work was supported by research deputy of Shahrekord University of Medical Sciences [Grant No. 2583]
	Possible conflicts of interest	Authors declare they have no conflict of interest.
Study characteristics	Aim/objectives of study	To evaluate the relationship between the concentration of metal(loid)s including Pb, As, Ni, Cu, Zn, Fe, and Se in drinking water with incidence of ulcerative colitis (UC).
	Study type/design	Case-control
	Study duration	Not applicable
	Type of water source (if applicable)	Not stated (drinking water)
Population characteristics	Population/s studied	35 UC patients and 35 healthy subjects in Hajar hospital, Shahrekord, Iran. Inclusion criteria were patients with UC who have passed at least one year of their diagnosis. Those who participated in the study did not receive any mineral supplements at least three months prior to sampling. Individuals who did not have UC or had consumed a mineral supplement were excluded.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	N=70 (35 UC patients, 35 controls).

Publication Reference: 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.		
Exposure and setting	Exposure pathway	Drinking water (oral)
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Mean: 3 µg/L in both groups (range 0-60 µg/L)
	Comparison group(s)	Control group (35 healthy patients)
Study methods	Water quality measurement used	Graphite furnace atomic absorption spectrophotometry
	Water sampling methods (monitoring, surrogates)	Not stated (drinking water samples of patients and controls were taken in 500 mL polyethylene bottles previously washed using Milli-Q water). The pH of the samples was adjusted to < 2 using concentrated nitric acid (65 %) and was kept in the dark at 4 °C until analysis.
Results (for each outcome)	Definition of outcome	• The average concentration of Se in patients and controls was similar and not significantly different (P = 0.359). • No significant difference between heavy metal concentrations in the drinking water of the two groups. • No significant correlation between Se in patients' intestinal tissue and drinking water.
	How outcome was assessed	
	Method of measurement	• Intestinal biopsies were obtained by colonoscopist after disease was confirmed by histopathological evaluation.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Statistical analysis was performed using IBM SPSS statistics software, version 23. An independent sample t-test and chi-square test were run for comparing the heavy metals concentration in colitis and in normal tissues. Pearson correlation coefficient was performed to investigate relationship between heavy metals concentration in the intestinal tissues and drinking water. The age ranges among two groups were matched and multivariate logistic regression was used to estimate the odd ratios and 95% confidence intervals for association risk of UC. P < 0.05 was considered as a statistically significant.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	1.002 (1.0008 ~ 1.003) (i.e. no significant increased risk of UC due to Se).
Author's conclusions	Interpretation of results	• The Se concentration in the control group samples was higher than that in the UC patients, but there was no significant difference between the two groups.
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	

Publication Reference: 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.		
	Notes on study quality, e.g. gaps, methods	• Small scale case-control study which indicated no association between Se in drinking water at low concentrations (3 µg/L) and UC. • Since study provides no dose response information for adverse effects, it was not subjected to risk of bias assessment.

Bao et al. 2020

Publication Reference: Bao X., Yan L., Lin J., Chen Q., Chen L., Zhuang Z., Wang R., Hong Y., Qian J., Wang J., Chen F., Liu F., Wang J. and He B. (2020). Selenoprotein genetic variants may modify the association between serum selenium and oral cancer risk. Oral Dis.		
General Information	Date of data extraction	08/06/2023
	Authors	Bao X, Yan L, Lin J, Chen Q, Chen L, Zhuang Z, Wang R, Hong Y, Qian J, Wang J, Chen F, Liu F, Wang J, and He B
	Publication date	2020
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	Program for New Century Excellent Talents in Fujian Province, Grant/Award Number: 2018B029; High-level Talents research Start-up Project of Fujian Medical University, Grant/Award Number: XRCZX2018001; Scientific Research Talents Training Project of Health and Family Planning Health Commission in Fujian Province, Grant/Award Number: 2019-ZQN-68, 2018-1-71 and 2017-ZQN-57; Fujian Natural Science Foundation Program, Grant/Award Number: 2019J01314; Startup Fund for Scientific Research of Fujian Medical University, Grant/Award Number: 2017XQ1011; Joint Funds for the Innovation of Science and Technology of Fujian province, Grant/Award Number: 2017Y9103
	Possible conflicts of interest	Authors declare they have no conflict of interest.
Study characteristics	Aim/objectives of study	To investigate the potential effect of selenoprotein genes (including GPx and TXNRD) in the association of serum Se with oral cancer risk.
	Study type/design	Case-control
	Study duration	September 2011-December 2018 (~7 years)
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: Bao X., Yan L., Lin J., Chen Q., Chen L., Zhuang Z., Wang R., Hong Y., Qian J., Wang J., Chen F., Liu F., Wang J. and He B. (2020). Selenoprotein genetic variants may modify the association between serum selenium and oral cancer risk. Oral Dis.		
Population characteristics	Selection criteria for population (if applicable)	Hospital-based case-control study in Fujian province, China. Cases were consecutively recruited from Department of Oral and Maxillofacial Surgery, the First Affiliated Hospital of Fujian Medical University, and histologically confirmed to be primary oral cancer. All patients were defined according to the World Health Organization classification of oral tumours. Controls were all patients with various acute non-neoplastic conditions admitted to other departments of the same hospital at the same time. All cases did not have previous history of chemotherapy and radiotherapy and controls without history of any malignant disease. Subjects without whole blood sample and with unqualified Deoxyribonucleic acid (DNA) quality were also excluded.
	Subgroups reported	235 oral cancer cases, 406 controls
	Size of study	N=641
Exposure and setting	Exposure pathway	Not stated (exposure was measured by serum Se levels)
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Median serum Se levels: • 115.25 µg/L (P25–P75: 78.29–148.48) for case group • 154.39 µg/L (P25–P75: 140.30–175.94) for control group
	Comparison group(s)	Controls (n=406)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Compared with the lowest tertile of Se concentration, those with Se levels in the third tertile were associated with the lower risk of oral cancer (OR = 0.228; 95% CI: 0.135, 0.384). After additional adjustment for genetic risk score (GRS, derived from selenoprotein genetic variants), the model demonstrated the superior goodness of fit. When stratified by GRS, the negative correlation of serum Se was more pronounced among those with low risk (i.e., lower GRS). Moreover, there is a multiplicative interaction between serum Se and GRS for the risk of oral cancer (p = .001). • More cases than controls were male and with lower BMI. Additionally, cases more often had higher education and were more likely to be smokers and drinkers. The case and control groups were balanced in terms of age and marital status. Median serum Se concentration was 115.25 µg/L (P25–P75: 78.29–148.48) for case group and 154.39 µg/L (P25–P75: 140.30–175.94) for control group and the difference was statistically significant (p < 0.001).
	How outcome was assessed	
	Method of measurement	• Genotyping on peripheral blood performed by MassARRAY system. • Se levels in serum measured by ICP-MS.

Publication Reference: Bao X., Yan L., Lin J., Chen Q., Chen L., Zhuang Z., Wang R., Hong Y., Qian J., Wang J., Chen F., Liu F., Wang J. and He B. (2020). Selenoprotein genetic variants may modify the association between serum selenium and oral cancer risk. Oral Dis.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Comparisons of demographic characteristic distributions between cases and controls were examined with chi-square test or t test. Serum levels of Se were expressed as median (quartile25–quartile75), and differences between cases and controls were assessed by Wilcoxon rank sum test. Considering the limited capacity of a single SNP, genetic risk score (GRS) was calculated by adding up the number of risk alleles of the total seven SNPs. Scores of the different genes were added together to obtain the genetic risk score. Unconditional logistic regression was used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All p-values were two-sided, and $p < .05$ was considered as statistically significant.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Compared with the lowest tertile of Se concentration, those with Se levels in the third tertile were associated with the lower risk of oral cancer (OR = 0.228; 95% CI: 0.135, 0.384).
Author's conclusions	Interpretation of results	• The results of the study showed an association between low concentration of serum Se and risk of oral cancer after adjustment for selenoprotein-related genetic variants and others factors. This study supported the hypothesis that selenoprotein-related gene polymorphisms may modify the association between serum Se and oral cancer risk.
	Assessment of uncertainty (if any)	These results are very preliminary in nature, and further prospective studies are warranted on larger populations.
Reviewer comments	Results included/excluded in review (if applicable)	• Case-control study suggesting an inverse association between serum Se levels and oral cancer risk. • Since study provides no dose response information for adverse effects (and no intake or drinking water concentrations), it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Bleys et. al. 2008

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Bleys, J., Navas-Acien, A., Guallar, E.
	Publication date	Reprinted Feb 25, 2008
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA

Publication Reference: 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.		
	Source of funding	This study was supported by grants R01 ES012673 from the National Institute of Environmental Health Sciences and 0230232N from the American Heart Association.
	Possible conflicts of interest	None reported
Study characteristics	Aim/objectives of study	Authors evaluated the association between selenium levels and all-cause and cause-specific mortality in a representative sample of US adults.
	Study type/design	Cohort
	Study duration	Followed up for mortality for up to 12 years.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Adult participants were recruited from 1988 to 1994 from the Third National Health and Nutrition Examination Survey (NHANES)
	Selection criteria for population (if applicable)	
	Subgroups reported	Tertiles of serum selenium levels based on the weighted population distribution (Tertile 1 <117.31 ng/mL, Tertile 2 117.32 - 130.38 ng/mL), Tertile 3 >130.39 ng/mL)
	Size of study	16,469 adults aged 20 to 90 years who participated in NHANES III interviews and physical examinations.
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Various (likely diet)
	Exposure concentrations (if applicable)	See serum concentrations in 'subgroups reported'
	Comparison group(s)	Tertile 1 <117.31 ng/mL
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Diabetes mellitus was defined as a fasting plasma glucose level of at least 126 mg/dL, a non-fasting plasma glucose level of at least 200 mg/dL (to convert to millimoles per litre, multiply by 0.0555), self-report of a physician diagnosis of diabetes, or current use of insulin.

Publication Reference: 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.		
	How outcome was assessed	• Hypercholesterolemia was defined as a serum total cholesterol level of at least 240 mg/dL (to convert to millimoles per litre, multiply by 0.0259), self-report of a physician diagnosis, or current medication use. • Participants were interviewed in NHANES III to obtain information on age, sex, race/ethnicity, education, family income, menopausal status, smoking, alcohol consumption, physical activity, and use of vitamin and/or mineral supplements. Height and weight were measured, and body mass index was calculated by dividing weight in kilograms by height in meters squared. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, a self-report of a physician diagnosis, or current medication use.
	Method of measurement	Serum selenium was measured using atomic absorption spectrometry
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	The cohort analysis was based on 13 887 NHANES III participants. Authors excluded 288 participants who were pregnant at the time of the survey, 1107 with missing information on serum selenium, 1172 with missing values on other variables of interest, and 15 participants with no follow-up information.
Statistics (if any)	Statistical method used	Study participants were divided in tertiles of serum selenium levels based on the weighted population distribution. The hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality associated with each tertile of selenium level compared with the first tertile were calculated using Cox proportional hazards regression. To further assess the dose response relationship of serum selenium levels with total and cause-specific mortality, the authors used restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the serum selenium distribution. Using restricted quadratic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles resulted in similar findings (data not shown). The P values for these relationships were obtained from likelihood ratio tests comparing models with and without serum selenium terms Authors analysed the data using SUDAAN statistical software (version 9.0; Research Triangle Institute, Research Triangle Park, North Carolina) to account for the NHANES weights and complex design.
	Details on statistical analysis	

Publication Reference: 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.		

	Relative risk/odds ratio, confidence interval?	• HRs for all-cause mortality: Tertile 2 = 0.84 (95% CI, 0.73-0.96) and Tertile 3 = 0.83 (95% CI, 0.72- 0.96). Note:
		  • At the higher levels (150 ng/mL), however, there was a gradual increase in mortality with increasing selenium (Figure 1)
		• HRs for cancer mortality: Tertile 2 = 0.73 (95% CI, 0.57-0.94) and Tertile 3 = 0.69 (95% CI, 0.53-0.90). Note:
		  • For all-cancer and lung cancer mortality, there was no further decrease but a potential increase with serum selenium levels of greater than 150 ng/mL. (Figure 2)
		• HRs for cardiovascular mortality: Tertile 2 = 0.95 (95% CI, 0.78-1.17) and Tertile 3 = 0.94 (95% CI, 0.77-1.16).
		• HRs for coronary heart disease mortality: Tertile 2 = 1.02 (95% CI, 0.71-1.46) and Tertile 3 = 0.99 (95% CI, 0.67-1.47).
		• HRs for stroke mortality: Tertile 2 = 0.73 (95% CI, 0.41-1.30) and Tertile 3 = 1.23 (95% CI, 0.66-2.28).

Author's conclusions	Interpretation of results	• In a representative sample of the US population, the authors found a nonlinear association between serum selenium levels and all-cause and cancer mortality. • Increasing serum selenium levels were associated with decreased mortality up to 130 ng/mL. • The study, however, raises the concern that higher serum selenium levels may be associated with increased mortality
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	Authors are claiming increase in all-cause mortality and cancers from 150 ng/mL based on an increase in HR which are below unity, confidence intervals that cross unity for all-cause mortality and no mention of confidence intervals for all-cancers. The results of the study found no statistically significant increase in all-cause mortality, cancer mortality, and mortality from cardiovascular, coronary heart disease and stroke. This study was subject to a RoB assessment.

Dettori et al. 2022

Publication Reference: Dettori M., Arghittu A., Deiana G., Castiglia P. and Azara A. (2022). The revised European Directive 2020/2184 on the quality of water intended for human consumption. A step forward in risk assessment, consumer safety and informative communication. Environ Res 209: 112773.		
General Information	Date of data extraction	07/06/2023
	Authors	Dettori M, rghittu A, Deiana G, Castiglia P
	Publication date	2022
	Publication type	Journal article
	Peer reviewed?	Yes

Publication Reference: Dettori M., Arghittu A., Deiana G., Castiglia P. and Azara A. (2022). The revised European Directive 2020/2184 on the quality of water intended for human consumption. A step forward in risk assessment, consumer safety and informative communication. Environ Res 209: 112773.		
	Country of origin	Italy
	Source of funding	This research was supported by "Fondo di Ricerca 2020", University of Sassari.
	Possible conflicts of interest	The author declares no conflicts of interest.
Study characteristics	Aim/objectives of study	To summarise the main features of the updated European Directive 2020/2184 (only aspects relevant to Se are summarised here).
	Study type/design	Report/review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Dettori M., Arghittu A., Deiana G., Castiglia P. and Azara A. (2022). The revised European Directive 2020/2184 on the quality of water intended for human consumption. A step forward in risk assessment, consumer safety and informative communication. Environ Res 209: 112773.		
Author's conclusions	Interpretation of results	• Outlines changes from EU Directive 98/83 for the Se DWG from 10 µg/L to 20 µg/L (with the value of 30 µg/L applying for regions where geological conditions could lead to high levels of Se in groundwater). • Deficiency of Se intake can lead to adverse effects related to general state of health and nutrition. • Several studies have shown inverse correlation between blood Se levels and prevalence of certain types of cancers. • High intakes of Se (generally >900 µg/day) may also be associated with certain disorders (gastrointestinal, discolouration of the epidermis, tooth decay, hair and nail loss and peripheral nerve and biochemical changes). • The upper tolerance limit for Se as per the WHO is 400 µg/day.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• This review provides a summary of the new EC Directive for drinking water, which revised the DWG for Se from 10 to 20µg/L, which is consistent with the adaptation of guidance values from the various jurisdictions around the World undertaken in the Stage 1 report. • This report is a review/summary of the new EC Directive; no new/additional health information was provided that would alter the conclusions made in the Stage 1 report, therefore no risk of bias analysis was undertaken. • Nevertheless, this report is in agreement with conclusions of Stage 1 report.
	Notes on study quality, e.g. gaps, methods	

Evans et al. 2019

Publication Reference: 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.		
General Information	Date of data extraction	07/06/2023
	Authors	Evans SO, Jacobson GM, Goodman HJB, Bird S, Jameson MB
	Publication date	2019
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	New Zealand
	Source of funding	Funding sources (Waikato Medical Research Foundation, Genesis Oncology Trust, Cycle for Life).
	Possible conflicts of interest	The authors declare no conflicts of interest.

Publication Reference: 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.		
Study characteristics	Aim/objectives of study	To determine the dose and form of Se that can be most safely and effectively used in clinical trials in combination with anticancer therapies. Secondary objectives include characterisation of the clinical and laboratory safety profile of the Se compounds, determination of plasma PK, evaluation of DNA damage in peripheral blood mononuclear cells (PBMCs) and exploration of PD markers in plasma and PBMC.
	Study type/design	Human controlled trial (HCT) – Phase Ib, randomised, double-blinded
	Study duration	8 weeks
	Type of water source (if applicable)	Not applicable (Se given via capsule)
Population characteristics	Population/s studied	Inclusion criteria consisted of patients with either proven chronic lymphocytic leukaemia (CCL) or metastatic solid cancers, in who use of chemotherapy was anticipated in the next 3 months. Additional inclusion criteria included: age > 18 years; ECOG performance status ≤2; adequate renal, liver and bone marrow function; and life expectancy > 6 months. Exclusion criteria included patients currently taking more than 100 µg of elemental Se daily, or those who had received chemotherapy, RT or anti-VEGF treatments in the preceding 4 weeks.
	Selection criteria for population (if applicable)	
	Subgroups reported	MSC, SLM or SS
	Size of study	24 patients
Exposure and setting	Exposure pathway	Oral (via capsule)
	Source of chemical/contamination	Purposeful administration of sodium selenite (SS), Se-methylselenocysteine (MSC) or seleno-1-methionine (SLM) All Se compounds were manufactured and supplied by Sabinsa Corporation, 20 Lake Drive, East Windsor, NJ 08520-5321, USA.
	Exposure concentrations (if applicable)	400 µg of elemental Se/day
	Comparison group(s)	Not applicable (each person acted as their own control with baseline clinical and lab evaluations).
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: 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.		
	How outcome was assessed	• Clinical and laboratory evaluations undertaken twice at baseline at least 1 week apart, then on day 2 of dosing, at weeks 4 and 8 of treatment then 4 weeks after last dose (week 12). • All treatment-emergent adverse events, or of greater severity than at baseline, were recorded and graded using the NCI CTCAE version 4.03. • At each study visit, the following tests were conducted for safety evaluation: urinalysis, ECG and blood tests (complete blood count, renal and liver function, glucose, urate, calcium, phosphate and coagulation). Plasma Se samples were taken once at baseline, 4 h post-dose on day 2, then trough levels were taken on weeks 4 and 8, and finally at week 12. • DNA damage was measured using a qPCR-based technique that calculates nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) lesion rates relative to DNA extracted from pre-treatment blood samples.
	Method of measurement	See above
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	24 exposed (each person acted as their own control).
Statistics (if any)	Statistical method used	• All statistical analysis was conducted using Prism v. 7.0; two-sided $p < 0.05$ was considered statistically significant. • Descriptive statistics were used to summarise the safety, toxicity and pharmacokinetic data. Baseline characteristics were analysed using one-way ANOVA for continuous data and the chi-square test for categorical variables. One-way ANOVA was used to identify the statistical significance of variance among group means for plasma Se AUC values by treatment arm. • Pairwise assessment of the treatment arms was carried out using Tukey's multiple comparison test. One-way ANOVA and Dunnett's multiple comparison test was used to compare variance among group means from measurements at baseline and subsequent time points for all treatment arm/disease group combinations for both DNA damage rates and baseline-corrected total lymphocyte count. Estimations of baseline variation are plotted as 95% confidence intervals for both relative DNA damage rates and total lymphocyte counts calculated from two baseline samples obtained prior to Se dosing.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: 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.		
Author's conclusions	Interpretation of results	Safety related results: • Of 24 randomised patients, 23 completed the 56-day treatment schedule; one patient discontinued on day 35 after an episode of grade 2 constipation, possibly attributable to Se. • Two episodes of ≥grade 2 toxicity were attributable to other causes: anaemia due to bleeding from an undiagnosed colon cancer while on dabigatran, and transient confusion associated with an undiagnosed brain metastasis. • Levels of DNA damage, calculated as mtDNA and nDNA lesion rates relative to baseline, were observed to be low across all treatment groups and time points, by both disease cohort and DNA subtype (mtDNA or nDNA), with mean lesion rates in each patient/Se compound cohort being < 1 per 10 kb of DNA. • No significant changes in total lymphocyte counts over time (n=4 per Se compound per disease cohort) in either the metastatic cancer or CLL cohorts. • All 3 compounds were well tolerated and assessed as safe to use at 400 µg Se/day in this study, with no clinically-significant treatment-related adverse events attributable to Se.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• This HCT, although limited endpoints were examined in a relatively small population, supports the notion that 400 µg/day of Se in different forms can be tolerated safely by cancer patients. • As study provides human information potentially informing the dose response of Se, it was subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Fairweather-Tait et al. 2011

Publication Reference: Fairweather-Tait S. J., Bao Y., Broadley M. R., Collings R., Ford D., Hesketh J. E. and Hurst R. (2011). Selenium in human health and disease. Antioxid Redox Signal 14(7): 1337-1383.		
General Information	Date of data extraction	14/06/2023
	Authors	Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE, Hurst R
	Publication date	2011
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	UK

Publication Reference: Fairweather-Tait S. J., Bao Y., Broadley M. R., Collings R., Ford D., Hesketh J. E. and Hurst R. (2011). Selenium in human health and disease. Antioxid Redox Signal 14(7): 1337-1383.		
	Source of funding	This review was carried out with partial financial support from the Commission of the European Communities, specific RTD Programme ''Quality of Life and Management of Living Resources,'' within the 6th Framework Programme (Contract No. FP6-036196-2 EURRECA: EURopean micronutrient RE Commendations Aligned) (R.C. and R.H.). Other financial support was provided from the University of East Anglia (SJF-T), the BBSRC (Agri-Food Committee Industry Partnering Award, BB-G013969-1), and by Yara (UK) Ltd. (M.R.B.).
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	To review current knowledge of selenium in the environment, dietary intakes, metabolism and status, functions in the body, thyroid hormone metabolism, antioxidant defence systems and oxidative metabolism, and the immune system. (Note only information directly relevant to Stage 2 RQs has been extracted here).
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
	Definition of outcome	

Results (for each outcome)	How outcome was assessed	• Although much less common than selenium deficiency, selenium toxicity can affect individuals as a result of over-supplementation, accidental or deliberate (suicidal) ingestion of very high doses, or through high levels in the food supply.
		• Characteristic features of selenosis occur in population groups exposed to unusually high levels of dietary selenium, and include brittle hair and brittle, thickened, stratified nails, leading to loss in some cases, along with an odour of garlic on the breath and skin. Additional symptoms, including vomiting and pulmonary oedema, are a feature of more acute selenium poisoning.
		• Where doses were reported:
		  ○ Chinese province with outbreak of selenosis in 1961-1964: average daily intake ~4,990 µg.
		  ○ Punjab state with high Se in crops and fodder, with signs of Se tox in people consuming locally grown food: average daily intake 632 µg and 475 µg/day in men and women, respectively.
		  ○ Inuit in North Greenland can tolerate high doses ~193-5885 µg/day from meat sources with no signs of tox.
		• Cardiovascular disease: Observational evidence that low selenium concentrations are associated with cardiovascular risk should be treated as suggestive but not definitive. There is uncertainty about cause and effect; therefore, time-resolved and prospective studies are needed in different pathological settings.
		• Cancer: Although direct comparisons of odds ratios, hazard ratios (HR), and relative risks for many studies are not possible because the results are study specific, there is a consistent trend throughout several of the human studies demonstrating potential protective effects with plasma/serum selenium between ~120–160 ng/ml and reduced risk of some types of cancer when compared with the low plasma selenium status, namely <120 ng/ml. Above 160 ng/ml the cancer protective effect is likely to diminish and the risk perhaps increases for some types of cancer. Literature from the 1950s and 1960s showed that an inappropriately high dose range of selenium may actually increase the incidence of certain types of cancer in animal models and selenium used to be classed as a carcinogen in animals when used at high exposure. Therefore, a careful balance ensuring selenium intakes and selenium status fall in the relatively narrow base of the U-shaped risk-response curve is critical for potential modulation of certain cancer-type-specific risk profiles.
		• Diabetes: Current evidence implies that both low and high selenium intakes could influence the risk of diabetes, and this relationship requires further investigation through good quality human studies.
		• Inflammatory conditions: Although there appears to be good evidence from case-control studies suggesting lower selenium status in patients with inflammatory conditions compared with healthy controls, there is little supporting evidence from high-quality RCTs for a therapeutic effect of selenium

Publication Reference: Fairweather-Tait S. J., Bao Y., Broadley M. R., Collings R., Ford D., Hesketh J. E. and Hurst R. (2011). Selenium in human health and disease. Antioxid Redox Signal 14(7): 1337-1383.		
		supplementation. This could, in part, be explained by the dual functionality of selenium, influencing both antioxidant and immune responses. Further high-quality interventions are required to establish these relationships. • Fertility: Evidence to date suggests that high dietary intakes (although below the upper safety limits) may be as detrimental as deficiency to male fertility, and therefore determining the optimal range for health is all the more pertinent. • The range of intake between which selenium deficiency and toxicity occurs is relatively narrow, with current estimates suggesting that intakes below 30 µg/day are inadequate and those exceeding 900 µg/day are potentially harmful
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	
Author's conclusions	Interpretation of results	• The relationships between selenium intake/status and health, or risk of disease, are complex but require elucidation to inform clinical practice, to refine dietary recommendations, and to develop effective public health policies.
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• This comprehensive review provides information on the doses of dietary Se that have been associated with selenosis overseas (475-4,990 µg/day) as well as a summary of the studies examining associations between different health endpoints. The review concluded more research needed to be done in order to refine nutrient requirement levels and upper safe levels of intake. There are suggestions for a U-shaped response for many endpoints, including diabetes and potentially some cancers. However the data in this review do not lend themselves to defining a dose response for these effects for potential revision of a guidance value. • As this paper is a review, it was not subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Fan and Kizer 1990

Publication Reference: Fan A. M. and Kizer K. W. (1990). Selenium. Nutritional, toxicologic, and clinical aspects. West J Med 153(2): 160-167.		
General Information	Date of data extraction	14/06/2023
	Authors	Fan AM, Kizer KW
	Publication date	1990
	Publication type	Journal article
	Peer reviewed?	Uncertain
	Country of origin	USA
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Review of the nutritional, toxicologic, and clinical aspects of selenium in an effort to assist physicians with questions and concerns about this compound.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
	Definition of outcome	

Publication Reference: Fan A. M. and Kizer K. W. (1990). Selenium. Nutritional, toxicologic, and clinical aspects. West J Med 153(2): 160-167.		
Results (for each outcome)	How outcome was assessed	• Se occurs naturally in four oxidation states: elemental selenium, selenite, selenide, and selenate. The valence state affects selenium's toxicity and bioavailability. Selenium, in the forms of selenite and selenate, is found in water, principally as a result of leaching from seleniferous rocks and soils. Water is generally not a biologically significant source of intake. • Symptoms observed in humans suffering from chronic selenium intoxication include depression, lassitude, nervousness, giddiness, emotional lability, dermatitis, gastrointestinal disturbances (primarily nausea and vomiting), a garlic odour of the breath and sweat, excess dental caries, and, in extreme cases, loss of hair and fingernails. In all reported cases, symptoms and signs have abated after excess exposure ceases. • The results of long-term human studies relating serum selenium levels to the development of coronary heart disease are conflicting. • Selenium sulfide, an ingredient in certain antidandruff shampoos, has been carcinogenic for rats and female mice when given by gavage, producing hepatocellular carcinomas in male and female rats and female mice and alveolar or bronchiolar carcinomas and adenomas in female mice. But selenium sulfide is a separate and distinct compound, rather than just another salt of selenium; therefore, it cannot be assumed that the results show that other inorganic selenium compounds (selenite or selenate) are carcinogenic.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable (no statistical analysis undertaken)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Clinicians should be familiar with the possible toxicity of selenium, as well as its possible benefits, because of growing public use of this compound as a dietary supplement and because of concerns raised by the occurrence of environmental selenium contamination and resultant wildlife toxicity in several areas of the western United States
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	• Review of Se toxicity and essentiality. Provides no new information to what has already been summarised in other reviews. Unlikely to be a critical paper. As this is a review, it was not subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Frisbie et al. 2015

Publication Reference: *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. Environmental health 14(1): 1-15.*		
General Information	Date of data extraction	07/06/2023
	Authors	Frisbie S. H., Mitchell E. J. and Sarkar B.
	Publication date	13 August 2015
	Publication type	Peer-reviewed journal article
	Peer reviewed?	Yes
	Country of origin	Canada
	Source of funding	Study was supported by Norwich University, The Research Institute of The Hospital for Sick Children, and the University of Toronto.
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	To review the 2011 changes to the WHO drinking water guidelines for manganese, molybdenum, nitrite, aluminium, boron, nickel, uranium, mercury, and selenium.
	Study type/design	Review/opinion piece
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable (drinking water guideline review)
Population characteristics	Studies referenced	Not applicable (drinking water guideline review)
	Types of studies referenced	
Exposure and setting	Exposure concentrations (if applicable)	Not applicable (drinking water guideline review)
	Comparison group(s)	
Study methods	Study approach	Not applicable (drinking water guideline review)
Results (for each outcome)	Definition of outcome	Not applicable (drinking water guideline review)
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	
Statistics (if any)	Statistical method used	Not applicable (drinking water guideline review)
	Relative risk/odds ratio, confidence interval?	

Publication Reference: *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. Environmental health 14(1): 1-15.*		
Author's conclusions	Interpretation of results	Authors critiqued the recent revision of the WHO DWG for Se for the following reasons: • The 400 µg/day upper level of intake calculated by US NAS applies specifically to adults. The authors state it is therefore not clear why the age-weight based differences specified by the NAS were not taken into account by WHO when establishing the DWG. • WHO increased the allocation for exposure to Se in drinking water from 10 to 20% without providing any references to support this increase, which resulted in a doubling of the guideline value. • Since the 2011 DWG for Se is based on a 2000 recommendation from NAS, it does not take into account subsequent studies which found reason to question whether the 400 µg/day UL for total Se intake or the former WHO guideline of 10 µg/L for Se in drinking water were sufficiently protective (Fairweather-Tait et al. 2011, Vinceti et al. 2009, 2010, 2012; Stranges et al. 2007).
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This review raises questions with regards to the reliability of the revised WHO DWG for Se. The references identified to be critical references by this review were sourced and included / individually assessed in this Stage 2 review.
	Notes on study quality, e.g. gaps, methods	

References:

Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE, et al. Selenium in human health and disease. Antioxid Redox Signal. 2011;14(7):1337–83. *As cited in Frisbie et al. 2015.*

Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes. Ann Intern Med. 2007;147:217–23. *As cited in Frisbie et al. 2015.*

Vinceti M, Maraldi T, Bergomi M, Malagoli C. Risk of chronic low-dose selenium overexposure in humans: Insights from epidemiology and biochemistry. Rev Environ Health. 2009;24(3):231–48. *As cited in Frisbie et al. 2015.*

Vinceti M, Bonvicini F, Rothman KJ, Vescovi L, Wang F. The relation between amyotrophic lateral sclerosis and inorganic selenium in drinking water: A population-based case–control study. Environ Health. 2010;9:77. *As cited in Frisbie et al. 2015.*

Vinceti M, Crespi CM, Malagoli C, Bottecchi I, Ferrari A, Sieri S, et al. A case–control study of the risk of cutaneous melanoma associated with three selenium exposure indicators. Tumori. 2012;98(3):287–95. *As cited in Frisbie et al. 2015.*

Gebreeyessus and Zewge 2019

Publication Reference: Gebreeyessus G. D. and Zewge F. (2018). A review on environmental selenium issues. SN Applied Sciences 1(1): 55.		
General Information	Date of data extraction	07/06/2023
	Authors	Gebreeyessus GD and Zewge F
	Publication date	2019
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Ethiopia
	Source of funding	Support received from the African Center of Excellence for Water Management, Addis Ababa University, Ethiopia
	Possible conflicts of interest	The authors declare no conflicts of interest.
Study characteristics	Aim/objectives of study	To review environmental Se issues.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	

Publication Reference: Gebreeyessus G. D. and Zewge F. (2018). A review on environmental selenium issues. SN Applied Sciences 1(1): 55.		
	Relative risk/odds ratio, confidence interval?	-
Author's conclusions	Interpretation of results	• Selenium carries the narrowest range between its nutritional deficiency (< 40 µg/d) and toxicity (> 400 µg/d) with respect to the daily intake. • Selenium exposure can result in either acute or chronic health problems. An acute exposure is explained by selenium neurotoxicity while the chronic exposure is explained by the toxic effect on endocrine function especially in the synthesis of thyroid hormones and if the dose exposed is relatively lower. For instance, a report from China indicated that clinical and biochemical signs occur at a daily intake above 0.8 mg (no reference cited after this statement). • An outbreak in US identified median estimated dose of Se of 41,749 µg/day (??) was associated with diarrhoea, fatigue, hair loss, joint pain, nail discolouration or brittleness and nausea. • The daily intake of Venezuelan children with clinical signs was estimated to be about 0.7 mg. • No clinical or biochemical signs of selenium toxicity were reported in a group of 142 persons with a mean daily intake of 0.24 mg (maximum 0.72 mg) from food.
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	• Review paper which identifies some potentially critical papers that have been sourced from the bibliography and reviewed separately in this Stage 2 report.
	Notes on study quality, e.g. gaps, methods	

Gore et al. 2020

Publication Reference: Gore F., Fawell J. and Bartram J. (2010). Too much or too little? A review of the conundrum of selenium. J Water Health 8(3): 405-416.		
General Information	Date of data extraction	07/06/2023
	Authors	Gore F, Fawell J, Bartram J
	Publication date	2020
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Switzerland, UK and USA
	Source of funding	No source of funding declared.

Publication Reference: Gore F., Fawell J. and Bartram J. (2010). Too much or too little? A review of the conundrum of selenium. J Water Health 8(3): 405-416.		
	Possible conflicts of interest	The corresponding author is a staff member of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization. No conflict of interest statement specifically included in paper.
Study characteristics	Aim/objectives of study	To review the risks associated with insufficient and excessive intake of Se in the diet, focusing on drinking water.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	-

Publication Reference: Gore F., Fawell J. and Bartram J. (2010). Too much or too little? A review of the conundrum of selenium. J Water Health 8(3): 405-416.		
Author's conclusions	Interpretation of results	• A study by Vinceti et al. (2001) suggested thatselenium species exhibit a bivalent effect in cancer, either increasing or decreasing risk. However, the studies carried out by Vinceti et al. (1994; 2000a,b; 2001) are difficult to interpret due to small size, difficulties in assessing total exposure or difficulties in accounting for confounding factors with what are essentially multifactorial diseases. The debate remains unresolved over the protective effect of selenium for various cancers or cardiovascular disease. • The adverse effect of chronic high selenium exposure has been widely reported from various regions in China, where populations exhibited typical symptoms of chronic exposure to selenium, fatigue, lesions of the skin, loss of nails and hair, loss of appetite, gastrointestinal disturbances, cardiac insufficiency and congestive heart failure. • Other studies reporting signs of selenium toxicity as a result of excessive exposure through drinking-water have been conducted in rural families living in seleniferous areas in Nebraska and South Dakota (USA). Values as high as 92 mg Se/L in drinking water were reported; however, intake from other sources was not clear. Symptoms included gastrointestinal disturbances, discoloration of the skin and decayed teeth. • The average dietary intake of selenium associated with selenosis has been reported to be >900 mg/day. • One case of selenium poisoning directly attributable to a water source has been reported in a family that was exposed for about three months to well water containing 9,000 mg/L of selenium. They suffered hair loss, weakened nails, and neurological symptoms, but recovered once they ceased consuming water from the contaminated well.
	Assessment of uncertainty (if any)	Not applicable
Reviewer comments	Results included/excluded in review (if applicable)	• Review paper which identifies some potentially critical papers that have been sourced from the bibliography and reviewed separately in this Stage 2 report.
	Notes on study quality, e.g. gaps, methods	

Hao et al. 2016

Publication Reference: Hao Z., Liu Y., Li Y., Song W., Yu J., Li H. and Wang W. (2016). Association between Longevity and Element Levels in Food and Drinking Water of Typical Chinese Longevity Area. J Nutr Health Aging 20(9): 897-903.		
General Information	Date of data extraction	08/06/2023
	Authors	Hao Z, Liu Y, Li Y, Song W, Yu J, Li H, Wang W

Publication Reference: Hao Z., Liu Y., Li Y., Song W., Yu J., Li H. and Wang W. (2016). Association between Longevity and Element Levels in Food and Drinking Water of Typical Chinese Longevity Area. J Nutr Health Aging 20(9): 897-903.		
	Publication date	2016
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	This work was supported by the National Science Foundation of China (grant no. 41171082).
	Possible conflicts of interest	Authors declare they have no conflict of interest.
Study characteristics	Aim/objectives of study	To detect the association between longevity and daily element intake from food and drinking water.
	Study type/design	Cross-sectional (observational)
	Study duration	Not applicable (samples collected in Feb 2012 and Jan 2013)
	Type of water source (if applicable)	Well water (collected from each centenarian's home)
Population characteristics	Population/s studied	Population data were collected from the Chinese demographic database of the 6th census. For each county in Hainan province, the percentage of the population aged 65+ and 90+ was calculated. Number of centenarians per 100,000 inhabitants was also calculated.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Unclear (18 provinces in China)
Exposure and setting	Exposure pathway	Oral (drinking water and rice)
	Source of chemical/contamination	Not stated.
	Exposure concentrations (if applicable)	Mean concentrations of Se in well water in the 18 provinces ranged from 0.33 to 2.88 µg/L
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively coupled plasma mass spectrometry
	Water sampling methods (monitoring, surrogates)	Well water samples were collected using a mineral water bottle and a standard collection method for water quality studies. Approximately 0.5 mL of concentrated nitric acid was immediately added to the water samples at a 1:1 ratio to prevent adsorption of dissolved metals onto the interior walls of the storage bottle and to minimise post-sampling microbial activity. All water samples were immediately transported to the laboratory and stored at 0–4°C until analysis (generally 1–2 days).
Results (for each outcome)	Definition of outcome	• Daily element intake from water (1.82 µg/d) was much lower than that from rice (20 µg/d); therefore, food represents the primary source of trace elements in Hainan Province. • Se intake from food and water had high positive correlation coefficients with the aging and longevity indexes (i.e. a potential beneficial effect at higher intakes).
	How outcome was assessed	
	Method of measurement	Not applicable (see stats)

Publication Reference: Hao Z., Liu Y., Li Y., Song W., Yu J., Li H. and Wang W. (2016). Association between Longevity and Element Levels in Food and Drinking Water of Typical Chinese Longevity Area. J Nutr Health Aging 20(9): 897-903.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	The association between longevity and element concentration in water and rice were assessed using Spearman correlation analysis. Statistical analyses performed using SPSS 16.0 for Windows (IBM, Chicago, IL, USA). Distribution maps of population and longevity indexes at a county level were generated using ArcGIS version 10.0 software.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The quality of food and water in Hainan Province are good and compared with water, food is a more important source of trace elements. An appropriate supply of Cu, Se, and Zn is important, whereas excessive intake of Pb should be avoided. The findings also provide basic data to support further studies on regional variations in longevity and their relationship to diet and drinking water.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This observational study found a beneficial effect of Se on longevity, however the estimated intakes of Se from drinking water and rice were relatively low concentration (i.e. mean drinking water ranged from 0.33 to 2.88 µg/) (below required levels) therefore this study only provides support for the essentiality of Se and does not provide any dose response information for the potential adverse effects of Se exposure. • Therefore it was not subjected to risk of bias analysis.
	Notes on study quality, e.g. gaps, methods	

Hadrup and Ravn-Haren 2020

Publication Reference: Hadrup N. and Ravn-Haren G. (2020). Acute human toxicity and mortality after selenium ingestion: A review. Journal of Trace Elements in Medicine and Biology 58: 126435.		
General Information	Date of data extraction	09/06/2023
	Authors	Hadrup N and Ravn-Haren G
	Publication date	2020
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Denmark
	Source of funding	No funding details provided.
	Possible conflicts of interest	Authors declare they have no conflict of interest.
Study characteristics	Aim/objectives of study	To review the published literature on the acute toxicity of oral selenium.
	Study type/design	Review

Publication Reference: Hadrup N. and Ravn-Haren G. (2020). Acute human toxicity and mortality after selenium ingestion: A review. Journal of Trace Elements in Medicine and Biology 58: 126435.		
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	See outcomes below
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• The published literature on the acute toxicity of oral selenium was gathered and reviewed. • Reported symptoms and signs include abdominal symptoms, such as vomiting, diarrhoea, pain, and nausea, as well as garlic-like odour on the breath. In cases of severe toxicity, cardiac and pulmonary symptoms may develop and ultimately lead to mortality. • Mortality has been described after the ingestion of gun bluing solutions, which often contain selenous acid among other potentially toxic substances. Mortality has also been reported after the ingestion of other forms of selenium. • Ingested doses associated with mortality are in the range of 1–100 mg Se/kg body weight. Blood levels associated with mortality are above 300 µg Se/L (normal level: 100 µg/L), whereas urinary levels associated with the same endpoint are above 170 µg Se/L (normal level: 20–90 µg/L).
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: Hadrup N. and Ravn-Haren G. (2020). Acute human toxicity and mortality after selenium ingestion: A review. Journal of Trace Elements in Medicine and Biology 58: 126435.		
Author's conclusions	Interpretation of results	• The acute toxicity associated with oral selenium ingestion and the blood and urinary levels of selenium in different cases of poisonings were reviewed. Mortality is a risk of acute selenium poisoning. • Concentrations of selenium in blood and urine samples in non-fatal cases are close to those observed in fatal cases.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• The review reviewed a number of case reports of selenium poisoning in humans. Ingested doses associated with mortality are in the range of 1–100 mg Se/kg body weight. As these doses are ~200-2,000x higher than the health-based guidance values used for derivation of candidate guideline values in the Stage 1 reports, the information in this review does not change the conclusions in the Stage 1 report. • As this was a review, it was not able to be subjected to risk of bias analysis, but it is noted no conflicts of interest were declared by the review authors who are both from government research organisations and/or universities.
	Notes on study quality, e.g. gaps, methods	

Karp et. al. 2013

Publication Reference: 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.		
General Information	Date of data extraction	15/06/2023
	Authors	Karp, D.D., Lee, S.J., Keller, S.M., Shaw Wright, G., 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., Khuri, F.R.
	Publication date	November 20 2013
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	US
	Source of funding	Supported in part by Public Health Service Grants No. CA037403, CA14958, CA80775, CA73590, CA107868, CA49957, CA31946, CA33601, CA32102, CA20319, CA25224, CA21661, and CA37422 and grants from the National Cancer Institute, National Institutes of Health, and Department of Health and Human Services.

Publication Reference: 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.		
	Possible conflicts of interest	• Employment or Leadership Position: None • Consultant or Advisory Role: Johnson, D.H., Peloton Therapeutics (C), Mirna Therapeutics (C) • Stock Ownership: None • Honoraria: None • Research Funding: None • Expert Testimony: None • Patents: None • Other Remuneration: None
Study characteristics	Aim/objectives of study	Conducted a double-blind, placebo-controlled trial to evaluate the incidence of second primary tumours (SPTs) in patients with resected non–small-cell lung cancer (NSCLC) receiving selenium supplementation.
	Study type/design	HCT, double-blind, placebo-controlled trial
	Study duration	6 to 36 months
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Patients with completely resected stage I non–small-cell lung cancer (NSCLC). One thousand seven hundred seventy-two participants were enrolled, with 1,561 patients randomly assigned.
	Selection criteria for population (if applicable)	
	Subgroups reported	Compliance was tested over a 4-week run-in period, and patients who qualified as compliant (taking ≥75% of their daily placebo tablets) by patient diary review and pill count were randomly assigned 2:1 to receive either selenium in the form of selenised yeast (n=1040) or an identical-appearing placebo (n=521).
	Size of study	1,561 patients
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Selenised yeast
	Exposure concentrations (if applicable)	200 µg/d
	Comparison group(s)	Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Incidence of lung second primary tumours (SPTs). Monitoring for Skin Cancer Incidence and Diabetic Incidences was also included. Diabetes-related questions were added in the on-study, toxicity, and long-term follow-up forms per the DMC's 2007 recommendation. Since then, 26 patients in the selenium arm and 12 patients in the placebo arm reported a diagnosis of diabetes during the long-term follow-up period.
	How outcome was assessed	
	Method of measurement	

Publication Reference: 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.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1,561 patients Eligibility criteria included the following: age ≥18 years; 6 to 36 months from complete resection of histologically proven stage IA (pT1N0) or stage IB(pT2N0) NSCLC (carcinoid tumours were excluded); pathologic stage N0 confirmed by sampling at least one mediastinal lymph node at resection; chest x-ray or computed tomography scan ≤8 weeks before registration without sign of new or recurrent lung cancer; no concurrent cancers or any other prior cancer history within the past 5 years, except localised nonmelanoma skin cancer; no synchronous lesions (lung + nonlung) or metastasis, even if resectable; no history of greater than one lung cancer primary tumour at any time; normal hepatic function (total bilirubin and AST or ALT ≤institutional upper limit of normal); laboratory values (including CBC) obtained within 8 weeks before registration; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
Statistics (if any)	Statistical method used	A two-sided, P = .05 level log-rank test was used to compare the groups, adjusted for sequential monitoring. The data as of June 2011 were analysed based on the intent-to-treat principle, including all patients regardless of eligibility and treatment status. The distribution of time-to-event data (time to lung SPT, disease-free survival [DFS], and overall survival [OS]) was estimated using the Kaplan-Meier method. Differences in treatment effect were evaluated using the log-rank test. All reported P values are based on two-sided testing. Incidence rate was estimated by dividing the number of patients with lung SPT by total number of person-years followed.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	• Lung and overall SPT incidence were 1.62 and 3.54 per 100 person-years, respectively, for selenium versus 1.30 and 3.39 per 100 person-years, respectively, for placebo (P= .294). • Five-year disease-free survival was 74.4% for selenium recipients versus 79.6% for placebo recipients. • Grade 1 to 2 toxicity occurred in 31% of selenium recipients and 26% of placebo recipients, and grade ≥3 toxicity occurred in less than 2% of selenium recipients versus 3% of placebo recipients. • Compliance was excellent.
Author's conclusions	Interpretation of results	• Overall, selenium was safe but conferred no benefit over placebo in the prevention of SPT in patients with resected NSCLC. • Two hundred fifty-two SPTs (from 224 patients) developed, of which 98 (from 97 patients) were lung cancer (38.9%). • No increase in diabetes mellitus or skin cancer was detected.
	Assessment of uncertainty (if any)	Not stated

Publication Reference: 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.		
Reviewer comments	Results included/excluded in review (if applicable)	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 selenium supplementation (200 µg/day as selenised yeast for 6-36 months). This study was subjected to RoB assessment.

Kilness and Hochberget 1977

Publication Reference: Kilness A. W. and Hichberg F. H. (1977). Amyotrophic lateral sclerosis in a high selenium environment. Jama 237(26): 2843-2844.		
General Information	Date of data extraction	16/06/2023
	Authors	Kilness AW, and Hochberg FH
	Publication date	June 27, 1977
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This investigation was supported in part by the State of South Dakota Department of Health.
	Possible conflicts of interest	No conflict of interest statement included in the paper.
Study characteristics	Aim/objectives of study	Authors report a cluster of amyotrophic lateral sclerosis (ALS) cases occurring under circumstances that suggest a possible cause for the disease.
	Study type/design	Case study
	Study duration	Not applicable (cases occurring during a ten-year period)
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: Kilness A. W. and Hichberg F. H. (1977). Amyotrophic lateral sclerosis in a high selenium environment. Jama 237(26): 2843-2844.		
Population characteristics	Selection criteria for population (if applicable)	Four confirmed ALS patients were unrelated farmer-ranchers without family histories of ALS. Their cases occurred in a sparsely populated county in west-central South Dakota (population 4,060 in 1975). The proximity of these persons is of particular importance; three were neighbouring farmer-ranchers living less than 3 km apart for their entire lives. Cases were: • Case 1: A 59-year-old farmer-rancher who lived his entire life on a farm in west-central South Dakota • Case 2: A farmer-rancher who lived his entire life on a farm less than 3 km from farmer in Case 1 • Case 3: A farmer-rancher who lived his entire life just 1 km south of the patient in Case 2 • Case 4: 61 yo patient raised on a farm south of the first three patients.
	Subgroups reported	Not applicable
	Size of study	4 patients
Exposure and setting	Exposure pathway	Oral. As a result of selenium contamination of the local food chain, the human population was exposed to high dietary selenium.
	Source of chemical/contamination	The cases occurred in a region where naturally occurring selenium toxication is endemic in farm animals.
	Exposure concentrations (if applicable)	Case 1: The first patient had a urinary selenium level of 0.45 mg/L and a whole blood level of 0.75 mg/L. The increased selenium intake is reflected in concentrations of urinary selenium above that of 0.03 mg/L expected for people in non-seleniferous areas.
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Persons diagnosed with ALS
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	4 patients
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	

Publication Reference: Kilness A. W. and Hichberg F. H. (1977). Amyotrophic lateral sclerosis in a high selenium environment. Jama 237(26): 2843-2844.		
	Relative risk/odds ratio, confidence interval?	Not applicable. Case details as follows: • Case 1: Symptoms started in December 1974. Diagnosis of ALS confirmed in June 1975. Patient died in June 1976 of terminal respiratory failure following an acute episode of dyspnoea and inability to swallow. • Case 2: Symptoms started in summer of 1964. February 1965, the diagnosis of ALS was confirmed. He died of terminal respiratory failure at the age of 57 years in September 1965. • Case 3: First symptoms in 1966. In 1967, the diagnosis of ALS was confirmed. He died of respiratory failure with bronchopneumonia in 1969. • Case 4: The patient was raised on a farm south of the first three patients (Case 1 to 3). First symptoms in 1969 and in 1970, a diagnosis of ALS was made. Death in 1974 was attributed to bulbar paralysis.
Author's conclusions	Interpretation of results	Authors have reported an unusual clustering of cases of ALS occurring in a farm locale where chronic selenium intoxication had been noted to be endemic in farm animals as early as 1936. The occurrence of a cluster of cases of ALS implies that an environmental factor may be present. The presence of selenium in high amounts in the Cretaceous soils of this area warrants examination of selenium as a possible environmental factor.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	Not included in the RoB assessment as does not provide dose-response information. Selenium blood levels in the farmer of Case 1 may be supporting information for the differences in uptake/toxicity of inorganic versus organic selenium. However, other confounding factors may be present (e.g. there is no mention of pesticide exposure, and all cases were farmers).

Klein et. al. 2011

Publication Reference: 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.		
General Information	Date of data extraction	15/06/2023
	Authors	2011 October 12
	Publication date	Klein, E.A., Thompson, I.M. Jr, Tangen, C.M. Dr, Crowley, J.J, Lucia, M.S., Goodman, P.J., Minasian, L., 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., Baker, L.H.

Publication Reference: 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.		
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	This work was supported in part by Public Health Service Cooperative Agreement grant CA37429 awarded by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and in part by the National Center for Complementary and Alternative Medicine (National Institutes of Health). Study agents and packaging were provided by Perrigo Company (Allegan, Michigan), Sabinsa Corporation (Piscataway, New Jersey), Tishcon Corporation (Westbury, New York), and DSM Nutritional Products Inc. (Parsipanny, New Jersey).
	Possible conflicts of interest	Dr. Gaziano reported receiving grant support (to his institution) from Wyeth (now Pfizer) in the form of vitamin and placebo pills and packaging. Dr. Chin reported receiving consultancy fees from Janssen, Amgen, Novartis and Firmagon; receiving payment for lectures from Firmagon; and payment for development of educational presentations from Astra Zeneca, Novartis and Firmagon. Dr. Meyskens reported being a co-founder of Cancer Prevention Pharmaceuticals. Dr. Baker reported Board Membership for Merck (no compensation). Dr. Karp reported receiving grants (to his institution) from Pfizer.
Study characteristics	Aim/objectives of study	To determine the long-term effect of vitamin E and selenium on risk of prostate cancer in relatively healthy men (SELECT).
	Study type/design	HCT, randomised, double-blind
	Study duration	Planned follow-up of a minimum of 7 and maximum of 12 years.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	SELECT randomized 35,533 men from 427 study sites in the United States, Canada and Puerto Rico in a double-blind manner between August 22, 2001 and June 24, 2004. Eligible men were 50 years or older (African Americans) or 55 years or older (all others) with a PSA ≤4.0 ng/mL and a digital rectal examination not suspicious for prostate cancer. Included in the analysis are 34,887 men randomly assigned to one of four treatment groups: selenium (n=8,752), vitamin E (n=8,737), both agents (n=8,702), or placebo (n=8,696). Data reflect the final data collected by the study sites on their participants through July 5, 2011.
	Selection criteria for population (if applicable)	
	Subgroups reported	Four treatment groups: selenium (n=8,752), vitamin E (n=8,737), both agents (n=8,702), or placebo (n=8,696)
	Size of study	34,887 men. Four treatment groups: selenium (n=8,752), vitamin E (n=8,737), both agents (n=8,702), or placebo (n=8,696)
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplements

Publication Reference: 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.		
	Exposure concentrations (if applicable)	200 µg/day from L-selenomethionine. (Vitamin E at 400 IU/d of all rac-α-tocopheryl acetate)
	Comparison group(s)	Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	The primary endpoint of the study was prostate cancer incidence as determined by routine clinical management and confirmed by central pathology review. Blinded follow-up continued until October 23, 2008, at which time participants discontinued use of study supplements. Prostate cancer status was determined by self-report at each 6-month study visit. Medical records were obtained thereafter and clinical stage and diagnostic method abstracted. The pathology report and tissue were forwarded to the SELECT central pathology laboratory for confirmation of diagnosis and for assignment of Gleason score. Median baseline and follow up plasma vitamin E and selenium levels are included in the authors' original report.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	The study enrolled healthy men at average risk of prostate cancer based on a baseline PSA of ≤ 4 ng/mL and normal digital rectal exam (DRE) commencing at age 50 for African Americans or age 55 for all others.
Statistics (if any)	Statistical method used	Authors reported two-sided p-values throughout because the comparison of prevention vs. increased risk of cancer is a two-sided question. A proportional hazards model was used to compare prostate cancer and other cancer incidence between placebo and each of the three arms with active agents. Those without the endpoint of interest were censored at their last contact date. An additional analysis was performed on all the data using a variable for selenium supplementation, a variable for vitamin E supplementation, and an interaction term. In all cases, the proportional hazards assumption was evaluated by assessing each study arm by time interaction. The cumulative incidence curves for prostate cancer were generated accounting for the competing risk of death. A chi-square test was used to test the difference in the relative risk of diabetes. Data were analysed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).
	Details on statistical analysis	

	Relative risk/odds ratio, confidence interval?	• Hazard ratios (99% confidence intervals [CI]) and numbers of prostate cancers vs. 1.00 (n=529) for placebo were:
		  • 1.17(99% CI 1.004-1.36, p=.008, n=620) for vitamin E
		  • 1.09 (99% CI 0.93-1.27, p=.18, n=575) for selenium
		  • 1.05 (99%CI 0.89-1.22, p=.46, n=555) for selenium + vitamin E
		• The absolute increase in risk compared with placebo for vitamin E, selenium and the combination were 1.6, 0.9 and 0.4 cases of prostate cancer per 1,000 person-years.

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• There was not a statistically significant increased risk of prostate cancer in the vitamin E and selenium combination group • In the initial SELECT report a non-statistically significant increased risk of type 2 diabetes mellitus (as defined by self-report or new use of glitazone medications) was observed in the selenium supplementation group (HR=1.07). In the updated results the hazard ratio has moved closer to 1(HR=1.04) and is not statistically significant (p=0.34) • For other pre-specified secondary endpoints of lung, colorectal, and total other cancers, deaths, and grade 4 cardiovascular events, there are no statistically significant differences in the hazard ratios between groups, suggesting neither benefit nor harm for dietary supplementation with selenium or vitamin E for these endpoints.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This randomised, double-blinded, placebo-controlled HCT found no statistically significant differences in hazard ratios for selenium administration (200 µg/day for uncertain period) with prostate cancer, type 2 diabetes, lung, colorectal, and total other cancers, deaths, and grade 4 cardiovascular events. This study was subject to a RoB assessment

Kristal et. al. 2014

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	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., Klein, E.A.
	Publication date	Published online February 22, 2014
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA

Publication Reference: 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.		
	Source of funding	This work was supported in part by Public Health Service Cooperative Agreement grant U10 CA037429 awarded by the National Cancer Institute, Division of Cancer Prevention, National Institutes of Health, Department of Health and Human Services, and by the National Center for Complementary and Alternative Medicine (National Institutes of Health). Study agents and packaging were provided by Sabinsa Corporation (Piscataway, NJ), Tishcon Corporation (Westbury, NY), and DSM Nutritional Products Inc (Parsipanny, NJ). Optional study multivitamins were provided by Perrigo Company (Allegan, MI).
	Possible conflicts of interest	The authors declare no competing financial interests.
Study characteristics	Aim/objectives of study	This case–cohort study investigates effects of selenium and vitamin E supplementation conditional upon baseline selenium status.
	Study type/design	Case–cohort study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Between July 2001 and May 2004, 35,533 men were block-randomised by study site. Selected from the US National Cancer Institute initiated the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which tested whether selenium (Se; 200 µg/d from L-selenomethionine), vitamin E (400 IU/d of all rac-α-tocopheryl acetate) or both could reduce prostate cancer (PCa) risk
	Selection criteria for population (if applicable)	
	Subgroups reported	Four groups: Se plus vitamin E; vitamin E plus placebo; Se plus placebo; or placebo plus placebo.
	Size of study	There were 1739 total and 489 high-grade (Gleason 7–10) PCa cases and 3117 men in the randomly selected cohort
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplements
	Exposure concentrations (if applicable)	Se; 200 µg/d from L-selenomethionine
	Comparison group(s)	Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Demographic and health-related characteristics were collected at baseline by self-administered questionnaire. All men were requested to provide toenail samples at baseline, and 89% complied.
	How outcome was assessed	
	Method of measurement	

Publication Reference: 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.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	427 participating sites across the United States, Canada, and Puerto Rico, black men aged 50 years or older or all other men aged 55 years or older, who had no history of PCa, and who had a serum prostate-specific antigen (PSA) of 4 ng/mL or less and nonsuspicious digital rectal exam were eligible to participate.
Statistics (if any)	Statistical method used	Proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for effects of supplementation within quintiles of baseline toenail selenium. Cox proportional hazards models were used to estimate hazard ratios, and all statistical tests are two-sided.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Selenium supplementation increased the risk of high-grade PCa among men with higher selenium status by 91% (P = .007). Statistically significant results for high-grade PCa: • Q5 Any Se: 1.96 (1.00,3.86) • Q4 Se and Vit E: 2.21 (1.10 to 4.45) • Q5 Se and Vit E: 2.24 (1.05 to 4.77) • Q4-5 Se and Vit E: 2.24 (1.34,3.75) • Q4-5 Any Se: 1.91 (1.20 to 3.05)
Author's conclusions	Interpretation of results	Selenium supplementation did not benefit men with low selenium status but increased the risk of high-grade PCa among men with high selenium status.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This case-cohort study found an association between increased risk of high-grade prostate cancer among men in SELECT trial and toenail selenium concentration (in patients receiving 200µg Se/day). This study was subjected to RoB assessment

Labunskyy et. al. 2011

Publication Reference: Labunskyy V. M., Lee B. C., Handy D. E., Loscalzo J., Hatfield D. L. and Gladyshev V. N. (2011). Both maximal expression of selenoproteins and selenoprotein deficiency can promote development of type 2 diabetes-like phenotype in mice. Antioxid Redox Signal 14(12): 2327-2336.		
General Information	Date of data extraction	15/06/2023
	Authors	Labunskyy, V.M., Cheon Lee, B., Handy, D.E., Loscalzo, J., Hatfield, D.L., Gladyshev, V.N.
	Publication date	2011
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA

Publication Reference: Labunskyy V. M., Lee B. C., Handy D. E., Loscalzo J., Hatfield D. L. and Gladyshev V. N. (2011). Both maximal expression of selenoproteins and selenoprotein deficiency can promote development of type 2 diabetes-like phenotype in mice. Antioxid Redox Signal 14(12): 2327-2336.		
	Source of funding	This work was supported by National Institutes of Health grants CA080946 and AG021518 (to VNG), HL61795, HL81587, HL70819, and HL48743 (to JL), and the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research (to DLH)
	Possible conflicts of interest	No competing financial interests exist.
Study characteristics	Aim/objectives of study	Examined the contribution of selenoproteins to increased risk of developing diabetes using animal models.
	Study type/design	Animal experiment
	Study duration	3 months
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	C57BL/6J mice
	Selection criteria for population (if applicable)	
	Subgroups reported	3 groups: nil, 0.1 and 0.4 parts per million Se.
	Size of study	3 groups: C57BL/6J mice (n =6–7 per group)
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Diet
	Exposure concentrations (if applicable)	C57BL/6J mice (n =6–7 per group) were fed either Se-deficient Torula yeast-based diet or diets supplemented with 0.1 and 0.4 parts per million Se.
	Comparison group(s)	Se-deficient group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Study looked at outcomes related to plasma glucose and insulin measurements, insulin sensitivity selenoprotein expression, and enzyme activity as follows: • To gauge the degree of regulation of selenoprotein expression by dietary Se. • Effect of dietary Se supplementation on insulin sensitivity and glycaemic control in C57BL/6J mice • Development of insulin resistance in GPx1-overexpressing mice is accompanied by elevated expression of several other selenoproteins • Selenoprotein deficiency leads to dysregulation of glucose homeostasis in i 6A - mutant Sec tRNA transgenic mice
	How outcome was assessed	
	Method of measurement	

Publication Reference: Labunskyy V. M., Lee B. C., Handy D. E., Loscalzo J., Hatfield D. L. and Gladyshev V. N. (2011). Both maximal expression of selenoproteins and selenoprotein deficiency can promote development of type 2 diabetes-like phenotype in mice. Antioxid Redox Signal 14(12): 2327-2336.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	3 groups: C57BL/6J mice (n =6–7 per group)
Statistics (if any)	Statistical method used	Statistical analysis of the data was performed using two-way ANOVA and Student's t-test. All results are represented as means –standard error of the mean (SEM).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Authors concluded that data show that mice maintained on a Se-supplemented diet develop hyperinsulinemia and have decreased insulin sensitivity. • These effects are accompanied by elevated expression of a selective group of selenoproteins. • Authors also observed that reduced synthesis of these selenoproteins caused by overexpression of an i6A - mutant selenocysteine tRNA promotes glucose intolerance and leads to a diabetes-like phenotype. • These findings indicate that both high expression of selenoproteins and selenoprotein deficiency may dysregulate glucose homeostasis and suggest a role for selenoproteins in development of diabetes.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This study was not subjected to a RoB assessment as it evaluated biomarkers of effects in animals and did not look at adverse effects *per se*.

Lacaustra et. al. 2010

Publication Reference: Laclaustra 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.		
General Information	Date of data extraction	15/06/2023
	Authors	Laclaustra, M., Stranges, S., Navas-Acien, A., Ordovas, J.M., Guallar, E.
	Publication date	2010 June
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA

Publication Reference: Laclaustra 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.		
	Source of funding	Supported by grants ES012673 from the National Institute of Environmental Health Sciences, DK075030 from the National Institute of Diabetes, Digestive, and Kidney Disease, 0230232N from the American Heart Association
	Possible conflicts of interest	The authors state they do not have potential conflicts of interest regarding this manuscript.
Study characteristics	Aim/objectives of study	Authors evaluated the association of serum selenium with fasting serum lipid levels in the National Health and Nutrition Examination Survey (NHANES) 2003–2004, the most recently available representative sample of the US population that measured selenium levels.
	Study type/design	Cross-sectional study
	Study duration	Not applicable (cross-sectional study design)
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Cross-sectional analysis of 1159 adults ≥40 years old from NHANES 2003–2004 [US Third National Health and Nutrition Examination Survey (NHANES III)]
	Selection criteria for population (if applicable)	
	Subgroups reported	Participants were divided into quartiles of serum selenium concentration based on the weighted population distribution.
	Size of study	1159 adults ≥40 years
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Diet
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Lowest quartile
Study methods	Water quality measurement used	Not applicable. (Note: Serum selenium was measured by inductively coupled plasma-dynamic reaction cell-mass spectrometry. Fasting serum total-cholesterol, triglycerides, and HDL cholesterol were measured enzymatically and LDL cholesterol was calculated).
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Participants were divided in quartiles of serum selenium concentration based on the weighted population distribution. Adjusted mean differences in serum lipids and total to HDL cholesterol ratio, comparing each quartile of serum selenium to the lowest quartile, were calculated using multivariable linear regression.
	How outcome was assessed	
	Method of measurement	

Publication Reference: Laclaustra 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.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Authors used data from NHANES 2003–2004 10, the most recent release with selenium data available in adults at the time. Participants aged ≥40 years (N = 3,299) were eligible for selenium measurement according to NHANES protocol. Among them, 1,302 participated in the morning examination and had a fasting blood sample. Authors excluded participants with missing serum selenium levels (N = 29), dietary intakes (N = 50), body mass index (N = 22), education level (N=2), cotinine levels (N = 3), and lipid levels (N = 3). They also excluded 34 participants with triglycerides > 400 mg/dL as LDL cholesterol could not be calculated in this group. The final sample size was 1,159.
Statistics (if any)	Statistical method used Details on statistical analysis	Multivariable linear regression using 2 models with progressive degrees of adjustment. Model 1 was adjusted for sex, age, race / ethnicity and education. Model 2 was further adjusted for body mass index, smoking, cotinine, menopausal status, cholesterol, total fat, saturated fatty acids, and selenium intakes, and use of vitamin / mineral supplements. Statistical analyses were performed using weights specific for the fasting morning sample in the survey package in the R Statistical Software (version 2.6.1, R Foundation for Statistical Computing, Vienna, Austria) to account for the complex sampling design and weights. Censored regression models were estimated using the cnreg command in Stata Statistical Software (Release 9.2, StataCorp LP, College Station, TX) weighted for NHANES survey weights.
	Relative risk/odds ratio, confidence interval?	The multivariable adjusted average differences (95% confidence interval) comparing the highest (≥147 µg/L) to the lowest (<124 µg/L) selenium quartiles were: • 18.9 (9.9, 28.0) mg/dL for total cholesterol • 12.7 (3.3, 22.2) mg/dL for LDL cholesterol • 3.9 (0.4, 7.5) mg/dL for HDL cholesterol • 11.5 (−7.6, 30.7) mg/dL for triglycerides.
Author's conclusions	Interpretation of results	• Mean serum selenium was 136.7 µg/L. • In spline regression models, total and LDL cholesterol levels increased progressively with increasing selenium concentrations. • HDL cholesterol increased with selenium but reached a plateau above 120 µg/L of serum selenium (20th percentile). • The triglyceride-selenium relationship was U-shaped. • In US adults, high serum selenium concentrations were associated with increased serum concentrations of total and LDL cholesterol. • Selenium was associated with increasing HDL cholesterol only at low selenium levels. • Given increasing trends in dietary selenium intake and supplementation, the causal mechanisms underlying these associations need to be fully characterised.

Publication Reference: Laclaustra 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.		
	Assessment of uncertainty (if any)	The present study is limited by its cross-sectional design, and authors 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. Besides, selenium data were only available for subjects above 40 years of age and the observed association could be different among younger individuals. The possibility of confounding by concomitant intake of high fat and high selenium foods was addressed through adjusting for cholesterol, total fat, saturated fatty acids, and selenium intakes, although measurement error in dietary data may result in residual confounding.
Reviewer comments	Results included/excluded in review (if applicable)	This cross-sectional study of the US general population found potential risk factors of cardiovascular disease (i.e. cholesterol) to be associated with Se levels in serum. A RoB assessment was undertaken for this study.

Lance et. al. 2017

Publication Reference: 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.		
General Information	Date of data extraction	15/06/2023
	Authors	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., Roe, D.J.
	Publication date	2017 January
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	USA
	Source of funding	This work was funded in part by Public Health Services grants R01 CA124862 (P. Lance), U10 CA37429 C.D. Blanke) and UM1 CA182883 (I. M. Thompson/C.M. Tangen)
	Possible conflicts of interest	None to declare
Study characteristics	Aim/objectives of study	The primary objective was to measure the effect of selenium (as selenomethionine) on colorectal adenomas occurrence, with the effect of vitamin E (as alpha tocopherol) supplementation on colorectal adenoma occurrence considered as a secondary objective. Exploratory objectives were to measure effect modification of the primary outcome by concomitant use of aspirin, body mass index (BMI), or a family history of colorectal cancer, defined as having 1 or more first-degree relatives (FDRs) previously diagnosed with the disease

Publication Reference: 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.		
	Study type/design	Randomised, placebo-controlled HCT (SELECT)
	Study duration	Follow-up of a minimum of 7 years and a maximum of 12 years
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a randomised, controlled trial of selenium (as selenomethionine) and vitamin E (as alpha tocopherol) for the prevention of prostate cancer, in which a total of 35,533 men were randomised at 427 clinical sites in the United States, Canada, and Puerto Rico. Participants who underwent lower endoscopy while in SELECT were identified from a subgroup of the 35,533 men randomiaed in the trial.
	Selection criteria for population (if applicable)	
	Subgroups reported	• Oral selenium (200 µg/day from L-selenomethionine) and matched vitamin E placebo • Vitamin E (400 IU/day of all rac-α-tocopheryl acetate [alpha tocopherol]) and matched selenium placebo • Selenium + vitamin E • Double placebo.
	Size of study	35,533 SELECT population. A total of 8,094 participants who underwent lower endoscopy during the trial consented to participate in the ancillary study
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplement
	Exposure concentrations (if applicable)	200 µg/day from L-selenomethionine
	Comparison group(s)	Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Adenoma occurrence was ascertained from the endoscopy and pathology reports for these procedures.
	How outcome was assessed	
	Method of measurement	Colonoscopies and sigmoidoscopies
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• Eligibility for SELECT included age ≥50 years (African American men) or ≥55 years (all other men), serum prostate-specific antigen ≤4 ng/mL, and a normal digital rectal examination. • SELECT exclusion criteria included a prior history of malignancies other than basal or squamous cell carcinoma of the skin within the previous 5 years and use of selenium and/or vitamin E supplements. Concomitant use of aspirin up to a daily dose of 175 mg was allowed.

Publication Reference: 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.		
Statistics (if any)	Statistical method used	Relative risk (RR) estimates and 95% confidence intervals (CI) of adenoma occurrence were generated comparing those randomised to selenium versus placebo and to vitamin E versus placebo based on the full factorial design. All analyses were performed based on the randomised treatment assignment (intent-to-treat). Statistical analysis was based on the factorial design and compared the presence of selenium (selenium alone and selenium + vitamin E groups) versus the absence (double placebo and vitamin E alone groups). Comparison of the presence versus the absence of vitamin E was assessed as a secondary outcome. Log-binomial regression was used to generate RR estimates and 95% CI. The initial models included the effects of selenium and vitamin E and their interaction; interaction was tested using a likelihood ratio test (LRT), comparing a model with and without the interaction term. In the absence of interaction, the selenium and vitamin E effects were estimated with the interaction terms excluded.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Compared with placebo, the RR for adenoma occurrence in participants randomised to selenium was 0.96 (95% CI, 0.90–1.02; P = 0.194). Vitamin E did not affect adenoma occurrence compared to placebo (RR = 1.03, 95% CI, 0.96–1.10; P = 0.38).
Author's conclusions	Interpretation of results	• Evaluable endoscopy information was obtained for 6,546 participants, of whom 2,286 had 1+ adenomas. Apart from 21 flexible sigmoidoscopies, all the procedures yielding adenomas were colonoscopies. • Adenomas occurred in 34.2% and 35.7%, respectively, of participants whose intervention included or did not include selenium. • Neither selenium nor vitamin E supplementation can be recommended for colorectal adenoma prevention.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This randomised, placebo-controlled HCT found no increased risk of colorectal adenoma in patients of SELECT trial administered 200 µg/ Se/day as selenomethionine. A RoB assessment was undertaken for this study.

Li et al. 2012

Publication Reference: Li S., Xiao T. and Zheng B. (2012). Medical geology of arsenic, selenium and thallium in China. Science of The Total Environment 421-422: 31-40.		
General Information	Date of data extraction	09/06/2023
	Authors	Li S, Xiao T, Zheng B
	Publication date	2012

Publication Reference: Li S., Xiao T. and Zheng B. (2012). Medical geology of arsenic, selenium and thallium in China. Science of The Total Environment 421-422: 31-40.		
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	No funding details provided.
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	To review the research progress of the human health impacts of a number of different elements (including Se) in China, particularly from the perspective of medical geology. Very little information on Se; relevant information has been pulled out in this data extraction table.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	See outcomes below
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• There are a few places in China which have observed a high prevalence of endemic selenosis. • Hair and nail loss were the prime symptoms of endemic selenosis, but disorders of the nervous system, skin, poor dental heath, garlic breath, and paralysis were also reported. Although no health investigations were carried out in the peak prevalence years of 1961 to 1964 in Enshi District, subsequent studies in these areas carried out in the 1970s revealed very high dietary intakes of 3.2–6.8 mg/day with a range of selenium in the blood of 1.3–7.5 mg/L and hair selenium levels of 4.1–100 mg/kg. • Due to increasingly less dependence on locally grown foodstuffs in the diet, no human cases of selenium toxicity have been reported since 1987 in these areas, but the local animals frequently suffer hoof and hair loss as a result of the high environmental selenium.
	How outcome was assessed	

Publication Reference: Li S., Xiao T. and Zheng B. (2012). Medical geology of arsenic, selenium and thallium in China. Science of The Total Environment 421-422: 31-40.		
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• This paper reviews the progress of medical geology of As, Se and Tl in China, and provides with some outlooks for future research directions. • The states of the endemic diseases of As, Se and Tl in China are still serious in some areas, and substantial research efforts regarding the health impacts of these elements are further required.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This review provides very limited information on endemic selenosis occurrence in Chinese villages but indicates dietary intakes of Se in these areas were very high 3.2–6.8 mg/day. These intakes are 8-17x higher than the upper tolerable intake of 0.4 mg/day referenced by WHO (2011) and others in the derivation of the candidate guideline values in the Stage 1 report. Thus this information would not change the outcomes of the Stage report. • As this is a review, it was not subjected to RoB assessment which is for assessing quality of primary studies.
	Notes on study quality, e.g. gaps, methods	

Lippman et. al. 2009

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	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. III, 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.A., Albanes, D., Taylor, P.R., Probstfield, J.L., Jagpal, T.J., Crowley, J.J., Meyskens, F.L. Jr, Baker, L.H., Coltman C.A., Jr.

Publication Reference: 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.		
	Publication date	2009 January 7
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	US
	Source of funding	This investigation was supported in part by Public Health Service Cooperative Agreement grant CA37429 awarded by the National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services DHHS, and in part by the National Center for Complementary and Alternative Medicine (NIH). Study agents and packaging were provided by Perrigo Company (Allegan, MI), Sabinsa Corporation (Piscataway, NJ), Tishcon Corporation (Westbury, NY) and DSM Nutritional Products, Inc (Parsipanny, NJ).
	Possible conflicts of interest	Dr. Gaziano reported (National Institutes of Health, the Veterans Administration, Veroscience, Amgen and BASF Corporation, BASF Corporation, Wyeth Pharmaceutical and DSM Nutritional Products Inc (formerly Roche Vitamins) and serving as a consultant or receiving honoraria from Bayer AG and Pfizer, and serving as an expert witness for Merck. Dr. Karp reported that he is Principal Investigator for the Eastern Cooperative Oncology Group (ECOG) E5597 Intergroup Study of Selenium Only vs. Placebo in Resected Stage I Lung Cancer. Dr. Lucia reported that he serves as a consultant for GlaxoSmithKline and Veridex, and is a member of the Advisory Board for GenProbe. Dr. Meyskens reported that he is Co-founder of Cancer Prevention Pharmaceuticals. Dr. Parsons reported that he receives grant support from the National Cancer Institute and the Department of Defense. Dr. Thompson reported that he serves as a consultant for Veridex and Mission Pharmacal (with fees paid to University of Texas HSC at San Antonio).
Study characteristics	Aim/objectives of study	To determine whether selenium or vitamin E or both could prevent prostate cancer with little or no toxicity in relatively healthy men.
	Study type/design	HCT, randomised double blinded, placebo-controlled trial (SELECT Trial)
	Study duration	A planned minimum of 7 and maximum of 12 years.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Randomisation of a planned 32,400 men to selenium, vitamin E, selenium plus vitamin E, and placebo in a double-blinded fashion. Participants were recruited and followed in community practices, local hospitals and HMOs, and tertiary cancer centres in the United States, Canada and Puerto Rico.
	Selection criteria for population (if applicable)	
	Subgroups reported	4 Groups: L-selenomethionine, matched vitamin E placebo, vitamin E (400 IU/day of all rac-α-tocopheryl acetate) and matched selenium placebo

Publication Reference: 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.		
	Size of study	35,533 men. Placebo (n=8,696), Vitamin E (n=8,737), Selenium (n=8,752), Combination (n=8,703)
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplement
	Exposure concentrations (if applicable)	Oral selenium (200 µg/day from L-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/day of all rac-α-tocopheryl acetate) and matched selenium placebo, or the two combined or placebo plus placebo for a planned minimum of 7 and maximum of 12 years.
	Comparison group(s)	Matched vitamin E placebo, vitamin E, and matched selenium placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Prostate cancer (as determined by routine community diagnostic standards) and prespecified secondary outcomes including lung, colorectal and overall cancer.
	How outcome was assessed	Authors report here the effects of selenium and vitamin E, alone or in combination, on the risk of prostate cancer and secondary endpoints in SELECT. Men were asked at their first 6-month clinic visit to report new events since entering the trial and thereafter to report new events since their last visit. Cardiac-event data were collected in detail from the trial beginning (2001); data on diabetes were added through self-reported glitazone-medication use (beginning in 2003) and diagnosis of diabetes (beginning in late 2005), which was initially asked retroactive to randomisation date and then reported at interval visits thereafter. A general question regarding any events considered severe or life- threatening (Grade 3 or 4), regardless of attribution to the study supplements, was also asked.
	Method of measurement	Self-reported, clinic visits
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Between 2001 and 2004, 35,533 men (10% more than planned because of a faster-than-expected accrual rate) were randomly assigned to the four study arms, which were well balanced with respect to all potentially important risk factors. Baseline eligibility included 50 years or older (African American) or 55 years or older (all others), a serum prostate-specific antigen (PSA) ≤ 4 ng/mL, and a digital rectal examination (DRE) not suspicious for prostate cancer.
Statistics	Statistical method used	

Publication Reference: 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.		
(if any)	Details on statistical analysis	The interim analyses tested the null hypothesis at a one-sided .0005 level (equivalent to a two-sided .001 level) using the proportional hazards regression model. In addition, the alternative hypothesis of a 25% reduction in prostate cancer incidence was tested at a one-sided level of .0005 (equivalent to a two-sided .001 level) using an extension of the proportional hazards regression model that allows for testing a relative risk not equal to 1. The purpose of the second analysis was to allow for the study to stop if it was determined that the expected reduction in prostate cancer would not be seen. The frequencies of the number of cardiac events and cases of diabetes were tested with a chi square test and were not corrected for multiple comparisons. For cardiac event and diabetes analyses, authors did not capture the report of the date of the event, which thus was not incorporated into the analysis.

	Relative risk/odds ratio, confidence interval?	• Hazard ratios (number of prostate cancers, 99% confidence intervals [CIs]) for prostate cancer compared with placebo (n=416) were
		  • 1.13 for vitamin E (n=473; CI, 0.91–1.41)
		  • 1.04 for selenium (n=432; CI, 0.83–1.30)
		  • 1.05 for the combination (n=437; CI, 0.83–1.31).
		• There were no significant differences (all p-values > 0.15) in any prespecified cancer endpoints.
		• There were nonsignificant increased risks of prostate cancer in the vitamin E arm (p=0.06; relative risk [RR]=1.13; 99% CI, 0.95–1.35) and of Type 2 diabetes mellitus in the selenium arm (p=0.16; RR=1.07; 99% CI, 0.94–1.22), but they were not observed in the combination arm.
		• Confidence intervals of hazard ratios for other adverse events were found to overlap 1 for the following in the selenium group:
		  • 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).

Author's conclusions	Interpretation of results	• Selenium or vitamin E, alone or in combination, did not prevent prostate cancer in this population at the doses and formulations used. • Study supplements were discontinued at the recommendation of the Data and Safety Monitoring Committee at a planned 7-year interim analysis because the evidence convincingly demonstrated no benefit from either study agent (p < 0.0001) and no possibility of a benefit to the planned degree with additional follow-up. • As of October 23, 2008, median overall follow-up was 5.46 years (range, 4.17 and 7.33)

Publication Reference: 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.		
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This large randomised, double-blind, placebo-controlled, long-term HCT in men susceptible of developing prostate cancer found no beneficial effect of Se on prostate cancer prevention and found no negative effect on cancer development. However, in the Se group (given 200 µg/d as selenomethionine) hazard ratios considered marginally significant were calculated for two mild adverse events: • 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). This study was subject to the RoB assessment as it found no statistical significance in selenium exposure and Type 2 diabetes in contrast to other studies (e.g. Stranges 2007)

Liu et al. 2018

Publication Reference: Liu Q., Han W., Han B., Shu M. and Shi B. (2018). Assessment of heavy metals in loose deposits in drinking water distribution system. Environ Monit Assess 190(7): 388.		
General Information	Date of data extraction	09/06/2023
	Authors	Liu Y, Yuan Y, Luo K
	Publication date	2018
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	Support for this research was provided by the National Natural Sciences Foundation of China (Nos. 41502329, 41472322, 41602124) and the Major State Basic Research Development Program of China (973 Program) (No. 2014CB238906).
	Possible conflicts of interest	The authors declare that they have no conflict of interest.
Study characteristics	Aim/objectives of study	To determine the spatial variation of longevity population and elements contained in the drinking water of longevity region in Jiangjin and investigate the relationship between the elements in drinking water and longevity.
	Study type/design	Cross-sectional (observational)
	Study duration	Not applicable (slice in time)

***Publication Reference*:** Liu Q., Han W., Han B., Shu M. and Shi B. (2018). Assessment of heavy metals in loose deposits in drinking water distribution system. Environ Monit Assess 190(7): 388.		
	Type of water source (if applicable)	Drinking water (including river water and shallow groundwater)
Population characteristics	Population/s studied	Statistical data for the centenarian and > 85-year-old populations were collected from the Jiangjin Bureau of Civil Affairs in 2015.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not clear
Exposure and setting	Exposure pathway	Drinking water (but other exposure pathways likely also operaple)
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Mean concentration of Se was 2.05 µg/L in drinking water in Jiangjin. Mean concentrations in other provinces used for comparison were 0.96, 0.87, 0.99, 0.98 and 2.46 µg/L.
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Se concentration in drinking water was measured by hydride generation atomic fluorescence spectrometry (HG-AFS).
	Water sampling methods (monitoring, surrogates)	Ninety-eight samples of drinking water (including river water and shallow groundwater) were collected in Jiangjin. Sampling containers are colourless polythene plastic barrels soaked in nitric acid for 24 h. The pH was determined *in situ*. All water samples were stored in clean plastic bottles at 4 °C before being analysed.
Results (for each outcome)	Definition of outcome	• The percentage of people above 85 years old (OE) in Jiangjin District was higher than that of the nation and Chongqing. Population statistics from population census in 2010 indicated that the number of centenarians per 100,000 inhabitants (OC) in Jiangjin (8.10) was 3.0 and 2.6 times more than that of national (2.70) and Chongqing level (3.09), respectively. • Mean concentrations of TDS, TH, Ca, Na, Sr, Li, Ba, Mn, Ni, and Se in drinking water from longevity township were significantly higher than those of non-longevity township (Mann–Whitney U test, $p < 0.05$).
	How outcome was assessed	
	Method of measurement	Three indexes were applied. The indexes are LI (ratio of ultra-nonagenarians to those above 65 years old, called longevity index), CI (ratio of centenarians within the ultra-nonagenarians, called centenarity index), and UC (number of centenarians per 10,000 over 65-year-old subjects).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Applied Mann–Whitney U and the Kruskal-Wallis methods in the non-parametric statistics methods to test the differences because the distribution of data did not follow normal distribution or logarithmic distribution. Effects were considered statistically significant with $p < 0.05$ based on two-tailed tests. SPSS 17.0 and Excel 2010 were used for the statistical analysis.
	Details on statistical analysis	

***Publication Reference*:** Liu Q., Han W., Han B., Shu M. and Shi B. (2018). Assessment of heavy metals in loose deposits in drinking water distribution system. Environ Monit Assess 190(7): 388.		
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Intake of safe drinking water with high concentrations of TH, Ca, Sr, Li, Mn, Ba, Ni, and Se might be good for human health and prolong lifespan. Therefore, a strict control of the concentrations of elements contained in drinking water might be an effective way to live longer.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This study suggests that higher concentrations of Se (and various other minerals) in drinking water compared to very low concentrations may be beneficial to health; however very crude endpoints (i.e. longevity) were used, the study did not adjust for any confounders, and the concentrations difference of Se in drinking water between provinces (i.e. ~0.95 µg/L vs. ~2.0 µg/L) were very minimal. • The reviewer considers the results of this study may simply be due to chance. • As the study provides no relevant information to inform the dose response of adverse effects due to Se exposure, it was not subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

MacFarquhar et. al. 2010

Publication Reference: 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.		
General Information	Date of data extraction	15/06/2023
	Authors	Jennifer K. MacFarquhar, Danielle L. Broussard,. Paul Melstrom, Richard Hutchinson, Amy Wolkin, Colleen Martin, Raymond F. Burk, John R. Dunn, Alice L. Green, Roberta Hammond, William Schaffner, Timothy F. Jones
	Publication date	2010
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA
	Source of funding	None reported
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Authors investigated an outbreak of acute selenium poisoning
	Study type/design	Case study
	Study duration	90-days

Publication Reference: 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.		
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	• 227 affected persons identified in 9 states: Florida, Georgia, Kentucky, Michigan, North Carolina, Pennsylvania, Tennessee, Texas, and Virginia • A case was defined as the onset of symptoms of selenium toxicity in a person within 2 weeks after ingesting a dietary supplement manufactured by "Company A," purchased after January 1, 2008.
	Selection criteria for population (if applicable)	
	Subgroups reported	None
	Size of study	227 affected persons identified in 9 states
Exposure and setting	Exposure pathway	Oral (supplement)
	Source of chemical/contamination	The source of the outbreak was identified as a liquid dietary supplement that contained 200 times the labelled concentration of selenium
	Exposure concentrations (if applicable)	The median estimated dose of selenium consumed was 41,749 µg/d (recommended dietary allowance is 55 µg/d). The median period over which patients had consumed the mis-formulated product was 29 days (range 1–109 days). Among 156 patients with data available, the median estimated amount of selenium ingested was 989 mg (range, 41–5875 mg), for a median of 41,585 µg/d (range, 3400–244,800 µg/d; recommended dietary allowance, 55 µg/d). Among 98 patients with weight and dose available, the median dose ingested was 12.8 mg/kg (range, 0.5–115.4 mg/kg).
	Comparison group(s)	No comparison group
Study methods	Water quality measurement used	Not applicable (Simplified fluorometric assay of total selenium in plasma and urine)
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Authors conducted case finding, administered initial and 90-day follow-up questionnaires to affected persons, and obtained laboratory data where available. • 5 states (Florida, Georgia, Michigan, North Carolina, and Tennessee) administered follow-up questionnaires approximately 90 days after the initial interviews. • Seven affected patients in Tennessee provided 24-hour urine specimens for testing of selenium concentration at the time of initial interview and at 1 week and 1 month thereafter. • Eight patients provided results of serum selenium testing ordered by their physicians from commercial laboratories.
	How outcome was assessed	
	Method of measurement	Questionnaire and lab analysis (15 patients only).

Publication Reference: 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.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• 201 cases identified in 10 states. • 104 of 150 patients were administered the follow-up questionnaire. • 26 consumers who did not meet the case definition reported no or mild symptoms.
Statistics (if any)	Statistical method used	Data were analysed by using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable. Results include: • Frequently reported symptoms included diarrhea (78%), fatigue (75%), hair loss (72%), joint pain (70%), nail discoloration or brittleness (61%), and nausea (58%). • Symptoms persisting 90 days or longer included fingernail discoloration and loss (52%), fatigue (35%), and hair loss (29%). • The mean initial serum selenium concentration of 8 patients was 751 µg/L (reference range, ≤125 µg/L). • The mean initial urine selenium concentration of 7 patients was 166 µg/24 h (reference range, ≤55 µg/24 h).
Author's conclusions	Interpretation of results	• Serum and urine selenium concentrations decreased gradually with time, with values returning to normal by weeks 1 to 2 for urine and starting at week 6 for serum. • Persistence of symptoms was also notable; patients often continued to experience symptoms 90 days after the exposure to selenium had ended. This was true not only for the hair and nail changes, which are expected to require substantial time to return to normal, but also for constitutional symptoms, including memory loss, mood swings, fatigue, musculoskeletal complaints, and garlic breath. • This episode of selenium toxicity caused by a mis-formulated commercially distributed dietary supplement presented unique clinical and public health challenges. Given the rarity of selenium toxicity, along with the array of nonspecific symptoms, recognising the diagnosis can be difficult. Furthermore, a substantial proportion of patients had not yet sought medical attention at the time they were contacted by public health investigators. • Because of nonspecific symptoms and limited health care–seeking behaviour among affected persons, the outbreak was probably even larger than recognised.
	Assessment of uncertainty (if any)	Not stated

Publication Reference: 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.		
Reviewer comments	Results included/excluded in review (if applicable)	The authors note that the serum selenium concentrations reported during this outbreak are high for subjects ingesting inorganic forms of selenium. Ingestion of organic selenium in the form of selenomethionine is associated with much higher serum selenium concentrations than ingestion of inorganic forms. This case series provides support for high doses of Se (median of ~41,600 µg/day) ingested for ~29 days resulting in selenosis-type adverse effects. As these doses are much higher than the upper levels of Se intake used to derive candidate guideline values in the Stage 1 report, this study was not subjected to RoB assessment.

Mandrioli et. al. 2017

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Mandrioli, J., Michalke, B., Solovyev, N., Grill, P., Violi, F., Lunetta, C., Conte, A., Sansone, V.A., Sabatelli, M., Vinceti, M.
	Publication date	Published online: May 6, 2017
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	National, Modena, and Reggio Emilia sections of the Italian Amyotrophic Lateral Sclerosis Association (AISLA), the Local Health Unit of Reggio Emilia, and the Vignola Foundation (to Dr. Vinceti), the DAAD-SPbSU Dmitrij Mendeleev-Programme (2015, grant No. 91591663), and the Russian Foundation of Basic Research (grant 16-33-60004 mol_a_dk (to Dr. Solovyev).
	Possible conflicts of interest	The authors declare no conflicts of interest
Study characteristics	Aim/objectives of study	Hypothesising a multistep pathogenic mechanism (genetic susceptibility and environmental exposure), the authors aimed to study selenium species in ALS patients carrying disease-associated gene mutations as compared to a series of hospital controls.
	Study type/design	Genetic study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	ALS patients were recruited from 3 major Italian ALS referral centres (Milan, Modena, and Rome) from among all patients who were diagnosed with definite or probable ALS
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable

Publication Reference: 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.		
	Size of study	9 ALS patients included 5 men and 4 women, with a mean age at disease onset of 50 years (range 12–64), who underwent lumbar puncture (LP) during the diagnostic process. The 42 age-matched controls had a mean age of 46 years (range 15–68).
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable (Note: limited difference in selenium levels except for one ALS patient with very high comparative selenium levels in cerebrospinal fluid (CSF)).
	Comparison group(s)	Eligible controls were Italian residents who underwent LP because of suspected but later unconfirmed neurological disease and whose sample (≥1 mL of CSF) was still available.
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Authors determined the total selenium and the selenium species selenite (Se-IV), selenate (Se-VI), selenomethionine-bound selenium (Se-Met), selenocysteine-bound selenium (Se-Cys), thioredoxin reductase-bound selenium (Se-TrxR), glutathione-peroxidase-bound selenium (Se-GPx), selenoprotein-P-bound selenium (Se-PP), and albumin-bound selenium (Se-HSA) in the CSF samples using ion exchange chromatography coupled with inductively coupled plasma sector field mass spectrometry (ICP-sf-MS) in high-resolution mode in analogy to methodologies previously established for CSF. Authors reported the mean and 25th, 50th, and 75th percentiles of analytical results after inputting for values below the limit of detection half that limit. They compared the results for all of the familial cases except for the TUBA4A case and the control subjects using a 2-tailed t test for independent samples, and computed the odds ratio (as an estimate of the relative risk [RR]) of ALS using an unconditional logistic regression model adjusting for age and sex.
	How outcome was assessed	
	Method of measurement	ICP-MS
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	9 ALS patients and 42 age-matched controls. ALS patients selected from 164 CSF samples of consecutive ALS patients, authors selected those carrying an ALS-related gene mutation and having at least 1 mL of CSF still stored and available for the present study.
Statistics (if any)	Statistical method used	Authors compared the results for all of the familial cases except for the TUBA4A case and the control subjects using a 2-tailed t test for independent samples, and computed the odds ratio (as an estimate of the relative risk [RR]) of ALS using an unconditional logistic regression model adjusting for age and sex.
	Details on statistical analysis	

Publication Reference: 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.		
	Relative risk/odds ratio, confidence interval?	• Total selenium OR = 0.8, CI = 0.4 – 1.7, p = 0.607 • Inorganic selenium OR = 0.1, CI = 0.0 – 7.3, p = 0.329 • Organic selenium OR = 1.0, CI = 0.4 – 2.2, p = 0.913 • Se-IV OR = 0.6, CI = 0.0 – 59.3, p = 0.807 • Se-VI OR = 0.0, CI = 0 – 394.1, p = 0.214 • **Se-Met OR = 175.0, CI = 1.5 – 19,858.1**, p = 0.032 • Se-PP OR = 0.9, CI = 0.2 – 3.2, p = 0.842 • Se-HSA OR = 0.3, CI = 0.0 – 36.9, p = 0.645 • Se-GPx OR = 0.7, CI = 0.2 – 2.3, p = 0.556 • Se-TrxR OR = 1,653.2, CI = 0.0–∞ , p = 0.202
Author's conclusions	Interpretation of results	The authors found abnormally high levels of selenomethionine in the CSF of patients carrying various disease-associated gene mutations. They also found very high levels of organic and inorganic selenium compounds in a patient carrying the extremely rare TUBA4A mutation. Such increases in potentially neurotoxic selenium compounds might represent an innocent bystander due to a common genetic background or unmeasured confounding, or alternatively they might play an independent and relevant role in the etiopathogenesis of the disease.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This study investigated the OR of ALS in patients with specific genetic mutations through determination of various Se species in CSF. There were no statistically significant results (apart from for selenomethionine, where 95% CI were very large) and exposure/dose response could not be ascertained hence this study was not subject to a RoB assessment.

Marshall et. al. 2011

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	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., Thompson, I.M. Jr.
	Publication date	2011
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	Not stated

Publication Reference: 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.		
	Possible conflicts of interest	Other Commercial Research Support: JM Gaziano (Wyeth: vitamin pills and packaging). Honoraria from Speakers Bureau: WR Lee. No other authors declared a conflict of interest
Study characteristics	Aim/objectives of study	Investigate selenium supplementation on risk of prostate cancer (PC) and High-grade prostatic intraepithelial neoplasia (HGPIN)
	Study type/design	Human Controlled Trial (HCT), double-blind, randomised, placebo-controlled
	Study duration	3 years
	Type of water source (if applicable)	Not applicable (Note: Supplement)
Population characteristics	Population/s studied	This NCI Intergroup trial was coordinated by the Southwest Oncology Group (SWOG). Of 619 enrolled patients, 423 randomised men with HGPIN (212, selenium; 211, placebo) were eligible (by central pathology review) and included in the primary analysis.
	Selection criteria for population (if applicable)	The following eligibility criteria were required: 40 years of age or older; digital rectal examination; biopsy- confirmed diagnosis of HGPIN with no evidence of cancer; upper limit of prostate-specific antigen (PSA) of 10 ng/mL (as measured locally); American Urological Association (AUA) symptom score of less than 20 (41), signifying no debilitating urinary problems; ambulatory and able to carry out work of a light or sedentary nature. The following conditions were exclusion criteria: Diagnosis of any cancer, other than non-melanoma skin cancer, within 5 years prior to trial registration; taking selenium supplements containing more than 50 µg/day within 30 days prior to registration; taking finasteride or other 5-alpha reductase inhibitors.
	Subgroups reported	Subjects were stratified with dynamic balancing (45) for age (40–60 versus 61 or older), race (African-American versus other), pre-study PSA (< 4 ng/ml versus 4–10 ng/ml), and vitamin E supplementation (yes versus no). In addition, after the protocol was changed in November 2002, subjects were stratified on the number of cores in the initial biopsy (< 10 cores versus 10 or more cores).
	Size of study	619 enrolled patients, 423 randomised men with HGPIN (212, selenium; 211, placebo).
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplement
	Exposure concentrations (if applicable)	Selenium 200 (µg/day) as selenomethionine in men with HGPIN
	Comparison group(s)	Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable

Publication Reference: 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.		
Results (for each outcome)	Definition of outcome	The primary endpoint was progression of HGPIN to prostate cancer over a three-year period.
	How outcome was assessed	
	Method of measurement	Adverse events were graded by clinicians using the National Cancer Institute Common Toxicity Criteria (CTC) version 2.X.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	619 enrolled patients, 423 randomised men with HGPIN (212, selenium; 211, placebo) were eligible (by central pathology review) and included in the primary analysis.
Statistics (if any)	Statistical method used	The primary treatment comparison was to compare the proportion of men diagnosed with PC within three years ± 90 days of randomisation in the selenium arm versus this proportion in the placebo arm. The denominator was men with a known three-year endpoint status; men with missing/unknown status were excluded. The chi-square test was used to evaluate the statistical significance of the difference between the proportions. Cumulative incidence plots for time to PC were derived for the placebo arm and the selenium arm; patients not developing PC were censored at the earliest of the following dates: Last contact, three years plus 90 days post-randomisation, or at death if it occurred prior to a diagnosis of PC.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Non significantly reduced PC risk (RR = 0.82; 95% CI, 0.40–1.69) in selenium versus placebo patients in the lowest quartile of baseline selenium level (< 106 ng/ml). There were 21 grade-2 events in the selenium arm and 13 in the placebo arm (detailed data not shown). There was only one grade-3 event, which was dermatologic, in the selenium arm, and there were three grade-3 events—one cardiovascular, one gastrointestinal, and one renal/bladder— in the placebo arm.
Author's conclusions	Interpretation of results	The present study extends the findings of the massive SELECT trial in showing that selenium does not prevent prostate cancer in selenium-replete men. Selenium (200 µg/day) in the form of selenomethionine is clearly ineffective for reducing PC risk in selenium-replete men with HGPIN. The present trial's suggestion of a selenium benefit in selenium-deficient men, which is consistent with earlier NPC findings, and selenium pharmacogenetics may identify men who would benefit from selenium, suggesting an approach for future study of selenium.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This randomised, double-blinded, placebo-controlled HCT found 200 µg/day selenium (as selenomethionine) given to men at risk of prostate cancer did not reduce the risk of developing prostate cancer. Adverse events incidence was not markedly different from placebo group (no statistical analysis done). As this study is unlikely to affect the Stage 1 conclusions, this study was not subject to a RoB assessment.

Mix et al. 2015

Publication Reference: 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.		
General Information	Date of data extraction	09/06/2023
	Authors	Mix M, Ramnath N, Gomez J, de Groot C, Rajan S, Dibaj S, Tan W, Rustum Y, Jameson MB, Singh AK
	Publication date	2015
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	USA and New Zealand
	Source of funding	Supported by The Health Research Council of New Zealand
	Possible conflicts of interest	The authors declare that they have no conflict of interest.
Study characteristics	Aim/objectives of study	To prospectively determine the safety and tolerability of oral L-selenomethionine (SLM) with concurrent chemoradiation (CCRT) for Stage III non-small cell lung cancer (NSCLC) and estimate if the incidence and/or severity of adverse events could be reduced by its use.
	Study type/design	HCT
	Study duration	SLM 800 µg capsules (Sabinsa Corp., NJ) were dosed as follows for a total of 7 wk: patients received loading doses of SLM 4800 µg orally twice daily for one week prior to beginning CCRT followed by a maintenance dose of 4800 µg daily for six weeks, or until the completion of therapy.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	16 patients with stage III NSCLC from Roswell Park Cancer Institute (RPCI) and Waikato Hospital accrued to single arm, phase II study.
	Selection criteria for population (if applicable)	Patients were ineligible if they: were pregnant or of childbearing potential and refusing appropriate contraception; had a prior myocardial infarct within the preceding 6 mo or had symptomatic heart disease (angina, congestive heart failure, uncontrolled arrhythmia); had a serious concomitant infection including post-obstructive pneumonia; or had undergone major surgery other than biopsy in the previous 2 wk.
	Subgroups reported	Not applicable
	Size of study	N=16 patients
Exposure and setting	Exposure pathway	Oral (capsule)
	Source of chemical/contamination	Not applicable

Publication Reference: 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.		
	Exposure concentrations (if applicable)	4,800 µg twice daily (i.e. 9,600 µg/day), then once daily during treatment for 6 weeks (or until completion of therapy). This equates to ~3,840 µg Se/day, followed by ~1,920 µg Se/day.
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• No selenium-related toxicity was observed. Analysis revealed grade 3 or higher esophagitis in 3 of 16 patients (19%), pneumonitis in 0, leukopenia in 2 (12.5%), and anaemia in 1 (6%); the latter two were significantly reduced when compared to the protocol-stated expected rate of 35% (P = 0.045 for leukopenia, and P < 0.01 for anaemia). Median overall survival was 14.9 mo and median failure-free survival was 9 mo (95%CI: 3.3-21.5).
	How outcome was assessed	
	Method of measurement	• Pre-treatment evaluation included a complete medical history and physical examination with determination of the Eastern Cooperative Oncology Group (ECOG) performance status (PS) and questions about recent weight loss and concurrent non-malignant diseases. • A complete blood count with differential and platelet count was also required, along with a biochemical survey, measurement of electrolytes, magnesium and serum transaminase levels, all of which had to be performed within 14 d of enrolment. • Imaging studies included computed tomography (CT) scans of the chest and upper abdomen and CT or magnetic resonance imaging of the brain. At least weekly, an interval history and physical examination was performed by a member of the study team to prospectively assess and collect data regarding PS, weight loss, and symptoms of esophagitis and other toxicities. The complete blood count with differential, absolute granulocyte count, platelet count and serum creatinine levels were determined weekly. • Particular attention was paid to patients' pain levels and the medications required for control of symptomatic esophagitis. Toxicity was scored using National Cancer Institute Common Toxicity Criteria (CTC), version 3.0. Patients were evaluated with the same assessments 1 and 3 mo after treatment completion, at 3-mo intervals for 2 years then every 6 mo. CT scanning of the thorax was performed 3 mo after treatment and at each follow-up visit thereafter. • Blood selenium levels were drawn at baseline, then weekly for the duration of therapy in order to monitor response of serum levels to supplementation

Publication Reference: 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.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	The primary endpoint examined was toxicity resulting from SLM/CCRT (in particular, the anticipated esophagitis, pneumonitis and myelosuppression). Secondary endpoints included effects of SLM on efficacy and survival. A protocol-dictated 35% rate of CTC grade ≥ 3 esophagitis, pneumonitis, and myelosuppression was utilised for comparative statistics. The lower bound of the statistical power for correctly concluding acceptable toxicity of SLM/CCRT is 0.81 if the true toxicity rate is reduced by 20% compared to historical controls. A 0.05 level was set for Type 1 error, and 95%CI were calculated. One-sided P-values were calculated. Median, overall, and failure-free survival rates were calculated using the Kaplan-Meier method, with 95%CI.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• There may be some protective benefit of selenium in the setting of CCRT for inoperable NSCLC. The data suggests decreased rates of myelosuppression when compared to similarly-treated historical and contemporary controls. Further evaluation of selenium in this setting may be warranted. • The addition of SLM 4800 µg daily to CCRT in inoperable stage III NSCLC was safe and well-tolerated.
	Assessment of uncertainty (if any)	• Early closure due to poor accrual resulted in a smaller than intended cohort. This calls into question the observed decreased rate of myelosuppression (albeit a significant one), given small patient numbers. These results may be due to other factors, and their influence can't be assessed without a placebo group. • The 35% benchmark set for grade ≥ 3 oesophageal toxicity in this patient population may need to be reconsidered in light of newer radiation techniques, including the shift towards IFRT as opposed to ENI. The true rate of severe oesophagitis in this setting should perhaps be closer to 20%. Nevertheless, authors did see a decrease relative to the most closely-matched cohort.
Reviewer comments	Results included/excluded in review (if applicable)	

Publication Reference: 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.		
	Notes on study quality, e.g. gaps, methods	• This HCT was of a small size and investigated the toxicity of Se administered orally via capsule as selenomethionine in patients undergoing chemotherapy for inoperable stage III non-small cell lung cancer. • No adverse effects due to Se exposure were noted; doses administered (as Se) equate to ~3,840 µg Se/day for one week, followed by ~1,920 µg Se/day for ~6 weeks. These doses are approximately 5-10 times higher than the upper tolerable daily intake used for derivation of candidate guidelines in the Stage 1 report, and thus provide support for Stage 1 conclusions. • Study was subjected to RoB assessment.

Pan et al. 2022

Publication Reference: Pan Z., Zhu T., Zhu J. and Zhang N. (2022). Association between Maternal Selenium Exposure and Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis. Iran J Public Health 51(10): 2149-2158.		
General Information	Date of data extraction	09/06/2023
	Authors	Pan Z, Zhu T, Zhu J, Zhang N
	Publication date	2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	The research was supported by National Natural Science Foundation of China (No.81970738 and No.81600157), National Science and Technology Major Project of the Ministry of Science and Technology of China (No.2019ZX09201003-003), and Key Research and Development Program of Sichuan Province (No. 2020YFS0071), and Universal Application Program of Health Commission of Sichuan Province (No.21PJ047).
	Possible conflicts of interest	The authors declare that they have no conflict of interest.
Study characteristics	Aim/objectives of study	Systematically review and quantitatively analyse observational studies for a potential relationship between maternal Se exposure and congenital heart defects (CHDs) in the offspring.
	Study type/design	Systematic review and meta-analysis
	Study duration	All literature from PubMed, Embase, Web of Science and Scopus databases up until August 2021.
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: Pan Z., Zhu T., Zhu J. and Zhang N. (2022). Association between Maternal Selenium Exposure and Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis. Iran J Public Health 51(10): 2149-2158.		
Population characteristics	Selection criteria for population (if applicable)	Systematic review conducted in accordance with MOOSE guidelines. Eligibility criteria: 1) original observational studies, including cross-sectional, case-control, and cohort studies; 2) studies that examined the association between maternal Se exposure (including Se concentrations in blood, hair, urine, and in other biomarkers that can reflect Se exposure concentrations) and CHDs or one of the CHDs subtypes in offspring; 3) Full-text articles published in English. Reviews, letters, comments, case reports, and conference abstracts were excluded.
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: Pan Z., Zhu T., Zhu J. and Zhang N. (2022). Association between Maternal Selenium Exposure and Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis. Iran J Public Health 51(10): 2149-2158.		
	How outcome was assessed	• 186 articles initially identified. After removing duplicates, 128 articles entered screening stage, of which 119 articles did not meet eligibility criteria and were excluded after screening titles and abstracts. After viewing full text, four articles covering 5 studies were included in systematic review. For meta-analysis one article was excluded for no available effect size. One cohort, rest were case-controls. • The study showed that the relationship between maternal Se exposure and CHDs in the offspring was inconsistent. Guo et al. explored the correlation between maternal hair Se and CHDs, and found that high maternal Se concentrations were associated with increased incidence of total CHDs in offspring. As for CHDs subtypes, Se exposure ≥ 0.884 mg/g increased the risk of CTD, SPD, RVOTO, LVOTO, and APVR compared to 0.423–0.884 mg/g. • Conversely, one study of whole blood reported that Se at the highest concentrations reduced the risk of total CHDs and CHDs subtypes, including CTD, SPD, and RVOTO, compared to the lowest exposure categories • The association between Se in cord serum and CHDs was also explored by Guo et al., and the results illustrated that Se exposure < 15.705 µg/L was associated with an approximate 4-fold greater risk of total CHDs (odds ratio (OR) = 4.14, 95% CI: 1.79, 9.56) when compared to a higher Se exposure concentration of 15.705 - 52.722 µg/L. • Nevertheless, no significant association was found between serum Se levels and CHDs. • Pooled results showed that Se levels (in circulation) were significantly decreased in mothers with CHDs offspring compared to controls (SMD = -36.31, 95% CI: -42.72, -29.89), with substantial heterogeneity (I2 = 99.7%, P < 0.001). Subgroup analysis subsequently showed decreased Se levels in the circulation of mothers with CHDs offspring (SMD = -108.27, 95% CI: -192.72, -23.82), with statistically significant heterogeneity (I2 = 99.8%, P < 0.001). However, no significant difference in maternal hair Se levels were found between the CHDs and control groups.
	Method of measurement	• Used the nine-star Newcastle-Ottawa Scale (NOS) to assess the methodological quality and evaluate possible sources of bias in the included case-control and cohort studies, based on the three parts of the NOS, including selection, comparability, and outcomes. • Studies with scores ≥ 6 were defined to be high quality, studies with scores < 6 were considered of relatively low quality.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics	Statistical method used	

Publication Reference: Pan Z., Zhu T., Zhu J. and Zhang N. (2022). Association between Maternal Selenium Exposure and Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis. Iran J Public Health 51(10): 2149-2158.		
(if any)	Details on statistical analysis	Statistical analysis was conducted using STATA 16.0 (StataCorp, College Station, TX, USA). The standard mean difference (SMD) and corresponding 95% confidence interval (CI) were calculated to evaluate maternal Se levels between CHDs groups and control groups. The pooled effect was considered significant at $P < 0.05$. If the studies provided data as median ± interquartile range (IQR) or median ± range, a standard method was used to estimate the mean ± standard deviation (SD). Statistical heterogeneity was assessed using the I2 statistic. If $P < 0.1$ or $I2 > 50\%$, significant heterogeneity was considered, and a fixed-effects model was used in the meta-analysis; otherwise, the random-effects model was utilised.
	Relative risk/odds ratio, confidence interval?	See outcome summary
Author's conclusions	Interpretation of results	• Low maternal Se status may be associated with an increased risk of CHDs in offspring.
	Assessment of uncertainty (if any)	• Due to the substantial heterogeneity among the included studies, the results should be interpreted with caution. • Further large-scale epidemiological studies with strict design methods are needed to explore the following problems: 1) to determine biomarkers that can accurately reflect the Se status in pregnant women; 2) to determine the association between Se status in different pregnancy periods and incidence of CHDs in offspring; and 3) to determine the effectiveness and safety of Se supplementation in pregnant women. Further laboratory research is also needed to clarify the role of Se in cardiac development.
Reviewer comments	Results included/excluded in review (if applicable)	• This meta-analysis of observational studies investigated the potential relationship between maternal Se exposure and congenital heart defects (CHDs) in the offspring. • The study found low maternal Se status may be associated with an increased risk of CHDs in offspring. • As the study is a meta-analysis and not a primary study, and the result does not readily inform the dose response for adverse effects of Se, it was not subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Rees et. al. 2013

Publication Reference: *Rees, K., Hartley, L., Day, C., Flowers, N., Clarke, A., Stranges, S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD009671. DOI: 10.1002/14651858.CD009671.pub2.*		
General Information	Date of data extraction	14/06/2023
	Authors	Rees, K., Hartley, L., Day, C., Flowers, N., Clarke, A., Stranges, S.
	Publication date	2013
	Publication type	Cochrane Review document
	Peer reviewed?	Not stated

Publication Reference: *Rees, K., Hartley, L., Day, C., Flowers, N., Clarke, A., Stranges, S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD009671. DOI: 10.1002/14651858.CD009671.pub2.*		
	Country of origin	UK
	Source of funding	Internal sources: Warwick Medical School, University of Warwick, UK; External sources: NIHR Cochrane Programme Grant, UK.
	Possible conflicts of interest	None known
Study characteristics	Aim/objectives of study	1. To determine the effectiveness of selenium only supplementation to prevent cardiovascular disease (CVD) events. 2. To determine the effects of selenium only supplementation on cardiovascular risk factors (blood pressure, lipid levels) and adverse effects including type 2 diabetes.
	Study type/design	Systematic review. Included studies were randomised controlled trials (RCTs) including 12 RCTs (14 papers) which met the inclusion criteria; seven RCTs had a duration of three months or more and contributed to the meta-analyses. Five short term trials of selenium supplementation (less than three months) were dealt with descriptively.
	Study duration	Varied: three months or more
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Adults of all ages from the general population and those at high risk of CVD were included (from 12 RCTs).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not stated
	Size of study	Twelve trials were included, with 19,715 participants randomised. Six trials recruited only male participants (17,843 randomised). Four trials (18,954 participants randomised) were conducted in the USA (Algotar 2010; Hawkes 2008; NCP; SELECT) and included the two largest trials, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) with 17,448 participants randomised and the Nutritional Prevention of Cancer trial (NCP) with 1312 participants randomised.
Exposure and setting	Exposure pathway	Oral (Supplements)
	Source of chemical/contamination	Supplements
	Exposure concentrations (if applicable)	The dose of selenium supplementation that was used varied from 36.4 to 800 µg/day.
	Comparison group(s)	Placebo or no intervention
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

Publication Reference: *Rees, K., Hartley, L., Day, C., Flowers, N., Clarke, A., Stranges, S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD009671. DOI: 10.1002/14651858.CD009671.pub2.*		
	How outcome was assessed	• Primary outcomes: Major CVD end-points: CVD, non-fatal myocardial infarction (MI), non-fatal stroke, and revascularisation procedures (CABG or PTCA). • Secondary outcomes: All cause mortality, CHD composite end-point: fatal CHD, non-fatal MI, or CABG or PTCA, Stroke composite end-point: fatal and non-fatal stroke, Peripheral artery disease, Type 2 diabetes (T2D), Changes in levels of blood pressure and blood lipids Note: T2D was used as a potential side effect of selenium. Other adverse effects were noted and data were collected on costs where available.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	19,715 participants Randomised controlled trials on the effects of selenium only supplementation on major CVD end-points, mortality, changes in CVD risk factors, and type 2 diabetes were included both in adults of all ages from the general population and in those at high risk of CVD. Trials were only considered where the comparison group was placebo or no intervention. Only studies with at least three months follow-up were included in the meta-analyses, shorter term studies were dealt with descriptively.
Statistics (if any)	Statistical method used	Data were processed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Dichotomous outcomes were expressed as relative risks (RR), and 95% confidence intervals (CI) were calculated for each study. For continuous variables net changes were compared (that is intervention group minus control group differences) and a weighted mean difference (WMD) and 95% CI were calculated for each study.
	Details on statistical analysis	

Publication Reference: *Rees, K., Hartley, L., Day, C., Flowers, N., Clarke, A., Stranges, S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD009671. DOI: 10.1002/14651858.CD009671.pub2.*		

	Relative risk/odds ratio, confidence interval?	There were no statistically significant effects of selenium supplementation on the following:
		• All-cause mortality (RR 0.97, 95% CI 0.88 to 1.08)
		• CVD mortality (RR 0.97, 95% CI 0.79 to 1.2)
		• Non-fatal CVD events (RR 0.96, 95% CI 0.89 to 1.04)
		• All CVD events (fatal and non-fatal) (RR 1.03, 95% CI 0.95 to 1.11)
		Findings for secondary outcomes:
		• There was a small increased risk of type 2 diabetes with selenium supplementation, but this did not reach statistical significance (RR 1.06, 95% CI 0.97 to 1.15).
		• Other adverse effects that increased with selenium supplementation, as reported in the SELECT trial, included:
		  • Alopecia (RR 1.28, 95% CI 1.01 to 1.62)
		  • Dermatitis grade 1 to 2 (RR 1.17, 95% CI 1.0 to 1.35).
		• Selenium supplementation reduced total cholesterol, but this did not reach statistical significance (WMD - 0.11 mmol/L, 95% CI - 0.3 to 0.07).
		Mean high density lipoprotein (HDL) levels were unchanged. There was a statistically significant reduction in non-HDL cholesterol (WMD - 0.2 mmol/L, 95% CI - 0.41 to 0.00) in one trial of varying selenium dosage.

Author's conclusions	Interpretation of results	Results of this review also highlight major gaps in the published literature. There is still a lack of definitive evidence on the effects of selenium only supplementation on CVD clinical events, lipid levels and type 2 diabetes, and for the primary prevention of CVD.
	Assessment of uncertainty (if any)	If there were sufficient trials that met the inclusion criteria, it was the authors' intention to perform sensitivity analyses excluding studies of low methodological quality and to undertake funnel plots and tests of asymmetry (Egger 1997) to assess possible publication bias. There were not sufficient trials for the authors to perform these analyses.
Reviewer comments	Results included/excluded in review (if applicable)	This report was not subject to a risk of bias assessment as it is a review document. This review assessed RoB in 12 RCTs and found: • Allocation: unclear in nine of the included studies and low risk of bias in remaining 3 (Hawkes 2008; NCP; UK PRECISE). • Blinding: 11 of the 12 included studies stated that they were double blind and were regarded as low risk of bias. (Unclear in Meltzer 1994). • Incomplete outcome data: Most studies reported losses to follow-up and these were judged to have low risk of bias. • Selective reporting: the risk of bias associated with selective reporting was unclear. • In most cases there was insufficient information to judge the risk of bias.

Stranges et. al. 2007

Publication Reference: Stranges S. (2007). Effects of Long-Term Selenium Supplementation on the Incidence of Type 2 Diabetes. Annals of Internal Medicine 147: 217.		
General Information	Date of data extraction	14/06/2023
	Authors	Stranges, S., Marshall, J.R., Natarajan, R., Donahue, R.P., Trevisan, M., Combs, G.F., Cappuccio, F.P., Ceriello, A., Reid, M.E.
	Publication date	21 August 2007
	Publication type	Journal Article
	Peer reviewed?	Not stated
	Country of origin	UK (Author), US (Study Population)
	Source of funding	This study was not supported by funding.
	Possible conflicts of interest	None disclosed
Study characteristics	Aim/objectives of study	To examine the effect of long-term selenium supplementation on the incidence of type 2 diabetes.
	Study type/design	Human Controlled Trial (HCT). Secondary analysis of a randomised, double-blind, placebo-controlled trial (NPC trial)
	Study duration	Follow-up of 7.7 years (time of exposure unclear)
	Type of water source (if applicable)	Not applicable (Note: Supplement)
Population characteristics	Population/s studied	1312 participants with a confirmed history of nonmelanoma skin cancer recruited in 1983 to 1991 from 7 dermatology clinics in areas of low selenium consumption of the eastern United States.
	Selection criteria for population (if applicable)	
	Subgroups reported	Selenium group (n=653), Placebo group (n=659)
	Size of study	1312 participants
Exposure and setting	Exposure pathway	Oral administration of selenium
	Source of chemical/contamination	High-selenium baker's yeast tablet
	Exposure concentrations (if applicable)	200 µg/d
	Comparison group(s)	Placebo (n=659)
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Clinical Examination, participants visited their respective clinics biannually to provide blood samples and report new illnesses and medications. Patient medical records from both study and non-study visits were periodically reviewed to ensure completeness and accuracy.
	How outcome was assessed	

Publication Reference: Stranges S. (2007). Effects of Long-Term Selenium Supplementation on the Incidence of Type 2 Diabetes. Annals of Internal Medicine 147: 217.		
	Method of measurement	• Participants who had a new diagnosis of type 2 diabetes during the blinded phase of the trial (15 September 1983 to 1 February 1996) were noted. The initial report of diabetes came from 3 sources: self-report during the clinical interview, reported use of drugs for diabetes, and reports in medical record documents. Medical record requests were then sent to the primary physicians for every patient with a report.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	1312 participants with a confirmed history of nonmelanoma skin cancer. Participants with a history of clinically important liver or kidney disorders and non-white persons were excluded. 1202 participants who did not have type 2 diabetes at baseline (600 selenium recipients and 602 placebo recipients).
Statistics (if any)	Statistical method used	t-tests and chi-square tests, respectively, to determine the statistical significance of any difference in the distribution of baseline variables between treatment groups. Cumulative incidence curves of type 2 diabetes by treatment group were constructed by comparing Nelson–Aalen cumulative hazard function estimates that were calculated at different time points of the trial and by using the 2-sided log-rank test. In unadjusted analyses, incidence data were statistically analysed by calculating relative risks as the ratios of the incidence density for the treatment groups, with corresponding 95% CIs. P values were derived from log-rank tests. In adjusted analyses, hazard ratios and 95% CIs were calculated by using the Cox proportional hazard model, which allowed adjustment for age, BMI (continuous variable), sex, and smoking status at baseline as covariates.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Statistically significant increased risk for type 2 diabetes • Hazard ratio = 1.55, 95% CI, 1.03 to 2.33, p=0.03. • Individuals with plasma selenium levels greater than the baseline top tertile (>121.6ng/mL): hazard ratio = 2.70, CI, 1.30 to 5.61, p = 0.008. • Individuals with plasma selenium levels greater than the baseline median value (>113.4ng/mL): hazard ratio = 2.50, CI, 1.32 to 4.77, p=0.005.
Author's conclusions	Interpretation of results	• The risk for type 2 diabetes was consistently higher in the selenium group within all subgroups of baseline age, sex, smoking status, and BMI. • However, in analyses stratified by BMI tertiles, the risk for type 2 diabetes did not differ between treatment groups within the top tertile of BMI.
	Assessment of uncertainty (if any)	Not stated

Publication Reference: Stranges S. (2007). Effects of Long-Term Selenium Supplementation on the Incidence of Type 2 Diabetes. Annals of Internal Medicine 147: 217.		
Reviewer comments	Results included/excluded in review (if applicable)	This double-blinded, randomised, placebo-controlled HCT found a significant increased risk of type 2 diabetes associated with selenium plasma concentration in participants given 200 µg/d selenium (as a selenium-containing yeast tablet) for an unknown exposure timeframe, but potentially 7 years. As this study provides information for a potentially new health effect compared to the Stage 1 report, it was subjected to a RoB assessment.

Stranges et. al. 2010

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Stranges, S., Marshall, J.R., Natarajan, R., Donahue, R.P., Trevisan, M., Combs, G.F., Cappuccio, F.P., Ceriello, A., Reid, M.E.
	Publication date	Published: 21 September 2010
	Publication type	Journal Article
	Peer reviewed?	Yes
	Country of origin	UK (Author), US (Study Population)
	Source of funding	Not stated
	Possible conflicts of interest	The authors declare that they have no competing interests.
Study characteristics	Aim/objectives of study	This study examined the prospective association between dietary selenium intake and risk of type 2 diabetes.
	Study type/design	Prospective Cohort
	Study duration	Mean follow-up: 16 years (5 years recruitment)
	Type of water source (if applicable)	Not appliable (Note: Diet)
Population characteristics	Population/s studied	The ORDET study (HORmones and Diet in the ETiology of Breast Cancer) is an ongoing prospective follow-up study of 10,786 women residents of Varese province in Northern Italy.
	Selection criteria for population (if applicable)	
	Subgroups reported	Quintiles for selenium intake
	Size of study	7,182 participants
Exposure and setting	Exposure pathway	Oral (via the diet)
	Source of chemical/contamination	Diet
	Exposure concentrations (if applicable)	Average selenium intake at baseline was 55.7 µg/day
	Comparison group(s)	Low quintile selenium intake
Study methods	Water quality measurement used	Not applicable

Publication Reference: 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.		
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Incident type 2 diabetes was defined as a self-report of a physician diagnosis, use of antidiabetic medication, or a hospitalisation discharge. • Dietary selenium intake was measured by a semi-quantitative food-frequency questionnaire at the baseline examination (1987-1992). • Participants were divided in quintiles based on their baseline dietary selenium intake.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• The final cohort comprised 7,182 participants. • The study excluded women who did not fill in the lifestyle questionnaire (N = 96), who reported the presence of type 2 diabetes at the baseline assessment (N = 203), who did not compile the food frequency questionnaire because it was not available at the beginning of the study (N = 1,552), or who had missing data in anthropometric variables (N = 54). • It also excluded participants in whom the ratio of total energy intake (determined from the food frequency questionnaire) to basal metabolic rate was at either extreme of the distribution (cut-offs 0.5 and 99.5 percentiles) (N = 73).
Statistics (if any)	Statistical method used	The study population was categorised in quintiles of energy-adjusted selenium intake at baseline using the residual method. Odds ratios (OR) for developing type 2 diabetes comparing the highest to the lowest quintile of selenium intake were estimated by logistic regression analysis. Authors used two levels of adjustment: model 1 (reduced model) was adjusted for age, education and menopausal status; model 2 (fully-adjusted model) was further adjusted for BMI (as a linear term), smoking (never, past, current), alcohol intake (abstainers, ≤ 12 g/day, > 12 g/day), energy intake (not from alcohol), saturated/polyunsaturated fat ratio, animal proteins, total carbohydrates, and body weight change (delta-weight) between the baseline and follow-up examinations. Tests for trend across selenium intake quintiles were derived from likelihood ratio tests comparing models with and without a variable including the median selenium intake at each quintile as a continuous variable. We tested the interaction of selenium intake with BMI categories (BMI ≤ 25 and > 25) and with menopausal status using a likelihood ratio test that compared the model that included the product term and the model that did not include it. We used STATA software (version 10.0; Stata Corp., TX) for statistical analysis.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Statistically significant increased risk for type 2 diabetes (fully adjusted model 2): • Comparison of the highest (75.1µg/day) to the lowest quintile (41.7 µg/day) of selenium intake: OR = 2.39, 95% CI: 1.32 - 4.32; P = 0.005). • A 10 µg/d increase in selenium intake OR = 1.29, 95% CI: 1.10 - 1.52.

Publication Reference: 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.		
Author's conclusions	Interpretation of results	Increased dietary selenium intake was associated with an increased risk of type 2 diabetes. These findings raise additional concerns about the association of selenium intake above the Recommended Dietary Allowance (55 µg/day) with diabetes risk.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	Most associations were not statistically significant. T2D was associated with elevated selenium intake in this prospective cohort study (highest quintile, ave = 75.1µg/day). As study may provide information to alter the Stage 1 conclusions, this study was subject to a RoB assessment.

Thompson et. al. 2016

Publication Reference: 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).		
General Information	Date of data extraction	14/06/2023
	Authors	Thompson, P.A., Ashbeck, E.L., Roe, D.J., Fales, L., Buckmeier, J., Wang, F., Bhattacharyya, A., Hsu, C., Chow, H.H.S., Ahnen, D.J., Boland, C.R., Heigh, R.I., Fay, D.E., Hamilton, S.R., Jacobs, E.T., Martinez, M.E., Alberts, D.S., Lance, P.
	Publication date	Published online August 16, 2016
	Publication type	Journal Article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	This trial was supported by grants P01 CA041108 (to PL), R01 CA151708 (to PL and PAT), and P30 CA23074 (to ASK).
	Possible conflicts of interest	The study funders had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.
Study characteristics	Aim/objectives of study	Final study investigated whether selenium supplementation prevents colorectal adenomas
	Study type/design	Human Controlled Trial (HCT) randomised, placebo-controlled
	Study duration	Six months
	Type of water source (if applicable)	Not applicable (Note: once-daily oral selenium 200 µg as selenised yeast)
	Population/s studied	

Publication Reference: 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).		
Population characteristics	Selection criteria for population (if applicable)	Participants were recruited through clinical centres in Arizona, Colorado, Texas, and New York following ambulatory colonoscopies. Eligible participants were between age 40 and 80 years and had undergone colonoscopic removal of one or more colorectal adenomas 3 mm or larger within six months prior to random assignment. Patients with a family history of familial adenomatous polyposis or Lynch syndrome or a diagnosis of invasive cancer within five years were excluded. Individuals with unstable cardiac disease, uncontrolled hypertension, poorly controlled diabetes mellitus or renal insufficiency were excluded.
	Subgroups reported	Participants with baseline advanced adenomas with outcome data
	Size of study	Baseline participant characteristics of the placebo and selenium arms were well balanced for three groups: 1) The entire 1824 participant cohort (1621 in the original cohort and an additional 203 in the Advanced Adenomas-Only cohort); 2) The 1374 participants (84.8%) with outcome data from the original 1621, on whom the primary analysis was based; 3) The combined total of 571 participants with baseline advanced adenomas with outcome data.
Exposure and setting	Exposure pathway	Oral (supplements)
	Source of chemical/contamination	SelenoExcell High Selenium Yeast tablets
	Exposure concentrations (if applicable)	200 µg/d
	Comparison group(s)	Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Sel/Cel was designed as a phase III, randomised, placebo-controlled, two-by-two factorial trial of celecoxib crossed with selenium for preventing colorectal adenomas • The celecoxib arm was suspended in December 2004 because of reported coxib-associated cardiovascular toxicity • The trial was modified to a two-arm design comparing selenium with placebo. • Participants randomly assigned during the factorial phase were retained in the appropriate selenium or placebo arm but were no longer allocated celecoxib or its placebo.
	How outcome was assessed	

Publication Reference: 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).		
	Method of measurement	• The primary outcome was any colorectal adenoma or cancer detected at a colonoscopy performed at least six months after random assignment until surveillance colonoscopy. Colorectal cancers diagnosed during follow-up were handled as adenoma recurrences and tabulated separately. Adenoma number, location, size, and histology were abstracted from endoscopic and pathology reports. Cumulative adenoma recurrence was ascertained over all follow-up colonoscopies. • Secondary outcomes included occurrences of multiple (3) or advanced adenomas (defined by one or more of the following features: 10 mm or more in size, with tubulovillous or villous villous tissue architecture, and/or with high-grade dysplasia). Toxicity outcomes included the development of T2D, brittle hair and/or nails, and squamous cell skin carcinoma (SCSC).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• n = 1,374, originally planned cohort. 689 with placebo and 685 with supplement • n = 571, Participants with advanced adenomas at baseline. 287 with placebo and 284 with supplement
Statistics (if any)	Statistical method used	• Log-binomial regression was used to estimate the relative risk (RR) and 95% confidence interval (CI) for the primary and secondary adenoma outcomes. • Poisson regression with robust variance was planned as an alternative method for calculating the relative risk and 95% CI in the event of convergence failure of the log-binomial model. • All models were adjusted for the design variables of random assignment to celecoxib, regular use of low-dose aspirin, and clinic site.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	• Adenoma detection in placebo versus selenium arm had relative risk [RR] = 1.03, 95% confidence interval [CI] 0.91 to 1.16, P = 0.68. • In participants with baseline advanced adenomas, adenoma recurrence was reduced by 18% with selenium, RR = 0.82, 95% CI 0.71 to 0.96, P = .01 • In participants receiving selenium, new-onset T2D RR = 1.25 (95% CI 0.74 to 2.11, P =.41), • Statistically significantly increased risk of selenium-associated T2D among older participants RR = 2.21; 95% CI 1.04 to 4.67, P =0.03).
Author's conclusions	Interpretation of results	• Overall, selenium did not prevent colorectal adenomas and showed only modest benefit in patients with baseline advanced adenomas. • With limited benefit and similar increases in T2D to other trials, selenium is not recommended for preventing colorectal adenomas in selenium-replete individuals.

Publication Reference: 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).		
	Assessment of uncertainty (if any)	Sensitivity analysis including only participants with an endpoint colonoscopy performed at least 2.5 years after the qualifying baseline colonoscopy did not change the overall findings, nor did adjustment for the total number of colonoscopies during follow-up.
Reviewer comments	Results included/excluded in review (if applicable)	In this randomised, placebo-controlled HCT (non-blinded), authors found a statistically significant increase in T2D with exposure to a supplement of selenised yeast (200 µg Se/day for 6 months). As this study provides potentially useful information with respect to dose response, it was subject to a RoB assessment.

Vinceti et. al. 1996

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Vinceti, M., Guidetti, D., Pinotti, M., Rovesti, S., Merlin, M., Vescovi, L., Bergomi, M., Vivoli, G.
	Publication date	Final version accepted April 11, 1996
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	Supported by the Ministry of the University and of Scientific and Technological Research (60%). Donata Guidetti was supported by Telethondtaly (Grant 163/1991-92).
	Possible conflicts of interest	Not stated (note page 531 missing)
Study characteristics	Aim/objectives of study	Authors examined 9 years' incidence of amyotrophic lateral sclerosis (ALS), a disease previously associated with a high-selenium environment, in a cohort of 5,182 residents of Reggio Emilia, Italy.
	Study type/design	Cohort
	Study duration	9-years follow up
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	A cohort of 5,182 residents of Reggio Emilia, Italy
	Selection criteria for population (if applicable)	
	Subgroups reported	Long-exposed subgroup in the main cohort
	Size of study	5,182 individuals in the main cohort (2,536 males and 2,646 females) and 2,065 individuals in the long-exposed group (1,021 males and 1,044 females)

Publication Reference: 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.		
Exposure and setting	Exposure pathway	This cohort had accidentally been exposed to drinking water with high selenium content.
	Source of chemical/contamination	The selenium was of geologic origin.
	Exposure concentrations (if applicable)	Municipal tap water supplied until 1988 contained the unusually high level of 7 µg/L of selenium in inorganic hexavalent form. Distribution in Rivalta of tap water with a high selenium content started in 1972. Selenium levels in tap water supplied in the remaining municipal and provincial territory were lower than 1 µg/L.
	Comparison group(s)	Residents from the remainder of the municipal population as the reference group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Authors identified all cases of ALS (including sporadic and familial forms) diagnosed during the follow-up in the population of the Province of Reggio Emilia. They used data from a survey for the 1986-1992 period and from the Hospital Discharge Registry of the Emilia Romagna Region, which allowed them to trace motor neuron disease discharges in regional hospitals for the period 1993-1994. They obtained clinical records of motor neuron disease patients identified through the Registry. These were reviewed by a neurologist (D. G.) who was blinded to the subject's exposure status. The neurologist used standard criteria to validate the ALS diagnosis. In the few cases of incomplete records or uncertain diagnosis, they contacted the family doctors of patients.
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	5,182 in the exposed group. Number of individuals in the unexposed group not disclosed
Statistics (if any)	Statistical method used	Authors calculated the standardised incidence ratio (SIR) for ALS in the cohort using two reference incidences: the gender-, 5-year-period-age-, and calendar-year-specific ALS incidence in the remaining municipal population and the gender- and age-specific 1986-1994 ALS incidence in the provincial population. They also calculated exact Poisson 95% confidence limits around the SIR.
	Details on statistical analysis	

Publication Reference: 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.		
	Relative risk/odds ratio, confidence interval?	Standardised incidence: 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)
Author's conclusions	Interpretation of results	Note: Page 531 of article is missing hence discussion and conclusion is not available. • During the follow-up, an initial diagnosis of ALS was made in four cohort members, one male and three females. All four cases were sporadic ALS and occurred in cohort members with the longest ascertainable period of exposure • The standardised incidence ratio was higher after limiting the analysis to the sub cohort with the longest ascertainable exposure period. • The findings appear to confirm a causal association between overexposure to environmental selenium and ALS.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This cohort study provides an indication that exposure to increasing Se concentration in drinking water may be associated with development of ALS. However, the study does not appear to mention adjustment for other potential confounders. Should be considered with weight of overall evidence. This study was subject to a RoB assessment as a positive statistically significant association was found for ALS with the long exposed and main cohort.

Vinceti et. al. 2001

Publication Reference: Vinceti M., Wei E. T., Malagoli C., Bergomi M. and Vivoli G. (2001). Adverse health effects of selenium in humans. Rev Environ Health 16(4): 233-251.		
General Information	Date of data extraction	19/06/2023
	Authors	Vinceti, M., Wei, E.T., Malagoli, C., Bergoini, M., Vivoli, G.
	Publication date	2001
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy and US

Publication Reference: Vinceti M., Wei E. T., Malagoli C., Bergomi M. and Vivoli G. (2001). Adverse health effects of selenium in humans. Rev Environ Health 16(4): 233-251.		
	Source of funding	The Italian National Research Council, the Foundation Angela Serra of Modena, and the California Department of Health supported the research work on selenium done by the authors and reported in part in this paper.
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Authors focus on the adverse health effects of chronic selenium exposure in humans, a topic of many recent reviews, of which publications /6—8/ are already out of date because of recent advances in epidemiology. They aim at presenting the epidemiological data that are currently available, discussing the uncertainties still existing in this field and addressing several public health issues, including the safe upper limit of intake of this element through diet and drinking water.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable (Various)
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not applicable (Various: diet, supplement, drinking water)
	Exposure concentrations (if applicable)	Various
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable (Various populations)
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	

Publication Reference: Vinceti M., Wei E. T., Malagoli C., Bergomi M. and Vivoli G. (2001). Adverse health effects of selenium in humans. Rev Environ Health 16(4): 233-251.			
	Relative risk/odds ratio, confidence interval?		Not applicable
Author's conclusions	Interpretation of results	Cancer	• Conclusive evidence about the ability of selenium compounds to counteract cancer growth *in vivo* and *in vitro* has been provided by a number of studies; yet, laboratory studies have shown that both the inorganic (selenite, selenate, selenium sulfide) and the organic (selenomethionine) species of this element are carcinogenic. • Until more data about the relation between selenium and cancer risk in humans become available, no definitive conclusion can be drawn on this topic.
		Neurotoxic Effects	• The occurrence of a cluster of four cases of amyotrophic lateral sclerosis (ALS) in a sparsely populated county in South Dakota, where the soil was so rich in selenium that it produced intoxication in livestock. • In view of this putative relation between selenium and ALS, is the observation of an 'epidemic' of spastic paraparesis in a population from Mozambique, attributed to chronic cyanide intoxication from cassava. The population residing in the affected area, characterised by high cassava consumption, showed considerably higher serum selenium levels than those determined in referent areas. • The plausibility of a link between selenium exposure and ALS finds support in animal studies demonstrating that selenium has a potent selective toxicity on motor neurons (the target cells in ALS neurodegeneration) in swine. • Abnormalities of the nervous system were observed in a Chinese population that was heavily intoxicated with selenium - possible association between selenium and ALS.
		Reproductive Health Effects	• No convincing evidence of adverse effects of environmental selenium exposure on human reproductive health has been provided. Nevertheless, the literature on this topic cannot by any means be considered complete, precluding a conclusive risk assessment of selenium compounds in human reproduction.

Publication Reference: Vinceti M., Wei E. T., Malagoli C., Bergomi M. and Vivoli G. (2001). Adverse health effects of selenium in humans. Rev Environ Health 16(4): 233-251.			
		Endocrine System Effects	• Convincing data have been provided for an adverse effect of selenium on thyroid hormone secretion, an apparent paradox because at low concentrations, selenium is essential for the synthesis, activation, and metabolism of thyroid hormones. • Four studies, including supplementation of selenium to children with iodine deficiency found an inhibitory effect of selenium on blood free thyroxine (T4) levels. • High selenium diet in men associated with drop in triiodo-thyronine (T3), 32% increase in serum TSH. • Experimental laboratory studies support the plausibility of an adverse effect of selenium on thyroid status. • Dietary selenium may also adversely affect growth hormone (GH) secretion and metabolism. • Much higher percentage of children below normal height in a seleniferous area of Venezuela than in a referent area. • Limited evidence indicates that excess selenium exposure may adversely affect secretion or metabolism of sex hormones in females.
		Immune System Effects	• Reports on the effect of selenium exposure on the immune system are conflicting.
		Hepatotoxicity	• High (28%) occurrence of icteroid discoloration of the skin among 100 residents in four ‘seleniferous’ counties from South Dakota and Nebraska. • An increased occurrence of history of jaundice and signs of frank hepatitis, although the relation with intoxication from environmental selenium was less clear.
		Dental Caries	• An analysis of the relation between urinary selenium concentrations and the prevalence of dental caries in children suggested that exposure to this element increases the susceptibility to caries. Further studies showed that the prevalence of caries was higher in high- than in low-selenium areas. Similarly, results of animal studies indicate that exposure to high levels of selenium during the period of tooth development can increase the incidence of dental caries.

Publication Reference: Vinceti M., Wei E. T., Malagoli C., Bergomi M. and Vivoli G. (2001). Adverse health effects of selenium in humans. Rev Environ Health 16(4): 233-251.			
		Dermatologic Effects	• Various communities with dermatologic manifestations (yellowish discoloration of the skin, skin eruptions of varying degrees of severity, diseased fingernails, brittle hair, dry scalp) from Se exposure via the diet or drinking water. • Occupational exposure to selenium has been associated with serious dermatological problems. Hair loss, conjunctivitis, skin problems (including acute irritant contact dermatitis and fungal infestation), and deformed and brittle nails. • No difference in the reporting of skin problems, brittle nails, abnormal loss of nail and hair in populations with drinking water exposure ranging from around 500 micrograms/L to less than 4 micrograms/L. • The finding in several observational and experimental animal studies that lesions of the integument, such as loss of hair and hoof lesions, commonly occur in several species following intoxication with selenium compounds.
		Other effects	• Severe congestion of the lung and diffuse (noncaseating, perivascular granulomas), gastrointestinal disturbances, diarrhoea, hypochromic anaemia.
		Safe range of selenium intake	• When considering the upper safe limit of intake of selenium, emphasis should be given to the toxicological profile of the various chemical forms of selenium, with selenomethionine and, particularly, selenite and selenate species being the more toxic forms of the element.
		Overall Conclusion	• Despite the difficulties in assessing an issue for which still limited epidemiological and clinical evidence has been provided, the authors believe that nearly 60 years later, the above cited statement can still be endorsed. They therefore stress the need to investigate this topic further, focusing, among other effects, on the possible toxicity on thyroid hormones and IGFs synthesis, NK cell activity, and motor neurons viability. Until more complete and confident data become available about risk assessment of this metalloid, they recommend limiting environmental exposure to the inorganic and to some organic forms of selenium, while being aware that current upper limits of exposure through drinking water, diet, and in occupational settings might be inadequate to protect human health.
	Assessment of uncertainty (if any)		-
Reviewer comments	Results included/excluded in review (if applicable)		This study was not subject to a RoB assessment as this document is a review and provides no dose-response information.

Vinceti et. al. 2009a

Publication Reference: Vinceti M., Maraldi T., Bergomi M. and Malagoli C. (2009a). Risk of chronic low-dose selenium overexposure in humans: insights from epidemiology and biochemistry. Rev Environ Health 24(3): 231-248.		
General Information	Date of data extraction	19/06/2023
	Authors	Vinceti M, Maraldi T, Bergomi M, Malagoli C.
	Publication date	2009
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Review the health effects of chronic low-dose Se overexposure in the human, with emphasis on the latest major achievements of the epidemiology and the biochemistry, which render the authors' previous evaluation of the topic out-of-date.
	Study type/design	Review
	Study duration	Not appliable
	Type of water source (if applicable)	Not appliable
Population characteristics	Population/s studied	Not appliable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not appliable
	Size of study	Not appliable
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Not applicable (Various: diet, supplement, drinking water)
	Exposure concentrations (if applicable)	Various
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics	Statistical method used	Not applicable

Publication Reference: Vinceti M., Maraldi T., Bergomi M. and Malagoli C. (2009a). Risk of chronic low-dose selenium overexposure in humans: insights from epidemiology and biochemistry. Rev Environ Health 24(3): 231-248.			
(if any)	Details on statistical analysis		
	Relative risk/odds ratio, confidence interval?		Not applicable
Author's conclusions	Interpretation of results	Cancer	• Overall, these observations further highlight the complexity of the Se-cancer relation, suggesting that ranges of Se exposures so far considered of 'nutritional' interest are actually associated with the stimulation of Se-dependent enzymes.
		Diabetes	• Overall, the currently available epidemiologic evidence from prospective studies, supports a diabetogenic effect of Se in humans, even for 'low dose' chronic dietary intakes, no matter from which source (diet or supplements) the metalloid enters the body. The authors outline that the Se amounts associated with excess diabetes risk were comparable to or even lower than those linked to other adverse effects in the human, and that these levels of exposure are lower that the upper safe limit of Se intake of 400 µg/d, set mainly on the basis of the observations published in 1983 by Yang et al.
		Amyotrophic Lateral Sclerosis (ALS)	• The possibility that excess environmental exposure to Se represents a risk factor for a devastating human neurodegenerative disease, amyotrophic lateral sclerosis (ALS), was suggested by two epidemiologic studies with different designs. • Overall, the possible aetiologic role of Se toxicity in ALS aetiology must be conclusively shown, but the evidence yielded by the only prospective study so far carried out, in turn generated by the original observation of a cluster in the South Dakota seleniferous area, and the suggestions coming from animal and *in vitro* studies strongly indicate the opportunity to further investigate this issue.

Publication Reference: Vinceti M., Maraldi T., Bergomi M. and Malagoli C. (2009a). Risk of chronic low-dose selenium overexposure in humans: insights from epidemiology and biochemistry. Rev Environ Health 24(3): 231-248.			
		Safe and recommended ranges of Selenium intake	• Different opinions exist in the scientific literature about the safe and the recommended daily intakes of Se in humans, • Daily Se amounts of 45 to 55 µg in adults were proposed by the US Institute of Medicine as the respective Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) because such doses should be able to maximise GPX activity (with a higher margin of safety for the RDA). • On the other hand, in 1996 an expert group of the World Health Organization proposed a lower Se intake as a guideline for an optimal intake of the metalloid, ranging from 21 to 40 µg in adult males and 16-30 µg in females, using GPX-1 as indicator of Se adequacy. • Recent indications from a northern European regulatory agency are comparable to those above, namely, 50 and 40 µg/d, respectively, for males and females. • If we assume, however, that GPX- 1 levels are associated only with the bioavailability of Se for its synthesis, the choice of setting the RDA for this metalloid at lower levels than those required to maximise enzyme activity appears to be erroneous and potentially dangerous, no matter which implications may arise for the classifications of countries regarding 'Se-deficiency'.
		Concluding remarks	• After decades of intensive research on the topic of the health effects of Se and its safe range of intake encompassing a large number of well-conducted epidemiologic and biochemical studies, we are still facing a number of inconsistencies and uncertainties on this issue, which calls not only for further research but also for extreme caution in approaching the Se-human health relation. Indeed, a comprehensive and integrated analysis of the most recent results from epidemiologic and biochemical studies indicates the potential for low-dose long-term toxicity of this metalloid at doses largely lower than until recently thought, both for the organic species generally found in foods and for the inorganic forms found in drinking water. The current upper allowable limits of Se intake through diet and the drinking water standard appear therefore to be inadequate to protect human health, indicating the need for cautionary reassessment whilst waiting for further clarification of these issues.
	Assessment of uncertainty (if any)		-
Reviewer comments	Results included/excluded in review (if applicable)		This study was not subject to a RoB assessment as this document is a review and provides no dose-response information. Note: It is stated by the Author that this review supersedes a previous review (presumably Vinceti et al. 2001).

Vinceti et. al. 2009b

Publication Reference: Vinceti M., Stranges S., Sieri S., Grioni S., Malagoli C., Muti P., Berrino F. and Krogh V. (2009b). Association Between High Selenium Intake and Subsequent Increased Risk of Type 2 Diabetes in an Italian Population. Epidemiology 20.		
General Information	Date of data extraction	16/06/2023
	Authors	Vinceti, M, Stranges, S., Sieri, S., Grioni, S., Malagoli, C., Muti, P., Berrino, F., Krogh, V.
	Publication date	November 2009
	Publication type	Abstract (Oral presentation)
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Authors analysed the association between selenium intake from foods and diabetes risk within a cohort study carried out in Italy.
	Study type/design	Cohort study
	Study duration	16-years follow-up
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	ORDET Cohort: A sample of 7,288 women from northern Italy enrolled in a prospective study on relation between diet and breast cancer.
	Selection criteria for population (if applicable)	
	Subgroups reported	Quintiles of dietary selenium intake
	Size of study	7,288 women
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Diet
	Exposure concentrations (if applicable)	Average intake of selenium in the cohort was lower than that estimated in the US population.
	Comparison group(s)	Lowest quintile of dietary selenium intake
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Development of Type 2 diabetes (as defined on the basis of a) self-reported physician diagnosis, b) use of anti-diabetic medication-self-reported or by linkage with regional prescription drug database, and c) linkage with medical discharge records
	How outcome was assessed	
	Method of measurement	Not applicable

Publication Reference: Vinceti M., Stranges S., Sieri S., Grioni S., Malagoli C., Muti P., Berrino F. and Krogh V. (2009b). Association Between High Selenium Intake and Subsequent Increased Risk of Type 2 Diabetes in an Italian Population. Epidemiology 20.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	7,288 women
Statistics (if any)	Statistical method used	Authors calculated in a logistic regression model the risk of diabetes according to quintile of baseline selenium intake, while adjusting for several demographic, anthropometric and lifestyle variables.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	In multivariate analysis, risk of diabetes was directly associated with baseline selenium intake (P trend 0.026), with a relative risk of 2.01 (95% confidence interval 1.11, 3.64) in the highest quintile of dietary selenium intake compared to the lowest one. Quintile dose divisions not specified in abstract.
Author's conclusions	Interpretation of results	Higher dietary intakes of selenium increased the risk of type 2 diabetes in this female population. Consistent with recent studies, these findings raise additional concerns about the possibility of sub-clinical metabolic toxicity induced by selenium at lower levels of exposure than previously thought.
	Assessment of uncertainty (if any)	Not stated.
Reviewer comments	Results included/excluded in review (if applicable)	This is an abstract for an oral presentation and similar published papers using the same cohort were prepared by Stranges et al. (2007, 2010) with the same outcome for type 2 diabetes (OR = 2.39, 95% CI: 1.32 - 4.32; P = 0.005, Stranges et al. 2010). Therefore, this abstract was not subject to a RoB assessment (however Stranges et al. 2010 was subject to a RoB assessment).

Vinceti et al. 2010a

Publication Reference: 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.		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti M, Bonvincini F, Rothman KJ, Vescovi L, Wang F
	Publication date	2010
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Italy
	Source of funding	Financial support to this study was provided by Pietro Manodori Foundation of Reggio Emilia and by the Local Health Unit of Reggio Emilia.
	Possible conflicts of interest	The authors declare that they have no conflict of interest.

Publication Reference: 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.		
Study characteristics	Aim/objectives of study	To determine whether an association of excess amyotrophic lateral sclerosis (ALS) with drinking water containing high Se concentrations found in an earlier study persisted during the years since the earlier report.
	Study type/design	Case-control
	Study duration	Study period: 1995-2006 (to update previous findings of 1986-1994).
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	Cases and matched controls in the Reggio Emilia municipality. Eligible cases were all Reggio Emilia residents who received a first-time diagnosis of ALS during the years 1995 to 2006, provided that they had been residents of Reggio Emilia for at least six months. Controls selected from the general population of Reggio Emilia, identifiable through annual directories of residents made available by the General Registry Office of the region. Using the calendar-year specific file of municipal residents corresponding to the year of diagnosis for each case, authors randomly selected two controls matched to the case for year of birth and sex, using the sample command of Stata statistical software.
	Selection criteria for population (if applicable)	
	Subgroups reported	Cases and controls
	Size of study	41 newly diagnosed cases 82 age- and sex-matched controls
Exposure and setting	Exposure pathway	Drinking water (oral)
	Source of chemical/contamination	Not stated
	Exposure concentrations (if applicable)	Before 1972 and after 1988, the water supplied to Rivalta was the same as that supplied to the rest of Reggio Emilia, but during this period water supplied to Rivalta residents came from two local wells having only one distinctive chemical characteristic, a high Se content. This water was sampled again for Se speciation for this study. The authors assigned a Se concentration of 8 µg/l to municipal tap water consumed by subjects residing in Rivalta for at least six months during 1972-88. They assigned a value of 0 µg of Se for all other consumption of municipal water, as the concentration of Se in the tap water never otherwise reached the detection limit of the analytical methodology. Then computed an estimate of overall Se intake through drinking water during the 35 years before the diagnosis date (or corresponding date for controls). This was derived by multiplying the number of days of exposure within the 35 year period by 2.6 L of water each day (estimate for pregnant women) and by Se concentration in water that was being consumed on the day it was measured.
	Comparison group(s)	≥ 1 µg/L vs. <1 µg/L

Publication Reference: 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.		
Study methods	Water quality measurement used	ICP-MS Se speciation (using HPLC) undertaken on all water samples with Se ≥ 1 µg/L
	Water sampling methods (monitoring, surrogates)	• For study participants who reported consuming well water, details, including year starting, year ending, and estimated percentage of total water consumed were obtained. Permission to sample this water was sought, when it was available. If subjects were no longer residing in the house that had the well, those currently living at that address were contacted and we asked for permission to sample the water. For three study subjects (all controls), the original well was not accessible in 2009 because it had collapsed, but after contacting a neighbouring family, authors were able to get a sample of water from a nearby well. • 21 well samples were collected. Concentrations of trace elements in well water was similar for cases and controls.
Results (for each outcome)	Definition of outcome	• Se in all the water samples was almost exclusively present as inorganic Se, in the form of hexavalent Se (selenate), the Se species found in the Rivalta municipal tapwater during 1972-88 period. • Consumption of drinking water containing ≥ 1 µg/L of inorganic Se was associated with a relative risk for amyotrophic lateral sclerosis of 5.4 (95% confidence interval 1.1-26) after adjustment for confounding factors. • Greater amounts of cumulative inorganic selenium intake were associated with progressively increasing effects, with a relative risk of 2.1 (95% confidence interval 0.5-9.1) for intermediate levels of cumulative intake and 6.4 (95% confidence interval 1.3-31) for high intake.
	How outcome was assessed	
	Method of measurement	• Questionnaire administered to all subjects was designed to collect information about residential history and sources of domestic drinking water during the thirty-five years before diagnosis for cases, and for the corresponding period for the matched controls. The questionnaire also asked about consumption of dietary supplements (types and duration), family history of ALS in first-degree relatives, occupational history, life-style factors (smoking habits, coffee and alcohol consumption), and history of trauma sufficient to result in admission to a hospital.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Most study subjects had consumed water from the municipal system that was low in Se. Three cases and four controls consumed the high Se municipal tap water that was distributed from 1972-88 in the Rivalta district. None of these study subjects consumed Rivalta municipal water for less than six months. Eleven cases and ten controls reported consuming at least 75% of their drinking water from private wells.
Statistics	Statistical method used	

Publication Reference: 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.		
(if any)	Details on statistical analysis	Authors estimated the relative risk (RR) of ALS following Se exposure through drinking water from Mantel-Haenszel odds ratios in a stratified analysis, and from odds ratios estimated from conditional logistic regression models that included the potential confounders (occupational exposures to pesticides, industrial chemicals and electromagnetic fields).
	Relative risk/odds ratio, confidence interval?	See outcome summary
Author's conclusions	Interpretation of results	• Based on these results, coupled with other epidemiologic data and with findings from animal studies that show specific toxicity of the trace element on motor neurons, the authors hypothesise that dietary intake of inorganic selenium through drinking water increases the risk for amyotrophic lateral sclerosis. • The findings are consistent with a Se-ALS relation that might be specific for the inorganic, soluble species of this element that is typically found in aquifers.
	Assessment of uncertainty (if any)	• Information on confounders was self-reported and thus subject to inaccurate recall, although such inaccuracies could not plausibly explain primary finding. • Caution that these results ought not be extended to the organic forms of the trace element found in foods and in Se-containing dietary supplements. • Weakness of study is limited size of exposed population, leading to broad confidence intervals for the effect estimates. • Some possibility of misclassification of exposure as the drinking water estimate of Se content was based on currently available Se levels for well waters and on historical data for Se municipal tap water content.
Reviewer comments	Results included/excluded in review (if applicable)	• This case-control observational study provides an indication that exposure to increasing Se concentration in drinking water may be associated with development of ALS. However the study is relatively small. Should be considered with weight of overall evidence. • It is noted the authors measured concentrations of Se at a point in time in 21 private wells; it is unclear from the paper how exposures for all cases and controls were assigned to either low of high Se from these data. • As this study provides some indication of dose-response, it was subjected to RoB assessment.
	Notes on study quality, e.g. gaps, methods	

Vinceti et al. 2010b

Publication Reference: 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.		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti M, Bonvincini F, Bergomi M, Malagoli C
	Publication date	2010
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Italy
	Source of funding	Financial support to this study was provided by Pietro Manodori Foundation of Reggio Emilia
	Possible conflicts of interest	The authors declare that they have no conflict of interest.
Study characteristics	Aim/objectives of study	To present an analysis of the evidence supporting an association between excess exposure to Se and amyotrophic lateral sclerosis (AML).
	Study type/design	Mini-review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• Biological effects of Se largely depend on its chemical form (i.e. inorganic/organic status and oxidation state).

Publication Reference: 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.		
	How outcome was assessed	• In humans, Se exposure generally occurs through diet, whilst drinking water and occupational environments are rarely a source of exposure. In foodstuffs, Se is generally in the form of organic Se, whilst in occupational settings and in groundwaters Se is generally found in its inorganic hexavalent and tetravalent forms, selenate and selenite, or as volatile Se compounds. Compared with the organic forms, inorganic Se is considerably more toxic, with an increase in toxicity in the order of fifty times for some of the adverse effects of the metalloid. • The epidemiologic evidence suggesting a causal relation between exposure to environmental Se and ALS is mainly based on two studies, one carried out in the US and the other in Northern Italy. The first investigation was carried out by Kilness and Hochberg, who reported in 1977 a cluster of four ALS cases in a "sparsely populated county", with a population of around 4000, located in west-central South Dakota. All these cases were male farmer/ranchers, with a age range between 57 and 66, living a few km away from each other. The investigators noted that the area was known to be affected by naturally occurring selenosis, as demonstrated by cases of Se intoxication in farm animals, and they hypothesised that the association between the high Se environment and the ALS cluster could be causal. • The second study was performed by Vinceti et al. in a Northern Italy municipality, Reggio Emilia, taking advantage of a so-called natural experiment, i.e. the distribution in a small area of that municipal territory of public tap water with unusually high Se content, 7-9 µg/L, compared to the remaining part of the municipal territory where tap water Se levels were lower than 1 µg/L. The high Se content in this "exposed area" was due to the high levels of Se in the waters of the two wells which were the source of municipal tap water in that area from 1972 to 1988. The origin of such high concentrations of Se were almost certainly natural, since no anthropogenic source of the metalloid in that area was ever identified. Selenium was almost entirely present in the inorganic hexavalent form, selenate
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• Overall, the epidemiologic evidence linking Se exposure to ALS risk, associated with the biological evidence, indicate that Se at least in its inorganic forms may actually represent a risk factor for ALS and suggest the need to further investigate this issue.
	Assessment of uncertainty (if any)	• Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This mini-review summarises information available for the association between overexposure to Se and ALS. The bibliography was consulted to source the original cited studies, which have been included in this report. No RoB assessment done.
	Notes on study quality, e.g. gaps, methods	

Vinceti et. al. 2012

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Vinceti, M., Crespi, C.M., Malagoli, C., Bottecchi, I., Ferrari, A., Sieri, S., Krogh, V., Alber, D., Bergomi, M., Seidenari, S., and Pellacani, G.
	Publication date	2013 May 01 (note publication date is 2012, but available online in 2013)
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	Financial support was provided by the Ministry of the University and of the Scientific and Technological Research (grant no. 2002063519_001), the 'Lega Italiana per la Lotta contro i Tumori' and the 'Fondazione Pietro Manodori' of Reggio Emilia and NIH P30 CA16042.
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	The study examined whether there is a direct association between exposure to the metalloid selenium and risk of cutaneous melanoma using multiple indicators of exposure.
	Study type/design	Case control
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
	Population/s studied	

Publication Reference: 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.		
Population characteristics	Selection criteria for population (if applicable)	Fifty-nine individuals residing in the province of Modena, northern Italy (population around 700,000) were recruited at the Department of Dermatology of Modena and Reggio Emilia University following the diagnosis of cutaneous melanoma from 1999 to 2002. Immediately after enrolment of each patient, which occurred at the beginning of clinical follow-up, the authors recruited one population control matched to the case on sex, age (± 5 years) and residence in the province, by approaching by phone potential participants identified from a general population database made available by the Local Health Unit of Reggio Emilia.
	Subgroups reported	Not applicable
	Size of study	59 cases and 59 controls
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Diet
	Exposure concentrations (if applicable)	Median intake of 54 µg/day (21 – 159 µg/day, 75th percentile = 68µg/day) for cases and 57 µg/day (22 – 96 µg/day, 75th percentile = 75µg/day) for controls. In the study sample as a whole, dietary selenium was mainly due to intake of fish (28% of overall intake), meat (22.7%), cereals (14.9%) and dairy products (12.6%), while the remaining food groups were minor contributors.
	Comparison group(s)	Control group
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Authors analysed the relation of selenium exposure with risk of cutaneous melanoma using two different biomarkers, plasma and toenail selenium concentration, and estimated dietary selenium intake in a community-based case-control series (54 cases, 56 controls) from an Italian community.
	How outcome was assessed	
	Method of measurement	• Right foot toenail clippings were obtained from the participants, cleaned, dried and analysed using instrumental neutron activation analysis • Authors determined selenium plasma concentrations using a direct electrothermal atomic absorption spectrometer. • For the dietary assessment, they used a semiquantitative food frequency questionnaire specifically developed for northern Italy that including 248 questions on frequency and quantity of consumption of 188 items.
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	59 cases and 59 controls. The participation rate was 72.0 % for cases, drawn from a consecutive series of patients, and 56.3% for referents.

Publication Reference: 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.		
Statistics (if any)	Statistical method used	Authors compared the distributions of each of the three selenium measures for cases and controls using two-sample Student's t-test. The associations among the three measures were quantified using Spearman rank correlation coefficients; this rank-based measure of association was used rather than Pearson correlation coefficients to reduce the influence of several moderate outliers. They estimated the relative risk (RR) of cutaneous melanoma associated with each indicator of selenium exposure by computing odds ratios in conditional and unconditional logistic regression models. Conditional logistic regression models used the case-control matching; unconditional logistic regression models controlled for age and gender. These analyses were conducted using the gam package in R version 2.9.2
	Details on statistical analysis	

	Relative risk/odds ratio, confidence interval?	Higher selenium levels were strongly associated with excess disease risk.
		A 10 µg/L increase in plasma selenium was associated with a RR of 1.41 (95% CI 1.11–1.79, P=0.005) in a matched analysis and 1.43 (95% CI 1.15–1.78, P=0.001) in unmatched analysis.
		
		Estimates of relative risk (RR) of melanoma with 95% confidence intervals (CI), by quartile of selenium exposure indicator – matched analysis
		• Plasma selenium
		  • Q2: RR = 2.13 (0.56 – 8.04), p = 0.266
		  • Q3: RR = 2.86 (0.79 – 10.32), p= 0.109
		  • Q4: RR = 5.86 (1.53 – 22.31), p = 0.010
		• Toenail selenium
		  • Q2: RR = 1.32 (0.43 – 4.07) p = 0.627
		  • Q3: RR = 1.41 (0.44 – 4.54), p = 0.566
		  • Q4: RR = 0.72 (0.22 – 2.38), p = 0.586
		• Dietary selenium
		  • Q2: RR = 1.50 (0.46 – 4.86), p = 0.500
		  • Q3: RR = 1.28 (0.45 – 3.63), p = 0.648
		  • Q4: RR = 0.64 (0.20 – 2.04), p = 0.454
		The relative risk estimates remained similar when adjusting for potential confounders including education, phototype and sunburn history, and when restricting the analysis to subjects without a family history of melanoma. The RR estimate was similar after these adjustments (1.43, 95% CI 1.13 – 1.81, P=0.003).

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• In unmatched and matched logistic regression models as well as nonparametric generalised additive models, higher plasma selenium levels were strongly associated with excess disease risk. • In contrast, toenail and dietary selenium exhibited little relation with melanoma risk. • The pattern of correlation among indicators of exposure differed by disease status, with dietary intake associated with plasma selenium levels in patients but not in controls.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This small case-control study looked at associations between melanoma and selenium in plasma, toenails and dietary selenium. A statistically significant positive association was found between plasma selenium level and melanoma in the high quartile group compared to the low quartile group. This study was subjected to RoB assessment.

Vinceti et al. 2013a

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Vinceti M, Crespi CM, Bonvincini F, Malagoli C, Ferrante M, Marmiroli S, Stranges S
	Publication date	2013
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Italy, US and UK
	Source of funding	Financial support to this study was provided by the "Fondazione Pietro Manodori di Reggio Emilia" and by the Italian Ministry of the University and of Scientific and Technological Research (COFIN grant 2002–063519).
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	To re-evaluate the potential hazard of selenium to human health when administered through drinking water, as well as the adequacy of current and proposed environmental standards in this regard.
	Study type/design	Review
	Study duration	Not applicable

Publication Reference: 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.		
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	

	How outcome was assessed	• Selenium is a recognised neurotoxin, with inorganic selenium appearing to be about 40 times more neurotoxic than organic selenium. The available evidence clearly indicates the importance of considering the different selenium compounds and of selenium speciation. Inorganic forms are not generally found in foods. • Risk assessment of organic (dietary) selenium benefitted from the results of two recent experimental studies, which showed that the dose of organic selenium that can be deemed safe is much lower than previously believed (Stranges et al. 2007; Bruhn et al. 2009; Lippman et al., 2009; Dennert et al. 2011; Suadicani et al. 2012). These studies found adverse dermatologic and endocrine effects at levels of about 250–300 µg/day of organic selenium intake, and recent observational studies (with one exception (Park et al. 2012)) appear to confirm that adverse endocrine effects of organic selenium species may start at considerably lower doses, of 50 µg/day. • The epidemiologic studies on health effects of selenium when administered through drinking water encompass three sets of investigations, two carried out in the United States (Tsongas and Ferguson 1977; Valentine et al. 1987; Valentine 1997) and the other in a northern Italy community (Vinceti et al. 1996, 1998, 2000a, 2000b, 2010). • In the first US study, tap water yielded Se content between 50-125 µg/L. Results showed consumption of the high-selenium drinking water was associated with higher urinary levels of selenium but not with study health endpoints. • Valentine et al. investigated three communities with unusually high selenium content in their drinking water supply systems, Red Butte and Jade Hills in Wyoming and Grants in New Mexico (1987). These communities had tap water with average selenium concentrations of 494, 194 and 327 µg/L Se, respectively, in undefined but most likely inorganic forms. Fifty consumers of this high-selenium drinking water were compared, as to body selenium burden and prevalence of several diseases, to 99 individuals from the Sun Valley (Nevada) and Casper (Wyoming) communities, which had drinking water with 3 and 2 µg/L Se, respectively. Analysis of biomarkers of exposure indicated that blood and hair selenium levels were higher in exposed subjects but the differences were small, despite the large difference in water selenium levels. In contrast, differences in urine selenium concentrations between exposed and unexposed subjects were much larger, though still less marked than the difference in water selenium content, and urine levels tended to correlate with water selenium concentrations. When disease prevalence was examined taking into account two biomarkers of exposure, i.e., urine and blood selenium, a tendency towards higher risk of diarrhoea, depression, dizziness, lassitude, pain in muscle and joints, and headaches in exposed subjects emerged, though these associations were statistically unstable. • Only the studies carried out in the Italian community of Reggio Emilia have so far investigated the long-term health

Publication Reference: 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.		
		effects of selenium in drinking water on risk of chronic diseases with a longitudinal design; the US studies were limited by their cross-sectional design and potential for uncontrolled confounding. Thus further investigations are clearly required to confirm these observations.
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• The excess incidence of several site-specific neoplasms and of ALS associated with chronic exposure of drinking water at around 8 µg/L, with the former effect apparently starting at levels ≥1 µg/L, together with evidence of toxicity at low levels in vitro and in animal studies, suggest that the current commonly used limit of 10 µg/L may be inadequate to protect against such health risks. • The limited investigations on selenium in drinking water in humans preclude the possibility of reliably identifying a Lowest Observed Adverse Effect Level (LOAEL) and therefore of conclusively identifying a safe upper limit. • However, a reasonable approach is to assume that selenium (as selenate) toxicity through drinking water occurs at concentrations as observed in epidemiologic studies (and which are consistent with laboratory studies) and apply an uncertainty factor to reach a presumably safe range of exposure (Renwick and Walker, 2008). Such factors are generally in the 3–10 range, though higher and lower values have been used (Ritter et al., 2007). Since in the Reggio Emilia studies selenium levels at 8 µg/L were shown to be toxic and concentrations from 1 to 8 µg/L of possible toxicity, the authors suggest that an acceptable level should be on the order of 1 µg/L for all inorganic selenium species combined, obtained by conservatively applying an uncertainty factor of 10 to 8–10 µg/L. Such a standard would be adequate to avoid increased risk of adverse health effects, including neoplasms and endocrine and neurological diseases, due to long-term exposure.
	Assessment of uncertainty (if any)	• Not done
Reviewer comments	Results included/excluded in review (if applicable)	• This review concludes that the EU drinking water standard of 10 µg/L (and recent WHO guideline of 40 µg/L) are likely too high to protect against the 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. As this is a review, no RoB assessment was undertaken.
	Notes on study quality, e.g. gaps, methods	

Vinceti et. al. 2013b

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Vinceti, M., Solovyev, N., Mandrioli, J., Crespi, C.M., Bonvicini, F., Arcolin, E., Georgoulopoulou, E., and Michalke, B.
	Publication date	2013 September
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	Financial support for this study was provided by the Pietro Manodori Foundation of Reggio Emilia, the national, Modena and Reggio Emilia sections of the Italian Amyotrophic Lateral Sclerosis Association (AISLA) and the Local Health Unit of Reggio Emilia to Dr. Vinceti, and by the US National Institute of Health for Dr. Crespi (grant NIH UL1TR000124).
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Authors conducted a case-control study to examine the hypothesis that Se species and particularly the inorganic ones are associated with ALS risk by using a CNS biomarker of exposure, cerebrospinal fluid (CSF), which appears to play a key role in assessing exposure to etiopathogenetic and therapeutic factors in this disease
	Study type/design	Case-control study
	Study duration	Not applicable
	Type of water source (if applicable)	Drinking water
Population characteristics	Population/s studied	ALS patients were recruited from a case series of residents of the Emilia-Romagna region, northern Italy, who were diagnosed with clinically definite or clinically probable ALS using the revised El Escorial Criteria (Georgoulopoulou et al. 2011) at the ALS Centre of the Modena University Neurological Department from May 1998 to April 2011, and who underwent lumbar puncture during diagnostic procedures.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	The 38 ALS cases included 16 men and 22 women, with mean age of 55.5 years (range 30.7–76.4 years),
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Drinking water with high content of inorganic Se as selenate
	Exposure concentrations (if applicable)	Not applicable

Publication Reference: 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.		
	Comparison group(s)	38 age- and gender-matched controls had mean age 52.6 years (range 30.2–85.5 years). Randomly selected 38 subjects matched 1:1 to ALS cases on age (± 10 years, in most cases ± 5 years) and gender from patients residing in the Emilia-Romagna region who were admitted to the same department between 1999 and 2010, inclusive, and underwent lumbar puncture because of suspected but later unconfirmed neurological disease, and had a sample of at least 1 mL of CSF still available in September 2011.
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Difference in selenium levels by species between case and controls
	How outcome was assessed	
	Method of measurement	Authors determined total Se and the Se species selenite, selenate, Se-MET, Se-Cys, Se-TrxR, Se-GPx, SePP and Se-HSA in the CSF samples using high pressure liquid chromatography (HPLC) coupled with inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) according to methodologies previously established for biological matrices, specifically for CSF. Selenium species tested: Selenite, selenate, selenomethionine (Se-MET), selenocysteine (Se-Cys), thioredoxin reductase (EC 1.8.1.9.)-bound selenium (Se-TrxR), glutathione peroxidase (EC 232–749-6)-bound selenium (Se-GPx)
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	38 cases and 38 controls
Statistics (if any)	Statistical method used	Authors tested differences in distribution of Se species in cases and controls using the Wilcoxon signed-rank test. They estimated the relative risk (RR) of ALS, as expressed by the odds ratio, associated with a one-unit increase in single Se species or categories using conditional logistic regression models. Sensitivity analyses were conducted by selectively omitting from analyses control patients with specific symptoms and signs leading to neurological examination (specifically, the 17 subjects suffering from headache, the 5 with paraesthesia and the 6 with diplopia).
	Details on statistical analysis	

Publication Reference: 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.		
	Relative risk/odds ratio, confidence interval?	Relative risks (RR) of ALS associated with 1 µg/L increase in CSF concentration of Se species: analysis using winsorized variables • Selenite RR= 1.9 (0.8–4.6) • Selenate RR = 0.9 (0.2–4.4) • Thioredoxin reductase-bound Se RR = 1.0 (0.9–1.0) • Glutathione peroxidase-bound Se RR = 1.0 (0.9–1.1) • Human serum albumin-bound Se RR= 1.5 (0.9–2.4) • Selenoprotein P-bound Se RR = 0.3 (0.08–0.8) • Total inorganic (adjusted for organic) RR = 1.7 (0.8–3.9) • Total organic (adjusted for inorganic) RR = 0.4 (0.2–0.9)
Author's conclusions	Interpretation of results	The authors concluded their results indicate a direct relation between ALS risk and the concentration of selenite in CSF of newly-diagnosed ALS patients, as well as an inverse association with the organic Se form SePP which might be a related phenomenon, supporting the hypothesis that overexposure to selenite may be an aetiological risk factor in the disease. Selenite may trigger neurodegenerative effects through its powerful toxicity, which appears to be unique among toxic chemicals, being highly specific towards motor neurons in some animal studies.
	Assessment of uncertainty (if any)	-
Reviewer comments	Results included/excluded in review (if applicable)	This small case-control study found higher risk ratios for Selenite, human serum bound Se and total organic Se in CSF and ALS but all RRs were not statistically significant (95% confidence intervals crossed over 1). This study was subjected to a RoB assessment.

Vinceti et al. 2014

Publication Reference: Vinceti M., Mandrioli J., Borella P., Michalke B., Tsatsakis A. and Finkelstein Y. (2014). Selenium neurotoxicity in humans: bridging laboratory and epidemiologic studies. Toxicol Lett 230(2): 295-303.		
General Information	Date of data extraction	14/06/2023
	Authors	Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, Zeegers MPA, Horneber M, D'Amico R, Del Giovane C
	Publication date	2014
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Italy, Germany, USA, Switzerland, Australia, Netherlands

Publication Reference: Vinceti M., Mandrioli J., Borella P., Michalke B., Tsatsakis A. and Finkelstein Y. (2014). Selenium neurotoxicity in humans: bridging laboratory and epidemiologic studies. Toxicol Lett 230(2): 295-303.		
	Source of funding	Several sources listed: • Funded in part by the Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena. The funding source had no role in designing, conducting or writing this systematic review. • Partially funded by the Dr. Ernst and Anita Bauer Foundation. • Funded in part by the EU CAM-Cancer Project. • Funded in part by the German Cancer Aid. • Funded in part by Grant Number R24 AT001293 from the National Center for Complementary and Alternative Medicine (NCCAM), USA. • Partially funded by Grant Number CA16042 from the National Institutes of Health, National Cancer Institute (NCI), USA. • Funded in part by the Italian League against Cancer (LILT), Reggio Emilia section and by the Fondazione Pietro Manodori of Reggio Emilia.
	Possible conflicts of interest	No conflict of interest for most authors, except MPA Zeggers who was the first investigator of one included observational study and one ongoing randomised controlled trial and is second author of another included observational study.
Study characteristics	Aim/objectives of study	This review is an update of the first Cochrane publication on selenium for preventing cancer, looking at what is the evidence for: 1. an aetiological relation between selenium exposure and cancer risk in humans? and 2. the efficacy of selenium supplementation for cancer prevention in humans?
	Study type/design	Systematic Review
	Study duration	Searches conducted in various databases from 1966 to 2013.
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Included prospective observational studies (cohort studies including sub-cohort controlled studies and nested case-control studies) and randomised controlled trials (RCTs) with healthy adult participants (18 years of age and older).
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable

Publication Reference: Vinceti M., Mandrioli J., Borella P., Michalke B., Tsatsakis A. and Finkelstein Y. (2014). Selenium neurotoxicity in humans: bridging laboratory and epidemiologic studies. Toxicol Lett 230(2): 295-303.		
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• 55 prospective observational studies (including more than 1,100,000 participants) and eight RCTs (with a total of 44,743 participants) were included. For the observational studies, they found lower cancer incidence (summary odds ratio (OR) 0.69, 95% confidence interval (CI) 0.53 to 0.91, N = 8) and cancer mortality (OR 0.60, 95% CI 0.39 to 0.93, N = 6) associated with higher selenium exposure. Gender-specific subgroup analysis provided no clear evidence of different effects in men and women (P value 0.47), although cancer incidence was lower in men (OR 0.66, 95% CI 0.42 to 1.05, N = 6) than in women (OR 0.90, 95% CI 0.45 to 1.77, N = 2). The most pronounced decreases in risk of site-specific cancers were seen for stomach, bladder and prostate cancers. Some studies suggested that genetic factors may modify the relation between selenium and cancer risk—a hypothesis that deserves further investigation. • In RCTs, they found no clear evidence that selenium supplementation reduced the risk of any cancer (risk ratio (RR) 0.90, 95% CI 0.70 to 1.17, two studies, N = 4765) or cancer-related mortality (RR 0.81, 95% CI 0.49 to 1.32, two studies, N = 18,698), and this finding was confirmed when the analysis was restricted to studies with low risk of bias. The effect on prostate cancer was imprecise (RR 0.90, 95% CI 0.71 to 1.14, four studies, N = 19,110), and when the analysis was limited to trials with low risk of bias, the interventions showed no effect (RR 1.02, 95% CI 0.90 to 1.14, three studies, N = 18,183). The risk of non-melanoma skin cancer was increased (RR 1.44, 95% CI 0.95 to 1.17, three studies, N = 1900). Results of two trials—the Nutritional Prevention of Cancer Trial (NPCT) and the Selenium and Vitamin E Cancer Trial (SELECT)—also raised concerns about possible increased risk of type 2 diabetes, alopecia and dermatitis due to selenium supplements. An early hypothesis generated by NPCT that individuals with the lowest blood selenium levels at baseline could reduce their risk of cancer, particularly of prostate cancer, by increasing selenium intake has not been confirmed by subsequent trials. As the RCT participants were overwhelmingly male (94%), gender differences could not be systematically assessed.
	How outcome was assessed	
	Method of measurement	For observational studies, authors conducted random effects meta-analyses when five or more studies were retrieved for a specific outcome. For RCTs, they performed random effects meta-analyses when two or more studies were available. The risk of bias in observational studies was assessed using forms adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies; the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions were used to evaluate the risk of bias in RCTs.

Publication Reference: Vinceti M., Mandrioli J., Borella P., Michalke B., Tsatsakis A. and Finkelstein Y. (2014). Selenium neurotoxicity in humans: bridging laboratory and epidemiologic studies. Toxicol Lett 230(2): 295-303.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Although an inverse association between selenium exposure and the risk of some types of cancer was found in some observational studies, this cannot be taken as evidence of a causal relation, and these results should be interpreted with caution. These studies have many limitations, including issues with assessment of exposure to selenium and to its various chemical forms, heterogeneity, confounding and other biases. Conflicting results including inverse, null and direct associations have been reported for some cancer types. • RCTs assessing the effects of selenium supplementation on cancer risk have yielded inconsistent results, although the most recent studies, characterised by a low risk of bias, found no beneficial effect on cancer risk, more specifically on risk of prostate cancer, as well as little evidence of any influence of baseline selenium status. Rather, some trials suggest harmful effects of selenium exposure. To date, no convincing evidence suggests that selenium supplements can prevent cancer in humans.
	Assessment of uncertainty (if any)	• These findings have limitations due to study design, quality and heterogeneity that complicate interpretation of the summary statistics
Reviewer comments	Results included/excluded in review (if applicable)	• This systematic review found limited evidence suggesting that individuals observed to have higher selenium levels have a lower incidence of cancer. However, it is not possible to conclude from these studies that selenium was the reason for the lower cancer risk, because a high selenium level might be associated with other factors that reduce cancer risk, such as healthier diet or lifestyle. • Recent randomised controlled trials that were judged to be well conducted and reliable have found no effects of selenium on reducing the overall risk of cancer or on reducing the risk of particular cancers, including prostate cancer. In contrast, some trials suggest that selenium may increase the risk of non-melanoma skin cancer, as well as of type 2 diabetes, raising concern about the safety of selenium supplements.
	Notes on study quality, e.g. gaps, methods	

Vinceti et al 2016

Publication Reference: 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.		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti, M., Ballotari, P., Steinmaus, C., Malagoli, C., Luberto, F., Malavolti, M., Giorgi Rossi, P.
	Publication date	Available online 24 June 2016
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	National Health Service – Local Health Authority of Reggio Emilia
	Possible conflicts of interest	None declared.
Study characteristics	Aim/objectives of study	To investigate the relationship between Se levels in water and mortality in the municipality of Reggio Emilia, Italy, where high levels of Se were previously observed in drinking water
	Study type/design	Cohort study (observational)
	Study duration	Not applicable
	Type of water source (if applicable)	Municipal water supply in a small northern Italian village (from wells that fed the local public aqueduct of Rivalta)
Population characteristics	Population/s studied	A main cohort of 5,182 exposed residents from the town of Rivalta (the exposed group) and 95,715 from the Reggio Emilia municipality (the unexposed group) For the Se-unexposed cohort, authors identified all 110,048 residents in the Reggio Emilia municipality since December 31, 1980 through December 31, 1985, excluding those identified in the Se exposed main cohort.
	Selection criteria for population (if applicable)	
	Subgroups reported	A sub-cohort from among this main cohort that only included subjects having the longest ascertainable exposure ('long-term exposed cohort').
	Size of study	N = 5,182 for main cohort, N = 2065 for long-term exposed cohort (a sub-group of the main cohort) and N = 110,048 for unexposed cohort
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	High Se levels in the water from these two wells and consequently in tapwater distributed in Rivalta was found to be geologic, and not associated to any possible anthropogenic source.
	Exposure concentrations (if applicable)	Testing for Se began during the 1980s, and Se levels in the tapwater distributed in Rivalta averaged 8 µg/L and in some cases approached the 10 µg/L European Union standard. In the main municipality tapwater supply, Se levels were always very low (0.6 µg/L).
	Comparison group(s)	Population of Reggio Emilia municipality excluding residents of the town of Rivalta.
Study methods	Water quality measurement used	Not stated.

Publication Reference: 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.		
	Water sampling methods (monitoring, surrogates)	Not stated.
Results (for each outcome)	Definition of outcome	The outcome of interest was all cause and cause-specific mortality. Causes of death were ascertained using Reggio Emilia mortality register, which contains death certificates of all deceased residents, and coded causes of death using the International Classification of Diseases - tenth revision (ICD-10). During the follow-up period the ICD codification system changed from the IX to X version, so all ICD codes of cohort members were carefully translated to the IX version by a physician with specific coding expertise (F.L.). The causes of death due to motor neuron disease (code=335.2) were recoded as amyotrophic lateral sclerosis (ALS). Because of new and updated cross-checks between mortality and population databases, unavailable at the time of the precedent study, the number and classifications of some causes of death among the long-term exposed cohort members were modified from a previous study (Vinceti et al. 2000). The person-time at risk was standardised by age (10 year age groups) and calendar time (5 year periods) in order to adjust for both time dependent covariates. Gender was considered as a stratification variable.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Long-term exposed cohort (1975-1985), subset of main cohort: • n = 2,065 'exposed' residents • n= 95,715 'unexposed' Main cohort (1981-1985): • n=5,182 'exposed' • n=110,048 'unexposed'
Statistics (if any)	Statistical method used	To compute RRs and their 95% confidence intervals (95%CI), authors ran multivariate Poisson models, with stratifications by sex and follow-up period (1986–1997 and 1998–2012). Record linkage and data analyses were performed using Stata (version 13.1, Stata Corp., College Station, TX 2015).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	In the long-term exposed cohort • buccal cavity and pharynx (RR 1.50, 95% CI 0.56–4.07), • colon-rectum cancers (RR 1.17, 95% CI 0.78–1.76) • melanoma (RR 2.30, 95% CI 0.84–6.29) • urinary tract neoplasms (RR 1.54, 95% CI 0.98–2.44) • Lymphohematopoietic cancers (mainly multiple myeloma, RR 2.24, 95% CI 1.05–4.78) Although some analyses involved small numbers and the point estimates were statistically imprecise. Death rates for nervous disease was also higher due to two neurodegenerative diseases • Parkinson's disease (RR 2.47, 95% CI 1.15–5.28) • Amyotrophic lateral sclerosis (ALS) (RR 2.79, 95% CI 1.01–7.67).

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• Excess rate ratios were seen for some site specific cancers such as neoplasms of buccal cavity and pharynx, urinary tract, lymphohematopoietic tissue, melanoma, and two neurodegenerative diseases, Parkinson's disease and amyotrophic lateral sclerosis. • Excess mortality in the exposed cohort for specific outcomes was concentrated in the first period of follow-up (1986–1997), and waned starting 10 years after the high exposure ended. • Authors also found lower mortality from breast cancer in females during the first period of follow-up. • Mortality patterns related to long-term exposure to inorganic hexavalent selenium through drinking water were elevated for several site-specific cancers and neurodegenerative disease.
	Assessment of uncertainty (if any)	Author makes reference to lifestyle factors as confounders that had little or no effect on RRs (but data not shown): • Some differences in occupations • Ethnic and religious factors were very homogeneous • Lung cancer from smoking and some occupational exposures • Liver cirrhosis from alcohol • Infectious diseases • Injury • Poisoning • Road Traffic Further research is needed to confirm the associations found.
Reviewer comments	Results included/excluded in review (if applicable)	RR are mostly not statistically significant except for melanoma, Parkinson's disease, and ALS in the long-exposed group (all subjects). In females, purported to be at home more often with higher drinking water intake, statistically significant results also observed for multiple myeloma but not Parkinson's disease. In men, kidney disease also had statistically significant RR. This paper was subjected to risk of bias assessment.

Vinceti et al 2017

Publication Reference: *Vinceti M., Filippini T., Cilloni S., Bargellini A., Vergoni A. V., Tsatsakis A. and Ferrante M. (2017). Health risk assessment of environmental selenium: Emerging evidence and challenges. Molecular Medicine Reports 15(5): 3323-3335.*		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti M., Filippini T., Cilloni S., Bargellini A., Vergoni A. V., Tsatsakis A. and Ferrante M.
	Publication date	February 20, 2017

Publication Reference: *Vinceti M., Filippini T., Cilloni S., Bargellini A., Vergoni A. V., Tsatsakis A. and Ferrante M. (2017). Health risk assessment of environmental selenium: Emerging evidence and challenges. Molecular Medicine Reports 15(5): 3323-3335.*		
	Publication type	Peer-reviewed journal article (literature review)
	Peer reviewed?	Yes
	Country of origin	Italy and Greece
	Source of funding	Not stated.
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Briefly updating the evidence generated by the most recent environmental and nutritional studies on the human health effects of Se, the biological plausibility of this relation, an overview of the challenges that these studies and their interpretation pose, and finally their implications on the adequacy of current environmental Se standards.
	Study type/design	Literature review
	Study duration	Not applicable (literature review)
	Type of water source (if applicable)	Not applicable (literature review)
Population characteristics	Population/s studied	Not applicable (literature review)
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (literature review)
	Size of study	Not applicable (literature review)
Exposure and setting	Exposure pathway	Not applicable (literature review)
	Source of chemical/contamination	Not applicable (literature review)
	Exposure concentrations (if applicable)	Not applicable (literature review)
	Comparison group(s)	Not applicable (literature review)
Study methods	Water quality measurement used	Not applicable (literature review)
	Water sampling methods (monitoring, surrogates)	Not applicable (literature review)
Results (for each outcome)	Definition of outcome	Not applicable (literature review)
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable (literature review)

Publication Reference: *Vinceti M., Filippini T., Cilloni S., Bargellini A., Vergoni A. V., Tsatsakis A. and Ferrante M. (2017). Health risk assessment of environmental selenium: Emerging evidence and challenges. Molecular Medicine Reports 15(5): 3323-3335.*		
Statistics (if any)	Statistical method used	Not applicable (literature review)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable (literature review)
Author's conclusions	Interpretation of results	• At amount of Se exposure (baseline dietary intake plus supplementation) of around 250-300 µg/day there is an increased risk of type-2 diabetes. • Overall selenium intake in the supplemented group of one of the largest trials averaged 300 µg/day and was associated with 'minor' adverse effects such as dermatitis and alopecia. • These effects indicate that the Se LOAEL is much lower than previously considered by regulatory agencies, calling for an update of the risk assessment of this element.
	Assessment of uncertainty (if any)	The newly available data from the clinical trials indicate the need of a substantial reassessment of the dose of Se toxicity, though they unfortunately do not allow to clearly identify a NOAEL and probably also a reliable LOAEL, since only one supplemental dose (200 µg/selenium/day) has been used in these trials and dose-response data are lacking.
Reviewer comments	Results included/excluded in review (if applicable)	The authors of this review raise the concern that the Chinese studies used by various agencies to derive guidance/guideline values for Se are outdated and there is a lot of new information available from experimental studies with Se. However, it is noted the authors themselves point out that only a single dose was often provided in the new available studies, and no increased risk of cancer was found at the single dose administered. It is unclear from this review which effects (if any) were observed that would be considered clinically significant without further detailed review. In another paper cited in this review by the same authors (Vinceti et al. 2014), risk estimates for the Se supplemented group (i.e. given 200 µg/day Se) were calculated for a number of secondary outcomes. Relative risks for alopecia and mild dermatitis grade 1-2 were significantly elevated compared with controls: • Alopecia: RR 1.28 (99% CI 1.01-1.62). • Dermatitis grade 1-2: RR 1.17 (99% CI 1.00-1.35). Although the review raises some concerns, it is noted the findings have not yet been reproduced in other studies. As the paper is a review, it was not subjected to a risk of bias assessment, but was used to identify other papers for detailed review.

Vinceti et al. 2018a

Publication Reference: 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.		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti, M., Vicentini, M., Wise, L.A. Sacchettini, C., Malagoli, C., Ballotari, P., Filippini, T., Malavolti, M., Giorgi Rossi, P.
	Publication date	Available online 24 April 2018
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	National Health Service - Local Health Authority of Reggio Emilia
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	Report investigated the long-term effects of selenium exposure on cancer incidence using data from a natural experiment in Northern Italy.
	Study type/design	Cohort study (observational)
	Study duration	Not applicable
	Type of water source (if applicable)	Municipal water supply in a small northern Italian village (from wells that fed the local public aqueduct of Rivalta)
Population characteristics	Population/s studied	2,065 residents in the long-term cohort and 5,182 from the Main Cohort from the town of Rivalta and 95,715 from long term unexposed cohort and 110,048 from the Main unexposed cohort. The study population is from the Reggio Emilia municipality.
	Selection criteria for population (if applicable)	
	Subgroups reported	Long-term cohort (1975-1985) and Main cohort (1981-1985) (Note: Data available for education. Status, occupation, age groups, end of follow up state, gender)
	Size of study	N = 97,780 residents from Reggio Emilia municipality for the Long-term exposed group and 115,230 from the Main cohort group
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	An unusually high content of selenium in the two wells that fed the local public aqueduct of Rivalta
	Exposure concentrations (if applicable)	Selenium from geologic origin found in tap water distributed in this exposed area was in the inorganic hexavalent form, selenate (8–10 µg/L), and its overall levels were slightly below the current drinking water standard in the European Union. (Note: no mention of Se levels in Rivalta drinking water after 1985 (post exposure period) and no mention of Se levels in Reggio Emilia drinking water for any period.
	Comparison group(s)	Population of Reggio Emilia municipality excluding residents of the town of Rivalta.
Study methods	Water quality measurement used	Not stated.
	Water sampling methods (monitoring, surrogates)	Not stated.

Publication Reference: 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.		
Results (for each outcome)	Definition of outcome	A retrospective follow-up of two cohorts of consumers of high selenium drinking water in the municipality of Reggio Emilia, Northern Italy during 1986–2013. To quantify cancer occurrence during follow-up, incidence data from the Reggio Emilia Cancer Registry at the Epidemiology Unit of the Local Health Authority was used, i.e. beginning on January 1, 1996. For the previous period, 1986–1995, mortality data as a proxy of incidence data was used, based on the death certificate directory of all residents available at the Epidemiology Unit, beginning on January 1, 1986. Outcomes of interest were all malignant tumours excluding non-melanoma skin cancers, chronic myeloproliferative disorders, and myelodysplastic syndromes
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N = 97,780 residents for the Long-term exposed group and 115,230 from the Main cohort group
Statistics (if any)	Statistical method used	Multivariate Poisson models, with stratification by sex and follow-up period.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	RR in men and women – overall long-term cohort, 1986-1985 • All cancers: 1.00 (0.90–1.11), 1.17 (0.94–1.46) • Buccal cavity and pharynx: 1.37 (0.68–2.76), 2.60 (0.63–10.76) • Stomach: 0.95 (0.62–1.44), 0.50 (0.19–1.35) • Colon-rectum: 1.03 (0.77–1.39), 1.59 (0.89–2.82) • Liver: 0.73 (0.33–1.64), 0.53 (0.07–3.83) • Biliary tract: 0.80 (0.30–2.16), 1.51 (0.37–6.16) • Pancreas: 1.15 (0.69–1.92), 0.64 (0.16–2.57) • Lung: 1.17 (0.91–1.49), 1.16 (0.75–1.81) • Melanoma: 1.11 (0.57–2.16), **7.11 (2.11–23.89)** • Breast: 0.94 (0.70–1.27), 0.49 (0.16–1.53) • Prostate: 0.85 (0.59–1.21), 1.80 (0.66–4.88) • Urinary tract: 1.27 (0.89–1.80), **2.16 (1.06–4.39)** • Lymphatic, hematop. Tissue 1.32 (0.96–1.80), 1.80 (0.96–3.38) • Hodgkin's lymphoma: 2.49 (0.78–7.95), 4.44 (0.57–34.57) • Non-Hodgkin's lymphoma: 1.25 (0.76–2.05), 1.56 (0.49–4.92) • Multiple myeloma: 1.56 (0.80–3.04), 2.37 (0.57–9.76) • All leukaemia: 1.14 (0.66–1.97), 1.56 (0.58–4.22)

Publication Reference: 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.		
Author's conclusions	Interpretation of results	• There is a general tendency of decreasing RRs over time, including overall cancer incidence • Several site-specific RRs were elevated, though imprecise, only in the first period, then flattening over time • Higher incidence of cancer at some sites, and for a few of them, namely cancers of the buccal cavity and pharynx, melanoma, urinary tract and lymphoid tissue, the excess incidence was particularly evident in the first period of follow-up but decreased over time. Overall, these results suggest that consumption of water with levels of selenium in its inorganic hexavalent form close to the European standard, 10 µg/L, may have unfavourable effects on cancer incidence.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	Authors noted that: • The exposure of interest has been overall selenium intake and not individual chemical forms of the element. However, the relevance of speciation analysis in studies on the health effects of selenium should not be overlooked because individual selenium forms may have different and in some instances opposite biological effects, which is relevant from both a toxicological and a nutritional perspective. • Concerning cancer, laboratory studies have provided evidence indicating that selenium and selenoproteins may both increase and decrease cancer risk, depending on the dose, specific organ, animal species and chemical form of selenium. There are clear concerns and biases with this study that cannot be understated. The reviewer does not account for smoking and drinking as a confounder for cancer incidence. There are large ranges in the confidence intervals that almost all cross 1 and therefore most RR are not statistically significant. Neither of these issues are raised by the authors, instead they claim a low risk of bias. There also seem to be multiple unnecessary references to the authors' previous works. This study was subjected to risk of bias assessment as human dose-response information could be estimated from drinking water concentrations and it informs of new potential adverse effects of Se.

Vinceti et al. 2018b

Publication Reference: Vinceti M., Filippini T. and Wise L. A. (2018b). Environmental Selenium and Human Health: an Update. Current environmental health reports 5(4): 464-485.		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti, M., Filippini, T., Wise, L.A.

Publication Reference: Vinceti M., Filippini T. and Wise L. A. (2018b). Environmental Selenium and Human Health: an Update. Current environmental health reports 5(4): 464-485.		
	Publication date	Published online: 2 October 2018
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Italy
	Source of funding	Not stated
	Possible conflicts of interest	Wise, L\.A. reports grants from National Institutes of Health (NICHD and NIEHS), while the study was conducted. Vinceti, M. and Filippini, T. declare that they have no conflict of interest.
Study characteristics	Aim/objectives of study	To provide an update on human health effects from exposure to environmental Se
	Study type/design	Report/Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Not applicable
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable

Publication Reference: Vinceti M., Filippini T. and Wise L. A. (2018b). Environmental Selenium and Human Health: an Update. Current environmental health reports 5(4): 464-485.		
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Risk assessments should be revised to incorporate the results of studies demonstrating toxic effects of selenium. • Particular attention should be given to the recent epidemiologic evidence indicating adverse effects of low-dose selenium overexposure. • Recent randomised trials have indicated that selenium overexposure is positively associated with type 2 diabetes and high-grade prostate cancer. In addition, a natural experiment has suggested an association between overexposure to inorganic hexavalent selenium and two neurodegenerative diseases, amyotrophic lateral sclerosis and Parkinson's disease. • A comprehensive assessment of the health effects of deficient and excess selenium exposure should also focus on neurological disease.
	Assessment of uncertainty (if any)	• Additional observational studies and secondary analyses of completed randomised trials are needed to address the uncertainties regarding the health risks of selenium exposure.
Reviewer comments	Results included/excluded in review (if applicable)	There are a number of reports referenced in this review (11 in total) that may be relevant to Se toxicity and attempts have been made to retrieve them and they have been evaluated separately. As this study was a review, it was not subjected to risk of bias assessment.

Vinceti et. al. 2018c

Publication Reference: 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.		
General Information	Date of data extraction	14/06/2023
	Authors	Vinceti, M., Filippini, T., Rothman, K.J.
	Publication date	Published online: 5 July 2018
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italian and US researchers
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in paper.

Publication Reference: 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.		
Study characteristics	Aim/objectives of study	Authors assessed the results of both experimental and nonexperimental epidemiologic studies linking selenium with type 2 diabetes incidence.
	Study type/design	Meta-analysis
	Study duration	Authors retrieved 50 potentially eligible nonexperimental studies and 5 randomised controlled trials published through June 11, 2018
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	• 18 studies included in the meta-analysis • 13 nonexperimental studies • 5 RCTs
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable (meta-analysis)
	Size of study	Authors retrieved 50 nonexperimental studies (18 cross-sectional, 25 case–control, and 7 cohort studies) and 5 randomised controlled trials (RCTs) potentially eligible for the review and the meta-analyses. Selenium exposure was assessed using levels of biomarkers [serum (n = 23), plasma (n = 9), whole blood (n = 5), (toe)nail (n = 7), urine (n = 5), hair (n = 1), tears (n = 1)], and from dietary assessment (n = 4) in 2801 cases and 5094 controls, while the cross-sectional and cohort studies involved over 50,000 and 22,000 participants
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	• Nonexperimental: Not stated. • Experimental: Supplementation
	Exposure concentrations (if applicable)	• Nonexperimental: Serum levels • Experimental: 200 µg/day supplement
	Comparison group(s)	• Nonexperimental studies: serum selenium levels of <45 µg/L • Experimental: Placebo
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Development of Type 2 Diabetes
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Nonexperimental: The cross-sectional and cohort studies involved over 50,000 and 22,000 participants. Experimental: A total of 11,469 and 10,796 subjects in the treatment and comparison group were involved and included in the present analysis.
Statistics	Statistical method used	

Publication Reference: 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.		
(if any)	Details on statistical analysis	To elucidate the possible dose–response relation, authors selected for further analysis those studies that included multiple exposure levels and serum or plasma levels. They computed a pooled summary risk ratio (RR) of diabetes according to selenium exposure in these studies. They also computed a RR for diabetes incidence following supplementation with 200 µg/day of selenium compared with placebo in trials.
	Relative risk/odds ratio, confidence interval?	Nonexperimental studies (six cross-sectional studies, one case–control study and three cohort studies): compared with the reference category of plasma or serum selenium levels of <45 µg/L, the following RRs were estimated: • 90 µg/L: 1.5 (95% CI 1.2–2.1) • 140 µg/L: 3.6 (95% CI 1.4–9.4) Meta-analysis of the risk ratio (RR), with 95% confidence interval (CI) of type 2 diabetes in all randomised controlled trials encompassing selective administration of selenium • Overall (I-squared = 0.0%) 1.11 (1.01, 1.22) • Thompson et al. 2016 1.25 (0.74, 2.09) • Lippmann et al. 2009 1.19 (0.61, 2.35) • Algotar et al. 2013 1.69 (0.68, 4.21) • Karp et al. 2013 1.08 (0.97, 1.19) • Stranges et al. 2007 1.49 (1.01, 2.20)
Author's conclusions	Interpretation of results	• In the nonexperimental studies, authors found a direct relation between selenium exposure and risk of diabetes, with a clear and roughly linear trend in subjects with higher plasma or serum selenium levels. • A dose–response meta-analysis focusing on studies with direct assessment of dietary selenium intake showed a similar trend. • In experimental studies, selenium supplementation increased the risk of diabetes when compared with the placebo-allocated participants (with a higher RR in women than in men). • Overall, results from both nonexperimental and experimental studies indicate that selenium may increase the risk of type 2 diabetes across a wide range of exposure levels. The relative increase in risk is small but of possible public health importance because of the high incidence of diabetes and the ubiquity of selenium exposure.
	Assessment of uncertainty (if any)	Not stated

Publication Reference: 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.		
Reviewer comments	Results included/excluded in review (if applicable)	In this meta-analysis for determining an association between selenium exposure and type 2 diabetes, the authors found an increased statistically significant risk of the disease with higher Se in serum (non-experimental studies) and in a meta-analysis of RCTs where Se was administered at 200 µg/day. 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 3 out of 3 RCTs for women and four out of the five RCTs 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. A RoB assessment was not done due to the study being systematic review including a meta- analysis.

Vinceti et al. 2019

Publication Reference: 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.		
General Information	Date of data extraction	13/06/2023
	Authors	Vinceti, M., Filippini,T., Malagoli, C., Violi, F., Mandrioli, J., Consonni, D., Rothman, K.J., Wise, L.A.
	Publication date	Available online 14 September 2019
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Italy
	Source of funding	National Health Service - Local Health Authority of Reggio Emilia
	Possible conflicts of interest	The authors have no conflict of interest to declare.
Study characteristics	Aim/objectives of study	Investigate the association between overexposure to selenium and risk of amyotrophic lateral sclerosis (ALS)
	Study type/design	Cohort study (observational)
	Study duration	Not applicable
	Type of water source (if applicable)	Municipal water supply in a small northern Italian village (from wells that fed the local public aqueduct of Rivalta)
Population characteristics	Population/s studied	2,065 residents from the town of Rivalta (the exposed group) and 95,715 from the Reggio Emilia municipality (the unexposed group)
	Selection criteria for population (if applicable)	

Publication Reference: 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.		
	Subgroups reported	Not applicable [Note: Analysis performed by gender, and by period (post exposure period from 1986-1994 and post exposure period from 1995-2015)]
	Size of study	N = 97,780 residents from Reggio Emilia municipality
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	An unusually high content of selenium in the two wells that fed the local public aqueduct of Rivalta
	Exposure concentrations (if applicable)	Both wells provided water later measured with a selenium content of around 8 µg/L, sometimes approaching the maximum allowed limit of 10 µg/L. These two wells were the only two sources of tap water in Rivalta since 1972 until June 1978. In early 1980s, some dilution of the selenium content of the tap water was noted however selenium level in Rivalta tap water was still close to the maximum allowable standard of 10 µg/L. From March 1989 selenium content of Rivalta municipal tap water was the same as the remaining municipality, < 1 µg/L.
	Comparison group(s)	Population of Reggio Emilia municipality excluding residents of the town of Rivalta.
Study methods	Water quality measurement used	Not stated.
	Water sampling methods (monitoring, surrogates)	Not stated.
Results (for each outcome)	Definition of outcome	ALS cases in the exposed and unexposed cohorts while they were still residing in the Reggio Emilia municipality or emigrated to other municipalities of the Reggio Emilia province. To identify ALS cases during the follow-up period, all administrative databases from the study area were used, including death records (as a proxy of disease incidence), available since 1986; registries of the neurological department, available since 1986; hospital discharge data, available since 1993; records of drug prescription (for the only specific drug for this disease, riluzole), available since 2001; data from the Emilia-Romagna Region ALS Registry, available since the date of its official start of operation: January 1st, 2009 (Mandrioli et al., 2014). All records were linked by sex and date of birth and, when a potential match was identified, by retrieving the exact name and surname of the resident or his/her taxpayer number, the only unique identification number available for Italian residents nationally. For subjects diagnosed with ALS in exposed and unexposed cohorts, clinical records and ALS Registry data were reviewed to obtain additional information about family history of the disease, and gene mutation. The latter information was used to classify sporadic and familial forms of ALS.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	N = 97,780 residents

Publication Reference: 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.		
Statistics (if any)	Statistical method used	Poisson regression models were used to compute incidence rate ratios (IRR) of ALS in the exposed and unexposed cohorts separately, taking into account age (time-dependent 5-year strata), sex, calendar-year of follow-up, educational attainment, and occupation. Stratified analyses by sex and calendar period were undertaken, which was split into two uneven periods (1986–1994 and 1995–2015).
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	• The IRR comparing exposed with unexposed cohorts was 2.8 (95% CI: 1.3, 6.0) in the crude model and 2.8 (95% CI: 1.3, 6.0) 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 • There were no substantial changes in the IRRs when they were controlled for broader categories of occupation.
Author's conclusions	Interpretation of results	• Individuals exposed to unusually high levels of inorganic hexavalent selenium in their drinking water experienced a higher incidence of sporadic ALS, and the excess ALS incidence waned over time
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	It was reported that none of the seven subjects with incident ALS in the exposed cohort (three men and four women) had a family history of ALS, nor was the disease found to be associated with genetic mutations in the two exposed cases who underwent genetic testing (specifically for mutations of the superoxide dismutase type-1 gene), since no such mutation was identified. All exposed cases were either administrative workers (men) or housewives (women), according to the information available at the General Registry Office directory. As human dose-response information could be estimated from drinking water concentrations and it informs of a new potential adverse effect of Se it was subjected to risk of bias assessment.

Walsh et al. 2021

Publication Reference: 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.		
General Information	Date of data extraction	13/06/2023
	Authors	Walsh, J.S., Jacques, R.M., Schomburg, L., Hill, T.R., Mathers, J.C., Williams, G.R., Eastell, R.

Publication Reference: 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.		
	Publication date	Published Online March 23, 2021
	Publication type	Journal Article
	Peer reviewed?	Yes (The full study report was subject to independent review through standard NIHR processes).
	Country of origin	UK
	Source of funding	National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME)
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	To determine if selenium supplementation in postmenopausal women with osteopenia decreases bone turnover, improves physical function score and grip strength, is safe (particularly for thyroid function and diabetes), increases biomarkers of selenium status, and decreases markers of oxidative stress and inflammation.
	Study type/design	Human Controlled Trial (HCT) randomised, double-blinded, placebo-controlled
	Study duration	6 months
	Type of water source (if applicable)	Not applicable (Note: selenite supplement at 0, 50 or 200µg per tablet per day)
Population characteristics	Population/s studied	Postmenopausal women with osteopenia or osteoporosis. Participants were recruited from a database of volunteers, by poster and email advertising, and from patients attending the metabolic bone centre for bone densitometry. Inclusion criteria were: age older than 55 years, at least 5 years since last menstrual period, osteopenia or osteoporosis, and willing and able to give informed consent. Exclusion criteria were: diabetes, thyroid dysfunction, any conditions known to affect bone metabolism, fracture or orthopaedic surgery in the last year, osteoporosis treatment or drugs known to affect bone metabolism in the last year, selenium supplements in the last 60 days, or previous adverse reaction to selenium or any of the selenite or placebo excipients.
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	115 participants, Placebo (n=37), Selenite 50 µg (n=39), and Selenite 200 µg (n=39) (Note: 120 participants at the start of the trial, 40 per group)
Exposure and setting	Exposure pathway	Oral (tablet)
	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	0, 50 or 200µg per person per day. Diet diaries were kept. 200µg per person per day was chosen as is was considered a safe dose and estimated to produce Se serum levels of 60 µg/L. (Note: All participants were given a single oral dose of 100 000 IU cholecalciferol at screening, to ensure they were vitamin D sufficient at the start of trial treatment).

Publication Reference: 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.		
	Comparison group(s)	Placebo group
Study methods	Water quality measurement used	Not applicable (Note: Blood and urine samples collected at week 13 and 26).
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	• The primary endpoint was between-group difference in the ratio of urine N-terminal cross-linking telopeptide of type I collagen (NTx) to creatinine at 26 weeks. • The secondary endpoints were: serum selenium and selenoprotein P; other bone turnover markers (pro collagen type I N propeptide [PINP], osteocalcin, C-terminal cross-linking telopeptide of type I collagen [CTx]), BMD of the lumbar spine and total hip by dual-energy x-ray absorptiometry, muscle function; antioxidant and inflammatory markers • Urine NTx to creatinine ratio (nmol bone collagen equivalent:mmol creatinine) did not differ significantly between treatment groups at 26 week • None of the secondary or mechanistic endpoint measurements differed between treatment groups at 26 weeks.
	How outcome was assessed	
	Method of measurement	
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	• 5 participants excluded as they did not complete follow-up • 7 participants withdrawn at 13 weeks due to abnormal thyroid-stimulating hormone concentrations (one in the 200 µg group, three in the 50 µg group, and three in the placebo group) and abnormal blood glucose (one in the 50 µg group).
Statistics (if any)	Statistical method used	• Baseline data were assessed for comparability between the treatment groups. Normality of distribution of variables was assessed from either the raw data or the residuals from the model using a density plot or histogram. • Analysis of covariance Hochberg testing was used with 26-week NTx to creatinine measurement as the dependent outcome variable and treatment group and baseline NTx to creatinine measurement as the independent variables.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	Selenium supplementation at these doses does not affect musculoskeletal health in postmenopausal women.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	Severe adverse events were judged by the principal investigator as unrelated to trial medication. Although limited health endpoints were investigated in this study, this double-blind placebo-controlled study indicates no adverse effects were observed in women ingesting 50 or 200 µg/day of selenite for 6 months. As study does provides dose-response human information it was subjected to risk of bias assessment.

Wang et. al. 2022

Publication Reference: Wang H., Wang J., Cao Y., Chen J., Deng Q., Chen Y., Qiu Y., Lin L., Shi B., Liu F., He B. and Chen F. (2022). Combined Exposure to 33 Trace Elements and Associations With the Risk of Oral Cancer: A Large-Scale Case-Control Study. Front Nutr 9: 913357.		
General Information	Date of data extraction	13/06/2023
	Authors	Wang, H., Wang, J., Cao, Y., Chen, J., Deng, Q., Chen, Y., Qiu, Y., Lin, L., Shi, B., Liu, F., He, B., Chen, F.
	Publication date	07 July 2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	Fiji
	Source of funding	Scientific Research Talents Training Project of Health and Family Planning Health Commission in Fujian Province (No. 2019-ZQN-68), the High-Level Talents Research Start-Up Project of Fujian Medical University (No. XRCZX2018001), and Fujian Natural Science Foundation Program (Nos. 2022J01239 and 2022J01235).
	Possible conflicts of interest	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Study characteristics	Aim/objectives of study	To comprehensively evaluate the independent and joint effects of 33 trace elements on oral cancer risk
	Study type/design	Case-control study
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Study participants recruited from the First Affiliated Hospital of Fujian Medical University (Fujian, China) between November 2010 and August 2019. It included 463 patient cases and 1,343 control participants.
	Selection criteria for population (if applicable)	Inclusion criteria for cases were: (1) all cases were those with histologically confirmed primary oral cancer; (2) all cases reside in the Fujian Province at least for 10 years; and (3) all cases aged 20 to 80 years. Exclusion criteria were as follows: (1) patients who have received neoadjuvant chemotherapy or radiotherapy prior to surgery; (2) patients with severe systemic diseases such as liver and kidney dysfunction; and (3) those with long-term dietary supplements. Control participants were recruited from the health examination centre of the same hospital without any history of malignancy. The exclusion criteria were as follows: (1) those who are occupationally exposed to inorganic elements, such as welders and potters; (2) those aged < 20 years or >80 years; (3) those who did not reside in the Fujian Province; and (4) those who take the long-term dietary supplements.
	Subgroups reported	Not applicable

Publication Reference: Wang H., Wang J., Cao Y., Chen J., Deng Q., Chen Y., Qiu Y., Lin L., Shi B., Liu F., He B. and Chen F. (2022). Combined Exposure to 33 Trace Elements and Associations With the Risk of Oral Cancer: A Large-Scale Case-Control Study. Front Nutr 9: 913357.		
	Size of study	N=1,806 (463 cases, 1,343 controls).
Exposure and setting	Exposure pathway	Oral (water and diet)
	Source of chemical/contamination	Dietary intake
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Control group (1,343 healthy patients)
Study methods	Water quality measurement used	Not applicable. [Note: serum samples measured by inductively coupled plasma mass spectrometry (ICP-MS)]
	Water sampling methods (monitoring, surrogates)	Not applicable. (Note: personal data received from questionnaire and routine health examination. Fasting peripheral blood samples collected and centrifuged)
Results (for each outcome)	Definition of outcome	• In single-element models, Se, other essential elements and non-essential elements showed significant association with oral cancer risk. • Higher levels of serum Se displayed favourable effects when all other essential elements were fixed at 25th or 50th percentiles. • Se performed complex interactions among essential metals. • This study provides supportive evidence that the overall mixture effect of essential and non-essential elements might be associated with oral cancer risk, especially for serum Zn, V, Cu, Sr, Se, Th, Li, and Y
	How outcome was assessed	
	Method of measurement	Serum samples measured by inductively coupled plasma mass spectrometry (ICP-MS).
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	• Baseline characteristics between oral cancer patients and control participants were assessed using chi-square analysis. • Propensity score matching was used to minimise the impact of potential confounders. • Conditional logistic regression was utilised to evaluate the association of each element individually with oral cancer risk. • Quantile g-computation and Bayesian kernel machine regression (BKMR) models were used to assess the joint effect of the overall element mixture and interactions.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable [Note: β coefficient-(confidence interval for Se: Q1 = reference, Q2 = 3.77 (-5.19, -2.36), Q3 = -4.77 (-6.22, -3.31), Q4 = 4.50 (-5.95, -3.05)]

Publication Reference: Wang H., Wang J., Cao Y., Chen J., Deng Q., Chen Y., Qiu Y., Lin L., Shi B., Liu F., He B. and Chen F. (2022). Combined Exposure to 33 Trace Elements and Associations With the Risk of Oral Cancer: A Large-Scale Case-Control Study. Front Nutr 9: 913357.		
Author's conclusions	Interpretation of results	Essential elements such as Zn, V, Cu, Sr, and Se displayed different degrees of contribution on oral cancer risk and interactive effects existed among them.
	Assessment of uncertainty (if any)	Not done
Reviewer comments	Results included/excluded in review (if applicable)	Authors also found that: "*Interactive effects and inverse associations for Se were identified in our findings. Se is characterized by antioxidant activity, enhancing immune function and scavenging free radicals (28, 29). Previous studies have indicated that Se could protect against oxidative stress by its immune-modulating and antiproliferative properties, reducing the incidence of head and neck cancer (30, 31). In addition, the effect of Se could be interfered by other elements (15).*" Since study provides no dose response information for adverse effects, it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Yang et. al. 2022

Publication Reference: Yang J., Chen E., Choi C., Chan K., Yang Q., Rana J., Yang B., Huang C., Yang A. and Lo K. (2022). Cross-Sectional Association of Blood Selenium with Glycemic Biomarkers among U.S. Adults with Normoglycemia in the National Health and Nutrition Examination Survey 2013-2016. Nutrients 14(19).		
General Information	Date of data extraction	13/06/2023
	Authors	Yang, J., Chen, E., Choi, C., Chan, K., Yang, O., Rana, J., Yang, Bo., Huang, C., Yang, A., Lo, K.
	Publication date	Published: 24 September 2022
	Publication type	Journal article
	Peer reviewed?	Yes
	Country of origin	China
	Source of funding	Hunan province (Grant number: No. 2021JJ70038)
	Possible conflicts of interest	The authors declare no conflict of interest
Study characteristics	Aim/objectives of study	To investigate the relationship between blood Se and glycaemic biomarkers among people with normoglycemia using a cross-sectional analysis of the U.S. National Health and Nutrition Examination Survey 2013–2016
	Study type/design	Cross-sectional
	Study duration	Not applicable (data from the U.S. National Health and Nutrition Examination Survey 2013–2016)
	Type of water source (if applicable)	Not applicable (Se presumably via diet and supplements)
	Population/s studied	

Publication Reference: Yang J., Chen E., Choi C., Chan K., Yang Q., Rana J., Yang B., Huang C., Yang A. and Lo K. (2022). Cross-Sectional Association of Blood Selenium with Glycemic Biomarkers among U.S. Adults with Normoglycemia in the National Health and Nutrition Examination Survey 2013-2016. Nutrients 14(19).		
Population characteristics	Selection criteria for population (if applicable)	Healthy population among U.S. adults with normoglycemia. 2706 participants in the final analysis selected from 20,146 participants enrolled in the 2013–2014 and 2015–2016 surveys and removal of participants aged <18 years (n = 8041), without data on blood metal concentrations (n = 6537), missing covariates (n = 2342), or with Type 2 Diabetes (T2D) (n = 520).
	Subgroups reported	Not Applicable. (note that subgroup analyses was performed by sex, age, BMI, hypertension history, and smoking status)
	Size of study	2706 participants in the final analysis
Exposure and setting	Exposure pathway	Diet and supplements
	Source of chemical/contamination	Diet and supplements
	Exposure concentrations (if applicable)	Not reported
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable.
	Water sampling methods (monitoring, surrogates)	Not applicable.
Results (for each outcome)	Definition of outcome	• A positive linear dose–response relationship existed between blood Se and FPG (Poverall = 0.003, Pnonlinear = 0.073) and insulin (Poverall = 0.004, Pnonlinear =0.060). • BMI, age, and smoking status modified the associations of the highest quartile of Se (compared with the lowest quartile) with glycaemic biomarkers. • Overall, positive associations of blood Se with glycaemic biomarkers were observed among U.S. adults with normoglycemia. • These findings imply that people with normoglycemia need to be aware of the level of Se and other mineral intakes from diet and supplements.
	How outcome was assessed	
	Method of measurement	Not applicable. (note1: FPG was measured by the hexokinase method, HbA1c was measured using a Tosoh Automated Glycohemoglobin Analyzer, insulin was measured by insulin radioimmunoassay and OGTT was measured by the Roche C501 instrument). [Note2: Se and parameters as reported in the U.S. National Health and Nutrition Examination Survey 2013–2016. Parameters included fasting plasma glucose (FPG), haemoglobin A1c (HbA1c), insulin, and the oral glucose tolerance test (OGTT)]. T2D was defined according to the harmonized definition as the presence of at least one of the following: (1) FPG ≥ 7.0 mmol/L (126 mg/dL); (2) HbA1c ≥ 6.5% (48 mmol/mol); (3) oral glucose tolerance test (OGTT) ≥200 mg/dL (11.1 mmol/L); (4) current use of medication to treat T2D; and/or (5) self-reported diabetes or sugar diabetes

Publication Reference: Yang J., Chen E., Choi C., Chan K., Yang Q., Rana J., Yang B., Huang C., Yang A. and Lo K. (2022). Cross-Sectional Association of Blood Selenium with Glycemic Biomarkers among U.S. Adults with Normoglycemia in the National Health and Nutrition Examination Survey 2013-2016. Nutrients 14(19).		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable. (Note: 2706 participants from the U.S. National Health and Nutrition Examination Survey 2013–2016 in the final analysis with >20,000 participants excluded).
Statistics (if any)	Statistical method used	Dose–response relationships examined by restricted cubic spline analysis. Descriptive statistics used to describe the demographics, Chi-square test for group comparison and multiple linear regression analysis for relationship between FPG, HbA1c, insulin and OGTT. All of the statistical analyses and graphical displays were carried out using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria)
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	Positive associations between blood Se concentration and glycaemic biomarkers in U.S. adults with normoglycemia. After adjusting for potential confounders, the highest quartile of blood Se was positively associated with four glycaemic biomarkers (FPG, OGTT, HbA1c, and Insulin). Significant interactions were observed between BMI, age, smoking status, and blood Se on glycaemic biomarkers
	Assessment of uncertainty (if any)	Not done.
Reviewer comments	Results included/excluded in review (if applicable)	This cross-sectional study found positive associations between blood Se concentration and glycaemic biomarkers (FPG, OGTT, HbA1c, and insulin) in US adults with normoglycaemia. Although this is not evaluating a disease state *per se*, it indicates a potential for Se exposure to influence glycaemia. As study provides human information potentially informing of a new potential adverse effect of Se, it was subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Zhang et. al. 2016

Publication Reference: Zhang X., Liu C., Guo J. and Song Y. (2016). Selenium status and cardiovascular diseases: Meta-analysis of prospective observational studies and randomized controlled trials. Eur J Clin Nutr 70(2): 162-169.		
General Information	Date of data extraction	14/06/2023
	Authors	Zhang, X., Liu, C., Guo, J., and Song, Y.
	Publication date	Published online 20 May 2015
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	US
	Source of funding	The study was supported by the Indiana University Health–Indiana University School of Medicine Strategic Research Initiative Grant (Drs XZ and YS).

Publication Reference: Zhang X., Liu C., Guo J. and Song Y. (2016). Selenium status and cardiovascular diseases: Meta-analysis of prospective observational studies and randomized controlled trials. Eur J Clin Nutr 70(2): 162-169.		
	Possible conflicts of interest	The authors declare no conflict of interest.
Study characteristics	Aim/objectives of study	Selenium was thought to have a role in cardiovascular disease (CVD) owing to its antioxidant properties; however, evidence from observational studies and randomised controlled trials (RCTs) has been inconsistent and controversial. The authors thus conducted a meta-analysis to assess the discrepancies between observational and randomised trial evidence.
	Study type/design	Meta-analysis of prospective observational studies and randomised controlled trials
	Study duration	Authors searched MEDLINE and EMBASE for eligible prospective studies regarding the relationship between selenium and CVD up to 15 December 2013
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Populations included in 16 prospective observational studies and 16 RCTs
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	35,607 participants from 16 prospective studies 37,572 participants (range: 23–17 448; median: 351) from 16 RCTS
Exposure and setting	Exposure pathway	Oral
	Source of chemical/contamination	Supplements with selenium formulation that included L-selenomethionine, sodium selenite, and selenium-enriched yeast
	Exposure concentrations (if applicable)	Of all 16 trials, 37 572 participants (range: 23–17 448; median: 351) took the median dose of 100 µg/day (range: 75–300 µg/day) selenium supplements for 2 weeks to 114 months duration (median: 12 months). Of all trials, 14 used a placebo-controlled double-blinded design and two used an open-label design. Selenium formulation included L-selenomethionine, sodium selenite, and selenium-enriched yeast
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	The study aimed to provide a comprehensive evaluation of the full spectrum of variation in baseline selenium concentrations and its dose–response relationship with incident CVD in prospective observational studies, and to determine whether any differences in selenium biomarkers by selenium supplementation could account for CVD risk in RCTs.
	How outcome was assessed	
	Method of measurement	Not applicable

Publication Reference: Zhang X., Liu C., Guo J. and Song Y. (2016). Selenium status and cardiovascular diseases: Meta-analysis of prospective observational studies and randomized controlled trials. Eur J Clin Nutr 70(2): 162-169.		
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	A total of 16 prospective studies involving 35 607 participants and 4421 incident CVD cases were included in this meta-analysis
Statistics (if any)	Statistical method used	Random effects model was used to estimate the pooled relative risk (RR). Generalised least-squares trend test and restricted cubic spline model were performed to assess a linear and a nonlinear dose–response relationship.
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	RR from Observational studies CVD Endpoint — No. of Studies — RR (95% CI) Cardiovascular disease — 6 — 0.88 (0.71, 1.09) Coronary heart disease — 8 — 0.72 (0.57, 0.92) Myocardial infarction — 7 — 0.81 (0.60, 1.09) Stroke — 4 — 0.69 (0.29, 1.63) RR from RCTs studies CVD Events — No. of Studies — RR (95% CI) Cardiovascular disease — 5 — 0.91 (0.72, 1.14) Coronary heart disease — 3 — 1.00 (0.84, 1.21) Myocardial infarction — 3 — 0.32 (0.07, 1.64) Stroke — 4 — 0.69 (0.29, 1.63) CVD Endpoints — No. of Studies — RR (95% CI) Incidence — 4 — 1.02 (0.93, 1.11) Mortality — 7 — 0.71 (0.47, 1.07)
Author's conclusions	Interpretation of results	The authors concluded that their meta-analysis in prospective studies demonstrated a significant inverse association between selenium status and CVD risk within a narrow selenium range and a null effect of selenium supplementation on CVD was observed in RCTs. These findings indicate the importance of considering selenium status, dose and safety in health assessment and future study design.
	Assessment of uncertainty (if any)	Not stated
Reviewer comments	Results included/excluded in review (if applicable)	This meta-analysis found the majority of RR for selenium exposure and CVD were not statistically significant as confidence intervals crossed 1. This includes for CVD from both observational studies and RCTs. The authors did not distinguish between form (organic and inorganic) of selenium. The review did not find critical adverse effects. As it is a review including a meta-analysis, no RoB assessment was undertaken.

Zietz et. al. 2015

Publication Reference: 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.		
General Information	Date of data extraction	09/06/2023
	Authors	Zietz, B.P., Richter, K., Laß, J., Suchenwirth, R., Huppmann, R.
	Publication date	Published online: 20 August 2014
	Publication type	Journal article
	Peer reviewed?	Not stated
	Country of origin	Germany
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	This study investigated in which amount abundant metals were released from different parts of domestic installations into the cold tap water
	Study type/design	Analytical study measuring metals in stagnant drinking water
	Study duration	Not applicable
	Type of water source (if applicable)	Domestic drinking water
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
Exposure and setting	Exposure pathway	Drinking water
	Source of chemical/contamination	Old lead pipes and valves
	Exposure concentrations (if applicable)	Selenium was not measured in amounts above the limits of quantification (<0.5 µg/L) or did not show an influence of different installation parts on tested values (nearly constant concentration courses in different water fractions).
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Inductively Coupled Plasma mass spectrometry (ICP-MS) following standards DIN EN ISO 17294-2 and DIN EN ISO 17294-1
	Water sampling methods (monitoring, surrogates)	A sequential water sampling protocol
Results (for each outcome)	Definition of outcome	Selenium was not measured in amounts above the limits of quantification (<0.5 µg/L) or did not show an influence of different installation parts on tested values (nearly constant concentration courses in different water fractions).
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics	Statistical method used	

Publication Reference: 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.		
(if any)	Details on statistical analysis	Variance of element testing results was examined using system H where sequential water samples were taken in five stagnation courses.
	Relative risk/odds ratio, confidence interval?	Not applicable to selenium as not detected in water
Author's conclusions	Interpretation of results	Not applicable to selenium as not detected in water
	Assessment of uncertainty (if any)	Not applicable to selenium as not detected in water
Reviewer comments	Results included/excluded in review (if applicable)	Not applicable to selenium as not detected in water. This study does not provide human dose-response information and does not inform of a new potential adverse effect of Se. Hence, it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

Zwolak and Zaporowska 2012

Publication Reference: Zwolak I. and Zaporowska H. (2012). Selenium interactions and toxicity: a review. Selenium interactions and toxicity. Cell Biol Toxicol 28(1): 31-46.		
General Information	Date of data extraction	14/06/2023
	Authors	Zwolak, I. and Zaporowska, H.
	Publication date	Published online: 14 September 2011
	Publication type	Journal Article
	Peer reviewed?	Not stated
	Country of origin	Poland
	Source of funding	Not stated
	Possible conflicts of interest	No conflict of interest statement included in paper.
Study characteristics	Aim/objectives of study	This review summarises recent studies on selenium interactions with arsenic and cadmium and selenium interactions with vanadium and chromium in mammals.
	Study type/design	Review
	Study duration	Not applicable
	Type of water source (if applicable)	Not applicable
Population characteristics	Population/s studied	Not applicable
	Selection criteria for population (if applicable)	
	Subgroups reported	Not applicable
	Size of study	Not applicable
	Exposure pathway	Not applicable

Publication Reference: Zwolak I. and Zaporowska H. (2012). Selenium interactions and toxicity: a review. Selenium interactions and toxicity. Cell Biol Toxicol 28(1): 31-46.		
Exposure and setting	Source of chemical/contamination	Not applicable
	Exposure concentrations (if applicable)	Not applicable
	Comparison group(s)	Not applicable
Study methods	Water quality measurement used	Not applicable
	Water sampling methods (monitoring, surrogates)	Not applicable
Results (for each outcome)	Definition of outcome	Not applicable
	How outcome was assessed	
	Method of measurement	Not applicable
	Number of participants (exposed/non-exposed, missing/excluded) (if applicable)	Not applicable
Statistics (if any)	Statistical method used	Not applicable
	Details on statistical analysis	
	Relative risk/odds ratio, confidence interval?	Not applicable
Author's conclusions	Interpretation of results	• Human studies have demonstrated that selenium may reduce arsenic accumulation in the organism and protect against arsenic-related skin lesions. • Selenium was found to antagonise the prooxidant and genotoxic effects of arsenic in rodents and cell cultures. • Studies on selenium effects against oxidative stress induced by cadmium in various animal tissues produced promising results. • Reports suggest that selenium protection against toxicity of arsenic and cadmium is mediated via sequestration of these elements into biologically inert conjugates. • Selenium-dependent antioxidant enzymes probably play a secondary role in arsenic and cadmium detoxification. • So far, few studies have evaluated selenium effects on chromium(III) and vanadium actions in mammals. Still, they show that selenium may interact with these minerals. • Taken together, the recent findings regarding selenium interaction with other elements extend our understanding of selenium biological functions and highlight selenium as a potential countermeasure against toxicity induced by arsenic and cadmium.
	Assessment of uncertainty (if any)	Not applicable

Publication Reference: Zwolak I. and Zaporowska H. (2012). Selenium interactions and toxicity: a review. Selenium interactions and toxicity. Cell Biol Toxicol 28(1): 31-46.		
Reviewer comments	Results included/excluded in review (if applicable)	Authors noted that: • Endemic chronic selenosis occurred in Chinese people who consumed crops with high Se content. It was estimated that the average daily intake of Se was 5 mg (Fan and Kizer 1990). Health consequences observed in affected persons included nail deformation, hair loss and skin lesions (Fan and Kizer 1990). • Acute Se poisoning has recently been described in people in the United States from ingestion of liquid dietary supplement that contained 200 times higher Se content than labelled (MacFarquhar et al. 2010). This review does not present dose-response human information for Se nor does it inform of a new potential adverse effect. As it is a review, it was not subjected to risk of bias assessment.
	Notes on study quality, e.g. gaps, methods	

APPENDIX C

Risk of Bias Tables

Algotar et al. 2013a

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Algotar et al. 2013a **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is indirect evidence that subjects were allocated to study groups using a method with a random component (i.e., authors state that allocation was random, without description of the method used).	-
2.	Allocation concealment	No	Double blinded study. There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable.	--
3.	Comparison groups appropriate	N/A	Comparison groups: not applicable	
	Confounding bias			
4.	Confounding (design/analysis)	N/A	Confounding: not applicable	
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	Double-blinded. There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure (including purity and stability of the test substance), but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable but not the gold standard) AND subjects had been followed for the same length of time in all study groups (if possible) AND there is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	-
	Other Sources of Bias			

11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Algotar et al. 2013b

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Algotar et al. 2013b **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is indirect evidence that subjects were allocated to study groups using a method with a random component (i.e., authors state that allocation was random, without description of the method used)	-
2.	Allocation concealment	No	There is indirect evidence that the research personnel and subjects did not know what study group subjects were allocated to and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable.	-
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is indirect evidence that the research personnel and subjects were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: there is insufficient information provided about numbers of subjects lost to follow-up	NR
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and subjects had been followed for the same length of time in all study groups	-

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

Risk of bias rating:

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

Bleys et al. 2008

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

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

Study ID: Bleys et. al. 2008 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardisation, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified and there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, and there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	--
	Performance Bias			

5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR. There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used.	NR
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, subjects had been followed for the same length of time in all study groups, and there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.	--
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Evans et al. 2019

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Evans et al. 2019 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component.	--

2.	Allocation concealment	No	Double blinded study. There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable.	--
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	Double-blinded. There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods AND subjects had been followed for the same length of time in all study groups AND there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.	--
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Karp et. al. 2013

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Karp et. al. 2013 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component.	--
2.	Allocation concealment	No	There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable (double blind study)	--
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods AND subjects had been followed for the same length of time in all study groups AND there is indirect evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Klein et. al. 2011

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Klein et. al. 2011 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is indirect evidence that subjects were allocated to study groups using a method with a random component	-
2.	Allocation concealment	No	There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable. (Note: Late in the study it became unblinded, October 23, 2008)	--
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study. (Note: Late in the study it became unblinded, October 23, 2008)	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR. There is insufficient information provided about numbers of subjects lost to follow-up.	NR
	Detection Bias			
8.	Exposure characterisation	Yes	NR. There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used	NR
9.	Outcome assessment	Yes	There is indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard) AND subjects had been followed for the same length of time in all study groups and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures.	-

			(Note: Prostate cancer incidence was determined by routine clinical management and confirmed by central pathology review).	
	Selective Reporting Bias			
10.	Outcome reporting	No	Indirect evidence that all of the study's measured outcomes have been reported.	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Kristal et al. 2014

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

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

Study ID: Kristal et al. 2014 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had similar participation/response rates.	--
	Confounding bias			
4.	Confounding (design/analysis)	Yes	NR. There is insufficient information provided about the distribution of known confounders	NR
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	It is deemed that the proportion lost to follow-up would not appreciably bias results	-

	Detection Bias			
8.	Exposure characterisation	Yes	NR. There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used	NR
9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods, subjects had been followed for the same length of time in all study groups, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (as an objective outcome measure applied).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Lacaustra et al. 2010

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

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

Study ID: Lacaustra et al. 2010 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate	Unknown	There is indirect evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had very different participation/response rates. (Note: It appears that demographics in Quartile 4 included a higher proportion of non-Hispanic black population and supplement users and lower proportion of females and smokers compared to other quartiles).	+
	Confounding bias			
4.	Confounding (design/analysis)	No	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-	--

			specific bias including standardisation, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, AND there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.	
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	--
	Detection Bias			
8.	Exposure characterisation	No	Exposure was assessed using indirect measures (e.g., questionnaire or occupational exposure assessment by a certified industrial hygienist) that have been validated or empirically shown to be consistent with methods that directly measure exposure.	-
9.	Outcome assessment	No	It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a particular outcome).	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Lance et. al. 2009

Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).
Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Lance et. al. 2009	**RoB: Yes/No**	**Notes**	**Risk of bias rating**

Study Type: Human Controlled Trial (HCT)		Unknown N/A		(--/-/+/++/NR)
Q				
	Selection bias			
1.	Randomization	No	There is indirect evidence that subjects were allocated to study groups using a method with a random component (i.e., authors state that allocation was random, without description of the method used),	-
2.	Allocation concealment	Yes	NR: there is insufficient information provided about allocation to study groups	NR
3.	**Comparison groups appropriate**	N/A	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	N/A	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	It is deemed that lack of adequate blinding during the study would not appreciably bias results (as objective measures were used to measure adenoma/tumour incidence)	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	It is deemed that the proportion lost to follow-up would not appreciably bias results	-
	Detection Bias			
8.	Exposure characterisation	Yes	NR. there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed that the outcome assessment methods used would not appreciably bias results	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Lippman et. al. 2009

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Lippman et. al. 2009 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component.	--
2.	Allocation concealment	Yes	NR: there is insufficient information provided about allocation to study groups	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR. there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and it is deemed that the outcome assessment methods used would not appreciably bias results	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Marshall et. al. 2011

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Marshall et. al. 2011 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is indirect evidence that subjects were allocated to study groups using a method with a random component (i.e. authors state that allocation was random, without description of the method used)	-
2.	Allocation concealment	No	There is indirect evidence that the research personnel and subjects did not know what study group subjects were allocated to and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable. (Note: It is a double-blind study, but it is not known if concealment applied to all research personnel).	-
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is indirect evidence that the research personnel and subjects were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study (Note: The central pathologist was blinded to study assignment but it is not known if all research personnel were blinded).	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR. There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using well-established methods and subjects had been followed for the same length of time in all study groups and there is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			

11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Mix et al. 2015

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Mix et al. 2015 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	Yes	Only one study group (no controls), therefore probably high risk of bias has been assigned.	+
2.	Allocation concealment	Yes	NR: There is insufficient information provided about allocation to study groups. Only one study group was included (no controls)	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	Yes	NR: There is insufficient information provided about blinding to study group during the study. However, only one study group was evaluated (no controls/placebo).	NR
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods AND subjects had been followed for the same length of time in all study groups (note only one study group in this study) AND it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results.	-

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

Risk of bias rating:

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

Stranges 2007

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Stranges et. al. 2007 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component	--
2.	Allocation concealment	Yes	There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable.	--
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	--
	Attrition/Exclusion Bias			

7.	Missing outcome data	No	There is direct evidence that there was no loss of subjects during the study and outcome data were complete	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR. there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome (T2D) was assessed using acceptable methods (i.e. self-reported during the clinical interview, reported use of drugs for diabetes, and reports in medical record documents). It is deemed lack of adequate blinding of outcome assessors would not appreciably bias results, as most outcome measures were objective (rather than subjective).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Stranges et. al. 2010

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

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

Study ID: Stranges et. al. 2010 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that differences between groups would not appreciably bias results	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, it is deemed that the measures used would not appreciably bias results, it is deemed that co-exposures present would not appreciably bias results.	-

	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from the study.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods and subjects had been followed for the same length of time in all study groups. Outcome measures were objectively assessed using diagnostic methods. There is indirect evidence that the outcome assessors were adequately blinded to the study group, as the exposures were not known to the medical practitioners undertaking the diagnoses.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Thompson et. al. 2016

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Thompson et. al. 2016 **Study Type: Human Controlled Trial (HCT)**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q			
	Selection bias		

1.	Randomization	No	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component	--
2.	Allocation concealment	Yes	NR: there is insufficient information provided about allocation to study groups	NR
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	It is deemed that lack of adequate blinding during the study would not appreciably bias results.	-
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR. there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern.	NR
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using acceptable methods (i.e. colonoscopy to identify adenomas). It is deemed lack of adequate blinding of outcome assessors would not appreciably bias results, as most outcome measures were objective (rather than subjective).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Vinceti et al. 1996

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

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

Study ID: Vinceti et al. 1996	**RoB: Yes/No Unknown**	**Notes**	**Risk of bias rating**
Study Type: Cohort (Co)			

		N/A		(--/-/+/++/NR)
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is insufficient information provided about the comparison group including a different rate of non-response without an explanation (note that the demographics and size of the unexposed group was not detailed).	+
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, it is deemed that the measures used would not appreciably bias results (i.e. it was reported in a later study of the same cohort but not demonstrated in the paper that confounding would not affect RR, Vinceti et al. 2016). It is deemed that co-exposures present would not appreciably bias results.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	There is insufficient information provided about numbers of subjects lost to follow-up.	+
	Detection Bias			
8.	Exposure characterisation	Yes	There is direct evidence that the exposure was assessed using methods with poor validity. It appears as though only two exposure groups were considered (<1 µg/L and ≥1 µg/L)	++
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using well-established methods and subjects had been followed for the same length of time in all study groups. Outcome measures were objectively assessed using diagnostic methods. There is indirect evidence that the outcome assessors were adequately blinded to the study group, as the exposures were not known to the medical practitioners undertaking the diagnoses.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported,	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Vinceti et al. 2010a

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

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

Study ID: Vinceti et al. 2010a **Study Type: Case-Control (CaCo)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that cases and controls were similar (e.g. recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made AND there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements AND there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			
8.	Exposure characterisation	Yes	There is direct evidence that the exposure was assessed using methods with poor validity or evidence of exposure misclassification. In this case the authors measured concentrations of Se at a point in time in 21 private wells; it is unclear from the paper how exposures for all cases and controls were assigned to either low of high Se from these data. It is also unclear how regression was undertaken using only two exposure groups (≥1 vs. <1 µg/L).	++
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed in cases (i.e. case definition) and controls using acceptable methods and subjects had been followed for the same length of time in all study groups. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results.	-
	Selective Reporting Bias			

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

Risk of bias rating:

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

Vinceti et. al. 2012

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

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

Study ID: Vinceti et. al. 2012 **Study Type: Case Control (CaCo)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that cases and controls were similar (e.g., recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome.	--
	Confounding bias			
4.	Confounding (design/analysis)	No	It is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			

7.	Missing outcome data	Yes	There is indirect evidence that exclusion of subjects from analyses was not adequately addressed	+
	Detection Bias			
8.	Exposure characterisation	Yes	NR. There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used	NR
9.	Outcome assessment	Yes	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure (e.g. serum levels)	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported,	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Vinceti et. al. 2013b

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

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

Study ID: Vinceti et. al. 2013b **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is direct evidence that cases and controls were similar (e.g., recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome.	--
	Confounding bias			
4.	Confounding (design/analysis)	Yes	NR. There is insufficient information provided about the distribution of known confounders in cases and controls	NR

	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR. There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used.	NR
9.	Outcome assessment	Yes	NR. There is insufficient information provided about blinding of outcome assessors	NR
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported,	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	Study authors over-interpreted the results of the paper, as they did not consider the statistical insignificance of risk ratios where confidence intervals crossed unity (or '1').	++

Risk of bias rating:

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

Vinceti et al. 2016

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

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

Study ID: Vinceti et al. 2016 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that differences between groups would not appreciably bias results.	-
	Confounding bias			

4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made; it is deemed that the measures used would not appreciably bias results (i.e. lifestyle factors including smoking, alcohol consumption, traffic etc. were considered but results not reported); it is deemed that co-exposures present would not appreciably bias results.	-
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	**Blinding of researchers during study?**	**N/A**	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about numbers of subjects lost to follow-up	NR
	Detection Bias			
8.	Exposure characterisation	Yes	There is direct evidence that the exposure was assessed using methods with poor validity. It appears as though only two exposure groups were considered (<1 µg/L and ≥1 µg/L); there is potential for exposure misclassification.	++
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using well-established methods and subjects had been followed for the same length of time in all study groups. Outcome measures were objectively assessed using diagnostic methods. There is indirect evidence that the outcome assessors were adequately blinded to the study group, as the exposures were not known to the medical practitioners undertaking the diagnoses.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	NR: there is insufficient information provided about selective outcome reporting [e.g. Risk Ratios (RR) and confidence intervals (CI) were calculated but no mention of statistical relevance for CI that crossed 1]	NR
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Vinceti et al. 2018a

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

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

Study ID: Vinceti et al. 2018a **Study Type: Cohort (Co)**	**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**

Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that differences between groups would not appreciably bias results (it was previously reported that there were differences in occupation between exposed and unexposed group, Vinceti et al. 2016).	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, it is deemed that the measures used would not appreciably bias results (i.e. it was previously reported but not demonstrated that confounding would not affect RR, Vinceti et al. 2016 where it was considered but not reported), it is deemed that co-exposures present would not appreciably bias results.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about numbers of subjects lost to follow-up	NR
	Detection Bias			
8.	Exposure characterisation	Yes	There is direct evidence that the exposure was assessed using methods with poor validity. It appears as though only two exposure groups were considered (<1 µg/L and ≥1 µg/L)	++
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using well-established methods and subjects had been followed for the same length of time in all study groups. Outcome measures were objectively assessed using diagnostic methods. There is indirect evidence that the outcome assessors were adequately blinded to the study group, as the exposures were not known to the medical practitioners undertaking the diagnoses.	-
	Selective Reporting Bias			
10.	Outcome reporting	Yes	NR: there is insufficient information provided about selective outcome reporting [e.g. Risk Ratios (RR and confidence intervals (CI) were calculated but no mention of statistical relevance for CI that crossed 1]	NR
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Vinceti et al. 2019

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

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

Study ID: Vinceti et al. 2019 **Study Type: Cohort (Co)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that differences between groups would not appreciably bias results (it was previously reported that there were no major differences in occupation between exposed and unexposed group, Vinceti et al. 2016).	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is indirect evidence that appropriate adjustments were made, it is deemed that the measures used would not appreciably bias results (i.e. it was previously reported but not demonstrated that confounding would not affect RR, Vinceti et al. 2016). It is deemed that co-exposures present would not appreciably bias results.	-
	Performance Bias			
5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	Yes	NR: There is insufficient information provided about numbers of subjects lost to follow-up	NR
	Detection Bias			
8.	Exposure characterisation	Yes	There is direct evidence that the exposure was assessed using methods with poor validity. It appears as though only two exposure groups were considered (<1 µg/L and ≥1 µg/L)	++
9.	Outcome assessment	No	There is indirect evidence that the outcome was assessed using well-established methods and subjects had been followed for the same length of time in all study groups. Outcome measures were objectively assessed using diagnostic methods. There is indirect evidence that the outcome assessors were adequately blinded to the study group, as the exposures were not known to the medical practitioners undertaking the diagnoses.	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported.	--
	Other Sources of Bias			

11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes		

Risk of bias rating:

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

Walsh et al. 2021

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

Questions and domains that are not applicable to Human Controlled Trials (HCT) greyed out.

Study ID: Walsh et al. 2021 **Study Type: Human Controlled Trial (HCT)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	No	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component (block randomisation sequence)	--
2.	Allocation concealment	No	There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable.	--
3.	**Comparison groups appropriate**	**N/A**	Comparison groups: not applicable	
	Confounding bias			
4.	**Confounding (design/analysis)**	**N/A**	Confounding: not applicable	
	Performance Bias			
5.	**Identical experimental conditions**	**N/A**	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	No	There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study.	--
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	Loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses.	--
	Detection Bias			
8.	Exposure characterisation	Yes	NR: there is insufficient information provided about the validity of the exposure assessment method (i.e. purity and stability of test item), but no evidence for concern	NR

9.	Outcome assessment	No	There is direct evidence that the outcome was assessed using well-established methods AND subjects had been followed for the same length of time in all study groups AND there is direct evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.	--
	Selective Reporting Bias			
10.	Outcome reporting	No	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported	--
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	N/A	No other threats applicable	

Risk of bias rating:

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

Yang et. al. 2022

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

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

Study ID: Yang et. al. 2022 **Study Type: Cross-sectional (CrSe)**		**RoB: Yes/No Unknown N/A**	**Notes**	**Risk of bias rating (--/-/+/++/NR)**
Q				
	Selection bias			
1.	Randomization	N/A	Randomization: not applicable	
2.	Allocation concealment	N/A	Allocation concealment: not applicable	
3.	Comparison groups appropriate	No	There is indirect evidence that subjects were similar (as they were recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status). The population was grouped by confounding factors (sex, age, BMI, hypertension history, and smoking status).	-
	Confounding bias			
4.	Confounding (design/analysis)	No	There is evidence that appropriate adjustments were made for known confounders (sex, age, BMI, hypertension history, and smoking status), but it is uncertain whether all potential covariates have been accounted for.	-
	Performance Bias			

5.	Identical experimental conditions	N/A	Experimental conditions: not applicable	
6.	Blinding of researchers during study?	N/A	Blinding of researchers: not applicable	
	Attrition/Exclusion Bias			
7.	Missing outcome data	No	There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.	-
	Detection Bias			
8.	Exposure characterisation	Yes	NR: There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used. Nevertheless, exposure was measured as Se in serum so this is a direct measure of Se exposure from a variety of sources (diet, drinking water and supplements).	NR
9.	Outcome assessment	No	It is deemed that the outcome assessment methods used would not appreciably bias results (given that data was not self-reported and outcome lack of blinding is unlikely to bias a particular outcome).	-
	Selective Reporting Bias			
10.	Outcome reporting	No	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported,	-
	Other Sources of Bias			
11.	Other threats (e.g. statistical methods appropriate; researchers adhered to the study protocol)	Yes	It is likely from the publication that statistical analysis used was appropriate. However, there is no information on dose received or discussion of Se background intakes hence the data could not have been adjusted for this factor which could influence outcome.	+

Risk of bias rating:

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

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