# EVIDENCE EVALUATIONS FOR AUSTRALIAN DRINKING WATER GUIDELINE CHEMICAL FACT SHEETS

**Selenium**
**Technical Report**

**Prepared for:**

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# BASIS OF REPORT

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

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# Abbreviations/Definitions

| Acronym | Definition |
|---|---|
| APVMA | Australian Pesticides and Veterinary Medicines Authority |
| ATSDR | US Agency for Toxic Substances and Disease Registry |
| BW, bw | Body Weight |
| DW | Drinking Water |
| DWG | Drinking Water Guideline |
| EFSA | European Food Safety Authority |
| FSANZ | Food Standards Australia New Zealand |
| ICP-MS(AES) | Inductively Coupled Plasma Mass Spectrometry (Atomic Emission Spectroscopy) |
| IPCS | International Programme on Chemical Safety |
| IRIS | Integrated Risk Information System |
| JECFA | Joint FAO/WHO Expert Committee on Food Additives |
| LOR | Limit of Reporting |
| MRL | Minimal Risk Level (ATSDR terminology) |
| NOAEL | No Observed Adverse Effect Level |
| NHMRC | National Health and Medical Research Council |
| OEHHA | Californian Office of Environmental Health and Hazard Assessment |
| PHG | Public Health Goal (in drinking water) (OEHHA terminology) |
| PPRTV | Provisional Peer-Reviewed Toxicity Value (US EPA terminology) |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RCT | Randomised Controlled Trial |
| ROS | Reactive Oxygen Species |
| Se | Selenium |
| The Guidelines | NHMRC and NRMMC (2011). Australian Drinking Water Guidelines 6 2011; Version 3.6 updated March 2021, National Health and Medical Research Council and Natural Resource Management Ministerial Council. Commonwealth of Australia, Canberra. |
| TRV | Toxicity Reference Value |
| UF | Uncertainty Factor |
| UL | Upper Limit (of Intake) |
| US EPA | United States Environmental Protection Agency |
| WHO | World Health Organization |
| WQAC | Water Quality Advisory Committee |

# 1 Introduction and Background

The National Health and Medical Research Council (NHMRC) have contracted SLR Consulting Australia Pty Ltd (SLR) to evaluate the existing guidance and evidence for 11 chemical factsheets in the 2011 *Australian Drinking Water Guidelines* (the Guidelines). The evidence reviews undertaken by SLR were governed by a newly designed methodological framework intended to increase transparency and quality control in the process of adopting or adapting existing guidelines. For each of the 11 chemicals, SLR was asked to:

- Customise and apply the 'Research Protocol' provided by NHMRC to answer research questions. The research questions varied slightly according to the chemical being evaluated.
- Produce a Technical Report and an Evaluation Report for each chemical factsheet.
  - 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 collaboration with the Water Quality Advisory Committee (WQAC) and NHMRC.

The report herein is the Technical Report for selenium (Se).

# 2 Research Questions

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

**Table 1 Research Questions for Evidence Evaluation of Selenium Factsheet Review**

| # | Research Questions |
|---|---|
| **Health-based** | |
| 1 | What is the critical human health endpoint for excess Se exposure? Therefore, what are the key adverse health hazards from exposure to Se in Australian drinking water? |
| 2 | What are the justifications for choosing this endpoint/health hazard? |
| 3 | What is the toxicological mode of action of Se for the critical human health endpoint? |
| 4 | Is Se an oral genotoxic carcinogen of relevance to humans? |
| 5 | What dose(s) are associated with the critical human health endpoint? |
| 6 | What is the guidance / guideline value? |
| 7 | Is the health-based guidance value expressed in the best way? |
| 8 | Is the proposed health-based guidance/guideline value relevant to the Australian context? |
| 9 | Are there groups of people in the general population who may be more sensitive to Se exposure? |
| 10 | Is there a knowledge gap from the time at which existing guideline values were developed? |
| 11 | Does any recent literature change the guideline value? (e.g. demonstrating a new critical endpoint?) |
| **Exposure-based** | |

| # | Research Questions |
|---|---|
| 12 | What are the typical Se levels in Australian drinking water? Do they vary around the country or under certain conditions e.g. source of water, drought? |
| 13 | Do Australian levels differ considerably from elsewhere? |
| 14 | What are the principal routes of exposure to Se in the Australian general population? |
| 15 | What are the typical levels of Australian exposure? (e.g. 'background' selenium intakes)? |
| **Risk-based** | |
| 16 | What are the risks to human health from exposure to Se in Australian drinking water? |
| 17 | Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review? |
| **Supporting Information** | |
| 18 | Is the general description current? |
| 19 | What are the indicators of the risks? How can we measure exposure? Is the information on measurement/analytical methods current? |
| 20 | Are there commercial analytical methods available that can measure at or below the guideline value? |
| 21 | Is the information for treatment options current in terms of current practices in Australia? |
| 22 | Can treatment technologies treat to the suggested level of the guideline value? |
| 23 | Are there any new sections that should be added? Should anything be removed? |

# 3 Evidence Evaluation Methods

## 3.1 Overview

This section summarises the methods followed to undertake the evidence evaluation review for Se. 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 Se 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 Se. 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).

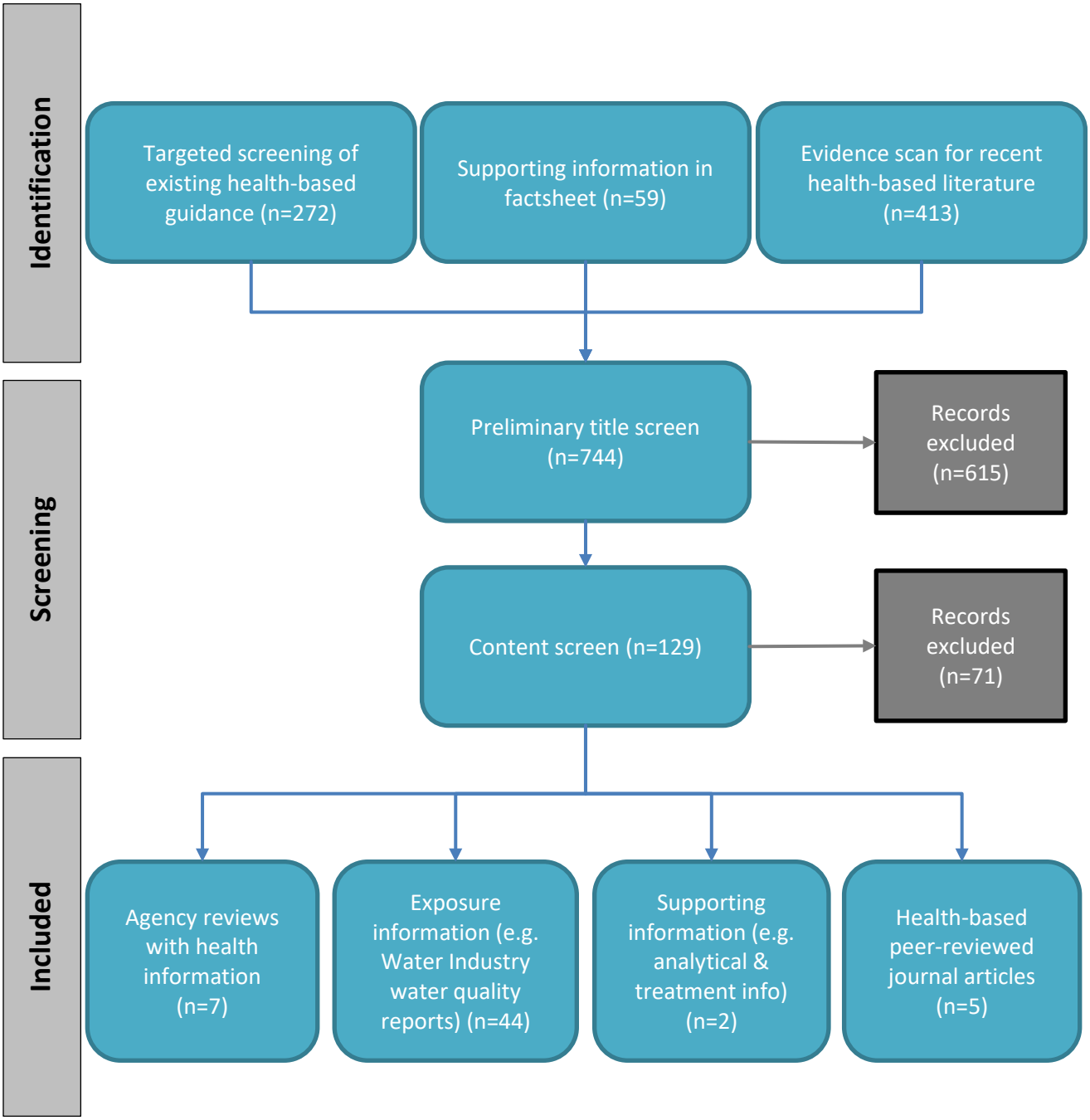


**Figure 1 Overview of literature search process followed for Selenium**

## 3.2 Targeted screening of existing health-based guidance

### Literature search strategy

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

## Table 2 Search strategy for Existing Guidance/Guidelines

| Parameter | Comments |
|---|---|
| Search terms | After a few trial runs of various combinations of search terms, it became apparent that the search terms would need to remain relatively broad so as not to miss pivotal references/reviews. Consequently, the selected search term was:<br>• (Selenium) |
| Databases/Agency websites | The following sources were searched:<br>• World Health Organization (WHO): https://www.who.int/ (in addition, 'Selenium in drinking water' was searched in Google®) [2].<br>• International Programme of Chemical Safety (IPCS Inchem): http://www.inchem.org/#/search<br>• Joint FAO/WHO Expert Committee on Food Additives (JECFA): (Included in IPCS Inchem search)<br>• European Food Safety Authority (EFSA): https://www.efsa.europa.eu/en<br>• United States Environmental Protection Agency (US EPA), specifically [1]:<br>  ○ Integrated Risk Information System (IRIS): https://www.epa.gov/iris<br>  ○ Provisional Peer-reviewed Toxicity Values (PPRTV): https://www.epa.gov/pprtv<br>• US Agency for Toxic Substances and Disease Registry (ATSDR): https://www.atsdr.cdc.gov/<br>• Californian Office of Health and Hazard Assessment (OEHHA) Public Health Goals (in Drinking Water): https://oehha.ca.gov/water/public-health-goals-phgs<br>• Food Standards Australia New Zealand (FSANZ), specifically [3]:<br>  ○ Publications page: https://www.foodstandards.gov.au/publications/Pages/default.aspx<br>  ○ Monitoring safety of food supply page: https://www.foodstandards.gov.au/science/surveillance/Pages/default.aspx<br>  ○ Chemicals in food page: https://www.foodstandards.gov.au/consumer/chemicals/Pages/default.aspx<br>• Australian Pesticides and Veterinary Medicines Authority (APVMA) Health Based Guidance Values: https://apvma.gov.au/node/26596<br>• National Health and Medical Research Council (NHMRC) Nutrient Reference Values (NRVs): https://www.nrv.gov.au/nutrients<br>The following additional sources were searched to provide exposure information in Australian drinking water supplies (to inform responses to Research Questions 12 and 15):<br>• Melbourne Water: https://www.melbournewater.com.au/<br>• Sydney Water: https://www.sydneywater.com.au/SW/index.htm<br>• TasWater: https://www.taswater.com.au/<br>• SA Water: https://www.sawater.com.au/<br>• Water Corporation of Western Australia: https://www.watercorporation.com.au/<br>• Power and Water Corporation Northern Territory Drinking Water Quality Reports: https://www.powerwater.com.au/about/what-we-do/water-supply/drinking-water-quality/past-drinking-water-quality-reports<br>• Seqwater: https://www.seqwater.com.au/<br>• Icon Water: https://www.iconwater.com.au/<br>• Water Research Australia: https://www.waterra.com.au/ |

| Parameter | Comments |
|---|---|
| Publication Date | If databases/agency websites allowed for specification of date ranges, searches were constrained to the following date range to coincide with the year of the last Australian drinking water guideline fact sheet update for Se:<br>• 1 January 1996 to July 2021 |
| Language | English |
| Study Type | Publicly available agency/industry reports and reviews. |
| Inclusion and exclusion criteria | The following exclusion criteria were used to screen relevance of agency reports/reviews:<br>• NR = Not Relevant. Information not directly relevant to answering research questions. Rationale for non-relevance was provided for transparency. E.g.<br>  ○ Not HH related = Not human health related (e.g. criteria are for protection of aquatic life).<br>  ○ Not a relevant exposure pathway = Since Se is not volatile, guidelines for non-oral and non-dermal routes of exposure are not considered relevant (e.g. inhalation).<br>  ○ Not relevant to chemical of interest.<br>  ○ Deficiency = Report focuses on toxicity resulting from Se deficiency, rather than excess.<br>• 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.<br>• Language = Language other than English. |
| Validation methods used | Preliminary searches were undertaken with more specific search terms [(Selenium) AND (toxicity or health); (Selenium) AND (exposure) AND (Australia)]. Upon scanning preliminary search results, the reviewer found these search terms to be too specific, as a number of agency reports did not appear in the results. The search terms were consequently refined.<br>In addition, from the preliminary search of the WHO website, it became evident that the latest background documentation for Se (dated 2010) did not come up in the general search results when using the search term 'Selenium'. Therefore, the WHO website search was supplemented by a Google® search to find the specific background document of interest. |
| Screening methods | Results were screened as follows:<br>*Preliminary title screen*<br>• Titles of results for each search were recorded in an Excel spreadsheet. Each website was on a separate tab of the spreadsheet.<br>• 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.<br>• 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.<br>*Content screen*<br>• 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. |

| Parameter | Comments |
|---|---|
| Documentation of search | Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.**<br>Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015). |
| Retrieval of publications | All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis. |

1. Preliminary search trials with the US EPA general search engine (https://www.epa.gov/) resulted in over 16,262 hits, regardless of search term refinement. This number of hits was considered unmanageable to screen through with the resources available for this project. Consequently, the search was targeted to specific sections of the website considered most relevant to answering the research questions.
2. From the preliminary search of the WHO website, it became evident that the latest background documentation for selenium (dated 2010) did not come up in the general search results when using the search term 'Selenium'. Therefore, the WHO website search was supplemented by a Google® search to find the specific background document of interest.
3. From the preliminary search of the FSANZ website, it became evident that the number of search results appeared infinite (there was no set number of hits provided, and no set pages of results; every time the final page of results was clicked on, additional pages appeared), regardless of search term refinement, with the vast majority of records being not relevant to the research questions. Consequently, specific sections of the website were consulted which were considered most relevant to answering the research questions.

## Data Extraction and Quality Assessment

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

- The full text was skimmed by a content expert.
- Where existing health-based guidance (in the form of drinking water guidelines or toxicity reference values, i.e. TRVs) was identified, relevant data on the guidance value in relation to the research questions were extracted using the format shown in **Table 3.** The individual data extraction tables are provided in **Appendix B**.
- For each health-based guidance review, quality of existing guidance/guidelines was assessed using the Assessment Tool (Appendix C in the Research Protocol). The individual completed Assessment tool tables for each guidance/guideline document are provided in **Appendix C**.

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

| **Agency Report Reference:** ***Insert full bibliographical reference for report*** | | |
|---|---|---|
| General Information | Date of data extraction | |
| | Authors | |
| | Publication date | |
| | Literature search timeframe | |
| | Publication type | |
| | Peer reviewed? | |
| | Country of origin | |
| | Source of funding | |
| | Possible conflicts of interest | |

| **Agency Report Reference:** ***Insert full bibliographical reference for report*** | | |
|---|---|---|
| Health considerations | Guideline value type (e.g. oral TRV, drinking water guideline) | |
| | Exposure timeframe | |
| | Critical human health endpoint | |
| | Justification provided by agency for critical endpoint | |
| | Critical study(ies) underpinning point of departure | |
| | Species for critical study(ies) | |
| | Point of departure type (e.g. NOAEL, LOAEL, $BMDL_{10}$, etc) | |
| | Point of departure value (include units) | |
| | Uncertainty factor(s) & rationale | |
| | Guideline value (include units) | |
| | Mode of action for critical health endpoint | |
| | Genotoxic carcinogen? | |
| | Identified sensitive sub-populations | |
| | Any non-health based considerations? | |
| Exposure considerations | Principal routes of exposure in general population | |
| | Levels in drinking water supplies (include location) | |
| | Any special considerations to exposure levels (e.g. higher in drought?) | |
| | Typical exposure in general population (include units for intakes & location) | |
| Risk Summary | Any risks to human health from drinking water identified in agency document? | |
| | Any emerging risks identified? | |

### Data summary/synthesis

In order to effectively compare data from different sources, the data has been presented side-by-side in tabular format for each individual research question.

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

## 3.3 Evidence scan for recent studies

### Literature search strategy

An evidence scan of recent literature was undertaken for research questions for which eligible guidance (for potential adoption or adaptation into the Guidelines) was identified in the targeted screening of existing health-based guidance (see **Section 3.2**). The aim of the evidence scan was to understand the availability of recent literature and to determine whether a formal systematic review to update the evidence underpinning available guidance is warranted.

The literature search strategy for undertaking the evidence scan for recent studies is summarised in **Table 4** below.

**Table 4 Search strategy for evidence scan of recent health-based studies**

| Parameter | Comments |
|---|---|
| Search terms | The selected search terms were:<br>• (Selenium) AND (toxicity) AND (oral)<br>• (Selenium) AND (health) AND (oral)<br>• (Selenium) AND (toxicity) AND (drinking water)<br>• (Selenium) AND (health) AND (drinking water)<br>• (Selenium) AND (exposure) AND (Australia) |
| Databases | The following sources were searched:<br>• MEDLINE/PubMed/TOXLINE |
| Publication Date | 2014– 2021, the bottom end of the range to coincide with the latest health-based agency review found in the targeted screening step. |
| Language | English |
| Study Type | Peer-reviewed, published, in press, unpublished and ongoing studies will be included.<br>Study types may include existing systematic reviews or literature reviews, human epidemiological studies, animal studies, and *in vitro* studies (the latter only if they inform on the mode of action for the critical health effect of concern). |
| Inclusion and exclusion criteria | The following exclusion criteria were used to screen relevance of information:<br>• NR = Not Relevant. Information not directly relevant to answering research questions.<br>• Language = Language other than English.<br>• UCC = Unlikely to Change Conclusions in Review. |

| Parameter | Comments |
|---|---|
| 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. |
| Screening methods | Results were screened as follows:<br>*Preliminary title and abstract screen*<br>• 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.<br>• 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.<br>• 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.<br>*Content screen*<br>• The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data extraction step. Only articles/reviews which provided information considered to potentially affect the overall conclusions made by other jurisdictions 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.**<br>Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015). |
| Retrieval of publications | All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis. |

## Data Extraction

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

- Where deemed to be relevant to the research questions and potentially providing information that could alter the existing assessments (identified in the targeted screening of existing health-based guidance), relevant data were extracted using the example format shown in **Table 5.** The format was more applicable to epidemiological studies and was adapted slightly for animal studies and/or reviews. The individual data extraction tables are provided in **Appendix E**.

### Table 5 Example of data extraction table format for evidence scan of recent health-based studies

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

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

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

### Data summary/synthesis

Data summary/synthesis for the evidence scan was limited to those aspects identified which have the potential to influence the overall conclusions made by the jurisdictions who have derived existing health-based guidance/guidelines (i.e. the health-based research questions only). Relevant data were summarised in tabular format by research question.

## 3.4 Supporting information in factsheet

In the first instance, the existing guidance/guideline documents identified as per the methods outlined in **Section 3.2** were consulted for supporting information in the factsheet (i.e. general description, uses, measurement techniques and limits of reporting in drinking water, treatment options, etc).

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

**Table 6 Example of data extraction table format for supporting information in factsheet**

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

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

## Table 7 Search strategy for evidence scan of supporting information in factsheet

| Parameter | Comments |
|---|---|
| Search terms | The selected search terms for the Scopus database were:<br>• (Selenium) AND (treatment) AND (drinking water) [(1)]<br>After a few trial runs of various combinations of search terms in the industry websites, it became apparent that the search capacities varied significantly between different webpages. Consequently, the selected search term (for industry websites) was kept relatively broad:<br>• (Selenium) |
| Databases/Other sources | The following source database was searched:<br>• Scopus<br>The following industry websites were searched:<br>• Water Services Association of Australia: https://www.wsaa.asn.au/<br>• Standard Methods for the Examination of Water and Wastewater: https://www.standardmethods.org/<br>• US EPA Drinking Water Treatability Database: https://tdb.epa.gov/tdb/home<br>The following Australian commercial laboratories were contacted directly via e-mail or website form for relevant information:<br>• National Measurement Institute<br>• SGS<br>• ALS<br>• Eurofins |
| Publication Date | Limited to last 5 years (2017-2021) |
| Language | English |
| Study Type | • Peer-reviewed, published, in press, unpublished and ongoing studies.<br>• Australian laboratory information sheets or e-mail responses on measurement methods and limits of determination. |
| Inclusion and exclusion criteria | The following exclusion criteria were used to screen relevance of information:<br>• NR = Not Relevant. Information not directly relevant to answering research questions.<br>• Research technique (analytical or treatment) = does not appear to be commercially applied.<br>• Language = Language other than English.<br>• NPA = Not publicly available.<br>• NL = Chemical not listed under specific treatment process. |
| Validation methods used | Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened. |

| Parameter | Comments |
|---|---|
| Screening methods | Results were screened as follows:<br>*Preliminary title and abstract screen*<br>• Titles of results for each search were recorded in an Excel spreadsheet. Each source was on a separate tab of the spreadsheet.<br>• 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.<br>• 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.<br>*Content screen*<br>• The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data extraction step. Only articles/reviews which provided information relevant to answering the research questions were taken through to the data extraction step. |
| Documentation of search | Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in **Appendix A.**<br>Overall results presented in **Figure 1**, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015). |
| Retrieval of publications | All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis. |
| 1. It became evident upon undertaking the initial searches using the following additional search term combinations ['(Selenium) AND (analysis) AND (drinking water)' OR '(Selenium) AND (testing) AND (drinking water)'] that these searches returned thousands of results that were not relevant to answering the research questions with respect to commercial analytical techniques used in Australia. Results obtained for analytical techniques in the peer-reviewed literature were research-based techniques for specific purposes and not currently commercially applied. It was considered more efficient and effective to contact Australian laboratories directly for information on their analytical techniques and commercial limits of reporting. Therefore, the search in the Scopus database was limited to information on treatment technologies. | |

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

- Citation information
- Name of treatment technology (as applicable)
- Name of analytical technique (as applicable)
- Associated Reporting Limit

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

# 4 Results

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

## 4.1 Health-based research question analysis

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

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 1 | What is the critical human health endpoint for Se exposure? Therefore, what are the key adverse health hazards from exposure to Se in Australian drinking water? | **ATSDR 2003** | Selenosis (i.e. morphological changes in fingernails, brittle hair, loss of fingernails and hair). In extreme cases, people may lose feeling and control in arms and legs. |
| | | **EFSA 2006, 2014a** | Selenosis (i.e. brittle hair with intact follicles, new hair with no pigment, thickened nails or brittle nails with spots and longitudinal streaks on surface). In extreme cases, symptoms of neurological disturbance have been observed (e.g. peripheral anaesthesia, acroparaesthesia, pain, hyperreflexia, numbness, convulsions, paralysis, motor disturbances). |
| | | **FSANZ 2008** | Brittleness and loss of hair and nails, gastrointestinal disturbances, skin rash, fatigue and effects on the nervous system |
| | | **NHMRC 2006** | Brittleness and loss of hair and nails in humans, as well as gastrointestinal disturbance, skin rash, fatigue, irritability and nervous system abnormalities. |
| | | **OEHHA 2010** | Hair loss and nail damage (i.e. selenosis) |
| | | **WHO 2011** | Selenosis (brittle hair and nails, skin lesions and changes in peripheral nerves). |
| 2 | What are the justifications for choosing this endpoint/health hazard? | **ATSDR 2003** | Selenosis is known to occur in humans at very high Se intakes. Very high amounts of Se have also caused decreased sperm counts, increased abnormal sperm, changes in the female reproductive cycle in rats, and changes in the menstrual cycle in monkeys. However, the relevance of reproductive effects of Se exposure in animals to potential reproductive effects in humans is not known. Se compounds have not been shown to cause birth defects. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **EFSA 2006, 2014a** | No indication of teratogenicity of Se has been shown in humans even in the areas of high Se intake in China.<br>Except for the studies of a population in seleniferous areas in the USA, more recent Chinese studies of endemic Se toxicity in humans and a 1991 American study, there are only anecdotal reports on chronic Se toxicity in humans. |
| | | **NHMRC 2006** | There are limited data on the toxicity of Se in humans, with the critical effects being the only ones shown in human studies of high Se intakes. |
| | | **OEHHA 2010** | The PHG is based on a comprehensive assessment of animal and human studies on both toxicity and essentiality of water-soluble and bioavailable Se compounds.<br>The extensive field studies on humans provide a database for the best estimates of the toxic doses to adult humans for chronic oral exposures to Se, including dietary and drinking water intakes. |
| | | **WHO 2011** | No justification provided *per se.* Because of concern about adverse effects resulting from exposure to excessive levels of Se, various national and international organisations have established upper limits of exposure to Se. The United States National Academy of Sciences Panel on Dietary Oxidants and Related Compounds set an upper tolerable limit for selenium at 400 µg/day (NAS 2000). This level was also recommended by FAO/WHO (1998) and the United Kingdom Expert Group on Vitamins and Minerals (EGVM 2002). The average dietary intake that is associated with selenosis has been found to be in excess of 900 µg/day. |
| | | **FSANZ 2008** → No information provided | |
| 3 | What is the toxicological mode of action of Se for the critical human health endpoint? | **ATSDR 2003** | Several mechanisms have been proposed to explain the various long-term toxic effects of excess Se. This includes information on mechanisms by which Se exerts effects as a component of glutathione peroxidase, thioredoxin reductase, and the iodothyronine deiodinases, although the roles of other Se-containing proteins in mammalian metabolism have not been clarified. Se also has strong interactions with other nutrients such as vitamin E, toxic metals such as mercury and cadmium, and various xenobiotics.<br>For example, selenosis is likely a consequence of high Se concentrations in hair and nails as a consequence of the substitution of Se for S in certain amino acids, including the disulphide bridges that provide tertiary structure and function to proteins. For example, substitution of Se for sulphur in keratin results in weakened physical protein structure and failure of keratinised tissues such as hair and hoof. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **EFSA 2006, 2014a** | Molecular mechanisms of Se toxicity remain unclear. Several mechanisms have been suggested:<br>• Redox cycling of auto-oxidisable Se metabolites.<br>• Glutathione depletion.<br>• Protein synthesis inhibition.<br>• Depletion of S-adenosyl-methionine (cofactor for selenide methylation).<br>• General replacement of sulphur and reactions with critical sulphydryl groups of proteins and cofactors. |
| | | **OEHHA 2010** | Possible mechanisms of Se toxicity have been suggested, such as substitution of Se for sulphur in protein synthesis, inhibition of methylation metabolism resulting in selenide accumulation, or membrane and protein damage from Se-generated reactive oxygen species (ROS). Other molecular mechanisms of Se toxicity that have been suggested include redox cycling of auto-oxidisable metabolites, glutathione depletion, protein synthesis inhibition, depletion of S-adenosylmethionine (the cofactor for selenide methylation), or reactions with critical sulfhydryl groups of proteins and cofactors. |
| | | **FSANZ 2008, NHMRC 2006, WHO 2011** → No information provided | |
| 4 | Is Se an oral genotoxic carcinogen of relevance to humans? | **ATSDR 2003** | No. Studies in laboratory animals and people show that most Se compounds probably do not cause cancer; in fact, some studies in humans suggest that lower than normal Se levels in diet might increase risk of cancer. Inorganic Se compounds have been observed to have both genotoxic and anti-genotoxic effects. |
| | | **EFSA 2006, 2014a** | Except for some Se compounds not used in food, i.e. Se sulphide, Se diethyldithiocarbamate, bis-amino-phenyl Se dihydroxide, experimental data do not indicate that inorganic Se salts or organic Se compounds relevant in food and nutrition are carcinogenic. Adequate human data do not exist. Genotoxicity has been seen in a number of *in vitro* systems and also *in vivo* at toxic doses. It is likely, however, that these effects may be related to the generation of reactive oxygen radicals, being dose dependent and showing a threshold *in vivo* and not occurring at nutritionally adequate intakes. |
| | | **OEHHA 2010** | Unlikely, as evaluation of cancer incidence in studies in which Se has been administered in high doses to humans provides credible evidence that moderate to high doses of Se are not associated with increases in human cancer rates. The weight of evidence actually points in the other direction, that Se may have cancer protective properties. Both mutagenic and antimutagenic activities have been observed with inorganic Se compounds; the effects are determined by the chemical form and dose of Se. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **WHO 2011** | The Se compounds studied are unlikely to act as carcinogens at low or moderate doses in experimental animals. |
| | | **FSANZ 2008, NHMRC 2006 →** No information provided | |
| 5 | What dose(s) are associated with the critical human health endpoint? | **ATSDR 2003** | NOAEL of 819 µg/day (i.e. 0.015 mg/kg/day based on 55kg body weight of individuals in study). |
| | | **EFSA 2006, 2014a** | NOAEL of 850 µg/day for clinical selenosis in Chinese subjects. |
| | | **FSANZ 2008** | The estimated Se intake associated with selenosis in adults is 0.91 mg/day (0.02 mg/kg bw/day). This figure is based on studies of people living in areas of the US and China with Se-rich soil, as Se content of food plants is directly related to levels of Se in the soil. Supplementation trials suggest that 0.2 mg/day for 10 years, or doses of up to 0.4 mg/day for shorter times, do not produce signs of selenosis. |
| | | **NHMRC 2006** | Adults: NOAEL in adults of 800 µg/day for selenosis.<br>Infants: NOAEL of 47 µg/day (7 µg/kg bw) in infants since human milk concentrations of 60 µg/L were not associated with adverse effects. |
| | | **OEHHA 2010** | NOAEL of 0.015 mg/kg bw/d in adults (this dose led to disappearance of selenosis symptoms in recovering adults). |
| | | **WHO 2011** | The average dietary intake that is associated with selenosis has been found to be in excess of 900 µg/day. Used upper tolerable daily intake of 400 µg/day for derivation of a DWG. |
| 6 | What is the guidance / guideline value? | **ATSDR 2003** | **0.005 mg/kg/d** (NOAEL of 0.015 mg/kg/d ÷ 3; UF of 3 applied for human variability). |
| | | **EFSA 2006, 2014a** | **0.0055 mg/kg/d** (NOAEL of 850 µg/day ÷ 3 = 283 µg/d, rounded to 300 µg/d; at 55kg body weight, this equates to dose of ~0.0055 mg/kg/d. UF of 3 applied for uncertainties of the studies used to derive the upper level of intake). |
| | | **NHMRC 2006, FSANZ 2008** | **400 µg/day for adults, i.e. ~0.0057 mg/kg/d** (NOAEL of 800 µg/day ÷ 2 = 400 µg/d; at 70 kg body weight for Australian adults, this equates to a dose of ~0.0057 mg/kg/d. UF of 2 applied to protect potentially sensitive individuals & data gaps).<br>**0.007 mg/kg/d for infants** (NOAEL of 7 µg/kg/d ÷ 1; no UF deemed required as there is no evidence that maternal intakes associated with human milk in this range cause toxicity for mothers or infants). |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **OEHHA 2010** | **0.005 mg/kg/d** (NOAEL of 0.015 mg/kg/d ÷ 3; UF of 3 applied for human variability and because exposures that NOAEL is based on were mainly to selenomethionine in food rather than Se in drinking water).<br><br>OEHHA (2010) also derived a guideline value of **30 µg/L** in drinking water as follows:<br>Adults: (0.005 mg/kg/d x 70kg x 0.2) ÷ 2L/day = 35 µg/L<br>Infants: (0.005 mg/kg/d x 10kg x 0.6) ÷ 1L/day = 30 µg/L<br>The lower of the two values was recommended. |
| | | **WHO 2011** | An upper tolerable intake (derived by others) of 400 µg/day was used to derive a drinking water guideline of 40 µg/L [(400 µg/day x 0.2) ÷ 2 L/day = 40 µg/L] (considered 'provisional' because of the uncertainties inherent in the scientific database). |
| 7 | Is the health-based guidance value expressed in the best way? | **ATSDR 2003** | All jurisdictions express guidance/guideline values as doses (mg/kg/d), intakes (µg/day) or concentrations in drinking water (µg/L). The doses per kilogram body weight lend themselves better to subsequent adaption to infant or child body weight when deriving drinking water guidelines. It is noted this was not done by WHO (2011) – only the adult upper level of intake (expressed as µg/day) was used for the derivation of a DWG. |
| | | **EFSA 2006, 2014a** | |
| | | **FSANZ 2008** | |
| | | **NHMRC 2006** | |
| | | **OEHHA 2010** | |
| | | **WHO 2011** | |
| 8 | Is the proposed health-based guidance / guideline value relevant to the Australian context? | **ATSDR 2003, EFSA 2006, 2014a; FSANZ 2008, NHMRC 2006, OEHHA 2010, WHO 2011** | Yes. |
| 9 | Are there groups of people in the general population who may be more sensitive to Se exposure? | **ATSDR 2003** | Data concerning human sub-populations with unusual susceptibility to the toxic effects of Se were not located. It is possible that persons exposed to high fluoride levels in DW might be at greater risk of adverse health effects from exposure to excessive levels of Se but evidence on this point is equivocal and requires further study. Individuals with vitamin E-deficient diets might also be at greater risk of liver damage from exposure to excess Se. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **EFSA 2006, 2014a** | None identified |
| | | **OEHHA 2010** | • It is possible that those undernourished with respect to protein or methionine, or patients with hepatitis or other liver diseases, could have compromised abilities to methylate and excrete Se before it reaches toxic levels.<br>• Mutations or polymorphisms in selenoprotein-related genes may cause differential sensitivity to Se.<br>• There are some data or speculations that some small children may be more or less sensitive to Se than adults. |
| | | **FSANZ 2008, NHMRC 2006, WHO 2011** → No information provided | |
| 10 | Is there a knowledge gap from the time at which existing guideline values were developed? | **ATSDR 2003** | Potentially. Bibliography contained literature up to 2003. |
| | | **EFSA 2006, 2014a** | Potentially. Bibliography contained literature up to 2000. |
| | | **FSANZ 2008** | Potentially. Review does not appear to be comprehensive. |
| | | **NHMRC 2006** | Potentially. Bibliography contained literature up to 2003. |
| | | **OEHHA 2010** | Potentially. Bibliography contained literature up to 2010. |
| | | **WHO 2011** | Potentially. Bibliography contained literature up to 2008. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 11 | Does any recent literature change the guideline value? (e.g. demonstrating a new critical endpoint?) | | Potentially.<br>A number of large randomised clinical trials (RCTs), which investigated the potential preventative effects of Vitamin E, Se, or the two combined on the incidence and mortality from prostate cancer were in progress when the various agencies published their guidance / guideline values. The agencies therefore did not have the benefit of including these findings in their reviews.<br><br>One of these, considered by Vinceti et al. (2017) to be of high quality, indicated that a Se dose of 200 µg/day given to men aged ≥ 50 years was associated with a significant increase in secondary outcomes (i.e. alopecia [RR 1.28, 99% CI 1.01-1.62] and grade 1-2 dermatitis [RR 1.17, 99% CI 1.00-1.35]. Unfortunately, only a single dose was tested in the study, therefore there is no dose response information for the effects.<br><br>Assuming that these effects could be regarded as a minimal LOAEL, a guidance value (for excess Se) of 67 µg/d could be derived [200 µg/d ÷ UF of 3 = 67 µg/d]. An UF of 3 is suggested instead of a default of 10 for use of a minimal LOAEL since Se is also an essential element. Using this guidance value, along with the default assumptions for deriving an Australian drinking water guideline (10% relative source contribution of drinking water, 2 L/d intake) results in a candidate DWG of 3 µg/L (rounded). As this candidate DWG is lower than both the current Australian DWG and the guideline values from other jurisdictions, it seems justifiable that a more detailed review and analysis of the more recent findings for Se is warranted before a revised DWG can be recommended. |

## 4.2 Exposure-related research question analysis

### Table 9 Synthesis of extracted data for exposure-related research questions – Water Corporations

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 12 | What are the typical selenium levels in Australian drinking water? Do they vary around the country or under certain conditions e.g. source of water, drought? | **Water Corporations (ICON Water 2020, Melbourne Water 2021, PWNT 2004-2020, Seqwater 2021, Tas Water 2014-2019)** | ACT, VIC: <0.001 mg/L<br>QLD: <0.002 mg/L<br>NT: mean range <0.0002 – 0.012 mg/L (high values at Kings Canyon and Daly Waters)<br>Tas: mean range <0.0001 – 0.0025 mg/L<br><br>In certain situations (e.g. drought), Se concentrations may be higher (OEHHA 2010). |
| 13 | Do Australian levels differ considerably from elsewhere? | Low levels of Se generally found in drinking water. In the US and most parts of the World Se levels are typically <10 µg/L (i.e. <0.01 mg/L) (ATSDR 2003, WHO 2011), with more than 90% of tap water samples collected throughout the USA being below the detection limit of 1 µg/L (i.e. <0.001 mg/L) (OEHHA 2010). This suggests Se concentrations around Australia are similar to those in the USA and most other parts of the World. | |

## Table 10 Synthesis of extracted data for other exposure-related research questions

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 14 | What are the principal routes of exposure to selenium in the Australian general population? | **ATSDR 2003** | Se is an essential nutrient for humans and animals. Primary source of exposure is through the diet, and to a lesser extent through water. |
| | | **OEHHA 2010** | Compared to drinking water, food is the major overall source of Se for humans. |
| | | **WHO 2011** | Most people obtain virtually all of their Se from the foods they eat. |
| | | **EFSA 2006, 2014a; FSANZ 2008, NHMRC 2006 →** No information provided (reviews focused on diet) | |
| 15 | What are the typical levels of Australian exposure (e.g. 'background' selenium levels)? | **ATSDR 2003** | No data for Australia. Estimates of average intake of Se from food for US population range from 71-152 µg/person/day. |
| | | **EFSA 2006, 2014a** | No data for Australia. The mean intakes of non-vegetarian adults in different studies are Belgium 28-61 µg/day, Denmark 41-57 µg/day, Finland 100-110 µg/day (due to Se fertilisation), France 29-43 µg/day, United Kingdom 63 µg/day, the Netherlands 40-54 µg/day, Norway 28-89 µg/day, Spain 79 µg/day, and Sweden 24-35 µg/day. |
| | | **FSANZ 2008** | Mean (95$^{th}$ percentile) intakes of Se in Australian general population:<br>• Infant: 14 (36) µg/d.<br>• Children (2-3 yrs): 37-41 (52-70) µg/d.<br>• Adults (19-29 yrs): 57-90 (88-143) µg/d. |
| | | **NHMRC 2006** | In Australia and New Zealand, the main dietary sources are seafood, poultry and eggs and, to a lesser extent, other muscle meats. The contribution of cereal products depends on the source. Much plant Se is in the form of selenomethionine, selenocysteine or selenocysteine metabolites. Meats and seafood also contain selenoproteins with Se in the form of selenocysteine. Low soil Se levels in New Zealand mean that dietary intakes and Se status are lower than in many other countries. |
| | | **OEHHA 2010** | In the USA, for adults, the overall mean Se intake from diet alone was estimated as 114 µg/day. The 90th percentile Se intake for diet plus supplements is estimated as 175 µg/day.<br>The average total daily Se consumption in infants zero to six months of age was estimated as 35 µg/day, which would correspond to Se derived from breast milk or formula, water, and any supplemental foods. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **WHO 2011** | Global Se intakes vary significantly; average intakes were relatively high in North America (85–150 µg/day), moderate in Europe (40–90 µg/day) and low in parts of China (10–20 µg/day). In Europe, dietary Se intakes have declined in recent decades: 29–39 µg/day in the United Kingdom and 30–80 µg/day in the Nordic countries in 1997, compared with earlier intakes of 40–90 µg/day. This decline has been attributed to reductions in the importation of higher-Se wheat grown in North America. |

## 4.3 Risk-based research question analysis

### Table 11 Synthesis of extracted data for risk-associated research questions

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 16 | What are the risks to human health from exposure to selenium in Australian drinking water? | **ATSDR 2003, OEHHA 2010** | None identified. |
| | | **FSANZ 2008** | No information on drinking water. A very small proportion (≤0.6%) of males aged 2-3, 4-8, 9-13 and 14-18 years had intakes greater than their respective ULs. However, as the ULs are highly conservative estimates extrapolated from infant ULs, according to FSANZ (2008) this finding is not considered to be of concern. All other groups had Se intakes below their respective ULs. On this basis, there is no evidence to suggest that intake of Se by the Australian population exceeds safe levels. |
| | | **WHO 2011** | Water is not normally a major source of Se intake, but it is important that a proper balance be achieved between recommended intakes and undesirable intakes in determining an appropriate guideline value for Se in drinking-water. |
| | | **EFSA 2006, 2014a; NHMRC 2006** → No information on drinking water. | |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 17 | Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review? | **ATSDR 2003, EFSA 2006, 2014a; FSANZ 2008, NHMRC 2006, OEHHA 2010, WHO 2011** | None identified. |
| | | **Literature from evidence scan** | As mentioned in response to research question No. 11, there is some concern in recent literature that Se guidance values and resulting DWGs may not be appropriate, as comprehensive experimental RCT studies suggest adverse effects from Se exposure may be observed at lower doses than those typically assumed to be NOAELs for derivation of a DWG. |

## 4.4 Supporting factsheet information research question analysis

The supporting information in the fact sheet for Se consists of the following (NHMRC and NRMMC 2011):

- **General Description:** "*Selenium and selenium salts are widespread in the environment. Selenium is released from natural and human-made sources, with the main source being the burning of coal. Selenium is also a by-product of the processing of sulfide ores, chiefly in the copper refining industry.*

  *The major use of selenium is in the manufacture of electronic components. It is used in several other industries, and selenium compounds are used in some insecticides, in hair shampoos as an anti-dandruff agent, and as a nutritional feed additive for poultry and livestock.*

  *Selenium concentrations in source waters are generally very low and depend on local geochemistry, pH and the presence of iron salts. Concentrations in drinking water supplies overseas are generally below 0.01 mg/L but groundwater concentrations as high as 6 mg/L have been reported in the United States.*

  *Food is the major source of intake for Australians. Cereal and grain products contribute most to intake, while fish and liver contain the highest selenium concentrations. Average daily intakes for Australian adults are between 0.06 mg and 0.13 mg."*
- **Typical values in Australian drinking water:** "*In major Australian reticulated supplies, selenium concentrations are less than 0.005 mg/L. Selenium concentrations in groundwater are not a problem in Australia, as they are in some overseas supplies*".
- **Treatment of drinking water:** "*Selenium concentrations in drinking water can be reduced by coagulation with ferric chloride and by lime softening. Coagulation with alum is much less effective. Activated alumina absorption is the most effective means of treatment, but only at low pH.".*
- **Measurement: "***The selenium concentration in drinking water can be determined by hydride generation followed by atomic absorption spectroscopy (APHA Method 3500-Se Part C 1992). The limit of determination is 0.001 mg/L***.**"

**Table 12 Synthesis of extracted data for research questions relevant to supporting factsheet information – Agency reviews**

| # | Research Questions | | Jurisdiction | Response to Research Questions |
|---|---|---|---|---|
| 18 | Is this information current? | Uses | **ATSDR 2003** | Yes, but some additional uses mentioned (e.g. used in some photographic devices, gun bluing, plastics, paints, and certain types of glass). |

| # | Research Questions | | Jurisdiction | Response to Research Questions |
|---|---|---|---|---|
| | | | **OEHHA 2010** | Yes, but some additional uses mentioned (e.g. used in rectifiers, photoelectric cells, blasting caps, xerography, electrostatic printing, stainless steel, optical lenses, exposure meters, and as a dehydrogenation catalyst; combinations of bismuth and Se are added to brasses to replace lead in plumbing applications; small amounts of Se are added to vulcanised rubber to increase its resistance to abrasion). |
| | | | **EFSA 2006, 2014a, FSANZ 2008, NHMRC 2006, WHO 2011 →** No information provided. | |
| | | Sources in DW | **ATSDR 2003** | Yes, with some additional detail provided that weathering of rocks and soils may result in low levels of Se in water, which may be taken up by plants. Disposal of Se in commercial products and waste could also increase the amount of Se in soil. |
| | | | **OEHHA 2010** | Yes, the major source of Se in the environment is the weathering of rocks and soils, but human activities also contribute. Selenates can leach from soil, transport to groundwater, and is the form of Se most readily taken up by plants. |
| | | | **EFSA 2006, 2014a, FSANZ 2008, NHMRC 2006, WHO 2011 →** No information provided. | |
| 19 | What are the indicators of the risks? How can we measure exposure? Is the information on measurement/analytical methods current? | | **ATSDR 2003** | Yes, information is current, except that ICP/AES is also mentioned.<br>• Atomic Absorption Spectrophotometry (AAS) (LOD 2 µg/L)<br>• ICP/AES (LOD 0.06 µg/L) |
| | | | **WHO 2011** | Yes, information is current, except the detection limit is listed as 0.5 µg/L instead of 1 µg/L and ICP is also mentioned as an alternative measurement technology with a similar detection limit. |
| | | | **EFSA 2006, 2014a, FSANZ 2008, NHMRC 2006, OEHHA 2010 →** No information provided. | |

## Table 13 Synthesis of extracted data for research questions relevant to supporting factsheet information – Other sources

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| 19 | What are the indicators of the risks? How can we measure exposure? Is the information on measurement / analytical methods current? | **Correspondence with Australian Commercial Laboratories** | ICP-MS or ICP-AES (standard LOR 1 µg/L, trace 0.1-0.2 µg/L). |
| | | **Water Corporations (ICON Water 2020, Melbourne Water 2021, PWNT 2004-2020, Seqwater 2021, Tas Water 2014-2019)** | USEPA 200.8 (LOR 1 µg/L). |
| | | **Ma et al. 2017** | ICP-AES (no LOR provided). |
| | | **Taseidifar et al. 2019** | ICP-MS (no LOR provided). |
| 20 | Are there commercial analytical methods available that can measure at or below guideline value? | **Correspondence with Australian Commercial Laboratories** | Yes, standard LORs in Australian laboratories are 1 µg/L with trace LORs at 0.1-0.2 µg/L. Candidate guideline values range from 10 µg/L (the current Australian DWG) to 40 µg/L (the WHO DWG). It is noted, even if the DWG resulting from using the information obtained in the evidence scan were used (3 µg/L), this would still be measurable with current analytical methods. |
| | | **Water Corporations (ICON Water 2020, Melbourne Water 2021, PWNT 2004-2020, Seqwater 2021, Tas Water 2014-2019)** | |
| | | **Ma et al. 2017, Taseidifar et al. 2019** → No information provided. | |
| 21 | Is the information for treatment options current in terms of current practices in Australia? | **Correspondence with Australian Commercial Laboratories** | No information provided |
| | | **Water Corporations (ICON Water 2020, Melbourne Water 2021, PWNT 2004-2020, Seqwater 2021, Tas Water 2014-2019)** | |
| | | **Ma et al. 2017** | Does not provide information on commercial treatment technologies. This publication investigated the use of $MoS4^{2-}$ intercalated Mg/Al layered double hydroxide as a sorbent (MgAl-MoS4-LDH, abbr. MoS4-LDH) for Se ions. |

| # | Research Questions | Jurisdiction | Response to Research Questions |
|---|---|---|---|
| | | **Taseidifar et al. 2019** | Does not provide information on commercial treatment technologies. This publication investigated the use of a natural, biodegradable surfactant obtained using a novel and efficient chemical reaction between cysteine (a thiol-based amino acid) and an octanoyl (C8) compound, for its application to the ion flotation removal of low levels of different contaminant ions from aqueous solution. |
| 22 | Can treatment technologies treat to the suggested level of the guideline value? | **Correspondence with Australian Commercial Laboratories** | No information from this source. |
| | | **Water Corporations (ICON Water 2020, Melbourne Water 2021, PWNT 2004-2020, Seqwater 2021, Tas Water 2014-2019)** | Although no direct information was available from these sources, the majority of tap water supplied water across Australia contains Se concentrations <2.5 µg/L, which is lower than all candidate guideline values (including the one that would result using the minimal LOAEL from RCT study identified in the evidence scan). This suggests that current source waters contain only low Se concentrations and/or treatment technologies would be effective to maintain Se concentrations below any suggested guideline value. |
| | | **Ma et al. 2017** | Achieves concentrations <10 µg/L which is the current Australia DWG. |
| | | **Taseidifar et al. 2019** | This technology was not very effective at removing Se. |
| 23 | Is there any new information which should be added? Should anything be removed? | | Typical values in Australian drinking water can be amended to be less than 2.5 µg/L in line with the literature sourced for this report. Measurement section should also include ICP-MS and ICP-AES and their limits of detection since these techniques appear to be the ones used by commercial laboratories to measure Se in drinking water. |

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# APPENDIX A

## Literature search screening outcome spreadsheets

Appendix A contents here

# APPENDIX B

## Data extraction tables – Health-based guidance/guidelines

## Existing Health-Based Guidance for Selenium

# ATSDR 2003

| **Agency Report Reference:** ***ATSDR (2003). Toxicological Profile for Selenium. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. September 2003.*** | | |
|---|---|---|
| General Information | Date of data extraction | 08/12/2021 |
| | Authors | Risher J, McDonald AR, Citra MJ, Bosch S, Amata RJ |
| | Publication date | September 2003 |
| | Literature search timeframe | Not stated, but bibliography contained literature up to 2003. |
| | Publication type | Agency review |
| | Peer reviewed? | Yes, profile underwent numerous internal ATSDR reviews, was peer reviewed by a non-governmental panel and was released for public comment prior to finalisation. |
| | Country of origin | United States |
| | Source of funding | Not stated, but assumed to be United States government |
| | Possible conflicts of interest | Not indicated |
| Health considerations | Guideline value type (e.g. oral TRV, drinking water guideline) | Oral Minimal Risk Level (MRL). |
| | Exposure timeframe | Chronic exposure (>365 days) |
| | Critical health endpoint(s) – oral exposure | Selenosis (i.e. morphological changes in fingernails, brittle hair, loss of fingernails and hair). In extreme cases, people may lose feeling and control in arms and legs. |
| | Justification provided by agency for critical endpoint | Selenosis is known to occur in humans at very high Se intakes. Very high amounts of Se have also caused decreased sperm counts, increased abnormal sperm, changes in the female reproductive cycle in rats, and changes in the menstrual cycle in monkeys. However, the relevance of reproductive effects of Se exposure in animals to potential reproductive effects in humans is not known. Se compounds have not been shown to cause birth defects. |
| | Critical study(ies) underpinning point of departure | Yang and Zhou 1994 [study of human populations in villages in China (including 5 study participants exhibiting signs of selenosis) where people were exposed to foods high in Se for months to years]. |
| | Species for critical study(ies) | Humans |
| | Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc) | NOAEL |
| | Point of departure value (include units) | 819 µg/day (i.e. 0.015 mg/kg/day based on 55kg body weight of individuals in study) |

| **Agency Report Reference:** ***ATSDR (2003). Toxicological Profile for Selenium. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. September 2003.*** | | |
|---|---|---|
| | Uncertainty factor(s) & rationale | 3 (for human variability).<br>This UF was considered appropriate because the individuals in this study were sensitive individuals drawn from a larger population and due to supporting studies which show NOAEL is consistent with NOAELs observed for other human populations. |
| | The derivation: | NOAEL of 0.015 mg/kg/d ÷ 3 = 0.005 mg/kg/d |
| | Guidance value (include units) | **0.005 mg/kg/d**<br>(The MRL does not represent a threshold for toxicity, but a daily intake that ATSDR considers to be safe for all populations). |
| | Mode of action for critical health endpoint | Several mechanisms have been proposed to explain the various long-term toxic effects of excess Se, such as alterations in the hair, skin, nails, liver, thyroid, and nervous system. This includes information on mechanisms by which Se exerts effects as a component of glutathione peroxidase, thioredoxin reductase, and the iodothyronine deiodinases, although the roles of other Se-containing proteins in mammalian metabolism have not been clarified. Se also has strong interactions with other nutrients such as vitamin E, toxic metals such as mercury and cadmium, and various xenobiotics.<br>For example, selenosis is likely a consequence of high Se concentrations in hair and nails as a consequence of the substitution of Se for S in certain amino acids, including the disulphide bridges that provide tertiary structure and function to proteins. For example, substitution of selenium for sulphur in keratin results in weakened physical protein structure and failure of keratinised tissues such as hair and hoof. |
| | Genotoxic oral carcinogen? | No. Studies in laboratory animals and people show that most Se compounds probably do not cause cancer; in fact, some studies in humans suggest that lower than normal Se levels in diet might increase risk of cancer.<br>Inorganic Se compounds have been observed to have both genotoxic and anti-genotoxic effects.<br>No further investigation is needed since humans have not been shown to have an increased risk of malignancy from selenium exposure. |
| | Identified sensitive sub-populations | Data concerning human sub-populations with unusual susceptibility to the toxic effects of Se were not located.<br>It is possible that persons exposed to high fluoride levels in drinking water might be at greater risk of adverse health effects from exposure to excessive levels of Se but evidence on this point is equivocal and requires further study.<br>Individuals with vitamin E-deficient diets might also be at greater risk of liver damage from exposure to excess Se.<br>Babies born early may be more sensitive to not having enough Se, and this deficiency may contribute to lung effects. |
| | Any non-health-based considerations? | No. |

| **Agency Report Reference:** ***ATSDR (2003). Toxicological Profile for Selenium. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. September 2003.*** | | |
|---|---|---|
| Exposure considerations | Principal routes of exposure in general population | Se is an essential nutrient for humans and animals. Primary source of exposure is through the diet, and to a lesser extent through water. |
| | Levels in drinking water supplies (include location) | Low levels of Se generally found in drinking water. In the US Se levels are typically <10 µg/L. |
| | Any special considerations to exposure levels (e.g. higher in drought?) | None noted for drinking water. |
| | Typical exposure in general population (include units for intakes & location) | Estimates of average intake of Se from food for US population range from 71-152 µg/person/day (approximately 1–2 µg/kg/day in adults). |
| Risk Summary | Any risks to human health from drinking water identified in agency document? | No. |
| | Any emerging risks identified? | No. |
| **References:**<br>Yang G and Zhou R (1994). Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electrolytes Health Dis 8:159-165. *As cited in ATSDR 2003.* | | |

## EFSA 2006, 2014a

| ***Agency Report Reference: EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority (EFSA). European Food Safety Authority.***<br><br>***Agency Report Reference: EFSA (2014a). Scientific Opinion on Dietary Reference Values for selenium. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2014;12(10):3846.*** | | |
|---|---|---|
| General Information | Date of data extraction | 08/12/2021 |
| | Authors | Authors not listed. |
| | Publication date | February 2006<br>(EFSA 2014a refers back to EFSA 2006, but does not appear to specifically re-evaluate the information in relation to Se excess). |
| | Literature search timeframe | Not stated, but bibliography contains literature up to 2000. |
| | Publication type | Agency review |
| | Peer reviewed? | Not stated |
| | Country of origin | Europe |
| | Source of funding | European Union |

| | | |
|---|---|---|
| ***Agency Report Reference: EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority (EFSA). European Food Safety Authority.***<br><br>***Agency Report Reference: EFSA (2014a). Scientific Opinion on Dietary Reference Values for selenium. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2014;12(10):3846.*** | | |
| | Possible conflicts of interest | No information provided. |
| Health considerations | Guideline value type (e.g. oral TRV, drinking water guideline) | Upper Level (UL) of Intake |
| | Exposure timeframe | Chronic exposure |
| | Critical health endpoint(s) – oral exposure | Selenosis (i.e. brittle hair with intact follicles, new hair with no pigment, thickened nails or brittle nails with spots and longitudinal streaks on surface). In extreme cases, symptoms of neurological disturbance have been observed (e.g. peripheral anaesthesia, acroparaesthesia, pain, hyperreflexia, numbness, convulsions, paralysis, motor disturbances). |
| | Justification provided by agency for critical endpoint | • No indication of teratogenicity of Se has been shown in humans even in the areas of high Se intake in China.<br>• Except for the studies of a population in seleniferous areas in the USA, more recent Chinese studies of endemic Se toxicity in humans and a 1991 American study, there are only anecdotal reports on chronic Se toxicity in humans. |
| | Critical study(ies) underpinning point of departure | Yang et al. 1989b, Yang and Zhou 1994 |
| | Species for critical study(ies) | Humans |
| | Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc) | NOAEL |
| | Point of departure value (include units) | 850 µg/day for clinical selenosis in Chinese subjects (349 study participants). |
| | Uncertainty factor(s) & rationale | 3 (for uncertainties of the studies used in deriving an upper level) |
| | The derivation: | 850 µg/day ÷ 3 = 283 (rounded to **300 µg/day**). Value is for adults.<br><br>No data are available to suggest that other life-stage groups have increased susceptibility to adverse effects of high Se intake. Therefore, the UL of 300 µg per day should be considered to apply also to pregnant and lactating women. |
| | Guideline value (include units) | **300 µg/day** in adults<br>(at 55 kg body weight, this would be 5.5 µg/kg/d)<br>(this was extrapolated to children using standard body weights) |

| | | |
|---|---|---|
| ***Agency Report Reference: EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority (EFSA). European Food Safety Authority.***<br><br>***Agency Report Reference: EFSA (2014a). Scientific Opinion on Dietary Reference Values for selenium. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2014;12(10):3846.*** | | |
| | Mode of action for critical health endpoint | Molecular mechanisms of Se toxicity remain unclear. Several mechanisms have been suggested:<br>• Redox cycling of auto-oxidisable Se metabolites.<br>• Glutathione depletion.<br>• Protein synthesis inhibition.<br>• Depletion of S-adenosyl-methionine (cofactor for selenide methylation).<br>• General replacement of sulphur and reactions with critical sulphydryl groups of proteins and cofactors. |
| | Genotoxic oral carcinogen? | Except for some Se compounds not used in food, i.e. Se sulphide, Se diethyldithiocarbamate, bis-amino-phenyl Se dihydroxide, experimental data do not indicate that inorganic Se salts or organic Se compounds relevant in food and nutrition are carcinogenic. Adequate human data do not exist. Genotoxicity has been seen in a number of *in vitro* systems and also *in vivo* at toxic doses. It is likely, however, that these effects may be related to the generation of reactive oxygen radicals, being dose dependent and showing a threshold *in vivo* and not occurring at nutritionally adequate intakes. |
| | Identified sensitive sub-populations | None identified. |
| | Any non-health-based considerations? | No. |
| Exposure considerations | Principal routes of exposure in general population | No information provided (review focused on foods). |
| | Levels in drinking water supplies (include location) | No information provided. |
| | Any special considerations to exposure levels (e.g. higher in drought?) | No information provided. |

| | | |
|---|---|---|
| ***Agency Report Reference: EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority (EFSA). European Food Safety Authority.***<br><br>***Agency Report Reference: EFSA (2014a). Scientific Opinion on Dietary Reference Values for selenium. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2014;12(10):3846.*** | | |
| | Typical exposure in general population (include units for intakes & location) | The mean intakes of non-vegetarian adults in different studies are Belgium 28-61 µg/day, Denmark 41-57 µg/day, Finland 100-110 µg/day (due to Se fertilisation), France 29-43 µg/day, United Kingdom 63 µg/day, the Netherlands 40-54 µg/day, Norway 28-89 µg/day, Spain 79 µg/day, and Sweden 24-35 µg/day.<br>In follow-up studies of a Chinese population of about 400 individuals which was evaluated for clinical and biochemical signs of Se toxicity, the average daily intakes based on lifetime exposures were 70, 195 and 1438 µg, and 62, 198 and 1288 µg for adult males and females, respectively, in the low-, medium- and high-Se areas (clinical signs of selenosis were only seen in subjects living in the high Se area). |
| Risk Summary | Any risks to human health from drinking water identified in agency document? | None for drinking water or food in western countries.<br><br>Based on the information on Se toxicity, there are areas in the world where there is a human intake of Se with no or only very small safety margins to levels where toxicity may occur. However, in most European countries the mean intake levels are much lower, in the lower range of 30-90 µg Se/day, except for Norway, that has a somewhat higher mean intake (60 µg Se/day) due to import of wheat rich in Se. Finland has an intake of 100-110 µg Se/day because of Se fertilisation. The margin between the present mean intake, excluding supplements, in the European population and an UL (adult) of 300 µg Se/day would be between 2.7 to 10. The 97.5 percentile intake was 81 and 90 µg Se/day in Italy and The Netherlands, respectively, giving a margin to the UL of about 2.7. |
| | Any emerging risks identified? | No |

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Yang G and Zhou R (1994). Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electolytes Health Dis 8: 159-165. *As cited in EFSA 2006.*

## FSANZ 2008

| **Agency Report** ***Reference: FSANZ (2008). The 22nd Australian Total Diet Study. Food standards Australia and New Zealand.*** | | |
|---|---|---|
| General Information | Date of data extraction | 09/12/2021 |
| | Authors | No authors listed |
| | Publication date | 2008 |
| | Publication type | Agency evaluation |
| | Description | No guidance value was derived in this document, however it contains relevant information on dietary exposure by the Australian general population. |

| **Agency Report** ***Reference: FSANZ (2008). The 22nd Australian Total Diet Study. Food standards Australia and New Zealand.*** | | |
|---|---|---|
| | Findings | • Se is a naturally occurring trace element and essential nutrient.<br>• Indications of chronic Se poisoning (selenosis) include brittleness and loss of hair and nails, skin lesions, gastrointestinal disturbances and effects on the nervous system. The estimated Se intake associated with selenosis in adults is 0.91 mg/day (0.02 mg/kg bw/day). This figure is based on studies of people living in areas of the US and China with Se-rich soil, as Se content of food plants is directly related to levels of Se in the soil. Supplementation trials suggest that 0.2 mg/day for 10 years, or doses of up to 0.4 mg/day for shorter times, do not produce signs of selenosis.<br>• Acute selenium poisoning appears to occur at doses higher than 0.5 mg/kg bw or a single dose of 250 mg. Daily intakes below 400 µg (0.4 mg) are considered safe for almost all individuals.<br>• Australian reference health standards for Se in different population groups have been established by the NHMRC (2006) – see summary for NHMRC (2006).<br>• The UL for adults of 400 µg/day is based on the No Observable Adverse Effect Level (NOAEL) of 800 µg/day for brittleness and loss of hair and nails, gastrointestinal disturbances, skin rash, fatigue and effects on the nervous system, and using an uncertainty factor of two to protect sensitive individuals and because of data gaps.<br>• The ULs for infants are based on a NOAEL of 7 µg/kg bw from studies showing that human milk concentrations of 60 µg/L are not associated with adverse effects. ULs for children and adolescents are extrapolated from the infant UL on a body weight basis.<br>• Mean (95$^{th}$ percentile) intakes of Se in Australian general population:<br>  ○ Infant: 14 (36) µg/d.<br>  ○ Children (2-3 yrs): 37-41 (52-70) µg/d.<br>  ○ Adults (19-29 yrs): 57-90 (88-143) µg/d.<br>• Bread made the highest contribution (~15 to 30%) to Se intake for all age and gender groups assessed, other than for infants where infant formula was the most important dietary source of Se.<br>• A very small proportion (≤0.6%) of males aged 2-3, 4-8, 9-13 and 14-18 years had intakes greater than their respective ULs. However, as the ULs are highly conservative estimates extrapolated from infant ULs, which were derived using an uncertainty factor of one, this finding is not considered to be of concern. All other groups had selenium intakes below their respective ULs. On this basis, there is no evidence to suggest that intake of Se by the Australian population exceeds safe levels. |

# NHMRC 2006

| **Agency Report Reference: NHMRC *(2006). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. National Health and Medical Research Council. Version 1.2, updated September 2017.*** | | |
|---|---|---|
| General Information | Date of data extraction | 09/12/2021 |
| | Authors | Not listed. |
| | Publication date | 2006 |
| | Literature search timeframe | Not specifically stated, but an expert review of recommendations relevant to Australia published in 2001 and an evidence-based review of several international recommendations published in 2003 were available to the committee. Bibliography contains literature up to 2003. |
| | Publication type | Agency review |
| | Peer reviewed? | An expert Working Party was appointed to oversee the process with representation from Australia and New Zealand, including end users from the clinical and public health nutrition research sector, the food industry, the dietetics profession, the food legislative sector and the Australian and New Zealand governments. The current publication, its recommendations and its associated Appendix, are the result of that review process. |
| | Country of origin | Australia/New Zealand joint initiative |
| | Source of funding | New Zealand Ministry of Health funded some initial work for review process that provided expert input into revision of iodine and selenium. NHMRC was then commissioned to manage the joint Australian/New Zealand revision process. |
| | Possible conflicts of interest | Not stated. |
| Health considerations | Guideline value type (e.g. oral TRV, drinking water guideline) | Upper Level of intake (UL) |
| | Exposure timeframe | Chronic (long-term exposure) |
| | Critical health endpoint(s) – oral exposure | Brittleness and loss of hair and nails in humans, as well as gastrointestinal disturbance, skin rash, fatigue, irritability and nervous system abnormalities. |
| | Justification provided by agency for critical endpoint | There are limited data on the toxicity of Se in humans, with the critical effects being the only ones shown in human studies of high Se intakes. |
| | Critical study(ies) underpinning point of departure | Adults: Studies in China (Yang et al. 1983, 1989b, Yang and Zhou 1994), consistent with one US study (Longnecker et al. 1991)<br><br>Infants: Shearer & Hadjimarkos (1975) |
| | Species for critical study(ies) | Humans |

| **Agency Report Reference: NHMRC *(2006). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. National Health and Medical Research Council. Version 1.2, updated September 2017.*** | | |
|---|---|---|
| | Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc) | Adults: NOAEL in adults of 800 µg/day for selenosis<br>Infants: NOAEL of 47 µg/day (7 µg/kg bw) in infants since human milk concentrations of 60 µg/L were not associated with adverse effects. |
| | Point of departure value (include units) | Adults: 800 µg/day<br>Infants: 47 µg/day (7 µg/kg/d) |
| | Uncertainty factor(s) & rationale | Adults: UF of 2 to protect sensitive individuals because of gaps in data and incomplete knowledge, bearing in mind that the toxic effect of Se is not severe but may be irreversible.<br><br>Infants: UF of 1, as there is no evidence that maternal intakes associated with human milk in this range cause toxicity for mothers or infants.<br><br>Older children: As there is no evidence of increased toxicity in older children and adolescents, the ULs for these groups were estimated on a body weight basis from the younger infant data using the level of 7 µg/kg/d. |
| | The derivation: | Adults: 800 µg/day ÷ 2 = 400 µg/day<br>Infants, children & adolescents: 7 µg/kg/d |
| | Guidance value (include units) | **Adults (including pregnant & lactating women): 400 µg/day**<br>**Infants (0-6 months): 45 µg/day**<br>**Infants (7-12 months): 60 µg/day**<br>**Children (1-3 years): 90 µg/day**<br>**Children (4-8 years): 150 µg/day**<br>**Children (9-13 years): 280 µg/day** |
| | Mode of action for critical health endpoint | Not provided. |
| | Genotoxic oral carcinogen? | No information provided. |
| | Identified sensitive sub-populations | No information provided. |
| | Any non-health-based considerations? | No (except that Se is an |
| Exposure considerations | Principal routes of exposure in general population | Not stated, but diet is primarily discussed. |
| | Levels in drinking water supplies (include location) | No information provided. |
| | Any special considerations to exposure levels (e.g. higher in drought?) | No information provided. |

| **Agency Report Reference: NHMRC *(2006). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. National Health and Medical Research Council. Version 1.2, updated September 2017.*** | | |
|---|---|---|
| | Typical exposure in general population (include units for intakes & location) | In Australia and New Zealand, the main dietary sources are seafood, poultry and eggs and, to a lesser extent, other muscle meats. The contribution of cereal products depends on the source. Much plant selenium is in the form of selenomethionine, selenocysteine or selenocysteine metabolites. Meats and seafood also contain selenoproteins with selenium in the form of selenocysteine. Low soil selenium levels in New Zealand mean that dietary intakes and selenium status are lower than in many other countries. |
| Risk Summary | Any risks to human health from drinking water identified in agency document? | No information provided. |
| | Any emerging risks identified? | No. |

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Yang G-Q, Zhou R-H. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electrolytes Hlth Dis 1994;8:159–65. *As cited in NHMRC 2006.*

## OEHHA 2010

| **Agency Report Reference: *OEHHA (2010). Public health goals for chemicals in drinking water – Selenium. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2010.*** | | |
|---|---|---|
| General Information | Date of data extraction | 10/12/2021 |
| | Authors | Wang Y |
| | Publication date | December 2010 |
| | Literature search timeframe | Not stated, but bibliography contains literature up to 2010. |
| | Publication type | Agency review |

| **Agency Report Reference:** ***OEHHA (2010). Public health goals for chemicals in drinking water – Selenium. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2010.*** | | |
|---|---|---|
| | Peer reviewed? | Yes |
| | Country of origin | USA (Californian Government) |
| | Source of funding | Not stated, however appears to be the Government of California. |
| | Possible conflicts of interest | Not stated in this document. |
| Health considerations | Guideline value type (e.g. oral TRV, drinking water guideline) | Public Health Goal (PHG) or Drinking water guideline |
| | Exposure timeframe | Chronic (long-term exposure) |
| | Critical human health endpoint | Hair loss and nail damage (i.e. selenosis) |
| | Justification provided by agency for critical endpoint | The PHG is based on a comprehensive assessment of animal and human studies on both toxicity and essentiality of water-soluble and bioavailable selenium compounds.<br>The extensive field studies on humans provide a database for the best estimates of the toxic doses to adult humans for chronic oral exposures to Se, including dietary and drinking water intakes. |
| | Critical study(ies) underpinning point of departure | Yang et al. (1981; 1982a,b; 1983; 1987; 1988a,b; 1989a,b), Yang (1987), Yang and Zhou (1994), and Yang and Xia (1995) |
| | Species for critical study(ies) | Humans |
| | Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc) | NOAEL |
| | Point of departure value (include units) | Adults: 0.015 mg/kg bw/d (this dose led to disappearance of selenosis symptoms in recovering adults) |
| | Uncertainty factor(s) & rationale | Adults: 3x to account for potentially sensitive sub-populations such as infants, pregnant women and their foetuses, the undernourished with respect to proteins and methionine and patients with liver diseases.<br>The uncertainty factor is also recommended because the human exposures that the NOAEL is based on were mainly to selenomethionine (in food) rather than Se in drinking water. |
| | The derivation: | Adults:<br>0.015 ÷ 3 = 0.005 mg/kg/d<br>0.005 mg/kg/d x 70 kg bw = 0.35 mg/d (i.e. 350 µg/d).<br><br>Adults:<br>(0.005 mg/kg/d x 70kg x 0.2) ÷ 2L/day = 35 µg/L<br><br>Infants:<br>(0.005 mg/kg/d x 10kg x 0.6) ÷ 1L/day = 30 µg/L |
| | Guideline value (include units) | 30 µg/L |

| **Agency Report Reference:** ***OEHHA (2010). Public health goals for chemicals in drinking water – Selenium. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2010.*** | | |
|---|---|---|
| | Mode of action for critical health endpoint | Possible mechanisms of Se toxicity have been suggested, such as substitution of Se for sulphur in protein synthesis, inhibition of methylation metabolism resulting in selenide accumulation, or membrane and protein damage from Se-generated reactive oxygen species (ROS). Other molecular mechanisms of Se toxicity that have been suggested include redox cycling of auto-oxidisable metabolites, glutathione depletion, protein synthesis inhibition, depletion of S-adenosylmethionine (the cofactor for selenide methylation), or reactions with critical sulfhydryl groups of proteins and cofactors. |
| | Genotoxic carcinogen? | Unlikely, as evaluation of cancer incidence in studies in which Se has been administered in high doses to humans provides credible evidence that moderate to high doses of Se are not associated with increases in human cancer rates. The weight of evidence actually points in the other direction, that Se may have cancer protective properties.<br>Both mutagenic and antimutagenic activities have been observed with inorganic Se compounds; the effects are determined by the chemical form and dose of Se. |
| | Identified sensitive sub-populations | • It is possible that those undernourished with respect to protein or methionine, or patients with hepatitis or other liver diseases, could have compromised abilities to methylate and excrete Se before it reaches toxic levels.<br>• Mutations or polymorphisms in selenoprotein-related genes may cause differential sensitivity to selenium.<br>• There are some data or speculations that some small children may be more or less sensitive to selenium than adults. |
| | Any non-health based considerations? | No. |
| Exposure considerations | Principal routes of exposure in general population | Compared to drinking water, food is the major overall source of selenium for humans. |
| | Levels in drinking water supplies (include location) | Drinking water in the U.S. generally has low Se concentrations. One study reported Se in range of 0.12 to 0.44 µg/L, with selenate as the primary Se species. The total dissolved Se level was less than 0.32 µg/L in one U.S. study, less than 1 to 2 µg/L in another study, and less than 0.2 µg/L in New York. More than 90 percent of 4,200 tap water samples collected throughout the U.S. were below the method detection limit of 1 µg/L; the mean Se concentration of the rest (less than 10 percent) was 3.5 µg/L, with a range from 1 to 6.5 µg/L. |
| | Any special considerations to exposure levels (e.g. higher in drought?) | In certain situations (e.g. drought), Se concentrations may be higher. For example, in 1975 during a period of drought in rural south-eastern Colorado (USA), Se levels in well water used for drinking ranged from 50-125 µg/L. |

| **Agency Report Reference:** ***OEHHA (2010). Public health goals for chemicals in drinking water – Selenium. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2010.*** | | |
|---|---|---|
| | Typical exposure in general population (include units for intakes & location) | In the USA, for adults, the overall mean Se intake from diet alone was estimated as 114 µg/day. The 90th percentile Se intake for diet plus supplements is estimated as 175 µg/day.<br>The average total daily Se consumption in infants zero to six months of age was estimated as 35 µg/day, which would correspond to Se derived from breast milk or formula, water, and any supplemental foods. |
| Risk Summary | Any risks to human health from drinking water identified in agency document? | No. |
| | Any emerging risks identified? | - |

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

**References:**

Yang GQ, Wang SZ, Zhou RH, Sun SS, Man RG, et al. (1981). Investigation on loss of hair and nail of unknown etiology endemic selenosis. Acta Acad Med Sinica (Zhong Kuo Yi Xue Ke Xue Yuan Xue Bao, China) 3(Suppl 2):1-6. *As cited in OEHHA 2010.*

Yang GQ, Zhou RH, Sun SZ, Wang SS, Li SS (1982a). Endemic selenium intoxication of man in China and the selenium levels of human body and environment. Acta Nutr Sinica (Ying Yang Xue Bao, China) 4(2):81-9. *As cited in OEHHA 2010.*

Yang GQ, Wang GY, Yin TA, Sun SZ, Zhou RH, et al. (1982b). Relationship between the distribution of Keshan disease and selenium status. Acta Nutri Sinica (Ying Yang Xue Bao, China) 4(3):191-200. *As cited in OEHHA 2010.*

Yang GQ, Wang SZ, Zhou RH, Sun SZ (1983). Endemic selenium intoxication of humans in China. Am J Clin Nutr 37(5):872-81. *As cited in OEHHA 2010.*

Yang GQ, Zhu LZ, Liu SJ, Gu LZ, Qian PC, Huang JH, Lu MD (1987). Human selenium requirements in China. In: Selenium in Biology and Medicine, Proc Third Internatl Sympos on Selenium in Biology and Medicine, May 27-June 1, 1984, Chinese Academy of Medical Sciences, Beijing, China, Combs GF Jr, Spallholz JE, Levander OA, Oldfield JE, eds. Van Nostrand Reinhold, New York, New York, pp. 589-607. *As cited in OEHHA 2010.*

Yang GQ (1987). Research on selenium-related problems in human health in China. In: Selenium in Biology and Medicine, Proc Third Internatl Sympos on Selenium in Biology and Medicine, May 27-June 1, 1984, Chinese Academy of Medical Sciences, Beijing, China. Combs GF Jr, Spallholz JE, Levander OA, Oldfield JE, eds, Van Nostrand Reinhold, New York, New York, pp. 9-32. *As cited in OEHHA 2010.*

Yang GQ, Ge KY, Chen JS, Chen XS (1988a). Selenium-related endemic diseases and the daily selenium requirement of humans. In: Sociological and Medical Aspects of Nutrition, World Rev Nutr Diet, Bourne GH, ed. Karger, Basel, Switzerland, Vol 55, pp. 58-97. *As cited in OEHHA 2010.*

Yang GQ, Gu L, Zhou R, Yin S (1988b). Studies of human maximal safe intake and requirements of selenium. In: Selenium in Biology and Meducine, Proc Fourth Internatl Symposium on Selenium in Biology and Medicine, July, 1988, Tubingen, West Germany, Wendel A, ed. Springer-Verlag, New York, New York, pp. 223-8. *As cited in OEHHA 2010.*

Yang GQ, Yin S, Zhou RH, Gu L, Yan B, Liu Y, Liu Y (1989a). Studies of safe maximal daily dietary Se-intake in a seleniferous area in China, part II: relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J Trace Elem Electrolytes Health Dis 3(3):123-30. [Erratum in 3(4):250, 1989.] *As cited in OEHHA 2010.*

Yang GQ, Zhou RH, Yin S, Gu L, Yan B, Liu Y, Liu Y, Li X (1989b). Studies of safe maximal daily dietary selenium intake in a seleniferous area in China, I, selenium intake and tissue selenium levels of the inhabitants. J Trace Elem Electrolytes Health Dis 3(2):77-87. *As cited in OEHHA 2010.*

Yang GQ, Xia YM (1995). Studies on human dietary requirements and safe range of dietary intakes of selenium in China and their application in the prevention of related endemic diseases. Biomed Environ Sci 8(3):187-201. *As cited in OEHHA 2010.*

Yang G-Q, Zhou R-H. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electrolytes Hlth Dis 1994;8:159–65. *As cited in NHMRC 2006.*

# WHO 2011

| **Agency Report Reference:** ***WHO (2011). Selenium in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization.*** | | |
|---|---|---|
| General Information | Date of data extraction | 10/12/2021 |
| | Authors | Fawell JK and Combs GF |
| | Publication date | 2011 |
| | Literature search timeframe | Not stated, however bibliography contains literature up to 2008. |
| | Publication type | Agency review |
| | Peer reviewed? | Yes |
| | Country of origin | Not specified (World Health Organization - concerted effort). |
| | Source of funding | Not specified; likely WHO |
| | Possible conflicts of interest | Individual experts are invited to serve as members of the Drinking Water Quality Committee (DWQC). Members are selected primarily on the basis of excellence, independence, relevance of their expertise and willingness to support the work of the DWQC (WHO 2009). All members sign a Declaration of Interest as a pre-requisite to participation.<br>Members refrain from participating in decision-making processes related to their particular area of conflicting interest (if applicable) (WHO 2009, JECFA 2017a). |
| Health considerations | Guideline value type (e.g. oral TRV, drinking water guideline) | Provisional drinking water guideline |
| | Exposure timeframe | Chronic (long-term exposure) |
| | Critical human health endpoint | Selenosis (brittle hair and nails, skin lesions and changes in peripheral nerves). |
| | Justification provided by agency for critical endpoint | No justification provided *per se.* Because of concern about adverse effects resulting from exposure to excessive levels of Se, various national and international organisation have established upper limits of exposure to Se. The United States National Academy of Sciences Panel on Dietary Oxidants and Related Compounds set an upper tolerable limit for selenium at 400 µg/day (NAS 2000). This level was also recommended by FAO/WHO (1998) and the United Kingdom Expert Group on Vitamins and Minerals (UK EGVM 2002).<br>The average dietary intake that is associated with selenosis has been found to be in excess of 900 µg/day. |
| | Critical study(ies) underpinning point of departure | Not stated (point of departure is upper tolerable daily intake of 400 µg/day derived by other agencies). |
| | Species for critical study(ies) | Humans |
| | Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc) | Upper tolerable daily intake of 400 µg/day |

| **Agency Report Reference:** ***WHO (2011). Selenium in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization.*** | | |
|---|---|---|
| | Point of departure value (include units) | Upper tolerable daily intake of 400 µg/day |
| | Uncertainty factor(s) & rationale | Not stated (point of departure is upper tolerable daily intake of 400 µg/day derived by other agencies). |
| | The derivation: | (400 µg/day x 0.2) ÷ 2 L/day = 40 µg/L |
| | Guideline value (include units) | **40 µg/L** ('Provisional' because of the uncertainties inherent in the scientific database). |
| | Mode of action for critical health endpoint | No information provided. |
| | Genotoxic carcinogen? | The Se compounds studied are unlikely to act as carcinogens at low or moderate doses in experimental animals. |
| | Identified sensitive sub-populations | No information provided. |
| | Any non-health based considerations? | No. |
| Exposure considerations | Principal routes of exposure in general population | Most people obtain virtually all of their Se from the foods they eat. |
| | Levels in drinking water supplies (include location) | In most parts of the world, Se concentrations in drinking water do not normally exceed 10 µg/L, except in certain seleniferous areas. Therefore, it would be unusual for drinking-water to make a significant contribution to total Se intake. |
| | Any special considerations to exposure levels (e.g. higher in drought?) | There are circumstances in which Se may be elevated above normal concentrations. |
| | Typical exposure in general population (include units for intakes & location) | Global Se intakes vary significantly; average intakes were relatively high in North America (85–150 µg/day), moderate in Europe (40–90 µg/day) and low in parts of China (10–20 µg/day). In Europe, dietary Se intakes have declined in recent decades: 29–39 µg/day in the United Kingdom and 30–80 µg/day in the Nordic countries in 1997, compared with earlier intakes of 40–90 µg/day. This decline has been attributed to reductions in the importation of higher-Se wheat grown in North America. |
| Risk Summary | Any risks to human health from drinking water identified in agency document? | Water is not normally a major source of Se intake, but it is important that a proper balance be achieved between recommended intakes and undesirable intakes in determining an appropriate guideline value for Se in drinking-water. |
| | Any emerging risks identified? | - |

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

**References:**

UK EGVM (2002) Revised review of selenium. United Kingdom Expert Group on Vitamins and Minerals (EVM/99/17.REVISEDAUG2002). *As cited in WHO 2011.*

FAO/WHO (1998) Preparation and use of food-based dietary guidelines. Report of a joint FAO/WHO consultation. Geneva, World Health Organization (WHO Technical Report Series, No. 880). *As cited in WHO 2011.*

JECFA (2017a). Joint FAO/WHO Expert Committee on Food Additives (JECFA) - Working Procedures. Joint FAO/WHO Expert Committee on Food Additives. Geneva, February 2017. https://www.who.int/foodsafety/chem/jecfa/JECFA-WP-REV2017.pdf?ua=1.

NAS (2000) Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. A report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington, DC, National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *As cited in WHO 2011.*

WHO (2009). WHO Guidelines for Drinking-water quality: Policies and procedures used in updating the WHO Guidelines for Drinking-water Quality. World Health Organization.

## Exposure-Related Information for Selenium

# ICON Water 2020

| ***ICON Water (2020). Icon Water (2020). Water Quality Report (2020). Australian Capital Territory, Canberra.*** | | |
|---|---|---|
| General Information | Date of data extraction | 29/11/2021 |
| | Authors | Not stated. |
| | Publication date | 2020 |
| | Publication type | Annual water quality report |
| | Description | No guidance value derived in this document *per se* but contains relevant information on Se exposure levels in Australian drinking water supply system (may or may not be relevant for context). |
| | Findings[1] | Minimum (mean): <0.001 mg/L<br>Maximum (range): <0.001 – 0.007 mg/L<br>Mean (mean): <0.001 mg/L |

[1]Summary data for all drinking water quality zones in the supply system

## Melbourne Water 2021

| *Agency Report Reference: Melbourne Water (2021). Testing water quality- Monthly Report, June 2021, Melbourne Water.* | | |
|---|---|---|
| General Information | Date of data extraction | 29/11/2021 |
| | Authors | Not stated. |
| | Publication date | June 2021 |
| | Publication type | Monthly report |
| | Description | No guidance value derived in this document *per se* but contains relevant information on Se exposure levels in Australian drinking water supply system (may or may not be relevant for context). |
| | Findings[1] | Mean: <0.001 mg/L [(2)] |

1. Summary data for all drinking water quality zones in the supply system
2. At measuring points Cardinia, Greenvale, Silvan, and Winneke.

## PWNT 2004, 2005, 2006, 2007a, 2008a, 2009a, 2009b, 2010a, 2010b, 2011a, 2011b, 2012, 2014, 2015, 2016a, 2016b, 2017, 2018, 2019, 2020

| Agency Report Reference: *See bibliography* | | |
|---|---|---|
| General Information | Date of data extraction | 26/09/2021 |
| | Authors | Not stated. |
| | Publication date | 2004-2020 |
| | Publication type | Drinking Water Corporation report. |
| | Description | No guidance value derived in this document *per se* but contains relevant information on Se exposure levels in Australian drinking water supply system (may or may not be relevant for context). |
| | Findings[1] | Australian Drinking Water Guideline: 0.01 mg/L<br>Range (mean): <0.0002 – 0.012 mg/L [(2)] |

1. Summary data for all drinking water quality zones in the supply system
2. Exceedances of the DWG have been recorded in 2004 at measuring points Kings Canyon and Daly Waters.

## Seqwater 2021a, 2021b, 2021c, 2021d, 2021e, 2021f

| Agency Report Reference: *See biblioghraphy* | | |
|---|---|---|
| General Information | Date of data extraction | 23/11/2021 |
| | Authors | Not stated. |
| | Publication date | 2021 |

| Agency Report Reference: *See bibliography* | | |
|---|---|---|
| | Publication type | Drinking Water Corporation report. |
| | Description | No guidance value derived in this document *per se* but contains relevant information on Se exposure levels in Australian drinking water supply system (may or may not be relevant for context). |
| | Findings[1] | Australian Drinking Water Guideline: 0.01 mg/L<br>Minimum: <0.002 mg/L across all measuring sites<br>Mean: <0.002 mg/L across all measuring sites<br>Maximum: <0.002 mg/L across all measuring sites |
| [1]Summary data for all drinking water quality zones in the supply system | | |

## Tas Water 2014, 2015a, 2015b, 2016a, 2016b, 2016c, 2017a, 2017b, 2017c, 2017d, 2018a, 2018b, 2018c, 2019a, 2019b, 2020

| Agency Report Reference: *See bibliography* | | |
|---|---|---|
| General Information | Date of data extraction | 03/09/2021 |
| | Authors | Not stated. |
| | Publication date | 2014-2019 |
| | Publication type | Drinking Water Corporation report. |
| | Description | No guidance value derived in this document *per se* but contains relevant information on Se exposure levels in Australian drinking water supply system (may or may not be relevant for context). |
| | Findings[1] | Australian Drinking Water Guideline): 0.01 mg/L<br>Mean: <0.0001 – 0.0025 mg/L<br>Minimum: <0.0001 – 0.002 mg/L<br>Maximum: <0.0001 – 0.0097 mg/L |
| [1]Summary data for all drinking water quality zones in the supply system | | |

# APPENDIX C

## Existing guideline/guidance assessment tables

## Criteria for assessing existing guidance or guidelines

### Administrative and technical criteria for assessing existing guidance or guidelines

Criteria have been colour-coded to assess minimum requirements as follows: 'Must have', 'Should have' or 'May have'

# ATSDR 2003

**Agency Report Reference:** ***ATSDR (2003). Toxicological Profile for Selenium. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. September 2003.***

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Overall guidance/advice development process | | |
| | Are the key stages of the organisation's advice development processes compatible with Australian processes? | Y | |
| | Are the administrative processes documented and publicly available? | Y | Yes, in the toxicological profile for Se. |
| | Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported? | Y | Yes, proposed minimal risk levels (MRLs) are reviewed by the Health Effects/MRL Workgroup within the Division of Toxicology and Human Health Sciences; an expert panel of external peer reviewers; the agency wide MRL Workgroup, with participation from other federal agencies, including EPA; and are submitted for public comment.<br>Regarding potential conflicts of interest, this was not stated in the document reviewed. However, ATSDR (2018) states that non-peer-reviewed studies considered relevant to the health effects of a substance undergo peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. This statement suggests such screening may be commonplace for selection of experts to sit on the relevant committees. |
| | Are funding sources declared? | Y | Although funding sources are not declared in the tox profile, the profiles are produced by congressional mandate, indicating they are likely government-funded. |
| | Was there public consultation on this work? If so, provide details. | Y | Yes, a draft for public comment was released in September 2001. |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Is the advice peer reviewed? If so, is the peer review outcome documented and/or published? | Y | Independent peer review panel provided comments. Scientists from the ATSDR have reviewed the peer reviewers' comments and determined which comments to include in the profile, with a brief explanation of the rationale for their exclusion; this exists as part of the administrative record. |
| | Was the guidance/advice developed or updated recently? Provide details. | NA | |
| | Evidence review parameters | | |
| | Are decisions about scope, definitions and evidence review parameters documented and publicly available? | N | Not specifically provided in the Se toxicological profile |
| | Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards? | Y | Yes, quality or shortcomings of individual studies is discussed in the text. However, no attempt appears to have been made by ATSDR to weight selected studies for quality. |
| | Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly? | N | ATSDR has recently begun incorporating systematic review methodology into profile development. However, it is unclear from the Se toxicity profile whether systematic or methodical review approaches have been utilised for production of this document. |
| | If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded? | Y | A list of databases reviewed and a list of unpublished documents cited are included in the administrative record. |
| | Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided? | N | No information provided on the details of the literature search in the Se tox profile. |
| | Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings? | NA | ATSDR has undertaken its own review of the information. |
| | Can grey literature such as government reports and policy documents be included? | Y | |
| | Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation? | Y | |
| | Evidence search | | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Are databases and other sources of evidence specified? | Y | Although the bibliography provides references for all literature consulted, and all literature referenced in the profile is tagged, the databases consulted for the literature review are not listed in the profile. Nevertheless, the peer review stated a list of databases reviewed and a list of unpublished documents cited are included in the administrative record. |
| | Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)? | NA | Unable to be ascertained from the information in the profile. |
| | Is it specified what date range the literature search covers? Is there a justification? | N | Literature search details are not specified, however the dates of publications in the bibliography suggest a literature search cutoff date of 2003. |
| | Are search terms and/or search strings specified? | N | Literature search details are not specified. |
| | Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate? | NA | Literature search details are not specified. |
| | Critical appraisal methods and tools | | |
| | Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality? | N | No information given regarding whether risk of bias assessment was undertaken for individual studies. However, the shortcomings of some studies (where identified by the authors) have been provided in the text. |
| | Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details. | Y | ATSDR summarises health endpoint information in the form of figures organised by route of exposure. This allows the reader to quickly assimilate the most sensitive health effects associated with Cd exposure. |
| | Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details. | N | Yes, typically done in newer tox profiles where a systematic review was undertaken. However, this has not been done for the Se tox profile. |
| | Derivation of health-based guideline values | | |
| | Is there justification for the choice of uncertainty and safety factors? | Y | |
| | Are the parameter value assumptions documented and explained? | Y | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Are the mathematical workings/algorithms clearly documented and explained? | Y | |
| | Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)? | NA | No, non-health related matters do not appear to be considered in guideline development. Recorded as 'not applicable'. |
| | Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values? | N | Guidance documentation is not cited. |
| | What processes are used when expert judgement is required and applied? Is the process documented and published? | Y | ATSDR only derives MRLs if quantitative or qualitative information is available for all potential systemic, neurological and developmental effects. If insufficient data are judged to be available, an MRL is not derived (ATSDR 2018). |
| | Is dose response modelling (e.g. BMDL) routinely used? | Y | However, BMD modelling was not used for the Se MRL derivation. |
| | What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded? | Y | ATSDR only derives MRLs for non-cancer health endpoints. |
| | If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value? | NA | |

**Summary:**
Total # of 'Must-Have' criteria met (or not applicable): 15/20 = 75%
Total # of 'Should-Have' criteria met (or not applicable): 7/10 = 70%
Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100%

**References:**
ATSDR (2018). DRAFT guidance on the preparation of toxicological profiles. Agency for Toxic Substances and Disease Registry. April 2018.
https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf

## EFSA 2006, 2014a

***Agency Report Reference: EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority (EFSA). European Food Safety Authority.***

***Agency Report Reference: EFSA (2014a). Scientific Opinion on Dietary Reference Values for selenium. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2014;12(10):3846.***

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Overall guidance/advice development process | | |
| | Are the key stages of the organisation's advice development processes compatible with Australian processes? | Y | |
| | Are the administrative processes documented and publicly available? | Y | |
| | Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported? | Y | Yes, a working group comprised of experts in toxicology and nutrition drawn from the SCF or NDA Panel which was complemented by additional experts were involved in drafting and/or review of the reports. |
| | Are funding sources declared? | Y | Although funding sources are not declared in the report, EFSA is funded by the European Union that operates independently of the European legislative and executive institutions and EU Member states. |
| | Was there public consultation on this work? If so, provide details. | N | Done on a case-by-case basis; does not appear to have been done for this piece of work. |
| | Is the advice peer reviewed? If so, is the peer review outcome documented and/or published? | Y | Not stated in document, however in 2007 a proposal document was published for various levels of peer review (EFSA 2007). This indicates the 2014a document was likely peer reviewed. |
| | Was the guidance/advice developed or updated recently? Provide details. | NA | |
| | Evidence review parameters | | |
| | Are decisions about scope, definitions and evidence review parameters documented and publicly available? | Y (1/2) | The terms of reference given by the European Commission, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF. |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards? | Y | |
| | Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly? | ? | Typically, yes for more recent documents, however literature searching details were not provided for either of these publications so it is unclear whether this was done. |
| | If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded? | Y | All cited literature in the profile bibliography appears to be publicly available. |
| | Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided? | N | No details provided on literature searches undertaken. |
| | Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings? | NA | |
| | Can grey literature such as government reports and policy documents be included? | Y | |
| | Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation? | Y | |
| | Evidence search | | |
| | Are databases and other sources of evidence specified? | N | No details provided on literature searches undertaken. |
| | Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)? | ? | No details provided on literature searches undertaken. |
| | Is it specified what date range the literature search covers? Is there a justification? | N | No details provided on literature searches undertaken. |
| | Are search terms and/or search strings specified? | N | No details provided on literature searches undertaken. |
| | Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate? | N | No details provided on literature searches undertaken. |
| | Critical appraisal methods and tools | | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality? | Y (1/2) | Brief mentions of risk of bias of some studies provided in text. However, the formal tools used to assess risk of bias are not provided or discussed. |
| | Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details. | N | Unclear from the documentations consulted. |
| | Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details. | N | Does not appear to have been done for Se. |
| | Derivation of health-based guideline values | | |
| | Is there justification for the choice of uncertainty and safety factors? | Y | |
| | Are the parameter value assumptions documented and explained? | Y | |
| | Are the mathematical workings/algorithms clearly documented and explained? | Y | |
| | Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)? | NA | No, non-health related matters do not appear to be considered in guidance value development. Recorded as 'not applicable'. |
| | Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values? | N | Guidance documentation is not cited. |
| | What processes are used when expert judgement is required and applied? Is the process documented and published? | Y | Unclear from the documentation consulted. However, the Panels consist of a group of experts which discuss and agree on the contents of the reports. |
| | Is dose response modelling (e.g. BMDL) routinely used? | Y | Yes, where data allows or where it is deemed to add value. Was not done for Se. |
| | What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded? | Y | Yes (EFSA 2012). Until 2005, the advice given by EFSA was to reduce exposures to such substances to a level that is as low as reasonably achievable (ALARA principle). Since then, EFSA has employed a margin of exposure (MOE) approach using a BMDL10 for cancer incidence in animals or humans. |
| | If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value? | NA | - |

| Criteria | Y/N/?/NA | Notes |
|---|---|---|
| **Summary:**<br>Total # of 'Must-Have' criteria met (or not applicable): 14/20 = 70%<br>Total # of 'Should-Have' criteria met (or not applicable): 5/10 = 50%<br>Total # of 'May-Have' criteria met (or not applicable): 1/2 = 50% | | |
| **References:**<br>EFSA (2007). Scientific advice by the Scientific Committee (Question No EFSA-Q-2007-060) adopted by written procedure on 3 August 2007. Proposal for a review system for EFSA's scientific activities. European Food Safety Authority. The EFSA Journal 2007. 526: 1-15.<br><br>EFSA (2012). Scientific opinion. Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Scientific Committee, European Food Safety Authority. The EFSA Journal 2012. 10(3): 2578. | | |

## NHMRC 2006

**NHMRC *(2006). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. National Health and Medical Research Council. Version 1.2, updated September 2017.***

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Overall guidance/advice development process | | |
| | Are the key stages of the organisation's advice development processes compatible with Australian processes? | Y | Refer to Appendix of NHMRC (2006) and the guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines (NHMRC 1999). |
| | Are the administrative processes documented and publicly available? | Y | |
| | Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported? | Y | |
| | Are funding sources declared? | Y | |
| | Was there public consultation on this work? If so, provide details. | Y | |
| | Is the advice peer reviewed? If so, is the peer review outcome documented and/or published? | Y | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Was the guidance/advice developed or updated recently? Provide details. | NA | |
| | Evidence review parameters | | |
| | Are decisions about scope, definitions and evidence review parameters documented and publicly available? | Y | Refer to Appendix of NHMRC (2006) and the guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines (NHMRC 1999). |
| | Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards? | Y | |
| | Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly? | Y | |
| | If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded? | NA | |
| | Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided? | Y | |
| | Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings? | Y | |
| | Can grey literature such as government reports and policy documents be included? | Y | |
| | Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation? | Y | |
| | Evidence search | | |
| | Are databases and other sources of evidence specified? | Y | Refer to Appendix of NHMRC (2006) and the guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines (NHMRC 1999). |
| | Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)? | Y | |
| | Is it specified what date range the literature search covers? Is there a justification? | Y | |
| | Are search terms and/or search strings specified? | Y | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate? | NA | |
| | Critical appraisal methods and tools | | |
| | Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality? | Y | Refer to Appendix of NHMRC (2006) and the guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines (NHMRC 1999). |
| | Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details. | Y | |
| | Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details. | Y | |
| | Derivation of health-based guideline values | | |
| | Is there justification for the choice of uncertainty and safety factors? | Y | Refer to Appendix of NHMRC (2006) and the guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines (NHMRC 1999). |
| | Are the parameter value assumptions documented and explained? | Y | |
| | Are the mathematical workings/algorithms clearly documented and explained? | Y | |
| | Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)? | Y | |
| | Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values? | Y | |
| | What processes are used when expert judgement is required and applied? Is the process documented and published? | Y | |
| | Is dose response modelling (e.g. BMDL) routinely used? | Y | |
| | What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded? | Y | |
| | If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value? | NA | |

| Criteria | Y/N/?/NA | Notes |
|---|---|---|
| **Summary:**<br>Total # of 'Must-Have' criteria met (or not applicable): 20/20 = 100%<br>Total # of 'Should-Have' criteria met (or not applicable): 10/10 = 65%<br>Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100% | | |
| **References:**<br>NHMRC (1999). A guide to the development, implementation and evaluation of clinical practice guidelines. National Health and Medical Research Council. https://www.health.qld.gov.au/__data/assets/pdf_file/0029/143696/nhmrc_clinprgde.pdf<br><br>NHMRC (2006) Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. Selenium. Australian National Health and Medical Research Council (NHMRC). https://www.nhmrc.gov.au/about-us/publications/nutrient-reference-values-australia-and-new-zealand-including-recommended-dietary-intakes#block-views-block-file-attachments-content-block-1 | | |

## OEHHA 2010

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

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Overall guidance/advice development process | | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Are the key stages of the organisation's advice development processes compatible with Australian processes? | Y | The process for OEHHA Public Health Goal (PHG) development is:<br>• Literature search/review.<br>• Critical endpoint/study selection.<br>• Dose-response analysis.<br>• Exposure assessment.<br>• Risk characterisation.<br>• Calculation of health-protective concentration for contaminant in drinking water.<br>These stages of the risk assessment framework are compatible with the Australian risk assessment process. |
| | Are the administrative processes documented and publicly available? | Y | A preface has been provided with the document that outlines the administrative processes for preparing the technical document |
| | Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported? | ? | Not a committee *per se* however the PHG technical support document for Se was discussed at the PHG workshop held on May 19, 2010, or as revised following the workshop (OEHHA 2010b).<br>Although not stated, potential conflicts of interest are managed through the University of California contract as part of the process for acquiring peer reviewers. OEHHA is not involved in the selection of peer reviewers. |
| | Are funding sources declared? | N | Funding sources are not declared in the report. |
| | Was there public consultation on this work? If so, provide details. | Y | Yes. First draft released for public comment on April 2, 2010 and a public workshop was held on May 19, 2010. The revised report was then released for a second public comment period prior to finalisation (OEHHA 2010b). |
| | Is the advice peer reviewed? If so, is the peer review outcome documented and/or published? | Y | Yes, document was reviewed by six scientists as well as the general public. |
| | Was the guidance/advice developed or updated recently? Provide details. | NA | |
| | Evidence review parameters | | |
| | Are decisions about scope, definitions and evidence review parameters documented and publicly available? | N | Not clear from the document reviewed. |
| | Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards? | NA | No, all valid studies are considered. |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly? | ? | For this review, the literature searches undertaken are not detailed so it is not known if the review has been undertaken systematically. PHG scientists have typically undertaken literature searches. Review of the information has been based on expert scientific judgment. However, OEHHA is increasingly incorporating more systematic/methodological processes (e.g., evidence mapping) for selection of key studies. |
| | If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded? | Y | Yes. PHG technical support documents provide summaries of studies but not raw data. Nonetheless, companies and other entities are informed that any information submitted to OEHHA will become public information. |
| | Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided? | N | Not detailed in document. |
| | Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings? | NA | |
| | Can grey literature such as government reports and policy documents be included? | Y | Yes, but its role in the risk assessment would depend on the quality of the data. |
| | Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation? | Y | |
| | Evidence search | | |
| | Are databases and other sources of evidence specified? | Y (1/2) | Databases not specified, but all references also cited in bibliography. |
| | Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)? | ? | No information provided on literature searches undertaken. |
| | Is it specified what date range the literature search covers? Is there a justification? | N | However, the bibliography lists references up to the year 2010. |
| | Are search terms and/or search strings specified? | N | No information provided on literature searches undertaken. |
| | Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate? | NA | |
| | Critical appraisal methods and tools | | |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality? | N | No information given regarding whether risk of bias assessment was undertaken for individual studies. However, the shortcomings of some studies (where identified by the authors) have been provided in the text. |
| | Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details. | N | Doesn't appear to have been done for this document. However, recently, OEHHA has been collaborating with US EPA's Integrated Risk Information System (IRIS) Program on evidence mapping using DistillerSR software and the Health Assessment Workspace Collaborative (HAWC) web application. |
| | Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details. | N | Yes, typically done in newer reports where a systematic review was undertaken. However, this has not been done for the Se public health goal document. |
| | Derivation of health-based guideline values | | |
| | Is there justification for the choice of uncertainty and safety factors? | Y | - |
| | Are the parameter value assumptions documented and explained? | Y | - |
| | Are the mathematical workings/algorithms clearly documented and explained? | Y | - |
| | Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)? | NA | No. OEHHA are statutorily prohibited from doing so. This step is the responsibility of a sister agency, the State Water Resources Control Board when establishing regulatory Maximum Contaminant Levels for chemicals in drinking water. |
| | Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values? | Y (1/2) | Guidance documentation is not cited, however OEHHA considers mechanistic, mode of action, and other relevant information in PHG derivation (and relies on expert judgement of author and reviewers). |
| | What processes are used when expert judgement is required and applied? Is the process documented and published? | Y | When expert judgment is used, the rationale is provided in the technical support document. |
| | Is dose response modelling (e.g. BMDL) routinely used? | Y | Yes but not used for Se. |
| | What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded? | Y | Yes, OEHHA has guidance documents that are publicly available (https://oehha.ca.gov/air/air-toxics-hot-spots). For carcinogens that do not have a slope factor, an additional uncertainty factor of 10 is applied to the guideline derivation. |
| | If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value? | NA | The level of cancer risk used in developing PHGs is one in one million ($1 \times 10^{-6}$). |

| Criteria | Y/N/?/NA | Notes |
|---|---|---|
| **Summary:**<br>Total # of 'Must-Have' criteria met (or not applicable): 11.5/20 = 58%<br>Total # of 'Should-Have' criteria met (or not applicable): 6.5/10 = 65%<br>Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100% | | |
| **References:**<br>OEHHA (2010b). Final Public Health Goal for Selenium. December 10, 2010. Office of Environmental Health and Hazard Assessment. [Accessed 13/12/2021]. https://oehha.ca.gov/water/public-health-goal/final-public-health-goal-selenium | | |

## WHO 2011

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

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Overall guidance/advice development process | | |
| | Are the key stages of the organisation's advice development processes compatible with Australian processes? | Y | |
| | Are the administrative processes documented and publicly available? | Y | Yes. Documented in various different guidance documentation (WHO 1987, 1990, 1994, 1999, 2006, 2009, 2017). |
| | Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported? | Y | Yes. By the Drinking-Water Quality Committee (DWQC) (WHO 2009). All 6 WHO regional offices participated in the process of the latest revision, in consultation with Member States (WHO 2017). |
| | Are funding sources declared? | Y | Although funding sources are not declared in the document, it is likely funded by the WHO. |
| | Was there public consultation on this work? If so, provide details. | Y | The front matter of the text indicates the final version of the document takes into consideration comments from both peer reviewers and the public. |
| | Is the advice peer reviewed? If so, is the peer review outcome documented and/or published? | Y | The DWGs per se are the collective product of many experts and therefore the advice is internationally peer reviewed (WHO 2009).<br>The peer review outcomes are not made publicly available, however they are retained by the WHO Secretariat (WHO 2009). |
| | Was the guidance/advice developed or updated recently? Provide details. | NA | |
| | Evidence review parameters | | |
| | Are decisions about scope, definitions and evidence review parameters documented and publicly available? | N | Not specified. |
| | Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards? | NA | All valid studies appear to be considered. Validity appears to be determined by expert judgement. |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly? | N | Unclear in this document. |
| | If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded? | Y | Unpublished proprietary data are referenced as such in reference lists, and where they form pivotal information they are described in detail. |
| | Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided? | N | Not specified. |
| | Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings? | Y | WHO used upper tolerable limit for Se from the US National Academy of Sciences Panel on Dietary Oxidants and Related Compounds (NAS 2000) to derive the drinking water guideline. WHO states that the same level was also recommended by FAO/WHO (1998) and the UK Expert Group on Vitamins and Minerals (UK EGVM 2002). This suggests that consistency between agencies appears to be an important consideration when adopting review findings from other agencies. |
| | Can grey literature such as government reports and policy documents be included? | Y | Yes, where reviews are 'recognised of high quality' (WHO 2017). |
| | Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation? | Y | |
| | Evidence search | | |
| | Are databases and other sources of evidence specified? | Y (1/2) | Although the bibliography provides references for all literature consulted, the databases consulted for the literature review are not listed in the agency review. |
| | Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)? | N | Unable to be ascertained from the information in the document. |
| | Is it specified what date range the literature search covers? Is there a justification? | N | Literature search details are not specified, however the dates of publications in the bibliography suggest a literature search cutoff date of 2008 in the WHO (2011) review. |
| | Are search terms and/or search strings specified? | N | Literature search details are not specified. |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate? | NA | Literature search details are not specified. |
| | Critical appraisal methods and tools | | |
| | Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality? | N | No information given regarding whether risk of bias assessment was undertaken for individual studies. However, the shortcomings of some studies (where identified by the authors) have been provided in the text. |
| | Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details. | N | WHO (2011) relies on previous evaluations by NAS, WHO/FAO and UK EGVM for their toxicological endpoint evaluation and review. |
| | Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details. | N | Not specified. |
| | Derivation of health-based guideline values | | |
| | Is there justification for the choice of uncertainty and safety factors? | N | Not stated/described in WHO (2011) document. NAS (2000) document on which upper intake is based was not consulted. |
| | Are the parameter value assumptions documented and explained? | Y | |
| | Are the mathematical workings/algorithms clearly documented and explained? | Y | |
| | Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)? | NA | For Se, non-health related matters do not appear to have been considered in guideline development. Recorded as 'not applicable'. |
| | Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values? | Y | Guidance documentation is not cited. However, guidance document does exist (FAO/WHO 2009, WHO 2005, 2007). |
| | What processes are used when expert judgement is required and applied? Is the process documented and published? | N | Unclear from documentation consulted. |
| | Is dose response modelling (e.g. BMDL) routinely used? | Y | Yes, where data permit and where a BMDL would provide greater confidence in the point of departure (WHO 2009). However, in this case dose response modelling was not used as value was adopted from other agencies. |

| Criteria | | Y/N/?/NA | Notes |
|---|---|---|---|
| | What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded? | NA | For genotoxic carcinogens, the DWG represents an excess lifetime cancer risk of $1x10^{-5}$ for people drinking water containing the chemical at the DWG for 70 yrs (WHO 2009). Compounds shown to be a carcinogen are evaluated on a case-by-case basis, where evidence of genotoxicity & human relevance is considered to determine correct approach for risk assessment (WHO 2009). Not done for Se as not identified to be an oral genotoxic carcinogen. |
| | If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value? | NA | |

**Summary:**
Total # of 'Must-Have' criteria met (or not applicable): 12.5/20 = 63%
Total # of 'Should-Have' criteria met (or not applicable): 6/10 = 60%
Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100%

| Criteria | Y/N/?/NA | Notes |
|---|---|---|

**References:**

FAO/WHO (1998) Preparation and use of food-based dietary guidelines. Report of a joint FAO/WHO consultation. Geneva, World Health Organization (WHO Technical Report Series, No. 880). *As cited in WHO 2011.*

FAO/WHO (2009). Environmental Health Criteria 240: Principles and methods for the risk assessment of chemicals in food. Chapter 5: Dose-response assessment and derivation of health-based guidance values. Geneva: A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc240_chapter5.pdf.

JECFA (2017a). Guidance document for WHO monographers and reviewers evaluating contaminants in food and feed. Joint FAO/WHO Expert Committee on Food Additives (JECFA). January 2017. Version 1.0. http://apps.who.int/iris/bitstream/handle/10665/254630/9789241512008-eng.pdf;jsessionid=8AB23D3A0003A624A67704756BB3A938?sequence=1

JECFA (2017b). Guidance to JECFA Experts on Systematic Literature Searches. Prepared by WHO JECFA (Joint FAO/WHO Expert Committee on Food Additives) Secretariat. January 2017. https://www.who.int/foodsafety/chem/jecfa/Litertature_Search.pdf?ua=1.

NAS (2000) Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. A report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington, DC, National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *As cited in WHO 2011.*

UK EGVM (2002) Revised review of selenium. United Kingdom Expert Group on Vitamins and Minerals (EVM/99/17.REVISEDAUG2002). *As cited in WHO 2011.*

WHO (2005). Harmonization Project Document No. 2: Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration response assessment. World Health Organization (IPCS). http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf.

WHO (2007). Harmonization Project Document No. 4. Part 1: IPCS framework for analysing the relevance of a cancer mode of action for humans and case-studies Part 2: IPCS framework for analysing the relevance of a non-cancer mode of action for humans." World Health Organization (IPCS). http://www.who.int/ipcs/methods/harmonization/areas/cancer_mode.pdf?ua=1.

WHO (2009). WHO Guidelines for Drinking-water quality: Policies and procedures used in updating the WHO Guidelines for Drinking-water Quality. World Health Organization.

# APPENDIX D

## Data extraction tables – Supporting Information in Factsheet

## Supporting Information in Selenium Factsheet

# ATSDR 2003

| **Agency Report Reference:** ***ATSDR (2003). Toxicological Profile for Selenium. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. September 2003.*** | | |
|---|---|---|
| General Description | Uses | Se and its compounds are used in some photographic devices, gun bluing (a liquid solution used to clean the metal parts of a gun), plastics, paints, anti-dandruff shampoos, vitamin and mineral supplements, fungicides, and certain types of glass. For example, Se sulphide is used in anti-dandruff shampoos by the common trade name Selsun Blue. Se is also used to prepare drugs and as a nutritional feed supplement for poultry and livestock. |
| | Sources in drinking water | Weathering of rocks and soils may result in low levels of Se in water, which may be taken up by plants. Disposal of Se in commercial products and waste could also increase the amount of Se in soil. Elemental Se that cannot dissolve in water and other insoluble forms of Se are less mobile and will usually remain in the soil, posing smaller risk of exposure. Se compounds that can dissolve in water are sometimes very mobile. Thus, there is an increased chance of exposure to these compounds. Se may enter surface water in irrigation drainage waters. |
| | Other | - |
| Treatment of drinking water | Treatment technology | - |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | • Atomic Absorption Spectrophotometry (AAS) (LOD 2 µg/L)<br>• ICP/AES (LOD 0.06 µg/L) |
| | Limit of determination/ Limit of Reporting (LOR) | See above |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## EFSA 2006, 2014a

| ***Agency Report Reference: EFSA (2006). Tolerable upper intake levels for vitamins and minerals. European Food Safety Authority (EFSA). Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority.***<br><br>***Agency Report Reference: EFSA (2014a). Scientific Opinion on Dietary Reference Values for selenium. European Food Safety Authority (EFSA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2014;12(10):3846.*** | | |
|---|---|---|
| General Description | Uses | - (reviews focused on food and food additives) |
| | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | - |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | - |
| | Limit of determination/ Limit of Reporting (LOR) | - |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## FSANZ 2008

| **Agency Report *Reference: FSANZ (2008). The 22nd Australian Total Diet Study. Food standards Australia and New Zealand.*** | | |
|---|---|---|
| General Description | Uses | Se is a naturally occurring trace element and essential nutrient. |
| | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | - |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | - |

| **Agency Report *Reference: FSANZ (2008). The 22nd Australian Total Diet Study. Food standards Australia and New Zealand.*** | | |
|---|---|---|
| | Limit of determination/ Limit of Reporting (LOR) | - |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## NHMRC 2006

| **Agency Report *Reference:* NHMRC *(2006). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. National Health and Medical Research Council. Version 1.2, updated September 2017.*** | | |
|---|---|---|
| General Description | Uses | - |
| | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | - |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | - |
| | Limit of determination/ Limit of Reporting (LOR) | - |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## OEHHA 2010

| **Agency Report** ***Reference: OEHHA (2010). Public health goals for chemicals in drinking water – Selenium. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2010.*** | | |
|---|---|---|
| General Description | Uses | Elemental Se is used in rectifiers, photoelectric cells, blasting caps, xerography, electrostatic printing, stainless steel, optical lenses, exposure meters, and as a dehydrogenation catalyst. Gray Se conducts electricity better in light than in darkness, which has made it useful in photoelectric devices.<br>Combinations of bismuth and Se are added to brasses to replace lead in plumbing applications. Small amounts of Se are added to vulcanised rubber to increase its resistance to abrasion.<br>Se supplements, in the form of selenite, selenate, or selenomethionine, for human and livestock diets, are the largest pharmaceutical and agricultural uses of Se. |
| | Sources in drinking water | The major source of Se in the environment is the weathering of rocks and soils, but human activities contribute about 3,500 metric tons per year in the U.S.<br>Selenates can leach from soil, transport to groundwater, and is the form of Se most readily taken up by plants. |
| | Other | - |
| Treatment of drinking water | Treatment technology | - |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | - |
| | Limit of determination/ Limit of Reporting (LOR) | - |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## WHO 2011

| **Agency Report Reference:** ***WHO (2011). Selenium in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization.*** | | |
|---|---|---|
| General Description | Uses | - |
| | Sources in drinking water | Present in earth's crust, often in association with S-containing minerals. Acidic and reducing conditions reduce inorganic selenites to elemental Se, whereas alkaline and oxidising conditions favour the formation of selenates. Because selenites and selenates are soluble in water, Se is leached from well-aerated alkaline soils that favour its oxidation. |

| **Agency Report Reference:** ***WHO (2011). Selenium in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization.*** | | |
|---|---|---|
| | Other | - |
| Treatment of drinking water | Treatment technology | The most common forms of Se in water are selenite (Se(IV), SeO32−) and selenate (Se(VI), SeO42−). The formation of selenate from selenite is slow, and both forms exist together in solution. Neither can be oxidised or reduced easily. Selenate is more difficult to remove from water by processes such as coagulation compared with selenite; therefore, oxidation of selenite to selenate would be undesirable in this context.<br><br>It has been reported that chemical clarification with lime, ferric sulphate or aluminium sulphate and activated carbon adsorption are moderately effective in removing selenite from water and ineffective at removing selenate. Tests have shown that the greatest removal was achieved by clarification with ferric sulphate at a pH below 7.<br><br>Selenium can be adsorbed onto iron oxide–coated sand. Practically complete removal of Se(IV) from a 10 mg/l solution in contact with 100 g/l coated sand was achieved within 10 min, whereas Se(VI) removal required about 90 min. Similar results were reported using aluminium oxide–coated sand, although the adsorption capacities were lower.<br><br>Pilot plant trials have shown that adsorption by soil has the ability to remove Se from water. Se removal of 95% was achieved in the absence of nitrate. The presence of nitrate interferes with the adsorption of Se.<br><br>Laboratory research suggested that both selenite and selenate may be removed by ion exchange and reverse osmosis. |
| | Effectiveness | See above |
| | Any special conditions? | |
| | Other | - |
| Measurement | Analytical method | Atomic absorption spectrometry with hydride generation is the most convenient method for determining Se in drinking-water. Inductively coupled plasma/mass spectrometry is also used, with a similar detection limit. |
| | Limit of determination/ Limit of Reporting (LOR) | 0.5 µg/L |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## ICON Water 2020

| *ICON Water (2020). Drinking Water Quality Report 2019-20. ICON Water.* | | |
|---|---|---|
| General Description | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | Not stated. |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | Not stated. |
| | Limit of determination/ Limit of Reporting (LOR) | Method:<br>USEPA 200.8 LOR: <0.001 mg/L |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## Melbourne Water 2021

| *Melbourne Water (2021). Testing water quality- Monthly Report, June 2021, Melbourne Water.* | | |
|---|---|---|
| General Description | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | Not stated. |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | Not stated. |
| | Limit of determination/ Limit of Reporting (LOR) | Method:<br>USEPA 200.8 LOR: <0.001 mg/L |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## PWNT 2004, 2005, 2006, 2007a, 2008a, 2009a, 2009b, 2010a, 2010b, 2011a, 2011b, 2012, 2014, 2015, 2016a, 2016b, 2017, 2018, 2019, 2020

| *See bibliography* | | |
|---|---|---|
| General Description | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | Not stated. |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | Not stated. |
| | Limit of determination/ Limit of Reporting (LOR) | |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## Seqwater 2021a, 2021b, 2021c, 2021d, 2021e, 2021f

| **Agency Report Reference:** *See bibliography* | | |
|---|---|---|
| General Description | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | Not stated. |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | Not stated. |
| | Limit of determination/ Limit of Reporting (LOR) | |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## Tas Water 2014, 2015a, 2015b, 2016a, 2016b, 2016c, 2017a, 2017b, 2017c, 2017d, 2018a, 2018b, 2018c, 2019a, 2019b, 2020

| **Agency Report Reference:** ***See bibliography*** | | |
|---|---|---|
| General Description | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | Not stated. |
| | Effectiveness | - |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | Not stated. |
| | Limit of determination/ Limit of Reporting (LOR) | LOR: <0.0001 mg/L |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## Ma et al 2017

| ***Ma L., Islam S. M., Xiao C., Zhao J., Liu H., Yuan M., Sun G., Li H., Ma S. and Kanatzidis M. G. (2017). Rapid simultaneous removal of toxic anions [HSeO3]−,[SeO3] 2−, and [SeO4] 2−, and metals Hg2+, Cu2+, and Cd2+ by MoS42−intercalated layered double hydroxide. Journal of the American Chemical Society 139(36): 12745-12757.*** | | |
|---|---|---|
| General Description | Uses | - |
| | Sources in drinking water | Se contaminants have been normally generated from coal-fire power plants and mining and metal smelting industries. |
| | Other | - |
| Treatment of drinking water | Treatment technology | Use of $MoS4^{2-}$ intercalated Mg/Al layered double hydroxide as a sorbent (MgAl-MoS4-LDH, abbr. MoS4-LDH). |
| | Effectiveness | For the pair Se(VI)+$Hg^{2+}$ the MoS4-LDH exhibited >99.9% removal rates for both $Hg^{2+}$ and Se(VI), compared with 81% removal for $SeO_4^{2-}$ alone.<br><br>For individual $SeO_3^{2-}$ (without metal ions), 99.1% Se(IV) removal is achieved, while ≥99.9% removals are reached in the presence of $Hg^{2+}$, $Cu^{2+}$, and $Cd^{2+}$. Simultaneously, the removal rates for these metal ions are also >99.9%, and nearly all concentrations of the elements can be reduced to <10 ppb. |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | ICP-AES. |

| *Ma L., Islam S. M., Xiao C., Zhao J., Liu H., Yuan M., Sun G., Li H., Ma S. and Kanatzidis M. G. (2017). Rapid simultaneous removal of toxic anions [HSeO3]−,[SeO3] 2−, and [SeO4] 2−, and metals Hg2+, Cu2+, and Cd2+ by MoS42−intercalated layered double hydroxide. Journal of the American Chemical Society 139(36): 12745-12757.* | | |
|---|---|---|
| | Limit of determination/ Limit of Reporting (LOR) | - |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

## Taseidifar et al 2019

| *Taseidifar M., Ziaee M., Pashley R. M. and Ninham B. W. (2019). Ion flotation removal of a range of contaminant ions from drinking water. Journal of Environmental Chemical Engineering 7(4): 103263.* | | |
|---|---|---|
| General Description | Uses | - |
| | Sources in drinking water | - |
| | Other | - |
| Treatment of drinking water | Treatment technology | Use of a natural, biodegradable surfactant obtained using a novel and efficient chemical reaction between cysteine (a thiol-based amino acid) and an octanoyl (C8) compound, was investigated for its application to the ion flotation removal of low levels of different contaminant ions from aqueous solution. |
| | Effectiveness | Not very effective (i.e. 14% removal of Se after 60 minutes) as there was insignificant binding potential with the ion flotation conditions.<br>Starting concentration: 4.6 mg/L<br>Concentration after 60 mins: 4.4 mg/L |
| | Any special conditions? | - |
| | Other | - |
| Measurement | Analytical method | ICP-MS |
| | Limit of determination/ Limit of Reporting (LOR) | - |
| | Other | - |
| Additional information | Any additional non-health related information considered important? | - |

# APPENDIX E

## Data extraction tables – Evidence Scan for Recent (Health-based) Studies

## Recent Health-Based Studies for Selenium

# 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 | 13/12/2021 |
| | 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:<br>• 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.<br>• WHO increased the allocation for exposure to Se in DW from 10 to 20% without providing any references to support this increase, which resulted in a doubling of the guideline value.<br>• 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 DW 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. These points are taken into consideration in discussion of the candidate guideline values. |
| | 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.*

# Hadrup & 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 | 13/12/2021 |
| | Authors | Hadrup N and Ravn-Haren G |
| | Publication date | 2020 |
| | Publication type | Peer-reviewed journal article (review) |
| | Peer reviewed? | Yes |
| | Country of origin | Denmark |
| | Source of funding | Not stated |
| | Possible conflicts of interest | The authors declare that there are no conflicts of interest. |
| Study characteristics | Aim/objectives of study | To review the acute toxicity of high oral Se exposure. |
| | Study type/design | Literature review |
| | Study duration | Acute (single or short-term exposure) |
| | Type of water source (if applicable) | Not applicable |
| Population characteristics | Studies referenced | Various (literature review) |
| | Types of studies referenced | Acute Se intoxications (e.g. case reports, etc). |
| Exposure and setting | Exposure concentrations (if applicable) | 1-100 mg Se/kg bw |
| | Comparison group(s) | Not applicable (literature review) |
| Study methods | Study approach | Not applicable (literature review) |
| Results (for each outcome) | Definition of outcome | Adverse symptoms after oral acute Se exposure |
| | How outcome was assessed | Review of literature |
| | Method of measurement | Not applicable (literature review) |
| | Number of participants (exposed/non-exposed, missing/excluded) (if applicable) | Not applicable (literature review) |
| Statistics (if any) | Statistical method used | Not applicable (literature review) |
| | Relative risk/odds ratio, confidence interval? | |

| **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 | Acute symptoms of Se intoxication include abdominal symptoms such as vomiting, pain, and nausea, as well as garlic breath, and cardiac symptoms. Mortality has been described in several cases specifically following the ingestion of gun bluing agents, which contain selenous acid, but also with other inorganic forms of Se.<br>Mortality has been described in humans having ingested doses of 1–100 mg Se/kg bw but equally high intakes have been reported in humans who did not die. Mortality has been associated with blood/plasma levels between 300 and 30,000 µg/L (normal level: 100 µg/L). Nevertheless, there are also human cases of ingestion in which blood levels as high as 3000 µg/L are observed without mortality. |
| | Assessment of uncertainty (if any) | - |
| Reviewer comments | Results included/excluded in review (if applicable) | Acute doses associated with Se intoxication potentially range from 1-100 mg/kg bw. These doses are 67-6,700 times higher than the NOAELs used by agencies to derive candidate guideline values therefore this review is unlikely to change conclusions. |
| | Notes on study quality, e.g. gaps, methods | |

## Kopp et al 2018

| **Publication Reference:** ***Kopp T. I., Outzen M., Olsen A., Vogel U. and Ravn-Haren G. (2018). Genetic polymorphism in selenoprotein P modifies the response to selenium-rich foods on blood levels of selenium and selenoprotein P in a randomized dietary intervention study in Danes. Genes & nutrition 13(1): 1-10.*** | | |
|---|---|---|
| General Information | Date of data extraction | 13/12/2021 |
| | Authors | Kopp T. I., Outzen M., Olsen A., Vogel U. and Ravn-Haren G. |
| | Publication date | 2018 |
| | Publication type | Peer-reviewed research article |
| | Peer reviewed? | Yes |
| | Country of origin | Denmark |
| | Source of funding | The dietary intervention study was supported by funds from the Bjarne Saxhof Foundation. The Foundation had no influence on the design and conduct of the study, management, analysis, and interpretation of the data or preparation of the manuscript. |
| | Possible conflicts of interest | The authors declare that they have no competing interests. |
| Study characteristics | Aim/objectives of study | (1) investigate the effect of mussel and fish intake on glutathione peroxidase enzyme activity and<br>(2) examine whether single nucleotide polymorphisms in the GPX1, GPX4, and SELENOP genes modify the effect of mussel and fish intake for 26 weeks on whole blood Se, plasma selenoprotein P concentrations, and erythrocyte GPX enzyme activity in a randomised intervention trial in Denmark. |

| **Publication Reference:** ***Kopp T. I., Outzen M., Olsen A., Vogel U. and Ravn-Haren G. (2018). Genetic polymorphism in selenoprotein P modifies the response to selenium-rich foods on blood levels of selenium and selenoprotein P in a randomized dietary intervention study in Danes. Genes & nutrition 13(1): 1-10.*** | | |
|---|---|---|
| | Study type/design | Randomised dietary intervention study with primary aim of studying the influence of increased intake of fish and mussels on blood Se levels. |
| | Study duration | September 2010-March 2011 (26-weeks) |
| | Type of water source (if applicable) | None (dietary study) |
| Population characteristics | Population/s studied | Participants in intervention or control group, men and women aged 50-74 years with a BMI of 18.5-28 kg/m$^2$ (based on a power calculation where minimum detectable difference of 10 ng/mL or 30 ng/mL in Se concentration between groups with a statistical power of 87 or 99%, respectively, was allowed). |
| | Selection criteria for population (if applicable) | Exclusion criteria included current smoking, intake of dietary supplements containing selenium 3 months before baseline measurements, frequent intake of fish and shell-fish (> 300 g/week), excessive intake of alcohol (according to the official Danish guidelines at study recruitment: women > 14 units of alcohol/week, men > 21 units of alcohol/week), strenuous exercise (> 10 h/week), severe chronic disease, and frequent use of specified medication (including diabetic medicine, anticoagulant medicine, and medication for heart disease), or a cancer diagnosis within the past 5 years. |
| | Subgroups reported | Intervention group (n=49; provided with 1000 g raw fish and raw or processed mussels once/week for 26 weeks, i.e. ~50.3 µg Se/d)<br><br>Control group (n=45). |
| | Size of study | N=94 total |
| Exposure and setting | Exposure pathway | Ingestion |
| | Source of chemical/contamination | Not applicable (naturally Se-containing seafood) |
| | Exposure concentrations (if applicable) | Intervention group received ~50.3 µg Se/d |
| | Comparison group(s) | Controls (no dietary intervention) |
| Study methods | Analysis | Parameters analysed:<br>• Whole blood Se<br>• Plasma selenoprotein P concentrations<br>• Erythrocyte GPX enzyme activity |
| | Water sampling methods (monitoring, surrogates) | Not applicable (dietary study) |
| Results (for each outcome) | Study findings | CC homozygotes of the SELENOP/rs3877899 polymorphism who consumed 1000 g fish and mussels per week for 26 consecutive weeks had higher levels of both selenoprotein P (difference between means −4.68 ng/mL (95% CI −8.49, −0.871)) and whole blood Se (difference between means −5.76 (95% CI −12.5, 1.01)) compared to fish and mussel consuming T-allele carriers although the effect in whole blood Se concentration was not statistically significant. |

| **Publication Reference:** ***Kopp T. I., Outzen M., Olsen A., Vogel U. and Ravn-Haren G. (2018). Genetic polymorphism in selenoprotein P modifies the response to selenium-rich foods on blood levels of selenium and selenoprotein P in a randomized dietary intervention study in Danes. Genes & nutrition 13(1): 1-10.*** | | |
|---|---|---|
| | Number of participants (exposed/non-exposed, missing/excluded) (if applicable) | Intervention: n=49 (21 F, 28 M)<br>Control: n=45 (19 F, 26 M) |
| Statistics<br>(if any) | Statistical method used | Linear multiple regression analysis was applied using least square means adjusted for baseline concentrations of whole blood Se, plasma selenoprotein P, or erythrocyte GPX enzyme activity, respectively. Adjustment for baseline level was done to eliminate baseline levels' influence on the effect of the SNPs. In order to increase the statistical power, heterozygote variant allele and homozygote variant allele carriers were pooled in the analyses.<br><br>A mixed-model, repeated-measures analysis of variance (ANOVA) was used to determine the within-subject effect between genotype and erythrocyte GPX enzyme activity, whole blood selenium, or plasma selenoprotein P concentrations during the entire intervention period. |
| | Relative risk/odds ratio, confidence interval? | There was a statistically significant difference of −4.68 ng/mL (95% CI −8.49, −0.871) between mean concentration of plasma selenoprotein P at week 26 for variant T-allele and CC homozygotes of the SELENOP/rs3877899 polymorphism. A mean difference in whole blood Se for the SELENOP/rs3877899 polymorphism was also seen; however, this association was not statistically significant (difference between means −5.76 (95% CI −12.5, 1.01). |
| Author's conclusions | Interpretation of results | Study indicates that genetically determined variation in SELENOP leads to different responses in expression of selenoproteins following consumption of Se-rich foods. This study also emphasises the importance of taking individual aspects such as genotypes into consideration when assessing risk in public health recommendations. |
| | Assessment of uncertainty (if any) | Limitations include lack of blinding and that participants were non-fasting at blood sampling. However, results were based on whole blood which has been shown to reflect the long-term Se status as opposed to plasma Se, which has a short half-life.<br>With regard to the lack of blinding, this is not expected to influence on this study since the effect of genetic variation in the intervention group was mainly studies. The authors are well aware of the present study being underpowered due to the small sample size. Nevertheless, the study is in accordance with the SELGEN study, and therefore they are able to support the notion that variation in the SELENOP gene affects Se biomarker concentration after intake of both a Se dietary supplement and food with a high content of Se. |
| Reviewer comments | Results included/excluded in review (if applicable) | |

| Publication Reference: *Kopp T. I., Outzen M., Olsen A., Vogel U. and Ravn-Haren G. (2018). Genetic polymorphism in selenoprotein P modifies the response to selenium-rich foods on blood levels of selenium and selenoprotein P in a randomized dietary intervention study in Danes. Genes & nutrition 13(1): 1-10.* | | |
|---|---|---|
| | Notes on study quality, e.g. gaps, methods | This study provides some useful insights into a potential genetic polymorphism SELENOP that may affect expression of seleno-proteins. This may indicate some population variability in protein expression. However whether this translates to an increased susceptibility to the adverse effects of Se is unknown. Therefore it is unlikely to change the conclusions of the evaluation. |

## 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 | 13/12/2021 |
| | Authors | Vinceti M., Filippini T., Cilloni S., Bargellini A., Vergoni A. V., Tsatsakis A. and Ferrante M. |
| | Publication date | February 20, 2017 |
| | Publication type | Peer-reviewed journal article (literature review) |
| | Peer reviewed? | Yes |
| | Country of origin | Italy & Greece |
| | Source of funding | Not stated. |
| | Possible conflicts of interest | Not stated. |
| 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 | Studies referenced | Various |
| | Types of studies referenced | • Most studies had an observational study design, which the authors acknowledge suffer from bias due to unmeasured confounding and/or exposure misclassification.<br>• Many experimental studies have been undertaken as randomised controlled trials to investigate the effects on cancer risk of an increased intake of Se. |
| Exposure and setting | Exposure concentrations (if applicable) | Not applicable (literature review) |
| | Comparison group(s) | |

| **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.*** | | |
|---|---|---|
| Study methods | Study approach | 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) | |
| Statistics (if any) | Statistical method used | None (literature review) |
| | 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.<br>• 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.<br>• 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.<br>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:<br>• Alopecia: RR 1.28 (99% CI 1.01-1.62).<br>• Dermatitis grade 1-2: RR 1.17 (99% CI 1.00-1.35).<br>Although the review raises some concerns, it is noted the findings have not yet been reproduced in other studies. |
| | Notes on study quality, e.g. gaps, methods | |

| **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.*** |
|---|
| **References:**<br>Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, Zeegers MP, Horneber M, D'Amico R and Del Giovane C (2014). Selenium for preventing cancer. Cochrane Database Syst Rev 3: CD005195. |

## 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. European journal of clinical nutrition 70(2): 162-169.*** | | |
|---|---|---|
| General Information | Date of data extraction | 13/12/2021 |
| | Authors | Zhang X., Liu C., Guo J. and Song Y. |
| | Publication date | 2016 |
| | Publication type | Peer-reviewed journal article (meta-analysis) |
| | Peer reviewed? | Yes |
| | Country of origin | USA & China |
| | 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). |
| | Possible conflicts of interest | The authors declare no conflict of interest. |
| Study characteristics | Aim/objectives of study | To assess the discrepancies between findings of observational and randomised trial evidence for Se exposure & cardiovascular disease. |
| | Study type/design | Meta-analysis |
| | Study duration | Studies searches up to December 15, 2013 |
| | Type of water source (if applicable) | Not applicable (not drinking water studies) |
| Population characteristics | Population/s studied | Meta-analysis of 16 prospective observational studies and 16 randomised controlled trials |

| **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. European journal of clinical nutrition 70(2): 162-169.*** | | |
|---|---|---|
| | Selection criteria for population (if applicable) | Articles were chosen based on the following inclusion criteria:<br>(1) original studies (not reviews, meeting abstracts, editorials, letters or commentaries);<br>(2) adult human studies;<br>(3) prospective study design (for example, prospective cohort, nested case–control, case–cohort) or RCTs;<br>(4) prospective studies that provided the relative risk (RR) estimation between baseline circulating or toenail Se concentration and CVD incidence or mortality; and<br>(5) RCTs with Se-containing supplements (Se alone or a combination with other vitamins or minerals), which provided available data of Se dose and CVD incidence or mortality and/or circulating concentrations of Se or Se protein GPx activity.<br><br>Also manually searched bibliographies from recent reviews and retrieved articles for additional studies. |
| | Subgroups reported | - |
| | Size of study | See below |
| Exposure and setting | Exposure pathway | Various (mainly oral supplementation or diet) |
| | Source of chemical/contamination | - |
| | Exposure concentrations (if applicable) | For supplementation trials:<br>Median dose 100 µg/d, range: 75-300µg/d. |
| | Comparison group(s) | - |
| Study methods | Water quality measurement used | - |
| | Water sampling methods (monitoring, surrogates) | - |
| Results (for each outcome) | Definition of outcome | Meta-analysis of prospective studies showed:<br>• nonlinear relationship of CVD risk with blood Se concentrations across a range of 30–165 µg/l and<br>• a significant benefit of CVD within a narrow Se range of 55–145 µg/l.<br>Meta-analyses of RCTs showed that oral Se supplements (median dose: 200 µg/day) for 2 weeks to 144 months significantly raised the blood Se concentrations by 56.4 µg/l (95% confidence interval (CI): 40.9, 72.0 µg/l), whereas oral Se supplements (median: 100 µg/day) for 6 to 114 months caused no effect on CVD (RR = 0.91; 95% CI: 0.74, 1.10). |
| | How outcome was assessed | |
| | Method of measurement | |
| | Number of participants (exposed/non-exposed, missing/excluded) (if applicable) | 35,607 participants in 16 prospective studies<br><br>37,572 participants in 16 trials (median dose 100 µg/d, range: 75-300µg/d). |

| **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. European journal of clinical nutrition 70(2): 162-169.*** | | |
|---|---|---|
| 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? | See above |
| Author's conclusions | Interpretation of results | Meta-analysis in prospective studies demonstrated a significant inverse association between Se status and CVD risk within a narrow Se range and a null effect of Se supplementation on CVD was observed in RCTs. |
| | Assessment of uncertainty (if any) | • The observational nature of prospective studies included in the analysis cannot rule out residual confounding, although the consistency of results across multiple strata and sensitivity analyses minimises the likelihood that residual confounding explains the findings.<br>• All included observational studies used a single measurement of Se at baseline, which is not a time-integrated measure of Se status and thereby affect the association.<br>• Substantial between-study heterogeneity could influence the accuracy in the pooled estimates. Nevertheless, the strength and the direction of the associations were essentially unchanged after excluding the studies with extreme values.<br>• As in any meta-analysis, publication bias is possible, although it was attempted to retrieve all relevant data.<br>• The benefits of Se may only present in the deficient population. Owing to sparse data, the authors indicate they have insufficient statistical power to clearly illustrate this hypothesis. In addition, there is low power to explore the differential effects between Se supplements alone and combined Se supplements.<br>• Limited data from existing prospective studies and RCTs provided insufficient power to detect potential sources of heterogeneity and interactions. In addition, the authors cannot completely exclude the possibility that changes in treatment compliance for all the trials included and differential serum Se concentrations in response to supplementation may affect the explanation for observed differences between treatment and placebo, especially when relevant information was unavailable and trial duration was long. |
| Reviewer comments | Results included/excluded in review (if applicable) | The meta-analysis indicates at doses ranging from 75-300 µg/d of Se, there does not appear to be an adverse effect of Se on cardiovascular function. This supports the use of a NOAEL of 300 µg/d for cardiovascular effects. |
| | Notes on study quality, e.g. gaps, methods | |

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