EVIDENCE EVALUATIONS FOR AUSTRALIAN DRINKING WATER GUIDELINE CHEMICAL FACT SHEETS

Nickel Evaluation Report

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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 nickel (Ni). 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 ten relevant reports on Ni from four different jurisdictions: the World Health Organization (WHO), the European Food Safety Authority (EFSA), the US Agency for Toxic Substances and Disease Registry (ATSDR) and the Californian Office of Health and Hazard Assessment (OEHHA). The documents were found to be suitable to adopt/adapt based on an assessment against a number of administrative and technical quality requirement. Several candidate guidance/guideline values for Ni for potential adoption/adaptation were identified from these reports. Two out of the ten jurisdictional reports (ATSDR 2005, EFSA 2005) did not derive any guidance/guideline values that could be adopted/adapted.

The jurisdictional guidance/guideline values found for Ni are:

- EFSA (2015a, b, c): A guidance value or Chronic tolerable daily intake (TDI) of 2.8 µg/kg/day for oral exposure was derived. An acute benchmark dose at 10% effect ($BMDL_{10}$) of 1.1 µg/kg was identified for Ni sensitised individuals for use in a Margin of Exposure (MOE) assessment[1]. A MOE >10 was considered to represent an acceptable level of risk for acute exposure.
- EFSA (2020a, b): A guidance value or Chronic TDI of 13 µg/kg/day for oral exposure was derived. An acute Low Observed Adverse Effect Level (LOAEL) of 4.3 µg/kg was identified for Ni sensitised individuals for use in a MOE assessment. A MOE >30 was considered to represent an acceptable level of risk for acute exposure.
- OEHHA (2001): A guideline value or Public Health Goal (PHG) in drinking water of 12 µg/L which was based on a chronic guidance value of 1.12 µg/kg/day.
- WHO (2007, 2021): A guideline value or Drinking Water Guideline (DWG) of 70 µg/L which was based on a TDI or chronic guidance value of 13 µg/kg/day.

An evaluation of the critical toxicological studies and margin of exposure analysis was undertaken. There was general agreement across the guidance documents about the critical endpoint for Ni. The identified guidance values were based on either a NOAEL or $BMDL_{10}$ for developmental effects from the same two-generation reproductive study in rats (SLI 2000b).

[1] Margin of exposure is calculated by dividing a point of departure such as a NOAEL by the intake.

EXECUTIVE SUMMARY

It was found that there was higher confidence in the recent guidance from EFSA (2020a) and WHO (2021) based on the recentness of the reviews and the administrative/technical processes undertaken, the underpinning toxicological study and its interpretation by both jurisdictions. Both EFSA (2020a) and WHO (2021 draft) reports are updates to previous health-based guidance on Ni in food and drinking water. In contrast, there was less confidence in guidance/guideline values derived by NHMRC and NRMMC (2011) and other jurisdictions (OEHHA 2001, EFSA 2005, EFSA 2015b and WHO 2007) since they are not based on the most recent benchmark dose analysis undertaken by international jurisdictions. Potential adaption of the EFSA (2020a) or WHO (2021 draft) guidance values would result in a slight increase to the current health-based DWG in the Guidelines from 0.02 mg/L to 0.045 mg/L. This would be achievable with existing treatment technologies and readily measurable with current commercial analytical techniques. The evidence scan undertaken for this report did not identify any recently published studies that would alter the suggested guidance/guideline values evaluated.

CONTENTS

DOCUMENT REFERENCES

TABLES

FIGURES

CONTENTS

Abbreviations/Definitions

Acronym	Definition
ADI	Acceptable Daily Intake (APVMA terminology)
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
BMDL10	Lower Benchmark Dose for a 10% Response
BW, bw	Body Weight
DW	Drinking Water
DWG	Drinking Water Guideline
EFSA	European Food Safety Authority
FSANZ	Food Standards Australia New Zealand
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Low Observed Adverse Effect Level
LOR	Limit of Reporting
MOE	Margin of Exposure
MRL	Minimal Risk Level (ATSDR terminology)
Ni	Nickel
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level
OEHHA	Californian Office of Environmental Health and Hazard Assessment
PHG	Public Health Goal (in drinking water) (OEHHA terminology)
RfD	Reference Dose (US EPA terminology)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RSC	Relative Source Contribution
TDI	Tolerable Daily Intake (WHO and EFSA terminology)
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.
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[2] 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 Nickel (Ni).

1.1 Objectives

The factsheet for Ni 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 Ni in drinking water at levels higher or lower than the current Australian drinking water guideline (DWG) of 0.02 mg/L (i.e. 20 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 question guiding the review are provided in **Table 1**.

[2] 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 Nickel Factsheet Review

#	Research Questions
Health-based	
1	What is the critical human health endpoint for Nickel (if any)? Therefore, what are the key adverse health hazards from exposure to Nickel in Australian drinking water?
2	What are the justifications for choosing this endpoint/health hazard?
3	What is the toxicological mode of action of Nickel for the critical human health endpoint (if applicable)?
4	Is Nickel an oral genotoxic carcinogen of relevance to humans?
5	What dose(s) are associated with the critical human health endpoint?
6	Is the proposed health-based guideline value relevant to the Australian context?
7	Is the health-based guidance value expressed in the best way?
8	Are there groups of people in the general population who may be more sensitive to Nickel exposure?
9	What is the guidance value (if any)?
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 Nickel 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 Nickel in the Australian general population?
15	What are the typical levels of Australian exposure? (e.g. 'background' Nickel levels)?
Risk-based	
16	What are the risks to human health from exposure to Nickel 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 on Factsheet	
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	Is there any new information which 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).
- 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 Ni 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 Ni. 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).

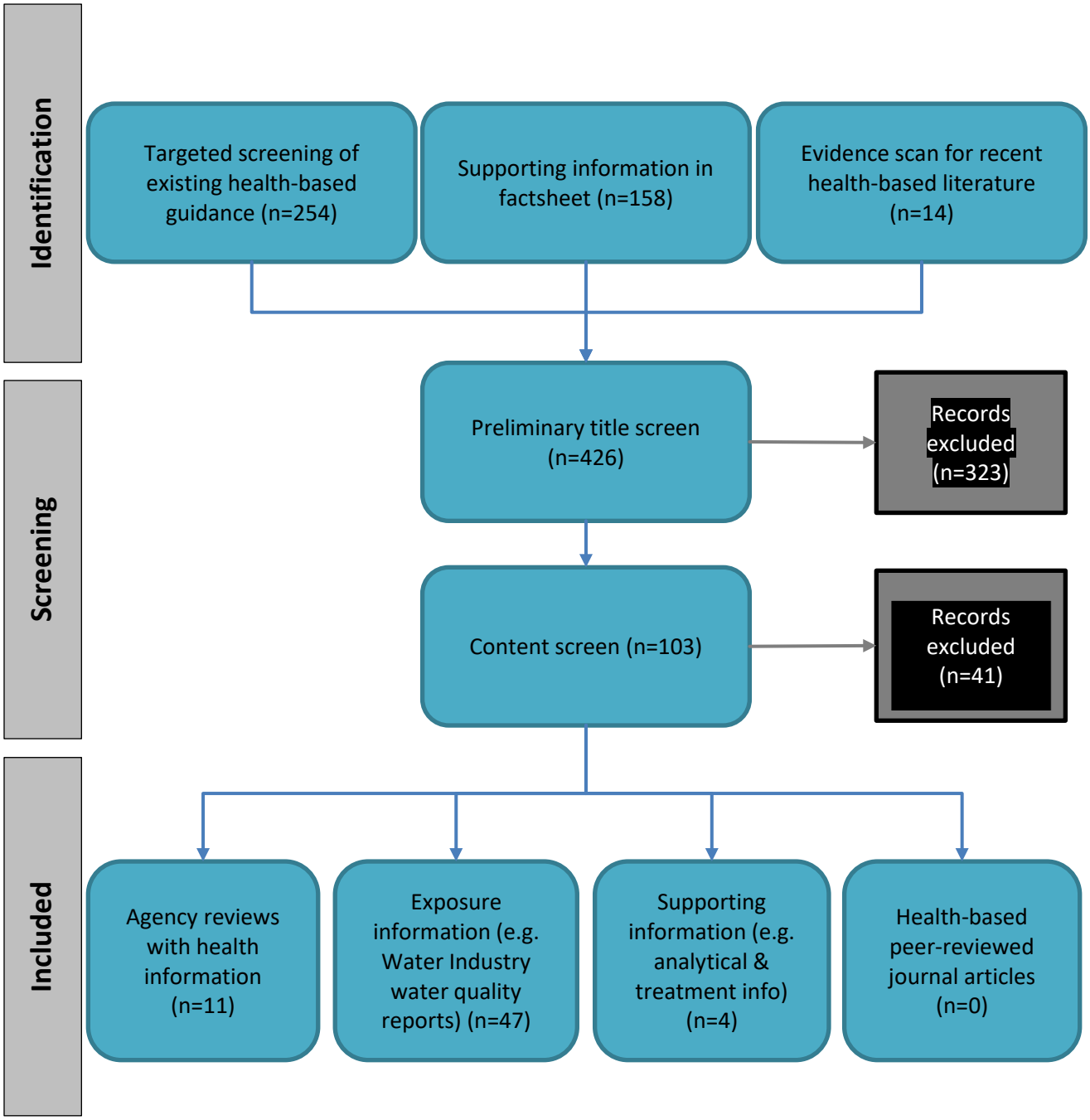

Figure 1 Overview of literature search process followed for Nickel

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 (Australian) 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 Section 6.3.3 of the current Guidelines (NHMRC and NRMMC 2011) 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), 10% (0.1) for the proportion of intake from drinking water, and 2 L/day of water consumption by an adult (1 L/day by a child).

4 Results

The targeted screening of existing health-based guidance found 11 relevant reports. From these sources the review identified four candidate guidance/guideline values for Ni for potential adoption/adaptation from three different jurisdictions. These values are:

- EFSA (2015a, b, c): A guidance value or Chronic TDI of 2.8 µg/kg/day for oral exposure was derived. An acute benchmark dose at 10% effect (BMDL10) of 1.1 µg/kg was identified for Ni sensitised individuals for use in a Margin of Exposure (MOE) assessment[3]. A MOE >10 was considered to represent an acceptable level of risk for acute exposure.
- EFSA (2020a, b): A guidance value or Chronic TDI of 13 µg/kg/day for oral exposure was derived. An acute Low Observed Adverse Effect Level (LOAEL) of 4.3 µg/kg was identified for Ni sensitised individuals for use in a MOE assessment. A MOE >30 was considered to represent an acceptable level of risk for acute exposure.
- OEHHA (2001): A guideline value or Public Health Goal (PHG) in drinking water of 12 µg/L which was based on a chronic guidance value of 1.12 µg/kg/day.
- WHO (2007, 2021): A guideline value or Drinking Water Guideline (DWG) of 70 µg/L which was based on a TDI or chronic guidance value of 13 µg/kg/day.

The other jurisdictional reports consulted (ATSDR 2005, EFSA 2005, FSANZ 2008) did not derive guidance/guideline values for Ni.

The contribution of drinking water to Ni intake was considered very small (EFSA 2020a) compared to intake from the diet. However, it is important to note that Ni-sensitised individuals may not know that they are sensitised and may have an acute reaction (eczematous flare-up reactions in the skin / systemic contact dermatitis) to Ni even if exposed to small amounts. Hence, EFSA and WHO have used a MOE approach to assess potential risk to Ni-sensitised individuals from acute exposure to Ni when considering derivation of chronic guidance / guideline values.

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.

[3] Margin of exposure is calculated by dividing a point of departure such as a NOAEL by the intake.

4.1 Health-based aspects

Research questions 1-12 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 Ni (if any)? Therefore, what are the key adverse health hazards from exposure to Ni in Australian drinking water?	The jurisdictions agree that developmental effects (post-implantation loss in rats) is the critical effect for chronic exposure. Systemic contact dermatitis from acute oral exposure in Ni-sensitised individuals should also be considered.	EFSA (2005) and ATSDR (2005) did not select a critical endpoint.
2	What are the justifications for choosing this endpoint/health hazard?	There is consistent evidence of increased pup mortality (stillbirth or post-implantation loss/perinatal lethality) after exposure of rats to Ni chloride or sulphate in several reproductive toxicity studies at doses ≥ 1.3 mg/kg bw per day. In Ni-sensitised humans, systemic contact dermatitis can be elicited in Ni-sensitive humans after acute oral exposure which is seen as eczematous flare-up reactions and worsening of allergic reactions (e.g. hand eczema, body erythema).	-
3	What is the toxicological mode of action of Ni for the critical human health endpoint (if applicable)?	EFSA noted that the mode of action appears to involve reactive oxygen species (ROS) for chronic exposure and Ni complexation with protamine 2 which is expressed in sperm chromatin. For acute exposures, antigens are taken up by antigen-presenting cells that migrate to draining lymph nodes, resulting in activation of Ni-specific T lymphocytes.	EFSA was the only jurisdiction to provide a mode of action for chronic effects.
4	Is Ni an oral genotoxic carcinogen of relevance to humans?	There is agreement between jurisdictions that Ni is not a genotoxic carcinogen in humans following oral exposures.	Nickel is a carcinogen with genotoxic potential following inhalation exposure.
5	What dose(s) are associated with the critical human health endpoint (if any)?	Points of departure for chronic effects were mostly similar (from 1.1 to 1.3 mg/kg/day) and were based on either a BMDL10 or a NOAEL except for a BMDL10 of 0.28 mg/kg/day from EFSA (2015). For acute effects, a LOAEL of 0.0043 mg/kg (or BMDL10 of 0.0011 mg/kg) was identified by most jurisdictions based on several studies. However, OEHHA (2001) identified a LOAEL of 0.0086 and 0.012 mg/kg and NOAEL of 0.00086 and 0.0012 mg/kg based on two studies.	EFSA in 2020 replaced the chronic BMDL10 of 0.28 mg/kg/day with a re-estimated BMDL10 of 1.3 mg/kg/day.

#	Research Questions	Is there agreement between different jurisdictions?	Any disagreement or things to note?
6	Is the proposed health-based guideline value relevant to the Australian context?	Yes, candidate health-based guidance/guideline values are relevant to the Australian context.	The exception is that OEHHA (2001) applied an additional uncertainty factor of 10x for potential carcinogenicity of Ni which is not in line with Australian risk assessment policy.
7	Is the health-based guidance value expressed in the best way?	Yes. Guidance values are consistently expressed as mg/kg/day (or µg/kg/day) and guideline values are expressed as mg/L (or µg/L).	-
8	Are there groups of people in the general population who may be more sensitive to Nickel exposure?	Yes. Nickel sensitised individuals (from acute effects).	Most individuals may not know that that they are sensitised to nickel.
9	What is the guidance value (if any)?	Guidance values for chronic effects ranged from 0.0028 mg/kg/day (TDI from EFSA 2015) to 0.013 mg/kg/day (EFSA 2020). For acute effects, the LOAEL and BMDL10 (refer to Question 5) were used as guidance values in a MOE assessment.	All jurisdictions applied an uncertainty factor (UF) of 100 to the identified points of departure for chronic effects, with the exception of OEHHA (2001) who applied an UF of 1,000. A MOE of ≥30 using a LOAEL or ≥10 using the BMDL10 were considered representative of low cause for concern for acute effects.
10	Is there a knowledge gap from the time at which existing guideline values were developed?	Unlikely considering two of the agency reviews were completed in 2020 and 2021 (draft) and the agencies have identified the sensitive critical endpoint for acute and chronic exposures.	-
11	Does any recent literature change the guideline value? (e.g. demonstrating a new critical endpoint?)	Evidence scan for recent studies did not reveal any new pivotal studies which may impact the findings of the jurisdictions summarised above.	

BW = Body weight. NOAEL = No Observed Adverse Effect Level, LOAEL = Low Observed Adverse Effect Level, BMDL = Benchmark Dose Level at 10% response

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 Ni 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 Ni in Australian drinking water supplies would currently 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 (of which FSANZ 2008 was added to the list as providing important exposure information for the Australian population).

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 Ni levels in Australian drinking water? Do they vary around the country or under certain conditions e.g. source of water, drought?	Mean concentrations of Ni in drinking water are mostly less than 0.001-0.01 mg/L but can range up to 0.015 mg/L. No particular indication that there is large variability across the country.
13	Do Australian levels differ considerably from elsewhere?	No, from literature reviewed levels in drinking water appear to be similar to those overseas. However, elevated Ni can be found in polluted areas (e.g. near Ni smelters) or in first flush drinking water.
14	What are the principal routes of exposure to Ni in the Australian general population?	The principal route of exposure to Ni is from dietary exposure. Drinking water makes a low contribution to overall Ni intake.
15	What are the typical levels of Australian exposure? (e.g. 'background' Ni levels)?	Dietary intake in Australian adults is around 150 µg/day in men and 115 µg/day in women (FSANZ 2008). This is similar to dietary intakes from other parts of the world (i.e. 170 µg/day in US, 150 µg/day in Denmark, 73 µg/day in Switzerland and 140-150 µg/day in the UK).

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 Ni in Australian drinking water?	No review found for Australia. Overseas the amount of Ni intake from drinking water alone is too low to be of concern.

#	Research Questions	Findings
17	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review?	Yes. The current factsheet is based on liver toxicity from a study by Ambrose et al. (1976). This is not the critical effect chosen by most agencies on which to base chronic health effects (developmental toxicity, post-implantation loss in rats). Further, it could be highlighted that individuals cannot be sensitised from oral exposure to Ni, but that individuals can have an allergic reaction from oral exposure if they are already sensitised and that most individuals do not know that they are sensitised.

4.4 Supporting information

The Ni factsheet contains a range of supporting information, including a brief general description (i.e. uses of Ni, 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.
19	What are the indicators of the risks? How can we measure exposure? Is the information on measurement/analytical methods current?	The method and limits of determination listed in the factsheet are now out of date. Ni concentrations in water are analysed by commercial laboratories in Australia using inductively coupled plasma-mass-spectrometry (ICP-MS) according to USEPA 6010D ICP-AES, USEPA 6020, USEPA 3010A, USEPA 3015A, APHA (21st Edition). Previously, the method used for analysis of Ni in water was graphic furnace atomic absorption spectroscopy (APHA Method 3500-Ni Part B and C 1992, refer to NHMRC and NRMMC 2021). There is a revised APHA Method 3500-Ni from 2018. Current standard limit of reporting is typically 0.001 mg/L. A trace level of determination is also reported by some commercial laboratories as low as 0.0001 mg/L. In the factsheet, the limit of determination is given as 0.02 mg/L and 0.005 mg/L (NHMRC and NRMMC 2011).
20	Are there commercial analytical methods available that can measure at or below the guideline value?	Commercial analytical methods can measure at or below the current Australian DWG value of 0.02 mg/L (with standard limits of determination of 0.001 mg/L).
21	Is the information for treatment options current in terms of current practices in Australia?	Current research is investigating improving removal efficiency and capacity of sorption processes using novel materials. Novel materials include granular iron-based sorption materials (ferric hydroxide), magnetic carbon nanotubes (CNT), macroporous cation exchange resins with chelate groups of iminodiacetic acid and graphene oxide (GO)

#	Research Questions	Findings
22	Can treatment technologies treat to the suggested level of the guideline value?	Current treatment technology (such as precipitation with iron and manganese oxides) can treat raw water to DWG. Novel materials may help improve capacity of existing systems and to lower Ni levels.
23	Is there any new information which should be added? Should anything be removed?	Nothing needs to be removed; however, the measurement section should be updated to reflect the latest test methods, type of test method and limit of determination.

DWG = Drinking Water Guideline.

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 health-based guidance for adoption/adaptation

Candidate health-based guidance/guideline values for Ni shown in **Section 4** and **5.2** for possible adoption/adaptation in Australia have been evaluated using the Assessment Tool (**Appendix C** in 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 that derived guidance values. It is evident from the figure that the international agencies met varying percentages of 'must-have' criteria, ranging from 63% (for OEHHA 2001) to 95% (for EFSA 2015b, 2020a). Most of the instances where these criteria were not met were related to lack of reporting of literature search and review details. Whilst most jurisdictions provided comprehensive bibliographies of the information relied upon, none of the international agencies except for EFSA (2015b, 2020a) reported any (or minimal) detail of the literature searches. The percentage of other criteria met was also highest for EFSA with 100% of 'should-have' criteria met, whereas for OEHHA (2001) and WHO (2007, 2021) this was 60-65%. All jurisdictions met 100% for 'may-have' criteria.

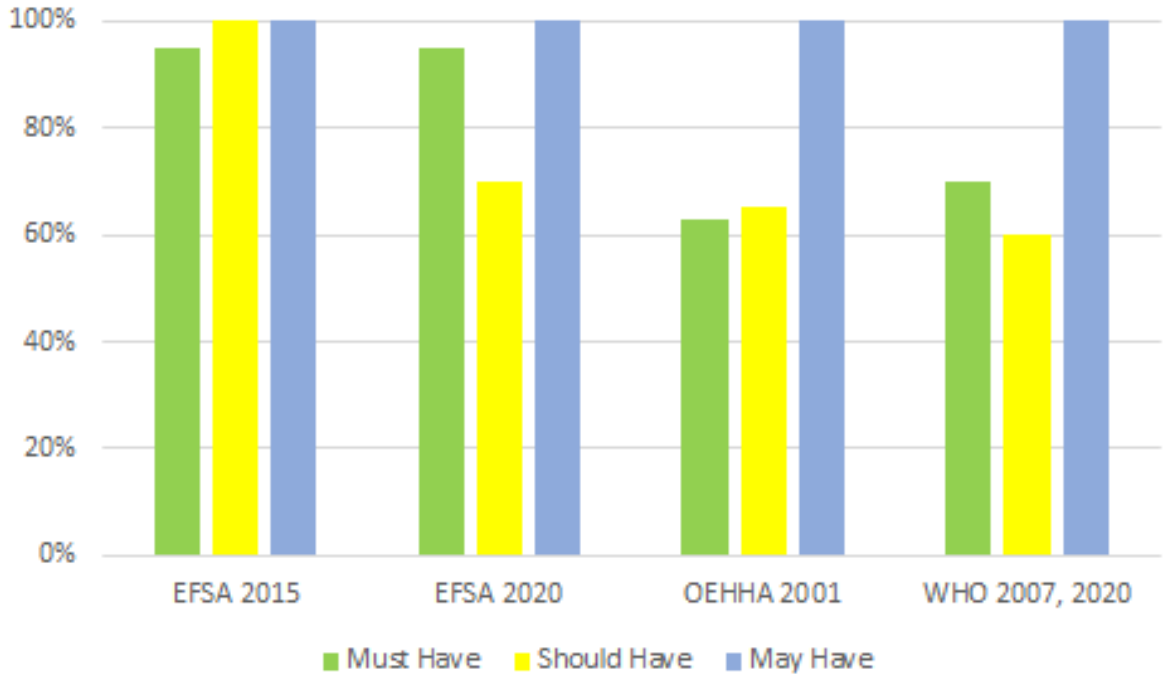

Figure 2 Overall proportion of 'must-have', 'should-have' and 'may-have' technical/administrative criteria met by jurisdictions who have derived candidate health-based guidance/guideline values for Nickel for possible adoption/adaptation in Australia

This analysis indicates that the highest proportion of criteria have been met by the EFSA (2015b, 2020a) evaluations.

5.2 Overall Evaluation

The analysis in **Section 5.1** indicated differences in suitability for adoption/adaption based on an assessment of administrative and technical characteristics of the available guidance documents. As there are a range of guidance values from the different jurisdictions, further analysis of the toxicological basis for these differences was undertaken.

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

- All jurisdictions have used the same critical health endpoint for chronic effects (i.e. developmental effects or post-implantation loss in rats) for derivation of a guidance/guideline value.
- Two jurisdictions, (EFSA 2005) and (ATSDR 2005) both elected not to identify a critical endpoint for chronic effects given the uncertainty associated with developmental toxicity identified in sub-chronic studies.
- The current factsheet in the Guidelines did not use developmental effects as the critical endpoint for derivation of a DWG for Ni. However, an uncertainty factor of 10 was used given the lack of adequate studies at the time.
- A margin of exposure (MOE) assessment was adopted in more recent publications to assess potential for acute health effects (i.e. systemic contact dermatitis in Ni-sensitised humans).

Chronic guidance values for Ni are either based on a NOAEL (1.1 mg/kg/day) or BMDL10 (0.28 to 1.3 mg/kg/day). Using Australian science policy for deriving drinking water guidelines, **Table 6** provides a summary of potential DWGs resulting from adaptation of Ni guidance values from other jurisdictions. The current Australian DWG of 0.02 mg/L (NHMRC and NRMMC 2011) is lower than the DWG of 0.07 mg/L derived by WHO (2007, 2021), but higher than the DWG of 0.012 mg/L derived by OEHHA (2001). DWGs shown in the table below were derived using Australian guidance (as per **Section 3**); in addition, the DWGs as derived by the relevant jurisdiction are also presented.

It can be seen from **Table 6** that:

- DWGs were not derived in the earlier guidance from 2005 (ATSDR 2005, EFSA 2005) given the potential for developmental effects (identified in rat studies) or available studies were considered inadequate on which to base a guidance value.
- Candidate DWGs derived using Australian procedures range between 0.0098 mg/L and 0.0455 mg/L (although most are around 0.04 mg/L).
- Using the BMDL10 of 1.3 mg/kg/day and an uncertainty factor of 100 from the latest agency reviews (EFSA 2020 and WHO 2021) and using Australian procedures for deriving a DWG results in a guidance value of 0.013 mg/kg/day and a DWG of 0.045 mg/L (rounded down).
- The current DWG (0.020 mg/L) is lower than the DWG derived using the latest agency reviews (0.045 mg/L) even though a higher point of departure is used for the current DWG (5 mg/kg/day versus 1.3 mg/kg/day). This is because an additional 10x uncertainty factor was used in the previous factsheet to account for database deficiencies. Such an uncertainty factor is no longer considered warranted based on the latest agency reviews.

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

Parameter	Jurisdiction							
	ATSDR 2005	EFSA 2005	EFSA 2015	EFSA 2020	OEHHA 2001	WHO 2007	WHO 2021	NHMRC 2011
Critical study (chronic effects)	Ambrose et al. 1976	Ambrose et al. 1976	SLI 2000a, SLI 2000b	RTI 1988a,b, SLI 2000b	SLI 2000b	SLI 2000b, EU 2004	SLI 2000b; EU, 2004	Ambrose et al. 1976
Study duration (chronic effects)	2 years (dogs), 3 years (rats).	2 years (dogs), 3 years (rats).	3 weeks (to birth) and 24 weeks (post birth) in rats	3 weeks (to birth) and 24 weeks (post birth) in rats	3 weeks (to birth) and 24 weeks (post birth) in rats	3 weeks (to birth) and 24 weeks (post birth) in rats	3 weeks (to birth) and 24 weeks (post birth) in rats	2 years (dogs), 3 years (rats).
Critical Effect (chronic)	Changes in liver / body / kidney weight in rats and dogs	Changes in liver / body / kidney weight in rats and dogs	Developmental toxicity	Post-implantation loss in rats	Increased perinatal mortality	Post-implantation / perinatal lethality	Reproductive and developmental toxicity	Altered organ-to-body-weight ratios
Chronic Point of Departure (mg/kg bw/d)	- (1)	- (2)	BMDL10: 0.28	BMDL10: 1.3	NOAEL: 1.12	NOAEL: 1.1	BMDL10: 1.3	NOAEL: 5
Uncertainty factor	-	-	100	100	100	100	100	1,000
Health-based guidance value (mg/kg bw/d)	-	-	0.0028	0.013	0.012	0.011	0.013	0.005
Resulting DWG with adaptation of Australian guidance(3) (mg/L)	-	-	0.0098	0.0455	0.042	0.0385	0.0455	0.020 (rounded)
DWG derived by the relevant jurisdiction (mg/L)	-	-	-	-	0.012	0.070	0.070 (0.080)	0.020

DWG = Drinking Water Guideline; Aus = Australian; NOAEL = No Observed Adverse Effect Level, LOAEL = Low Observed Adverse Effect Level, BMDL = Benchmark Dose Level at 10% response

1. ATSDR (2005) did not establish a point of departure because Intermediate-duration studies found significant decreases in survival of the offspring of rats exposed to ≥1.3 mg Ni/kg/day.
2. EFSA (2005) did not establish a point of departure as the available studies do not allow the establishment of a NOAEL and increased perinatal mortality was observed in a sub-chronic study.
3. 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 and NRMMC (2011):

DWG (mg/L) = [Guidance value (mg/kg bw/d) x 70 kg bw (adult) or 13 kg (child) x 0.1 (i.e. 10% relative contribution from DW)] ÷ 2 L/day (adult) or 1 L/day (child)

In order to determine whether the candidate DWGs also afford protection from the acute health effects of concern (i.e. systemic contact dermatitis), consistent with EFSA (2015, 2020), a MOE assessment was undertaken using a LOAEL of 0.0043 mg/kg identified in the most recent EFSA (2020a, b) review with the assumption an individual in a fasted state[4] may drink a glass of water (0.2 L). The results are presented in **Table 7**. MOE of more than 30 were estimated for all candidate DWGs (i.e. MOE range from 33 to 154). A MOE of 30 or more is considered acceptable amongst Ni-sensitised individuals given that a LOAEL is being used as a point of departure, the high incidence of positive reactions at the LOAEL (40%) in the pivotal study, the low number of individuals used in the pivotal study, and the uncertainty regarding the thresholds used. Thus, all candidate DWGs would be considered to afford appropriate protection from acute health effects of Ni exposure.

Table 7 MoE from candidate Ni drinking water guideline values (mg/L) for elicitation of systemic contact dermatitis in Ni-sensitised individuals

Parameter		Jurisdiction					
		EFSA 2015	**EFSA 2020**	**OEHHA 2001**	**WHO 2007**	**WHO 2021**	**NHMRC 2011**
Health-Based Guideline Value or DWG (mg/L) – see Table 6		0.0098	0.0455	0.042	0.0385	0.0455	0.020
Ni intake from drinking a glass of tapwater (ca. 200ml/day) for an adult (mg/kg) (1)		$2.8x10^{-5}$	0.00013	0.00012	0.00011	0.00013	$5.7x10^{-5}$
Acute Point of Departure - systemic contact dermatitis (mg/kg)	Identified in the agency review	BMDL10: 0.0011 (3)	LOAEL: 0.0043 (4)	-	LOAEL: 0.012 (5)	LOAEL: 0.0043	-
	Used in this assessment	LOAEL: 0.0043					
Margin of Exposure (unitless) (2)		154	33	36	39	33	75
Target Margin of Exposure (MoE)		30 or higher (comprising 10 for effects in Ni-sensitised individuals (6) and 3x for use of a LOAEL).					

DWG = Drinking Water Guideline; NOAEL = No Observed Adverse Effect Level, LOAEL = Low Observed Adverse Effect Level, BMDL10 = Benchmark Dose Level at 10% response

1. Ni Intake from drinking a glass of tapwater (mg/kg) = DWG (mg/L) x [Volume in a glass of water (0.2 L)] ÷ 70 kg bw (adult).
2. Margin of exposure = [Acute Point of Departure (0.0043 mg/kg)] ÷ [Ni Intake from drinking a glass of tapwater (mg/kg)].
3. The lowest BMDL10 of 0.08 mg Ni per person, corresponding to 1.1 µg Ni/kg bw, calculated from the data by Jensen et al. (2003), was selected by EFSA (2015) as a reference point for systemic contact dermatitis elicited in Ni-sensitive humans after acute oral exposure to Ni.
4. EFSA (2020a) decided to base their MOE assessment on a LOAEL rather than a BMDL10 as previously done (EFSA 2015b). This is because of the availability of new studies and the uncertainty in the resulting BMDL that spanned two orders of magnitude; in addition, the resulting BMDL (0.0124mg Ni per person) was outside the dose range, therefore a LOAEL was preferred.
5. WHO (2007) indicated the LOAEL established after provocation of fasted patients (highly sensitised population) with an empty stomach is 0.012 mg/kg.
6. A value of 10 (instead of 3) was considered appropriate for Ni-sensitised individuals considering the high incidence of positive reactions at the LOAEL (40%), the low number of individuals used in the pivotal study, and the uncertainty regarding the threshold (EFSA 2020a).

Based on the above analysis of the toxicological basis for the differences in guidance values, the following key points have been determined for consideration when determining which guidance value to adopt/adapt for the Guidelines:

- there is greater confidence in the critical endpoint of chronic developmental effects based on more recent data and general agreement across jurisdictions.

[4] Absorption of Ni from the gut is higher in individuals who are fasted.

- there is higher confidence in guidance values concomitantly informed by margin of exposure assessments to account for acute health effects from Ni exposure.
- there is less confidence in guidance values that do not use benchmark dose analysis.
- there is higher confidence in the EFSA (2020a) and WHO (2021) guidance values based on the recentness of the reviews and the methods used to synthesise the underpinning evidence.

The evidence scan undertaken for this report did not reveal any recently published studies which could potentially impact the conclusions made in this report.

6 Conclusions

Eight guidance documents from three jurisdictions for Ni were found to be suitable to adopt/adapt based on an assessment of the administrative and technical criteria described in **Appendix C** of the Technical Report.

Two of these documents did not provide guidance/guideline values to adopt/adapt. The guidance from ATSDR (2005) and EFSA (2005) did not identify a critical endpoint for chronic effects or derive guidance/guideline values for Ni due to uncertainty associated with developmental toxicity identified in sub-chronic studies.

As shown in **Table 6** there are several options to adopt/adapt existing guidance values in the Guidelines. Based on administrative and technical processes, the EFSA (2015) guidance is most suitable to adopt/adapt. However, based on an evaluation of the toxicological evidence and the methods underpinning the assessment there is higher confidence in the benchmark dose analysis approach taken by EFSA (2020) and WHO (2021). These guidance documents also represent the most recent reviews of the evidence.

Potential adaption of the $BMDL_{10}$ of 1.3 mg/kg/day used by EFSA (2020a) and WHO (2021) would translate to a DWG of 0.045 mg/L (rounded down). Both EFSA (2020a) and WHO (2021) are updates to previous health-based guidance on Ni in food and drinking water. This DWG is achievable with existing treatment technologies, and readily measurable with current commercial analytical techniques.

Potential adaption of the $BMDL_{10}$ of 0.28 mg/kg/day used by EFSA (2015) would translate to a DWG of 0.01 mg/L (rounded up). However, there is less certainty in this guidance value as EFSA (2020a) has superseded the EFSA (2015) guidance, which took a different approach for undertaking a benchmark dose analysis.

There is less confidence in guidance/guideline values derived by NHMRC and NRMMC (2011) and other jurisdictions (OEHHA 2001 and WHO 2007) than the latest available guidance values from EFSA (2020a) and WHO (2021) since the former are not based on the most recent benchmark dose analysis undertaken by international jurisdictions.

The evidence scan undertaken for this report did not identify any recently published studies that would alter the suggested guidance/guideline values. Updates of information in the factsheet are also suggested (see **Table 5**).

7 Review Team

Name	Position	Responsibilities
Mr Giorgio De Nola, MSc, RACTRA	Principal Consultant – Toxicology & Risk Assessment, SLR	Report author

Name	Position	Responsibilities
Dr Slavica Kandic, PhD	Project Consultant – Toxicology & Risk Assessment, SLR	Literature searching, preliminary title screen, compilation of Appendices
Ms Tarah Hagen, MSc, DABT, FACTRA	Technical Discipline Manager – Toxicology & Risk Assessment, SLR	Internal peer review, technical oversight of literature 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. • Provided advice on setting appropriate health-based Ni emission limits for loading of Ni containing ore concentrates at ports. • Undertaken numerous human health risk assessments of public exposure to dust from mine sites, where Ni was one of the substances evaluated.
Dr Slavica Kandic	No interest to declare.
Mr Giorgio De Nola	No interest to declare.

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