EVIDENCE EVALUATIONS FOR AUSTRALIAN DRINKING WATER GUIDELINE CHEMICAL FACT SHEETS

Selenium Evaluation Report

Prepared for:

National Health and Medical Research Council

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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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DOCUMENT CONTROL

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EXECUTIVE SUMMARY

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 underpinning the evaluations have been undertaken in line with a new methodological framework which employs a pragmatic, systematic adopt/adapt approach for reviewing health advice.

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

The targeted screening of existing health-based guidance identified five candidate guidance/guideline values for Se for potential adoption/adaptation from six different jurisdictions: the World Health Organization (WHO), the US Agency for Toxic Substances and Disease Registry (ATSDR), the European Food Safety Authority (EFSA), the Californian Office of Health and Hazard Assessment (OEHHA), Food Safety Australia New Zealand (FSANZ) and the National Health and Medical Research Council (NHMRC). The jurisdictional guidance values found for Se are:

- ATSDR (2003): A guidance value or Chronic Minimal Risk Level (MRL) of 0.005 mg/kg/d.
- EFSA (2006, 2014a): A guidance value or Upper Level of Intake (UL) of 300 µg/day in adults or 0.0055 mg/kg/d (at 55 kg body weight, consistent with body weight in the studies from which this value is derived).
- NHMRC (2006), FSANZ (2008): A guidance value or UL of 400 µg/day for adults (~0.0057 mg/kg/d at a 70kg average Australian body weight) and 0.007 mg/kg/d for infants.
- OEHHA (2018): A guideline value or Public Health Goal (PHG) of 30 µg/L (based on a guidance value of 0.005 mg/kg/d).
- WHO (2016): A provisional guideline value or Drinking Water Guideline (DWG) of 40 µg/L (based on a UL of 400 µg/day).

Potential adaptation of the guidance values from the various jurisdictions would result in a health-based DWG of 0.02 mg/L, which is higher than the current Australian DWG of 0.01 mg/L.

The evidence scan undertaken for this review revealed a number of recently published studies which could potentially impact the conclusions made in this report. Additional randomised controlled trial results have been published (Vinceti et al. 2014, 2017, 2018) which do not appear to have been critically evaluated by the most recent agency review (OEHHA 2018). This could have the potential to lower the recommended DWG to 0.003 mg/L. It was, however, beyond the scope of this work to undertake a detailed critical appraisal of the new information. It is therefore recommended that a more detailed review and analysis of the more recent findings for Se is warranted before considering revising the current DWG.

The concentration of both candidate DWGs of 0.003 mg/L and 0.02 mg/L appear to be achievable with existing treatment technologies and readily measurable with current commercial analytical techniques.

CONTENTS

DOCUMENT REFERENCES

TABLES

FIGURES

CONTENTS

Abbreviations/Definitions

Acronym	Definition
ADI	Acceptable Daily Intake
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)
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Low Observed Adverse Effect Level
LOR	Limit of Reporting
MRL	Minimal Risk Level (ATSDR terminology)
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
NRV	Nutrient Reference Value
OEHHA	Californian Office of Environmental Health and Hazard Assessment
PHG	Public Health Goal (in drinking water) (OEHHA terminology)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
RfD	Reference Dose (US EPA terminology)
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.
TDI	Tolerable Daily Intake
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 guidance/guideline[1] values. For each of the 11 chemicals, SLR was asked to:

- Customise and apply a 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 Evaluation Report for selenium (Se).

1.1 Objectives

The factsheet for Se within the Guidelines was last updated in 1996. The overarching objective of this review is to identify existing sources of guidance or guidelines on the impact of exposure to Se in drinking water at levels higher or lower than the current Australian drinking water guideline (DWG) of 0.01 mg/L (i.e. 10 µg/L) on human health outcomes. The intention is to identify candidate health-based guidance/guideline values for potential adoption/adaptation into the Guidelines.

Other objectives of the review are:

- To assess the currency of selected guidance/guidelines through a brief scan of recent literature to determine whether a more comprehensive review is required; and
- To undertake an evidence scan to inform an update to the supporting information (e.g. monitoring and treatment guidance) provided in the factsheet.

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 literature searches. The research questions guiding the review are provided in **Table 1**.

[1] A guidance value in this report refers to a health-based oral intake which can be ingested daily without adverse health effects; examples are Tolerable Daily Intakes (TDIs), Acceptable Daily Intakes (ADIs), Reference Doses (RfDs), Minimal Risk Levels (MRLs) etc. A guideline value transforms the health-based guidance value into a 'tolerable' concentration in various exposure media, e.g. a drinking water guideline (DWG). For derivation of a DWG, factors such as assumed intake of water by a person per day, body weight, and assumed percentage contribution of drinking water to the overall intake of a chemical are taken into account.

Table 1 Research Questions for Evidence Evaluation of Se 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 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	
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 Methodology Overview

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

- A targeted literature search of existing health-based guidance/guidelines. Jurisdictions included in this search were those previously identified by ToxConsult (2019) as providing reliable information and meeting a large proportion of pre-determined technical and administrative criteria. They included the World Health Organization (WHO) including the Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), United States Environmental Protection Agency (US EPA), US Agency for Toxic Substances and Disease Registry (ATSDR), Californian Office of Health and Hazard Assessment (OEHHA), Food Safety Australia New Zealand (FSANZ), and the Australian Pesticides and Veterinary Medicine Authority (APVMA). In addition, the Nutrient Reference Values (NRVs) from the NHMRC were also consulted.
- Where eligible guidance/guideline values existed, a brief evidence scan of published reviews and/or primary studies published after the guidance/guideline search date, with a view to determining whether a full systematic review is required.
- Consultation of identified existing guidance/guideline documents for supporting information in the factsheet (e.g. general description, uses, measurement techniques and limits of reporting in drinking water, treatment options, etc).
- An additional evidence scan of recent publicly available literature for supporting information in the factsheet.

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

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

Relevant data were extracted by populating various pre-constructed tables which focused on data needed to answer the research questions. Synthesis was conducted by presenting extracted data 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/interpretations may differ from Australian science policy. In addition, each candidate jurisdiction's guideline/guidance value for Se considered for potential adoption/adaptation into the Guidelines was evaluated with respect to defined list of administrative and technical criteria (previously defined by ToxConsult 2019 and NHMRC). The reader is referred to the accompanying Technical Report for the detailed methodology, records of the literature screening process (including all records that were excluded) and all data extraction tables.

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).

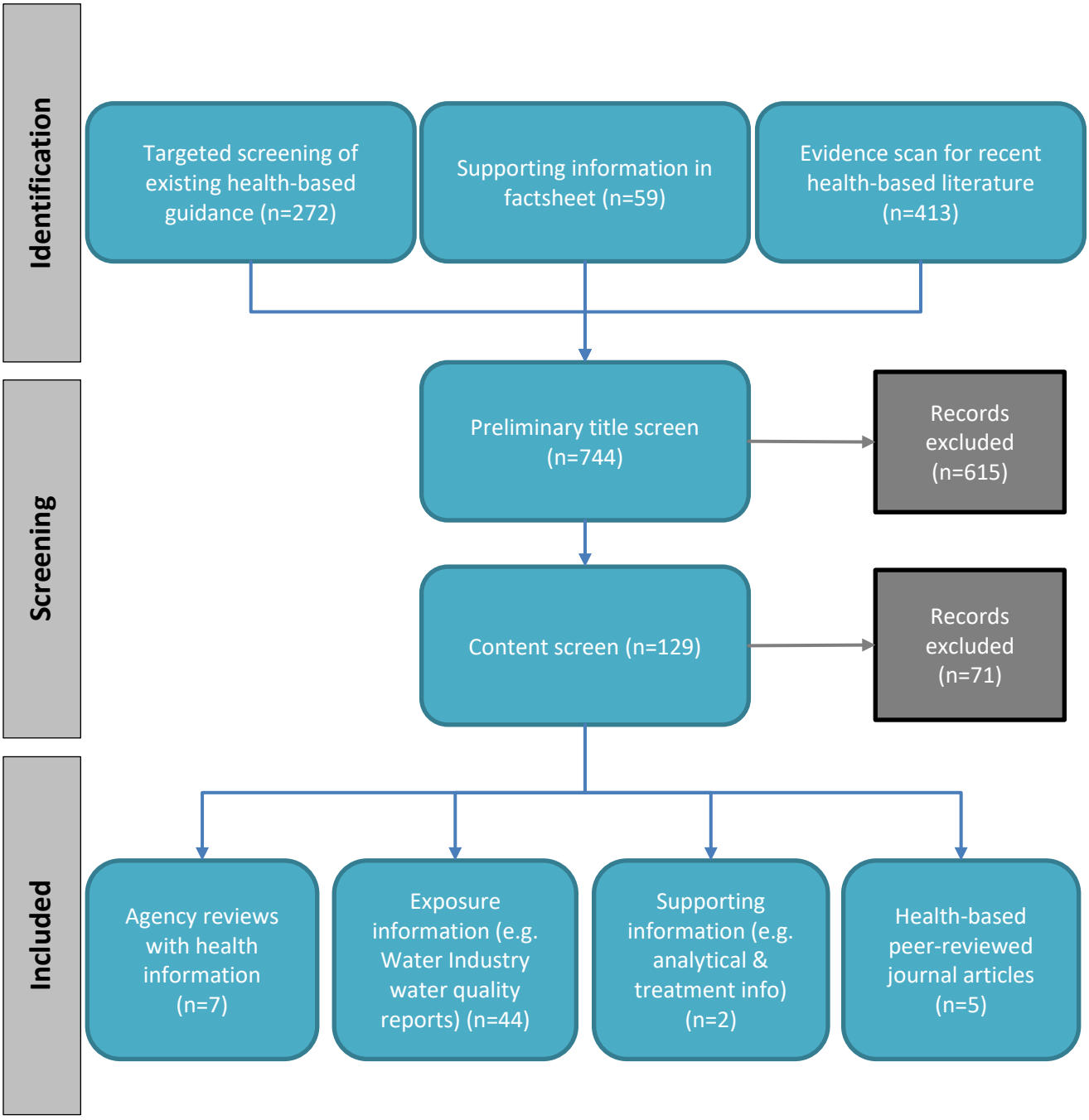

Figure 1 Overview of literature search process followed for Selenium

This report provides the summary of the findings (**Section 4**), a discussion of the results (**Section 5**), and conclusion and recommendations (**Section 6**). Where health-based guidance values were considered reasonable for potential adaptation into the Guidelines, calculations of prospective DWGs were undertaken using the methodology and assumptions outlined in the Guidelines (NHMRC and NRMMC 2011).

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

Guideline value (µg/L) =

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

.....**Equation 1**

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

4 Results

The targeted screening of existing health-based guidance identified seven sources of health-based information on Se for inclusion in the review. Upon further assessment, five candidate guidance/guideline values for Se for potential adoption/adaptation from six different jurisdictions were identified. These jurisdictions are:

- ATSDR (2003): A guidance value or Chronic Minimal Risk Level (MRL) of 0.005 mg/kg/d.
- EFSA (2006, 2014a): A guidance value or Upper Level of Intake (UL) of 300 µg/day in adults or 0.0055 mg/kg/d (at 55 kg body weight, consistent with body weight in the studies from which this value is derived).
- NHMRC (2006), FSANZ (2008): A guidance value or UL of 400 µg/day for adults (~0.0057 mg/kg/d at a 70kg average Australian body weight) and 0.007 mg/kg/d for infants.
- OEHHA (2018): A guideline value or Public Health Goal (PHG) of 30 µg/L (based on a guidance value of 0.005 mg/kg/d).
- WHO (2016): A provisional guideline value or Drinking Water Guideline (DWG) of 40 µg/L (based on a UL of 400 µg/day).

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

4.1 Health-based aspects

Research questions 1-11 all cover health-based aspects of the review; this is considered to be the most important information in the factsheet. **Table 2** provides a synthesis of the results by showing where there is and is not agreement between different jurisdictions.

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

#	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?
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?	The jurisdictions agree that the critical health endpoint is selenosis, manifested as brittle hair, nail damage (i.e. loss of fingernails), and in extreme cases, neurological disturbances.	No disagreements to note.
2	What are the justifications for choosing this endpoint/health hazard?	Selenosis is known to occur in humans at very high Se intakes. Other effects seen in animal studies are of unknown relevance to humans.	-
3	What is the toxicological mode of action of Lead for the critical human health endpoint (if applicable)?	Several mechanisms have been proposed but the exact mechanisms remain unclear. Mechanisms may involve: • Redox cycling of auto-oxidisable Se metabolites. • Glutathione depletion. • Protein synthesis inhibition. • Depletion of S-adenosyl-methionine (cofactor for selenide methylation). • General replacement of sulphur and reactions with critical sulphydryl groups of proteins and cofactors.	
4	Is Se an oral genotoxic carcinogen of relevance to humans?	There is agreement between jurisdictions that most Se compounds are probably not carcinogenic, although some may be genotoxic at toxic doses.	-
5	What dose(s) are associated with the critical human health endpoint (if any)?	Most jurisdictions indicate the human adult NOAEL for selenosis is 800-900 µg/day. This equates to ~0.015-0.02 mg/kg bw/day.	NHMRC (2006) also indicate the NOAEL in infants is ~7µg/kg bw/d since human milk concentrations of 60µg/L were not associated with adverse effects.
6	What is the guidance value?	All jurisdictions have guidance values (when converted to doses) in a relatively narrow range from 0.005 to 0.0057 mg/kg/d (and for infants 0.007 mg/kg/d, NHMRC 2006).	-
7	Is the health-based guidance value expressed in the best way?	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.	
8	Is the proposed health-based guidance / guideline value relevant to the Australian context?	Yes.	

#	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?
9	Are there groups of people in the general population who may be more sensitive to Se exposure?	Jurisdictions have generally not identified any particularly sensitive sub-populations. Some agencies speculate that it is possible that people who are malnourished (e.g. vitamin E deficient diets), have hepatitis or liver disease, and/or have certain mutations or polymorphisms in selenoprotein-related genes may have differential sensitivity to Se.	
10	Is there a knowledge gap from the time at which existing guideline values were developed?	Potentially. The bibliography in the most recent agency review contained literature up to the year 2010.	
11	Does any recent literature change the guideline value? (e.g. demonstrating a new critical endpoint?)	Potentially. 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. 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. 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.	

NOAEL = No Observed Adverse Effect Level. LOAEL = Low Observed Adverse Effect Level. BW = Body weight.

4.2 Exposure-related aspects

Another important aspect of the factsheet covers the exposure-related considerations. This is important for consideration of whether exposures to the chemicals evaluated by Australians are approaching the health-based guidance value used for deriving a DWG. It is also important for considerations of whether typical levels of the chemicals considered in Australian drinking water supplies would adhere to any revised DWG. Research questions 12-15 cover exposure-related aspects of the review. For these aspects, drinking water quality reports from various water corporations around Australia were consulted in addition to the agency reviews identified in the targeted search.

Table 3 provides a synthesis of the results by showing where there is and is not agreement between different sources.

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

#	Research Questions	Findings
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?	ACT, VIC: <0.001 mg/L QLD: <0.002 mg/L NT: mean range <0.0002 – 0.012 mg/L (high values at Kings Canyon and Daly Waters). Tas: mean range <0.0001 – 0.0025 mg/L In certain situations (e.g. drought), Se concentrations may be higher (OEHHA 2010).
13	Do Australian levels differ considerably from elsewhere?	Available data suggests Se concentrations around Australia are similar to those in the USA and other parts of the World.
14	What are the principal routes of exposure to Se in the Australian general population?	Se is an essential nutrient for humans and animals. Compared to drinking water, food is the major overall source of Se for humans. Most people obtain virtually al, of their Se from the foods they eat.
15	What are the typical levels of Australian exposure? (e.g. 'background' Se levels)?	Mean (95th percentile) intakes of Se in Australian general population: • Infant: 14 (36) µg/d. • Children (2-3 yrs): 37-41 (52-70) µg/d. • Adults (19-29 yrs): 57-90 (88-143) µg/d.

4.3 Risk-based aspects

Research questions 16 and 17 are risk-based considerations. The jurisdiction reviews subjected to detailed data extraction mentioned at the start of **Section 4** were also consulted to answer these questions. **Table 4** presents a summary of the findings.

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

#	Research Questions	Findings
16	What are the risks to human health from exposure to Se in Australian drinking water?	None identified for drinking water in Australia. 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.
17	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review?	None identified by the agencies. However, 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.
DWG = Drinking Water Guideline. RCT = Randomized Controlled Trials. NOAEL = No Observed Adverse Effect Levels.		

4.4 Supporting information

The Se factsheet contains a range of supporting information, including a brief general description (i.e. uses of Se, sources in drinking water), typical values in Australian drinking water, treatment of drinking water, and measurement (i.e. analytical) considerations. The remaining Research questions 18-23 cover the supporting information of the review. For these aspects, in addition to consulting the previously mentioned sources (e.g. the drinking water quality reports from various water corporations around Australia, the agency reviews identified in the targeted search), additional targeted searches were undertaken (for details, refer to Technical Report). **Table 5** provides a summary of the results.

Table 5 Summary of findings from data extraction for supporting information

#	Research Questions	Findings
18	Is the general description current?	Yes, but a few additional uses and additional detail on weathering of rocks as a source of Se in drinking water are mentioned in agency reviews.
19	What are the indicators of the risks? How can we measure exposure? Is the information on measurement/analytical methods current?	Yes, information is current, except that ICP/AES is also mentioned in the agency reviews. • Atomic Absorption Spectrophotometry (AAS) (LOD 2 µg/L) • ICP/AES (LOD 0.06 or 0.5 µg/L) Australian commercial laboratories tend to measure Se in drinking water with ICP-MS or ICP-AES (standard LOR 1 µg/L, trace 0.1-0.2 µg/L). Water Corporations measure Se in DW with method USEPA 200.8 (LOR 1 µg/L).
20	Are there commercial analytical methods available that can measure at or below the guideline value?	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.
21	Is the information for treatment options current in terms of current practices in Australia?	Only limited information on treatment options was found in the literature search undertaken for this report. The information found does not suggest any changes are required to what is already in the factsheet.
22	Can treatment technologies treat to the suggested level of the guideline value?	Although no direct relevant information was available from the sources consulted, 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.

#	Research Questions	Findings
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.

DWG = Drinking Water Guideline; LOAEL = Low Observed Adverse Effect Level; RCT = Randomised Controlled Trial. LOR = Limit of Reporting. ICP = Inductively Coupled Plasma. MS = Mass Spectrometry. AES = Atomic Emission Spectroscopy.

5 Discussion

This section provides a discussion of the strengths and limitations of the candidate guidance/guideline values for possible adoption/adaptation into the Guidelines.

5.1 Suitability of candidate health-based guidance for adoption/adaptation

Candidate health-based guidance/guideline values for Se shown in **Section 4** and **5.2** for possible adoption/adaptation in Australia have been evaluated using the Assessment Tool Appendix C in the Technical Report). This tool evaluates each document against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. The overall suitability of these guidance/guideline values for adoption/adaption can be gauged at least partially by examining the percentage of 'must-have', 'should-have', and 'may-have' criteria met by each jurisdiction.

Figure 2 presents the percentage of criteria (combined technical and administrative criteria) met by each jurisdiction. It is evident from the figure that NHMRC (2006) met the highest proportion of 'must-have' criteria (100%) with OEHHA (2010) and WHO (2011) meeting the lowest (58% and 63%, respectively). Most of the instances where these criteria were not met were related to lack of reporting of literature search and review details. Whilst all jurisdictions provided comprehensive bibliographies of the information relied upon, none except for NHMRC (2006) reported any detail of the literature searches. The 'should-have' criteria met by most agencies was similar ranging from 50-70%. All jurisdictions, except EFSA (2006, 2014a) met 100% of the 'may-have' criteria.

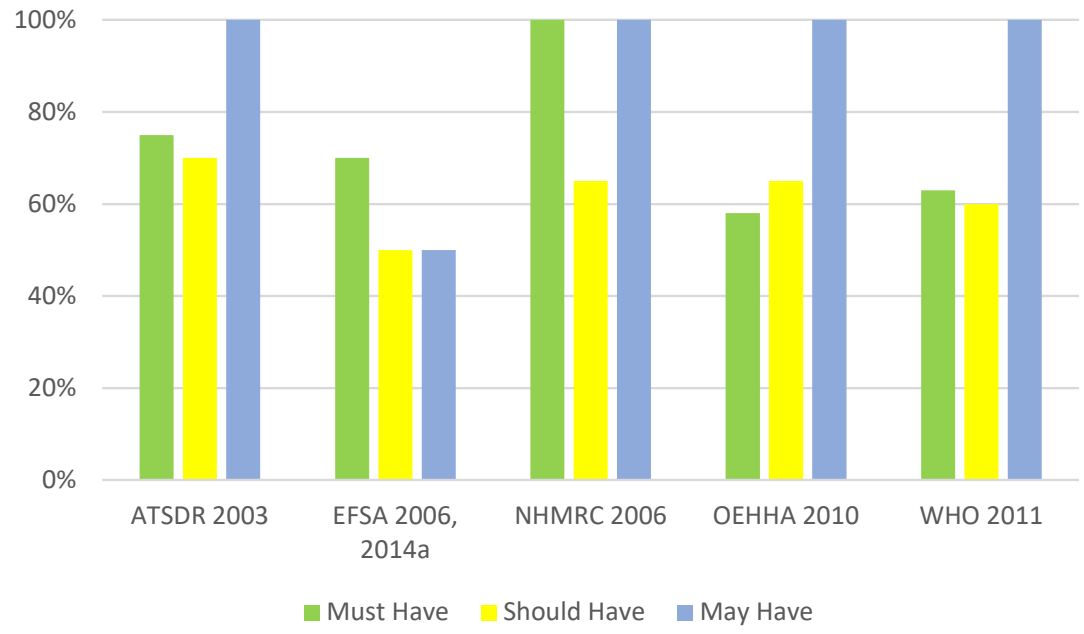

Figure 2 Overall proportion of 'must-have', 'should-have' and 'may-have' technical/administrative criteria met by jurisdictions who have derived candidate health-based guidance/guideline values for selenium for possible adoption/adaptation in Australia

This analysis indicates that the health assessments undertaken by all jurisdictions meet a similar proportion of overall technical and administrative criteria. NHMRC (2006) met a higher proportion of 'must have' criteria.

5.2 Overall Evaluation

The analysis in Section 5.1 indicated slight differences in suitability of the candidate guidance/guideline values for adoption/adaption based on an assessment of administrative and technical characteristics of the identified guidance documents. Further analysis of the toxicological basis and methods used for deriving the different guidance values was also undertaken.

The following summary comments are made with respect to the toxicological basis and methods for the health-based guidance values for Se cited or derived by the jurisdictions shown in **Section 5.1:**

- All jurisdictions agree that selenosis (manifested by brittle hair and nails) is the critical health endpoint on which a guidance/guideline value for Se should be based. Most of the agencies have used the various Chinese studies by Yang (various dates) in a population with high Se intakes as the basis for their point of departure with the data from a US study (Longnecker et al. 1991) providing support. However, the current Australian guideline value is based on the US study alone and does not mention the numerous Chinese studies.
- As a result of using essentially the same studies and point of departure (and very similar uncertainty factors ranging from 2-3), the guidance values derived by the various jurisdictions are very similar. In contrast the current Australian DWG in NHMRC and NRMMC (2011) is lower since it is based on a NOAEL from the US study.
- Adaptation of the guidance values from the various jurisdictions would result in the same DWG (i.e. 0.02 mg/L), which is higher than the current Australian DWG of 0.01 mg/L (see **Table 6**).

Although there is very good agreement between the agencies that a DWG for Se of 0.02 mg/L would be defensible, it is noted that 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. Agencies other than EFSA (2014a) did not have the benefit of including these findings in their reviews, and the EFSA (2014a) review focused mainly on Se requirements rather than adverse effects of Se excess.

One of these RCTs (the SELECT Trial), 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 statistically 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]. In a later paper (Vinceti et al. 2018) the same RRs were reported but 95% confidence intervals were 1.07-1.53 (alopecia, 265/206 cases in Se and placebo arms) and 1.03-1.29 (dermatitis, 619/524). Unfortunately, only a single dose was tested in the study, therefore there is no dose response information for the effects. It is noted Karp et al. (2013) found no such significant increases in alopecia or dermatitis in 865 patients given the same dose of Se for 2 years compared with 477 patients given placebo from a different RCT study, however the study participant numbers were much lower than in the SELECT trial.

Assuming that the effects noted by Vinceti et al. (2014, 2017, 2018) could be regarded as a minimal LOAEL, a guidance value (for excess Se) of 67 µg/d could theoretically be derived [200 µg/d ÷ uncertainty factor of 3 = 67 µg/d]. In this case, an uncertainty factor of 3 would be 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 potential candidate DWG of 3 µg/L (i.e. 0.003 mg/L) (rounded). This candidate DWG is lower than both the current Australian DWG (0.01 mg/L) and the adapted candidate guideline value from other jurisdictions (0.02 mg/L). It therefore 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.

Table 6 Potential drinking water guideline values (mg/L) resulting from adaptation of selenium guidance values from other jurisdictions

Parameter	NHMRC (2021) – Existing Aus DWG – last updated in 1996	ATSDR (2003)	EFSA (2006, 2014a)	NHMRC (2006)	OEHHA (2010)	WHO (2011)
Critical study	Longnecker et al. 1991	Yang and Zhou 1994	Yang et al. 1989b, Yang and Zhou 1994	Adults: Studies in China (Yang et al. 1983, 1989b, Yang and Zhou 1994), consistent with one US study (Longnecker et al. 1991) Infants: Shearer & Hadjimarkos (1975)	Yang et al. (1981; 1982a,b; 1983; 1987; 1988a,b; 1989a,b), Yang (1987), Yang and Zhou (1994), and Yang and Xia (1995)	Not stated (point of departure is upper tolerable daily intake derived by other agencies)
Study population	Humans	Humans	Humans	Humans	Humans	Humans

Parameter	NHMRC (2021) – Existing Aus DWG – last updated in 1996	ATSDR (2003)	EFSA (2006, 2014a)	NHMRC (2006)	OEHHA (2010)	WHO (2011)
Critical Effect	No adverse effects reported	Selenosis	Selenosis	Selenosis (adults) No adverse effects (infants)	Selenosis	Selenosis
Point of Departure (mg/kg/d or mg/day)	NOAEL 0.24 mg/day	NOAEL 0.015 mg/kg/d	NOAEL 0.85 mg/day	Adults: NOAEL 0.8 mg/day Infants: NOAEL of 0.047 mg/day (0.007 mg/kg bw/d)	NOAEL 0.015 mg/kg/d	Upper tolerable daily intake 0.4 mg/day
Uncertainty factor	None	3 (UF_H)	3 (UF_H)	Adults: 2 (UF_H) Infants: 1	3 (UF_H)	None
Health-based guidance or guideline value (mg/kg/d or mg/L)	0.24 mg/day (i.e. 0.0034 mg/kg/d) (2)	MRL of 0.005 mg/kg/d	0.3 mg/day (rounded) in adults (0.0055 mg/kg/d) (3)	Adults: 0.4 mg/day (i.e. 0.0057 mg/kg/d) (2) Infants: 0.007 mg/kg bw/d	0.005 mg/kg/d (PHG of 0.03 mg/L)	0.4 mg/day, DWG of 0.04 mg/L
Resulting adaptation to a Health Based DWG(1) (mg/L)	0.01	0.03 (infant) 0.02 (adult) (rounded)	0.04 (infant) 0.02 (adult) (rounded)	0.05 (infant) 0.02 (adult) (rounded)	0.02 mg/L (rounded)	0.02 mg/L

DWG = Drinking Water Guideline; Aus = Australian; LOAEL = Low Observed Adverse Effect Level; NOAEL = No Observed Adverse Effect Level; MRL = Minimal Risk Level. UF_H = Uncertainty factor for human variability.

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

   DWG (mg/L) = [Guidance value (mg/kg bw/d) x 5 kg bw (infant) or 70kg (adult) x 1 for infant (i.e. 100% relative contribution from DW) or 0.1 for adult] ÷ 0.75 L/day for infant or 2 L/day for adult

2. Assuming an average adult body weight of 70 kg.
3. Using a 55kg body weight as per the studies on which the NOAEL is based.

It is noted, however, Se intake from drinking water at a DWG of 0.02 mg/L is approximately 40 µg/day (= 0.02 mg/L x 2L/day x 1,000µg/mg). This intake is similar in proportion to the mean overall Se background intakes for Australian infants (14 µg/day), 2 – 3 year-old children (37-41 µg/d) and adults (57-90 µg/d). Summing the mean background intakes and the potential intake from drinking water, the intakes (up to 130 µg/day) are less than the potential minimal LOAEL (200 µg/day) for alopecia and dermatitis. However, at the 95th percentile background Se intakes, the highest overall intake from background sources and drinking water (i.e. 183 µg/day in adults) is approaching the minimal LOAEL, therefore it is considered the veracity of the minimal LOAEL be evaluated in more detail prior to making a definitive recommendation.

6 Conclusions

Five existing guidance/guideline values relevant to Se from six jurisdictions were found suitable to adopt/adapt based on an assessment of the administrative and technical criteria described in Appendix C of the Technical Report.

Potential adaptation of the similar guidance values from the various identified jurisdictions would result in a health-based DWG of 0.02 mg/L, which is higher than the current Australian DWG of 0.01 mg/L.

The evidence scan undertaken for this review revealed a number of recently published studies which could potentially impact the conclusions made in this report. The most recent agency reviews do not appear to have undertaken a detailed evaluation of the results from recent randomised controlled trial (RCT) studies in relation to adverse effects (alopecia and dermatitis) from excess Se exposure which could have the potential to lower the recommended DWG to 0.003 mg/L. It was, however, beyond the scope of this review to undertake a detailed critical appraisal of the new information. It is therefore recommended that a more detailed review and analysis of the more recent findings for Se is warranted before a revised DWG can be recommended.

The concentration of both candidate DWGs of 0.003 mg/L and 0.02 mg/L appear to be achievable with existing treatment technologies and readily measurable with current commercial analytical techniques.

7 Review Team

Name	Position	Responsibilities
Ms Tarah Hagen, MSc, DABT, RACTRA	Technical Discipline Manager – Toxicology & Risk Assessment, SLR	Report author and technical oversight of literature review
Dr Slavica Kandic, PhD	Project Consultant – Toxicology & Risk Assessment, SLR	Literature searching, preliminary title screen, compilation of Appendices
Mr Giorgio De Nola, MSc, RACTRA	Principal Consultant – Toxicology & Risk Assessment, SLR	Internal peer review

8 Declared Interests

Team Member	Declaration of Interest
Ms Tarah Hagen	As part day-to-day consulting activities at SLR Consulting and ToxConsult Pty Ltd, Ms Hagen has: • Provided the report "Assessment of International and National Agency Processes for Deriving HBGVs and DWGs" to NHMRC. This has been used to inform the methodological framework for this review as described in the Research Protocol.
Dr Slavica Kandic	No interest to declare.

Team Member	Declaration of Interest
Mr Giorgio De Nola	No interest to declare.

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10 References

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

European Food Safety Authority (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).

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

FSANZ (2008). The 22nd Australian Total Diet Study. Food standards Australia and New Zealand.

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

Longnecker M.P., Taylor P.R., Levander O.A., Howe M., Veillon C., McAdam P.A., Patterson K.Y., Holden J.M., Stampfer M.J., Morris J.S., Willett W.C. Selenium in diet, blood and toenails in relation to human health in a seleniferous area. Am J Clin Nutr 1991;53:1288–94. *As cited in NHMRC 2006.*

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

NHMRC (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. Commonwealth of Australia, Canberra.

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.

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

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

Vinceti M., 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.

Vinceti M., Filippini T., Del Giovane C., Dennert G., Zwahlen M., Brinkman M., Zeegers MPA, Horneber M, D'Amico R, Crespi CM (2018). Selenium for preventing cancer. Cochrane Database of Systematic Reviews. Issue 1. Art. No: CD005195. DOI: 10.1002/14651858.CD005195.pub4.

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

Yang G.Q., Wang S.Z., Zhou R.H., Sun S.S., Man R.G., 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 Medicine, 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.*

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