

# EVIDENCE EVALUATIONS FOR AUSTRALIAN DRINKING WATER GUIDELINE CHEMICAL FACT SHEETS

**Nickel**  
**Technical Report**

**Prepared for:**  
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**SLR** 

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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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## Abbreviations/Definitions

Acronym	Definition
APVMA	Australian Pesticides and Veterinary Medicines Authority
ATSDR	US Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
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
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Low Observed Adverse Effect Level
LOR	Limit of Reporting
MHC	Major Histocompatibility Complex
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)
POD	Point of Departure
PPRTV	Provisional Peer-Reviewed Toxicity Value (US EPA terminology)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROS	Reactive Oxygen Species
RP	Reference Point
TDI	Tolerable Daily Intake (WHO and EFSA terminology)
The Guidelines	NHMRC and NRMCC (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.
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WQAC	Water Quality Advisory Committee

## 1 Introduction and Background

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

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

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

The report herein is the Technical Report for Nickel (Ni).

## 2 Research Questions

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

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

#	Research Questions
<b>Health-based</b>	
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?)
<b>Exposure-based</b>	
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?

#	Research Questions
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)?
<b>Risk-based</b>	
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?
<b>Supporting Information on Factsheet</b>	
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 Evidence Evaluation Methods

### 3.1 Overview

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

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

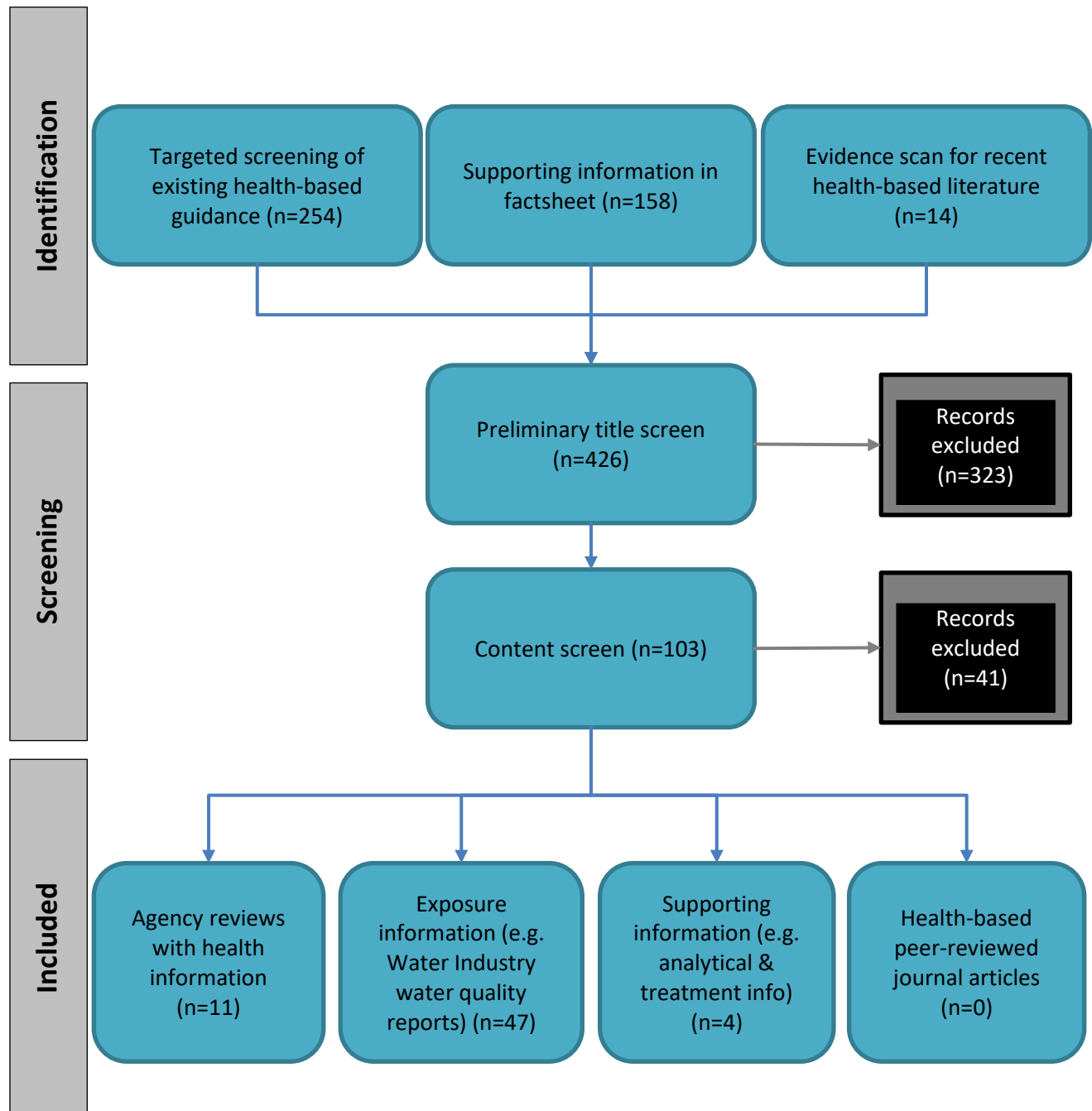


Figure 1 Overview of literature search process followed for Ni

## 3.2 Targeted screening of existing health-based guidance

### Literature search strategy

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

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**Table 2 Search strategy for Existing Guidance/Guidelines**

Parameter	Comments
Search terms	<p>After a few trial runs of various combinations of search terms, it became apparent that the search terms would need to remain relatively broad so as not to miss pivotal references/reviews. Consequently, the selected search term was:</p> <ul style="list-style-type: none"> <li>(Nickel)</li> </ul>
Databases/Agency websites	<p>The following sources were searched:</p> <ul style="list-style-type: none"> <li>World Health Organization (WHO): <a href="https://www.who.int/">https://www.who.int/</a> (in addition, 'Nickel in drinking water' was searched in Google®) <sup>(2)</sup>.</li> <li>International Programme of Chemical Safety (IPCS Inchem): <a href="http://www.inchem.org/#/search">http://www.inchem.org/#/search</a></li> <li>Joint FAO/WHO Expert Committee on Food Additives (JECFA): (Included in IPCS Inchem search)</li> <li>European Food Safety Authority (EFSA): <a href="https://www.efsa.europa.eu/en">https://www.efsa.europa.eu/en</a></li> <li>United States Environmental Protection Agency (US EPA), specifically <sup>(1)</sup>: <ul style="list-style-type: none"> <li>Integrated Risk Information System (IRIS): <a href="https://www.epa.gov/iris">https://www.epa.gov/iris</a></li> <li>Provisional Peer-reviewed Toxicity Values (PPRTV): <a href="https://www.epa.gov/pprtv">https://www.epa.gov/pprtv</a></li> </ul> </li> <li>US Agency for Toxic Substances and Disease Registry (ATSDR): <a href="https://www.atsdr.cdc.gov/">https://www.atsdr.cdc.gov/</a></li> <li>Californian Office of Health and Hazard Assessment (OEHHA) Public Health Goals (in Drinking Water): <a href="https://oehha.ca.gov/water/public-health-goals-phgs">https://oehha.ca.gov/water/public-health-goals-phgs</a></li> <li>Food Standards Australia New Zealand (FSANZ), specifically <sup>(3)</sup>: <ul style="list-style-type: none"> <li>Publications page: <a href="https://www.foodstandards.gov.au/publications/Pages/default.aspx">https://www.foodstandards.gov.au/publications/Pages/default.aspx</a></li> <li>Monitoring safety of food supply page: <a href="https://www.foodstandards.gov.au/science/surveillance/Pages/default.aspx">https://www.foodstandards.gov.au/science/surveillance/Pages/default.aspx</a></li> <li>Chemicals in food page: <a href="https://www.foodstandards.gov.au/consumer/chemicals/Pages/default.aspx">https://www.foodstandards.gov.au/consumer/chemicals/Pages/default.aspx</a></li> </ul> </li> <li>Australian Pesticides and Veterinary Medicines Authority (APVMA) Health Based Guidance Values: <a href="https://apvma.gov.au/node/26596">https://apvma.gov.au/node/26596</a></li> </ul> <p>The following additional sources were searched to provide exposure information in Australian drinking water supplies (to inform responses to Research Questions 12 and 15):</p> <ul style="list-style-type: none"> <li>Melbourne Water: <a href="https://www.melbournewater.com.au/">https://www.melbournewater.com.au/</a></li> <li>Sydney Water: <a href="https://www.sydneywater.com.au/SW/index.htm">https://www.sydneywater.com.au/SW/index.htm</a></li> <li>TasWater: <a href="https://www.taswater.com.au/">https://www.taswater.com.au/</a></li> <li>SA Water: <a href="https://www.sawater.com.au/">https://www.sawater.com.au/</a></li> <li>Water Corporation of Western Australia: <a href="https://www.watercorporation.com.au/">https://www.watercorporation.com.au/</a></li> <li>Power and Water Corporation Northern Territory Drinking Water Quality Reports: <a href="https://www.powerwater.com.au/about/what-we-do/water-supply/drinking-water-quality/past-drinking-water-quality-reports">https://www.powerwater.com.au/about/what-we-do/water-supply/drinking-water-quality/past-drinking-water-quality-reports</a></li> <li>Seqwater: <a href="https://www.seqwater.com.au/">https://www.seqwater.com.au/</a></li> <li>Icon Water: <a href="https://www.iconwater.com.au/">https://www.iconwater.com.au/</a></li> <li>Water Research Australia: <a href="https://www.waterra.com.au/">https://www.waterra.com.au/</a></li> </ul>

Parameter	Comments
Publication Date	If databases/agency websites allowed for specification of date ranges, searches were constrained to the following date range to coincide with the year of the last Australian drinking water guideline fact sheet update for Ni: <ul style="list-style-type: none"> <li>1 January 1996 to July 2021</li> </ul>
Language	English
Study Type	Publicly available agency/industry reports and reviews.
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of agency reports/reviews: <ul style="list-style-type: none"> <li>NR = Not Relevant. Information not directly relevant to answering research questions. Rationale for non-relevance was provided for transparency. E.g. <ul style="list-style-type: none"> <li>Not HH related = Not human health related (e.g. criteria are for protection of aquatic life).</li> <li>Not a relevant exposure pathway = Since Ni present in drinking water is not volatile, guidelines for non-oral and non-dermal routes of exposure are not considered relevant (e.g. inhalation).</li> <li>Not relevant to chemical of interest.</li> </ul> </li> <li>NPA = Basis of guideline value or information underpinning review conclusions are Not Publicly Available, e.g. health-based guideline value has used unpublished proprietary information which could not be verified.</li> <li>Language = Language other than English.</li> </ul>
Validation methods used	Preliminary searches were undertaken with more specific search terms [(Nickel) AND (toxicity or health); (Nickel) AND (exposure) AND (Australia)]. Upon scanning preliminary search results, the reviewer found these search terms to be too specific, as a number of agency reports did not appear in the results. The search terms were consequently refined.  In addition, from the preliminary search of the WHO website, it became evident that the latest background documentation for Ni (dated 2007) did not come up in the general search results when using the search term 'Nickel'. Therefore, the WHO website search was supplemented by a Google® search to find the specific background document of interest. Upon undertaking this search, a later version of a WHO background document (dated 2021) for Ni (Draft Version for public review) was found. Both documents have been included in this report.
Screening methods	Results were screened as follows: <i>Preliminary title screen</i> <ul style="list-style-type: none"> <li>Titles of results for each search were recorded in an Excel spreadsheet. Each website was on a separate tab of the spreadsheet.</li> <li>The researcher scanned the titles. In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required.</li> <li>Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included.</li> </ul> <i>Content screen</i> <ul style="list-style-type: none"> <li>The full text content of reports/reviews selected to be included from the preliminary title screen were reviewed by a subject expert to determine which reports/reviews to include in the data extraction step. Only reports/reviews which provided information relevant to answering the research questions were taken through to the data extraction step.</li> </ul>

Parameter	Comments
Documentation of search	Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in <b>Appendix A</b> . Overall results presented in <b>Figure 1</b> , adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015).
Retrieval of publications	All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.
<ol style="list-style-type: none"> <li>1. Preliminary search trials with the US EPA general search engine (<a href="https://www.epa.gov/">https://www.epa.gov/</a>) resulted in over 24,312 hits, regardless of search term refinement. This number of hits was considered unmanageable to screen through with the resources available for this project. Consequently, the search was targeted to specific sections of the website considered most relevant to answering the research questions.</li> <li>2. From the preliminary search of the WHO website, it became evident that the latest final and draft background documentation for Ni (dated 2007 and 2021, respectively) did not come up in the general search results when using the search term 'Nickel'. Therefore, the WHO website search was supplemented by a Google® search to find the specific background documents of interest.</li> <li>3. From the preliminary search of the FSANZ website, it became evident that the number of search results appeared infinite (there was no set number of hits provided, and no set pages of results; every time the final page of results was clicked on, additional pages appeared), regardless of search term refinement, with the vast majority of records being not relevant to the research questions. Consequently, specific sections of the website were consulted which were considered most relevant to answering the research questions.</li> </ol>	

## Data Extraction and Quality Assessment

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

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

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

Agency Report Reference: <i>Insert full bibliographical reference for report</i>		
General Information	Date of data extraction	
	Authors	
	Publication date	
	Literature search timeframe	
	Publication type	
	Peer reviewed?	
	Country of origin	
	Source of funding	
	Possible conflicts of interest	
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	

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

## Data summary/synthesis

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

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

### 3.3 Evidence scan for recent studies

#### Literature search strategy

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

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

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

Parameter	Comments
Search terms	The selected search terms were: <ul style="list-style-type: none"> <li>• (Nickel) AND (toxicity) AND (oral)</li> <li>• (Nickel) AND (health) AND (oral)</li> <li>• (Nickel) AND (toxicity) AND (drinking water)</li> <li>• (Nickel) AND (health) AND (drinking water)</li> <li>• (Nickel) AND (exposure) AND (Australia)</li> </ul>
Databases	The following sources were searched: <ul style="list-style-type: none"> <li>• MEDLINE/PubMed/TOXLINE</li> </ul>
Publication Date	2020 – 2021, the bottom end of the range to coincide with the latest health-based agency review found in the targeted screening step.
Language	English
Study Type	Peer-reviewed, published, in press, unpublished and ongoing reviews, meta-analyses and systematic reviews were included.
Inclusion and exclusion criteria	The following exclusion criteria were used to screen relevance of information: <ul style="list-style-type: none"> <li>• NR = Not Relevant. Information not directly relevant to answering research questions.</li> <li>• Language = Language other than English.</li> <li>• UCC = Unlikely to Change Conclusions in Review.</li> </ul>
Validation methods used	Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened.

Parameter	Comments
Screening methods	<p>Results were screened as follows:</p> <p><i>Preliminary title and abstract screen</i></p> <ul style="list-style-type: none"> <li>• Titles of results for each search were recorded in an Excel spreadsheet. The results for each combination of search terms were exported into a separate tab of the spreadsheet. To readily eliminate duplicate records, results from all search term combinations were subsequently collated into one spreadsheet.</li> <li>• The researcher scanned the titles (and abstracts, if required). In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required.</li> <li>• Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included.</li> </ul> <p><i>Content screen</i></p> <ul style="list-style-type: none"> <li>• The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data extraction step. Only articles/reviews which provided information considered to potentially affect the overall conclusions made by other jurisdictions were taken through to the data extraction step.</li> </ul>
Documentation of search	<p>Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in <b>Appendix A</b>.</p> <p>Overall results presented in <b>Figure 1</b>, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015).</p>
Retrieval of publications	<p>All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.</p>

## Data Extraction

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

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

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

Publication Reference: <i>Insert full bibliographical reference for report</i>		
General Information	Date of data extraction	
	Authors	
	Publication date	
	Publication type	
	Peer reviewed?	

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

**Publication Reference: *Insert full bibliographical reference for report***

	Notes on study quality, e.g. gaps, methods	
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**Data summary/synthesis**

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

**3.4 Supporting information in factsheet**

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

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

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

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

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

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

Parameter	Comments
Search terms	<p>The selected search terms for the Scopus database were:</p> <ul style="list-style-type: none"> <li>• (Nickel) AND (treatment) AND (drinking water)<sup>(1)</sup></li> </ul> <p>After a few trial runs of various combinations of search terms in the industry websites, it became apparent that the search capacities varied significantly between different webpages. Consequently, the selected search term (for industry websites) was kept relatively broad:</p> <ul style="list-style-type: none"> <li>• (Nickel)</li> </ul>
Databases/Other sources	<p>The following source database was searched:</p> <ul style="list-style-type: none"> <li>• Scopus</li> </ul> <p>The following industry websites were searched:</p> <ul style="list-style-type: none"> <li>• Water Services Association of Australia: <a href="https://www.wsaa.asn.au/">https://www.wsaa.asn.au/</a></li> <li>• Standard Methods for the Examination of Water and Wastewater: <a href="https://www.standardmethods.org/">https://www.standardmethods.org/</a></li> <li>• US EPA Drinking Water Treatability Database: <a href="https://tdb.epa.gov/tdb/home">https://tdb.epa.gov/tdb/home</a></li> </ul> <p>The following Australian commercial laboratories were contacted directly via e-mail or website form for relevant information:</p> <ul style="list-style-type: none"> <li>• National Measurement Institute</li> <li>• SGS</li> <li>• ALS</li> <li>• Eurofins</li> </ul>
Publication Date	Limited to last 5 years (2017-2021)
Language	English
Study Type	<ul style="list-style-type: none"> <li>• Peer-reviewed, published, in press, unpublished and ongoing studies.</li> <li>• Australian laboratory information sheets or e-mail responses on measurement methods and limits of determination.</li> </ul>
Inclusion and exclusion criteria	<p>The following exclusion criteria were used to screen relevance of information:</p> <ul style="list-style-type: none"> <li>• NR = Not Relevant. Information not directly relevant to answering research questions.</li> <li>• Research technique (analytical or treatment) = does not appear to be commercially applied.</li> <li>• Language = Language other than English.</li> <li>• NPA = Not publicly available.</li> <li>• NL = Chemical not listed under specific treatment process.</li> </ul>
Validation methods used	<p>Preliminary test searches were undertaken to assist with selecting search terms. Refinements were made as considered appropriate to ensure adequate, but also specific coverage in the sources screened.</p>

Parameter	Comments
Screening methods	<p>Results were screened as follows:</p> <p><i>Preliminary title and abstract screen</i></p> <ul style="list-style-type: none"> <li>• Titles of results for each search were recorded in an Excel spreadsheet. Each source was on a separate tab of the spreadsheet.</li> <li>• The researcher scanned the titles (and abstracts, if required). In a separate column a decision regarding relevance of the result was recorded as per the exclusion criteria. An additional column was included to provide commentary as (and if) required.</li> <li>• Where the researcher was uncertain as to the relevance of a particular result, the researcher discussed the matter with a subject expert prior to making a decision OR the result was considered potentially relevant and included.</li> </ul> <p><i>Content screen</i></p> <ul style="list-style-type: none"> <li>• The full text content of literature selected to be included from the preliminary title and abstract screen were reviewed by a subject expert to determine which articles to include in the data extraction step. Only articles/reviews which provided information relevant to answering the research questions were taken through to the data extraction step.</li> </ul>
Documentation of search	<p>Spreadsheets with full search results and screening outcomes (i.e. reasons for exclusion) are provided in <b>Appendix A</b>.</p> <p>Overall results presented in <b>Figure 1</b>, adapted from the PRISMA figure presented in Moher et al. (2009) and Figure 5 in NTP (2015).</p>
Retrieval of publications	<p>All relevant and potentially relevant results were recorded in an Endnote library and soft copies of files saved into a designated folder on the SLR server for review. The server is backed up on a daily basis.</p>
<p>1. It became evident upon undertaking the initial searches using the following additional search term combinations [‘(Nickel) AND (analysis) AND (drinking water)’ OR ‘(Nickel) AND (testing) AND (drinking water)’] that these searches returned thousands of results that were not relevant to answering the research questions with respect to commercial analytical techniques used in Australia. Results obtained for analytical techniques in the peer-reviewed literature were research-based techniques for specific purposes and not currently commercially applied. It was considered more efficient and effective to contact Australian laboratories directly for information on their analytical techniques and commercial limits of reporting. Therefore, the search in the Scopus database was limited to information on treatment technologies.</p>	

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

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

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

## 4 Results

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

### 4.1 Nickel Health-based research question analysis

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

#	Research Questions	Jurisdiction	Response to Research Questions
1	What is the critical human health endpoint for Ni (if any)? Therefore, what are the key adverse health hazards from exposure to Ni in Australian drinking water?	ATSDR 2005	A critical endpoint was not selected. Significant decreases in body weight and liver weights in rats and decreases in body weight, increases in liver weight, and adverse renal and lung effects in dogs were found in chronic studies. Intermediate-duration studies found significant decreases in survival of offspring of rats exposed to $\geq 1.3$ mg Ni/kg/day.
		EFSA 2005	A critical endpoint was not selected. The main targets for the toxicity of orally ingested Ni salts are kidneys, spleen, lungs, and the myeloid system. In addition, perinatal mortality has been reported to increase in rats.
		EFSA 2015a, b, c	Chronic exposure: Developmental toxicity (in rodents). Acute exposure: Hypersensitivity reactions (in humans).
		EFSA 2020 a,b	Chronic exposure: An increased incidence of post-implantation loss in rats was identified as the critical effect for the risk characterisation of chronic oral exposure. Acute Exposure: Eczematous flare-up reactions in the skin elicited in Ni -sensitised humans.
		OEHHA 2001	Increased perinatal mortality (or early pup mortality in rats) and dermatitis in people who are sensitive to nickel.
		WHO 2007, 2021	The critical effect for the risk characterisation of chronic oral exposure to Ni is reproductive and developmental toxicity.
2	What are the justifications for	ATSDR 2005	Not applicable (no critical endpoint selected as the database was considered inadequate).
		EFSA 2005	Not applicable (the available studies do not allow the establishment of a NOAEL).

#	Research Questions	Jurisdiction	Response to Research Questions
	choosing this endpoint/health hazard?	<b>EFSA 2015a, b, c</b>	Chronic exposure: Ni is considered to be a developmental toxicant inducing fetotoxicity, embryotoxicity and teratogenicity. Acute exposure: Systemic contact dermatitis elicited in Ni-sensitive humans after oral exposure seen as eczematous flare-up reactions and worsening of allergic reactions (e.g. hand eczema, body erythema) were identified as the critical effect for acute oral exposure to Ni of Ni-sensitised humans.
		<b>EFSA 2020 a,b</b>	Chronic exposure: 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 $\geq 1.3$ mg/kg bw per day. Acute exposure: A condition known as systemic contact dermatitis, was identified as the critical effect for the risk characterisation of acute oral exposure.
		<b>OEHHA 2001, 2021</b>	OEHHA concluded that the 1.1 mg/kg-day dose in the Springborn Laboratory (SLI 2000b) study represents the highest NOAEL which is lower than the lowest relevant LOAEL, and therefore selected it as the critical endpoint for risk assessment. It resulted in the lowest reference value when excluding other studies. A number of studies indicated that acute oral exposure of Ni could aggravate Ni dermatitis in people who are sensitive to Ni.
		<b>WHO 2007</b>	2007: In a well conducted two-generation study in rats, a NOAEL of 1.1 mg of Ni per kg of body weight per day was identified for all the end-points studied, including the variable of post-implantation/perinatal lethality (SLI 2000b; EU 2008). 2021: The reassessment takes into account improved science and methods, including a meta-analysis of epidemiological data and an updated Benchmark Dose (BMD) approach that enabled an improved determination of a Point of Departure (POD) for chronic oral exposure. The reassessment also identified weaknesses in the original study used to derive a guideline value (Nielsen et al. 1999, WHO 2005; note the latter reference was not cited in WHO 2021). Although this study no longer forms the basis for the guideline value, the guideline value remains the same.
3	What is the toxicological mode of	<b>ATSDR 2005</b>	Not applicable (no critical endpoint selected).
		<b>EFSA 2005</b>	Not applicable (no critical endpoint selected).

#	Research Questions	Jurisdiction	Response to Research Questions
	action of Ni for the critical human health endpoint?	<b>EFSA 2015a, b, c</b>	<p>Chronic exposure: Ni can cross-link amino acids to DNA, lead to formation of reactive oxygen species (ROS), moreover mimic hypoxia. These changes may lead to the activation of some signalling pathways, subsequent transcription factors and eventually to alterations in gene expression and cellular metabolism.</p> <p>Acute exposure: There is evidence that combination of Ni with circulating or tissue protein gives rise to antigen specific responses, and thus Ni can act as a contact allergen and cause sensitisation. The antigens are taken up by antigen-presenting cells that migrate to draining lymph nodes, resulting in activation of Ni-specific T lymphocytes. Contact sensitivity is either expressed as Type I or Type IV hypersensitivity, mediated by reagins and allergen-specific T lymphocytes, expressing in a wide range of cutaneous eruptions following dermal or systemic exposure. An alternative, but not mutually exclusive, hypothesis is that this metal interferes with the antigen recognition step of the immune response, i.e. binding to Major Histocompatibility Complex (MHC) and or MHC-bound peptides and T cell receptors leading to the activation of Ni-specific T cells.</p>
		<b>EFSA 2020 a,b</b>	<p>Chronic exposure: The mode of action appears to involve ROS, at least in part mediated by Ni complexation with protamine 2 which is expressed in sperm chromatin. Humans express both protamine 2 and protamine 1 at appreciable levels in sperm (43% protamine 2) and therefore may be more similar in this respect to the mouse (67–72% protamine 2 in various mouse species) than to the rat which expresses very little protamine 2 (2–5% in Norwegian rats). Thus, on the basis of protamine 2 expression levels, it appears that the susceptibility of humans to infertility might be more similar to that of the mouse rather than to that of the rat, although the relative level of antioxidant defence in sperm will undoubtedly also be a major determinant of susceptibility. There is also a possible interference with calcium ion channels. <i>In vitro</i>, Leydig cell toxicity and reduced testosterone production is related to increased ROS and there is evidence of altered extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) signalling which appears to inhibit testosterone synthetase.</p> <p>Acute exposure: Reduced interleukin (IL)-10 levels were noted in the desensitised individuals, indicating a role for IL-10 in the regulation of Ni -specific responses after oral uptake of Ni in Ni -sensitised individuals.</p> <p>Gingival fibroblasts may be involved in the induction of oral tolerance through Ni -induced alteration in nuclear factor kappa B (NF-kB) and hypoxia-inducible factor 1-alpha (HIF-1a) regulation. Increased IL1-b, chemokine ligand 20 and vascular endothelial growth factor protein levels, as well as decreased IL-10 levels, which predispose an individual to an inflammatory reaction in the skin due to Ni, seem to be inhibited in gingival/oral tissue.</p>
		<b>OEHHA 2001</b>	A mode of action for the critical endpoint was not provided.
		<b>WHO 2007, 2021</b>	Not stated for chronic effects (from oral exposure).

#	Research Questions	Jurisdiction	Response to Research Questions
4	Is Ni a genotoxic carcinogen of relevance to humans?	ATSDR 2005	There is some evidence to suggest that Ni is clastogenic and can damage DNA. Carcinogenicity of Ni has been found from inhalation exposure, whereas in lifetime drinking water studies in rats and mice, Ni acetate was not carcinogenic.
		EFSA 2005	While there is evidence that inhaled Ni salts are carcinogenic in rodents and humans, orally ingested Ni salts have not been shown to be carcinogenic. The genotoxicity of Ni salts, observed at chromosome level at high, toxic doses is likely due to indirect mechanisms.
		EFSA 2015a, b, c	The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) considered it unlikely that dietary exposure to Ni results in cancer in humans.
		EFSA 2020 a,b	No tumours have been observed in the carcinogenicity studies in experimental animals after oral administration of soluble Ni compounds. It is unlikely that dietary exposure to Ni results in cancer in humans. Ni and Ni compounds have been classified by the IARC as carcinogenic to humans (Group 1) causing cancers of the lung, nasal cavity and paranasal sinuses after inhalation.
		OEHHA 2001	All four oral rodent cancer bioassays reported in the literature failed to show that soluble Ni is an oral carcinogen.
		WHO 2007, 2021	There is a lack of evidence of a carcinogenic risk from oral exposure to Ni.
5	What dose(s) are associated with the critical human health endpoint?	ATSDR 2005	Not applicable (no critical endpoint selected).
		EFSA 2005	Not applicable (no critical endpoint selected).
		EFSA 2015a, b, c	Chronic exposure: A BMDL10 value of 0.28 mg Ni /kg b.w. per day for post-implantation loss as a reference point (RP) for chronic dietary exposure to Ni. Acute exposure: When applying the BMD approach for quantal data a BMDL10 of 1.1 µg Ni/ kg b.w. was calculated as a RP for eliciting systemic contact dermatitis in Ni-sensitive humans after acute oral exposure to Ni.
		EFSA 2020 a,b	Chronic exposure: A BMDL10 of 1.3 mg Ni/kg body weight (bw) per day was selected as the RP. Acute exposure: A LOAEL of 4.3 µg Ni/kg bw was selected as the RP.

#	Research Questions	Jurisdiction	Response to Research Questions
		<b>OEHHA 2001</b>	OEHHA identified the oral dose of 1.12 mg Ni/kg-d as the appropriate NOAEL value for chronic exposure, from the lower dose-range from the Springborn Laboratory (SLI 2000b) study. LOAELs of 8.6 and 12 µg Ni/kg were identified for acute effects (SCD) in nickel-sensitised women. An uncertainty factor of 10 was applied to derive NOAELs of 0.86 and 1.2 µg Ni/kg, considered upper bound estimates as studies were of people in fasted state and absorption of Ni is up to 30x higher in fasted individuals.
		<b>WHO 2007, 2021</b>	2007: 1.1 mg of Ni per kg of body weight per day. WHO (2007) indicated the LOAEL established after provocation of fasted patients (highly sensitised population) with an empty stomach is 12 µg/kg. 2021: The resulting BMDL10 for post-implantation loss of 1.3 mg /kg bw per day for the F0 and F1 data of the two-generation study was selected as a point of departure. A LOAEL of 4.3 µg/kg was identified for acute effects.
6	Is the proposed health-based guidance value relevant to the Australian context?	<b>ATSDR 2005</b>	Not applicable (no health-based guidance/guideline value was derived).
		<b>EFSA 2005</b>	Not applicable (no health-based guidance/guideline value was derived).
		<b>EFSA 2015a, b, c</b>	Yes
		<b>EFSA 2020 a, b</b>	Yes
		<b>OEHHA 2001</b>	Yes, except that the additional uncertainty factor of 10x applied by OEHHA (2001) for potential carcinogenicity of Ni is not in line with Australian risk assessment policy.
		<b>WHO 2007, 2021</b>	Yes
7	Is the health-based guidance value expressed in the best way?	<b>ATSDR 2005, EFSA 2005, EFSA 2015a, b, c, EFSA 2020 a, b, OEHHA 2001, WHO 2007, 2021</b>	Yes. Guidance values are expressed as µg/kg/day and guideline values are expressed as µg/L.
8	Are there groups of people in the general population who may be more sensitive to Ni exposure?	<b>ATSDR 2005</b>	The developing organism may be a sensitive target of Ni toxicity following intermediate-duration exposure.
		<b>EFSA 2005</b>	Ni-sensitised individuals. Ni salts are potent skin sensitisers in humans, causing allergic contact dermatitis.
		<b>EFSA 2015a, b, c</b>	Chronic exposure: The foetus might be particularly sensitive towards the adverse effects of Ni because it lacks effective means for eliminating excessive Ni. Acute exposure: Ni-sensitised individuals.

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#	Research Questions	Jurisdiction	Response to Research Questions
		<b>EFSA 2020 a,b</b>	Chronic exposure: Not stated. Acute exposure: Ni-sensitised individuals.
		<b>OEHHA 2001</b>	Individuals allergic to Ni are the sensitive sub-population.
		<b>WHO 2007, 2021</b>	Not stated although Ni sensitised individuals are discussed.
9	What is the guidance value (if any)?	<b>ATSDR 2005</b>	Not applicable (no guidance value was derived).
		<b>EFSA 2005</b>	Not applicable (no guidance value was derived).
		<b>EFSA 2015a, b, c</b>	Chronic exposure: A tolerable daily intake (TDI) of 2.8 µg/kg/day Acute exposure: 1.1 µg/kg using a Margin of Exposure (MOE) approach (MOE >10 = acceptable)
		<b>EFSA 2020 a,b</b>	Chronic exposure: A TDI of 13 µg/kg/day. Acute exposure: 4.3 µg Ni/kg bw (a LOAEL) using a MOE approach (MOE > 30 = acceptable).
		<b>OEHHA 2001</b>	Guideline value for chronic exposure: 0.012 mg/L (12 µg/L or 12 ppb) for soluble Ni compounds in drinking water, based on a NOAEL of 1.12 mg Ni/kg-d and application of an uncertainty factor of 1,000. No guideline value was derived for acute exposures.
		<b>WHO 2007, 2021</b>	2007: A TDI of 11 µg/kg of body weight to derive a guideline value of 70µg/L. 2021: A TDI of 13 µg/kg bw/day to derive a guideline value of 80µg/L. The previous guideline value of 70µg/L was maintained.
10	Is there a knowledge gap from the time at which existing guideline values were developed?	<b>ATSDR 2005</b>	Potentially. Bibliography contained literature up to 2005.
		<b>EFSA 2005</b>	Potentially. Bibliography contained literature up to 2005.
		<b>EFSA 2015a, b, c</b>	Potentially. Bibliography contained literature up to 2015.
		<b>EFSA 2020 a, b</b>	Unlikely as it was prepared in 2020.
		<b>OEHHA 2001</b>	Potentially. Bibliography contained literature up to 2000.
		<b>WHO 2007, 2021</b>	Unlikely as the update (draft publication) was prepared in 2021.
11	Does any recent literature change the guideline value? (e.g. demonstrating a new critical endpoint?)	No health-based studies which would potentially alter the conclusions of the evaluation were found in the evidence scan conducted.	



## 4.2 Exposure-related research question analysis

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

#	Research Questions	Jurisdiction	Response to Research Questions
12	What are the typical Ni levels in Australian drinking water? Do they vary around the country or under certain conditions e.g. source of water, drought?	<b>ICON Water 2019-2020 (ACT)</b>	Minimum <sup>(1)</sup> : <0.001 mg/L, maximum <sup>(1)</sup> : 0.003 & mean: <0.001, 95th percentile <sup>(1)</sup> : <0.001 mg/L. No info on variability around country.
		<b>Melbourne Water 2021</b>	Mean <sup>(1)</sup> : <0.001 mg/L. No info on variability around country.
		<b>PWNT 2005 – 2020 (NT)</b>	Range of means <sup>(1)</sup> : 0.001 – 0.015 mg/L. No info on variability around country.
		<b>Seqwater 2021 (QLD)</b>	Mean <sup>(1)</sup> : <0.001 mg/L. No info on variability around country.
		<b>Tas Water 2014-2020 (Tas)</b>	Mean range <sup>(1)</sup> : <0.0005 – 0.003 mg/L, minimum range <sup>(1)</sup> : <0.0005 – 0.0007 mg/L & maximum range <sup>(1)</sup> : 0.0005 – 0.007 mg/L. No info on variability around country.
		<b>WRA 2008 (rainwater tanks – Aus)</b>	Mean <sup>(1)</sup> : 0.002 mg/L, minimum <sup>(1)</sup> : 0.0005 mg/L, & maximum <sup>(1)</sup> : 0.005 mg/L. No info on variability around country.
13	Do Australian levels differ considerably from elsewhere?	No, from literature reviewed levels in drinking water appear to be similar to those overseas. Adult intakes of Ni in the diet in Australia seem to be higher than in the US where adult intakes have been estimated to fall in the range 79-105 µg/day, but lower than Canada where studies report that adults consume between 207-406 µg/day (FSANZ 2008).	
1. It is noted that it is not always clear from the various Water Corporation performance reports whether the data presented are for treated or untreated supplies. Thus the data presented may be for reticulated treated or raw water.			

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

#	Research Questions	Jurisdiction	Response to Research Questions
14	What are the principal routes of exposure to Nickel in the Australian general population?	ATSDR 2005	No data for Australia in this report. Overseas, food is the major source of exposure to Ni. You may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing Ni.
		EFSA 2005	In Europe, diet.
		EFSA 2015a, b, c	In Europe, diet and to a lesser extent from drinking water.
		EFSA 2020 a, b	In Europe, dietary exposure (food and drinking water).
		OEHHA 2001	Not stated <i>per se</i> but focus is on food and water.
		WHO 2007, 2021	In Europe, food is the dominant source of Ni exposure in the non-smoking, non-occupationally exposed population.
15	What are the typical levels of Australian exposure (e.g. 'background' Ni levels)?	ATSDR 2005	US: You eat about 170 micrograms ( $\mu\text{g}$ ; 1 $\mu\text{g}$ =1 millionth of a gram) of Ni in your food every day [equating to $\sim 2.4 \mu\text{g}/\text{kg}$ body weight/day for a 70kg adult]. Our daily intake of Ni from drinking water is only about 2 $\mu\text{g}$ .
		EFSA 2005	Europe: The intake of Ni from the average diet is estimated to be about 150 $\mu\text{g}/\text{day}$ (about 2.5 $\mu\text{g}/\text{kg}$ body weight/day) but may reach 900 $\mu\text{g}/\text{day}$ (about 15 $\mu\text{g}/\text{kg}$ body weight/day) or more, when large amounts of food items with high Ni contents are consumed.
		EFSA 2015a, b, c	Europe: Mean dietary acute exposure ranged from 3.4 $\mu\text{g}/\text{kg}$ b.w. in one survey for 'Adolescents' to 14.3 $\mu\text{g}/\text{kg}$ b.w. in one survey for 'Toddlers'.
		EFSA 2020 a,b	In 2015, dietary exposure assessments in European countries showed that mean adult exposure ranged from 90 to 361 $\mu\text{g}/\text{day}$ . Assuming a body weight of 70 kg, this range corresponds to 1.3–5.2 $\mu\text{g}/\text{kg}/\text{day}$ .
		OEHHA 2001	<ul style="list-style-type: none"> <li>US: 168<math>\pm</math>11 <math>\mu\text{g}/\text{day}</math>.</li> <li>Denmark: 150 <math>\mu\text{g}/\text{day}</math> (as high as 900 <math>\mu\text{g}/\text{day}</math> with certain foods with high Ni content).</li> <li>Switzerland: 73<math>\pm</math>9 <math>\mu\text{g}/\text{day}</math> (in a restaurant) and 142<math>\pm</math>20 <math>\mu\text{g}/\text{day}</math> (in a military canteen)</li> <li>United Kingdom (1981-84): 140-150 <math>\mu\text{g}/\text{day}</math>.</li> </ul>
		WHO 2007, 2021	<ul style="list-style-type: none"> <li>Food: Daily dietary intakes of Ni were 0.14–0.15 mg in the United Kingdom in 1981–1984 [140–150<math>\mu\text{g}/\text{day}</math>], 0.082 mg in Sweden in 1987 [or 82<math>\mu\text{g}/\text{day}</math>], 0.16 mg (mean; 95% fractile, 0.27 mg) in Denmark [160<math>\mu\text{g}/\text{day}</math>], and 0.16 mg in the USA [160<math>\mu\text{g}/\text{day}</math>].</li> <li>Water: 0.005–0.025 mg daily [5-25<math>\mu\text{g}/\text{day}</math>] (i.e. 2–11% of the total daily oral intake of Ni).</li> </ul>

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#	Research Questions	Jurisdiction	Response to Research Questions
		<b>FSANZ 2008</b>	Up to the age of 7-8, boys and girls had similar intakes. A divergence appeared during adolescence and led to different levels in adulthood, with men consuming an average of around 150 µg/day and women only around 115 µg/day. Adult intakes in Australia seem to be higher than in the US where adult intakes have been estimated to fall in the range 79-105 µg/day, but lower than Canada where studies report that adults consume between 207-406 µg/day.

### 4.3 Risk-based research question analysis

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

#	Research Questions	Jurisdiction	Response to Research Questions
16	What are the risks to human health from exposure to Ni in Australian drinking water?	<b>ATSDR 2005</b>	None identified (for US). The amount of Ni in foods and drinking water are too low to be of concern.
		<b>EFSA 2005</b>	None identified in Europe from water alone. Consumption of food with high Ni content and additional exposure from first-run drinking water and kitchen utensils could result in an intake higher than the critical dose [in Ni sensitised population].
		<b>EFSA 2015a, b, c</b>	None identified in Europe from water alone. However, there is a concern that Ni-sensitised individuals may develop eczematous flare-up skin reactions for acute exposures and daily intake is close to the chronic TDI or above it particularly when considering the young age classes.
		<b>EFSA 2020 a, b</b>	In Europe, none identified from water alone. Chronic exposure: The mean chronic dietary exposure to Ni is close to the TDI or above it particularly when considering the young age classes. Acute exposure: All the MOEs calculated are considerably below 10 for all age groups both for the estimated mean and 95th percentile exposure levels.
		<b>OEHHA 2001</b>	In California, current levels of Ni in drinking water are commonly higher than the PHG value.
		<b>WHO 2007, 2021</b>	None identified. Drinking a glass of tap water (c.a. 200 ml) would not elicit acute effects (systemic contact dermatitis) noting that the LOAEL in the Jensen et al. (2003) study was associated with a bolus dose under fasted conditions in contrast to the intermittent nature of a normal drinking-water exposure scenario.
17	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review?	<b>ATSDR 2005, EFSA 2005, EFSA 2015a, b, c, EFSA 2020 a, b, OEHHA 2001, WHO 2007, 2021</b>	Yes. The factsheet is based on liver toxicity from a study by Ambrose (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, however 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 factsheet information research question analysis

The supporting information in the fact sheet for Ni consists of the following (NHMRC and NRMCC 2021):

- **General Description:** *“Drinking water generally contains very low concentrations of nickel. Concentrations reported overseas are usually less than 0.01 mg/L. Higher concentrations, up to 0.5 mg/L, have been reported where water has been in prolonged contact with nickel-plated tap and plumbing fittings; however, these higher concentrations are unusual”.*

*Nickel is used in the electroplating industry and in alloys used in the chemical, marine, nuclear and aerospace industries. It is used as a catalyst in industrial processes, and in oil refining. Main releases to the environment are from the burning of fossil fuels and in waste discharges from electroplating industries.*

*Nickel is present in many foods. Highest concentrations occur in cocoa, soy beans and some cereals. It has been estimated that the average daily dietary intake is between 0.1 mg/day and 0.3 mg/day”.*

- **Typical values in Australian drinking water:** *“In major Australian reticulated supplies, concentrations of nickel range up to 0.03 mg/L, with typical concentrations less than 0.01 mg/L”.*
- **Treatment of drinking water:** *“Nickel can be co-precipitated with iron and manganese oxides”.*
- **Measurement:** *“The nickel concentration in drinking water can be determined using inductively coupled plasma emission spectroscopy or graphite furnace atomic absorption spectroscopy (APHA Method 3500-Ni Parts B and C 1992). The limits of determination are approximately 0.02 mg/L and 0.005 mg/L respectively. Lower concentrations can be determined with pre-concentration using chelation or solvent extraction techniques”.*

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

#	Research Questions	Jurisdiction	Response to Research Questions
18	Is the general description current?	Uses	ATSDR 2005, EFSA 2015a, b, c, OEHHA 2001 & WHO 2007, 2021
			EFSA 2005, EFSA 2020 a,b
		Sources in DW	ATSDR 2005, EFSA 2015a, b, c, EFSA 2005, EFSA 2020 a,b, OEHHA 2001 & WHO 2007, 2021
			Yes, the general description of uses in the factsheet is current.
			Not applicable (as uses are not discussed in this report).
			Yes, the general description of sources in DW in the factsheet is current.

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#	Research Questions	Jurisdiction	Response to Research Questions
19	What are the indicators of the risks? How can we measure exposure? Is the information on measurement/analytical methods current?	<b>ATSDR 2005</b>	<p>The measurement method listed is no longer current. There is a revised APHA Method 3500-Ni from 2018.</p> <p>The most common methods used to detect Ni in environmental samples are AAS, either flame or graphite furnace, ICP-AES, or ICP-MS. Ni in water and wastewater samples are analysed by commercial laboratories in Australia using one or more of the following methods:</p> <ul style="list-style-type: none"> <li>• ASTM Test Methods D1976 (ICP-AES)</li> <li>• ASTM Test Methods D5673 (ICP-MS)</li> <li>• EPA Test Method 249.1 (atomic absorption, direct aspiration)</li> <li>• EPA Test Method 249.2 (atomic absorption, furnace technique).</li> <li>• EPA Test Method 200.7 (ICP-AES),</li> <li>• EPA Test Method 200.8 (ICP-MS),</li> <li>• EPA Test Method 1638 (ICP-MS),</li> <li>• EPA Test Method 200.12 (atomic absorption, graphite furnace technique) or a direct current plasma atomic emission spectrophotometric method.</li> </ul>
		<b>EFSA 2005</b>	Not stated
		<b>EFSA 2015a, b, c</b>	Method types include atomic absorption spectrometry (AAS), either flame or graphite furnace (FAAS, GFAAS), inductively coupled plasma optical/atomic emission or mass spectrometry (ICP-OES/ICP-AES or ICP-MS), followed by spectrophotometric techniques (ultra-violet (UV)-visible absorption, photodiode array).
		<b>EFSA 2020 a, b</b>	Flame or graphite furnace with atomic absorption spectrometry (F- or GF-AAS), inductively coupled plasma-optical/atomic emission spectrometry (ICP-OES/ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS).
		<b>OEHHA 2001</b>	Not stated
		<b>WHO 2007, WHO 2021</b>	Flame atomic absorption spectrometry is suitable in the range of 0.1–10 mg/L, reaffirmed in 2017.
20	Are there commercial analytical methods available that can measure at or below guideline value?	<b>WHO (2007, 2021)</b>	Inductively coupled plasma atomic emission spectrometry can be used for the determination of Ni with a limit of detection of about 10 µg/L.
21	Is the information for treatment options current in terms of current practices in Australia?	<b>WHO (2007, 2021)</b>	Yes. Conventional surface water treatment, comprising chemical coagulation, sedimentation and filtration, can achieve 35–80% removal of Ni, depending on a number of factors including the coagulant dosage, the age of the activated carbon and pH.

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

#	Research Questions	Jurisdiction	Response to Research Questions
19	What are the indicators of the risks? How can we measure exposure? Is the information on measurement/analytical methods current?	<b>Correspondence with Australian Commercial Laboratories</b>	No. The method and limits of determination are now out of date.  Ni concentration in water can be determined by 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 (2021).  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. Previously, the limit of determination was 0.02 mg/L and 0.005 mg/L (NHMRC 2021).
		<b>Water Corporations (ICON Water 2019-2020, Melbourne Water 2021, PWNT 2005 – 2020, Seqwater 2021 Tas Water 2014-2020, WRA 2008)</b>	Method not stated
20	Are there commercial analytical methods available that can measure at or below guideline value?	<b>Correspondence with Australian Commercial Laboratories</b>	Yes. The current limit of determination (0.001 – 0.0001mg/L, i.e. 0.1-1 µg/L) are below candidate guideline values (20 – 70 µg/L).
		<b>Water Corporations (ICON Water 2019-2020, Melbourne Water 2021, PWNT 2005 – 2020, Seqwater 2021 Tas Water 2014-2020, WRA 2008)</b>	Yes, LOR is <0.001 mg/L for most water corporations.
21	Is the information for treatment options current in terms of current practices in Australia?	<b>Correspondence with Australian Commercial Laboratories</b>	-
		<b>Water Corporations (ICON Water 2019-2020, Melbourne Water 2021, PWNT 2005 – 2020, Seqwater 2021 Tas Water 2014-2020, WRA 2008)</b>	-

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#	Research Questions	Jurisdiction	Response to Research Questions
		<b>Barloková et al. 2021</b>	Yes however improved sorption methods are discussed in this paper. Adsorption of Ni on a suitable adsorption material is the most frequently used method in water treatment. Granular iron-based sorption materials (Oxides, oxyhydroxides and hydroxide containing iron) can be used to remove Ni from drinking water.
		<b>Khan et al. 2021</b>	Yes however improved sorption methods are discussed in this paper. Characteristics of magnetic carbon nanotubes (CNT) have led them to an extensive search for their utilisation in water purification.
		<b>Kurdiumov et al. 2020</b>	Yes however improved sorption methods are discussed in this paper. Studies have shown that the best extraction of non-ferrous metals (such as Ni) is provided by weakly acidic macroporous cation exchange resins with chelate groups of iminodiacetic acid.
		<b>Nujić et al. 2020</b>	Yes however improved sorption methods are discussed in this paper. Adsorption is still one of the most suitable technologies for heavy metal ions removal (such as Ni). Recent studies show that graphene oxide (GO), functionalised GO and their composites can efficiently remove heavy metal ions from water.
22	Can treatment technologies treat to the suggested level of the guideline value?	<b>Correspondence with Australian Commercial Laboratories</b>	-
		<b>(ICON Water 2019-2020, Melbourne Water 2021, PWNT 2005 – 2020, Seqwater 2021, Tas Water 2014-2020, WRA 2008)</b>	-
		<b>Barloková et al. 2021</b>	Yes. Bayoxide E33 (a ferric hydroxide granular iron-based sorption material) was the most suitable for Ni removal to below DWG of 0.02 mg/L in Slovakia as compared to other tested sorption materials.
		<b>Khan et al. 2021</b>	Presumably. Removal of nickel (Ni (II)) elevated around 25% with use of CNT.
		<b>Kurdiumov et al. 2020</b>	Presumably. In bicomponent systems, the extraction of Ni ions increases from 59 to 78 % (but does not discuss whether it can treat to guideline levels).
		<b>Nujić et al. 2020</b>	Presumably. Chitosan / graphene oxide (GO) nanocomposite, Chitosan/iron oxide and silica from rice husk ash/GO (RHA-SiO <sub>2</sub> /GO) adsorbents showed good adsorption properties for Ni ions with capacities of 72.04, 57.86 and 256 mg/g respectively (but does not discuss whether it can treat to guideline 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.



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# APPENDIX A

## Literature search screening outcome spreadsheets

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Appendix A contents here

# APPENDIX B

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

## Existing Health-Based Guidance for Nickel

## ATSDR 2005

Agency Report Reference: <i>ATSDR (2005). Toxicological Profile for Nickel. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. August 2005.</i>		
General Information	Date of data extraction	12/11/2021
	Authors	Fay, M., Wilbur, S., Abadin, H., Ingerman, L., and Swarts, S.G.
	Publication date	August 2005
	Literature search timeframe	Not stated, but bibliography contained literature up to 2005
	Publication type	Agency review
	Peer reviewed?	Yes, profile underwent numerous internal ATSDR reviews, was peer reviewed by a non-governmental panel and was released for public comment prior to finalisation.
	Country of origin	United States
	Source of funding	Not stated, but assumed to be United States government
	Possible conflicts of interest	Not indicated
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	Normally oral Minimal Risk Level (MRL), however the database for oral studies was inadequate and an oral MRL was not derived.
	Exposure timeframe	Not applicable – no oral MRLs derived.
	Critical health endpoint(s) – oral exposure	Data on the chronic toxicity of ingested Ni are limited to one animal study that found significant decreases in body weight and liver weights in rats exposed to 75 mg Ni/kg/day as Ni sulphate in the diet and decreases in body weight, increases in liver weight, and adverse renal and lung effects in dogs at 62.5 mg Ni/kg/day (Ambrose et al. 1976).
	Justification provided by agency for critical endpoint	The available chronic-duration database was considered inadequate for MRL derivation because Intermediate-duration studies found significant decreases in survival of offspring of rats exposed to Ni chloride at $\geq 1.3$ mg Ni/kg/day. The available data are not sufficient to establish a threshold for developmental effects to Ni chloride in rats; the lowest LOAEL values identified in the studies range from 1.3 to 90 mg Ni/kg/day and the highest NOAEL values range from 2.2 to 45 mg Ni/kg/day. Because decreased pup survival is considered a serious LOAEL and a NOAEL for developmental effects has not been clearly identified, an intermediate-duration oral MRL was not derived for Ni.
	Critical study(ies) underpinning point of departure	Not applicable (no critical endpoint selected).
	Species for critical study(ies)	Not applicable (no critical endpoint selected).
	Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc)	Not applicable (no critical endpoint selected).
	Point of departure value (include units)	Not applicable (no critical endpoint selected).
	Uncertainty factor(s) & rationale	Not applicable (no critical endpoint selected).

**Agency Report Reference: ATSDR (2005). Toxicological Profile for Nickel. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. August 2005.**

	The derivation:	Not applicable (no critical endpoint selected).
	Guideline value (include units)	Not applicable (no critical endpoint selected).
	Mode of action for critical health endpoint	Not applicable (no critical endpoint selected).
	Genotoxic oral carcinogen?	<p>In lifetime drinking water studies in rats and mice, nickel acetate (0.6 mg Ni/kg/day for rats; 0.95 mg Ni/kg/day for mice) was found to be noncarcinogenic (Schroeder et al. 1964, 1974). The incidence of tumours was comparable to that observed in controls.</p> <p>The Department of Health and Human Services (NTP 2002) has determined that metallic Ni may reasonably be anticipated to be a carcinogen and that Ni compounds are known to be human carcinogens. Similarly, IARC classified metallic Ni in group 2B (possibly carcinogenic to humans) and Ni compounds in group 1 (carcinogenic to humans).</p> <p>There is some evidence to suggest that Ni is clastogenic and can damage DNA.</p>
	Identified sensitive sub-populations	The developing organism may be a sensitive target of Ni toxicity following intermediate-duration exposure. However, additional studies are needed to confirm the identification of these effects as sensitive targets of Ni toxicity.
	Any non-health-based considerations?	Not in MRL development.
Exposure considerations	Principal routes of exposure in general population	Food is the major source of exposure to Ni. You may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing Ni. Skin contact with soil, bath or shower water, or metals containing Ni, as well as metals plated with Ni can also result in exposure. Stainless steel and coins contain Ni. Some jewellery is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in artificial body parts made from Ni -containing alloys. Exposure of an unborn child to Ni is through the transfer of Ni from the mother's blood to foetal blood.
	Levels in drinking water supplies (include location)	The average concentration of Ni in drinking water in the United States is between 2 and 4.3 ppb (1ppb = 1 µg/L). However, you may be exposed to higher-than-average levels of Ni in drinking water if you live near industries that process or use Ni. The highest levels of Ni in drinking water, about 72 ppb, were found near areas of a large natural Ni deposit where Ni is mined and refined.
	Any special considerations to exposure levels (e.g. higher in drought?)	Not for drinking water. The highest soil concentrations (up to 9,000 ppm) are found near industries that extract Ni from ore. High concentrations of Ni occur as dust that is released into air from stacks during processing and settles on the ground.

Agency Report Reference: <i>ATSDR (2005). Toxicological Profile for Nickel. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. August 2005.</i>		
	Typical exposure in general population (include units for intakes & location)	You eat about 170 micrograms ( $\mu\text{g}$ ; $1 \mu\text{g}=1$ millionth of a gram) of Ni in your food every day. Foods naturally high in Ni include chocolate, soybeans, nuts, and oatmeal. Our daily intake of Ni from drinking water is only about $2 \mu\text{g}$ . We breathe in between 0.1 and $1 \mu\text{g}$ Ni /day, excluding Ni in tobacco smoke. We are exposed to Ni when we handle coins and touch other metals containing Ni.  You may be exposed to higher levels of Ni if you work in industries that process or use Ni.
Risk Summary	Any risks to human health from drinking water identified in agency document?	No. The amount of Ni in foods and drinking water are too low to be of concern.
	Any emerging risks identified?	No
<p><b>References:</b></p> <p>Ambrose, A.M., Larson, P.S., Borzelleca, J.F., et al. 1976. Long term toxicologic assessment of nickel in rats and dogs. <i>J Food Sci Technol</i> 13:181-187. <i>As cited in ATSDR (2005).</i></p> <p>NTP (2002). Report on carcinogens. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. <a href="http://ehp.niehs.nih.gov/roc/toc10/html">http://ehp.niehs.nih.gov/roc/toc10/html</a>. June 06, 2003. <i>As cited in ATSDR (2005).</i></p> <p>Schroeder, H.A., Balassa, J.J., Vinton, W.H. Jr. (1964). Chromium, lead, cadmium, nickel and titanium in mice: Effect on mortality, tumors and tissue levels. <i>J Nutr</i> 83:239-250. <i>As cited in ATSDR (2005).</i></p> <p>Schroeder, H.A., Mitchener, M., Nason, A.P.. (1974). Life-term effects of nickel in rats: Survival, tumors, interactions with trace elements and tissue levels. <i>J Nutr</i> 104:239-243. <i>As cited in ATSDR (2005).</i></p>		

## EFSA 2005

Agency Report Reference: <i>EFSA (2005). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Nickel. European Food Safety Authority (EFSA). The EFSA Journal (2005) 146, 1-21.</i>		
General Information	Date of data extraction	12/11/2021
	Authors	Not listed.
	Publication date	2005
	Literature search timeframe	Not stated, but bibliography contained literature up to 2004
	Publication type	Agency review.
	Peer reviewed?	Not specifically stated.
	Country of origin	Europe (not further specified)
	Source of funding	Not specified; likely European governments.
	Possible conflicts of interest	Not stated.

Agency Report Reference: *EFSA (2005). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Nickel. European Food Safety Authority (EFSA). The EFSA Journal (2005) 146, 1-21.*

Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	None derived. European Food Safety Authority was asked 1) to review the upper levels of daily intakes that are unlikely to pose a risk of adverse health effects; 2) to provide the basis for the establishment of safety factors, where necessary. In the absence of adequate dose-response data for these effects, it is not possible to establish a tolerable upper intake level.
	Exposure timeframe	Not applicable (no guidance value was derived).
	Critical health endpoint(s) – oral exposure	In studies on subchronic toxicity, the main targets for the toxicity of orally ingested Ni salts are kidneys, spleen, lungs, and the myeloid system. In addition, perinatal mortality has been reported to increase in rats, even at the lowest administered dose of 1.3 mg Ni /kg body weight/day as Ni chloride. It is not possible to derive a threshold for provoking dermal reactions in Ni -sensitised subjects. Although only dermal exposure to Ni can lead to sensitisation, oral doses of Ni have been shown to exacerbate hand eczema in Ni -sensitised individuals. In some studies, as little as 8 and 12 µg Ni /kg body weight provoked such reactions.
	Justification provided by agency for critical endpoint	The available studies do not allow the establishment of a NOAEL.
	Critical study(ies) underpinning point of departure	Not applicable (no critical endpoint selected).
	Species for critical study(ies)	Not applicable (no critical endpoint selected).
	Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc)	Not applicable (no critical endpoint selected).
	Point of departure value (include units)	Not applicable (no critical endpoint selected).
	Uncertainty factor(s) & rationale	Not applicable (no critical endpoint selected).
	The derivation:	Not applicable (no critical endpoint selected).
	Guideline value (include units)	Not applicable (no critical endpoint selected).
	Mode of action for critical health endpoint	Not applicable (no critical endpoint selected).
	Genotoxic oral carcinogen?	While there is evidence that inhaled Ni salts are carcinogenic in rodents and humans, orally ingested Ni salts have not been shown to be carcinogenic. The genotoxicity of Ni salts, observed at chromosome level at high, toxic doses is likely due to indirect mechanisms.
	Identified sensitive sub-populations	Ni salts are potent skin sensitisers in humans, causing allergic contact dermatitis. In a number of oral challenge studies, single oral doses of a few mg Ni provoked dermal reactions in Ni -sensitised subjects.
	Any non-health-based considerations?	No

Agency Report Reference: *EFSA (2005). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Nickel. European Food Safety Authority (EFSA). The EFSA Journal (2005) 146, 1-21.*

Exposure considerations	Principal routes of exposure in general population	Diet.
	Levels in drinking water supplies (include location)	In Europe, first-run drinking water, may contain up to 1000 µg/L.
	Any special considerations to exposure levels (e.g. higher in drought?)	Average intakes from food are about one third of the lowest intake reported to aggravate hand eczema in Ni sensitised subjects.
	Typical exposure in general population (include units for intakes & location)	The intake of Ni from the average diet is estimated to be about 150 µg/day (about 2.5 µg/kg body weight/day) but may reach 900 µg/day (about 15 µg/kg body weight/day) or more, when large amounts of food items with high Ni contents are consumed. In addition, first-run drinking water, which may contain up to 1000 µg/L, and leaching from kitchen utensils into food may also contribute to Ni intake. Intakes of 150 and 900 µg/day are about 500 and 90-fold lower, respectively, than the lowest dose reported to cause adverse effects in rats.
Risk Summary	Any risks to human health from drinking water identified in agency document?	Consumption of food with high Ni content and additional exposure from first-run drinking water and kitchen utensils could result in an intake higher than the critical dose [in Ni sensitised population].
	Any emerging risks identified?	No. In the worst case, however, the first-run drinking water, which remained in the tap overnight, would be consumed and the release of Ni from kitchen utensils would cause an additional alimentary exposure. In that case, the margin between the dietary intake and toxic doses would be considerably lower.

## EFSA 2015 a, b, c

Agency Report Reference: *EFSA (2015a). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.*

Agency Report Reference: *EFSA (2015b). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.*

Agency Report Reference: *EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.*

General Information	Date of data extraction	12/11/2021
	Authors	Hellenic Food Authority (EFET)
	Publication date	12 February 2015 (NB: An editorial correction was carried out that does not materially affect the contents or outcome of this scientific output. Some minor editorial corrections were carried out so as to comply with the in-house style guide). A version released on 28 February 2018 replaces the previous output published.
	Literature search timeframe	Not stated. References span from 1943 to 2015.
	Publication type	Agency Review
	Peer reviewed?	In accordance with Art 29 (1) of Regulation (EC) No 178/2002, the Hellenic Food Authority asks the European Food Safety Authority to provide a scientific opinion on the risk to human health related to the presence of Ni in food addressing particularly the presence of Ni in vegetables.
	Country of origin	Italy, on request from the European Commission.
	Source of funding	Not specifically stated. Likely to be on request from the European Commission.
	Possible conflicts of interest	Non stated.
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	Chronic exposure: Tolerable daily intake Acute exposure: BMDL10 of 1.1 µg Ni/kg b.w. for a Margin of Exposure (MOE) approach
	Exposure timeframe	Acute (<1 day) or chronic (1yr+)
	Critical health endpoint(s) – oral exposure	Chronic exposure: Developmental toxicity (in rodents). Acute exposure: Hypersensitivity reactions (in humans)
	Justification provided by agency for critical endpoint	Chronic exposure: Ni is considered to be a developmental toxicant inducing fetotoxicity, embryotoxicity and teratogenicity. Acute exposure: Systemic contact dermatitis elicited in Ni-sensitive humans after oral exposure seen as eczematous flare-up reactions and worsening of allergic reactions (e.g. hand eczema, body erythema) were identified as the critical effect for acute oral exposure to Ni of Ni-sensitised humans.

Agency Report Reference: *EFSA (2015a). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.*

Agency Report Reference: *EFSA (2015b). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.*

Agency Report Reference: *EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.*

	Critical study(ies) underpinning point of departure	<p>Chronic exposure: The Panel used the combined data from a dose range finding unpublished 1-generation study (SLI 2000a) and a subsequent full 2-generation study in rats (SLI 2000b) and derived a lower 95 % confidence limit for a benchmark response at 10 % extra risk (BMDL10) value.</p> <p>Acute exposure: Three data sets on sensitised human individuals with a history of contact dermatitis or related symptoms exposed orally to Ni in clinical challenge studies were identified as suitable for dose-response analysis using the benchmark dose (BMD) approach (Gawkrödger et al. 1986, Hindsén et al. 2001, Jensen et al. 2003). Out of the human volunteer studies suitable for the dose response analysis, the CONTAM Panel selected the study by Jensen et al. (2003) resulting in the lowest BMDL10 for the derivation of the acute reference point (RP) (Jensen et al. 2003).</p>
	Species for critical study(ies)	Rats (chronic) or human volunteers (acute).
	Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc)	BMDL10 (chronic and acute)
	Point of departure value (include units)	<p>Chronic exposure: A BMDL10 value of 0.28 mg Ni /kg b.w. per day for post-implantation loss as RP for chronic dietary exposure to Ni.</p> <p>Acute exposure: When applying the BMD approach for quantal data a BMDL10 of 1.1 µg Ni/ kg b.w. was calculated as an RP for eliciting systemic contact dermatitis in Ni-sensitive humans after acute oral exposure to Ni.</p>
	Uncertainty factor(s) & rationale	<p>Chronic exposure: 100 to account for interspecies differences and human variability.</p> <p>Acute exposure: An MOE of 10 to be indicative of a low health concern.</p>
	The derivation:	<p>Chronic exposure: A tolerable daily intake of 2.8 µg Ni/kg body weight (b.w.) per day was derived from a BMDL10 of 0.28 mg/kg and an uncertainty factor of 100.</p> <p>Acute exposure: A lowest BMDL10 of 1.1 µg Ni/kg b.w. was derived and used in an MOE approach.</p>
	Guideline value (include units)	<p>Chronic exposure: A tolerable daily intake (TDI) of 2.8 µg/kg/day (chronic)</p> <p>Acute exposure: 1.1 µg/kg (acute) using a MOE approach</p>

Agency Report Reference: EFSA (2015a). *Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water*. European Food Safety Authority (EFSA). *EFSA Journal* 2015;13(2):4002.

Agency Report Reference: EFSA (2015b). *Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed*. European Food Safety Authority (EFSA). *EFSA Journal* 2015;13(4):4074.

Agency Report Reference: EFSA (2015c). *Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans*. European Food Safety Authority (EFSA). *Supporting Publications* 2015:EN-478.

	Mode of action for critical health endpoint	<p>Chronic exposure: Ni can cross-link amino acids to DNA, lead to formation of reactive oxygen species (ROS), moreover mimic hypoxia. These changes may lead to the activation of some signalling pathways, subsequent transcription factors and eventually to alterations in gene expression and cellular metabolism.</p> <p>Acute exposure: There is evidence that combination of Ni with circulating or tissue protein gives rise to antigen specific responses, and thus Ni can act as a contact allergen and cause sensitisation. The antigens are taken up by antigen-presenting cells that migrate to draining lymph nodes, resulting in activation of Ni-specific T lymphocytes. Contact sensitivity is either expressed as Type I or Type IV hypersensitivity, mediated by reagents and allergen-specific T lymphocytes, expressing in a wide range of cutaneous eruptions following dermal or systemic exposure. An alternative, but not mutually exclusive, hypothesis is that this metal interferes with the antigen recognition step of the immune response, i.e. binding to Major Histocompatibility Complex (MHC) and/or MHC-bound peptides and T cell receptors leading to the activation of Ni-specific T cells.</p>
	Genotoxic oral carcinogen?	<p>There is evidence for the induction of DNA damage by soluble Ni compounds both <i>in vitro</i> and <i>in vivo</i>.</p> <p>No tumours were found in animals that received soluble Ni compounds by the oral route.</p> <p>The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) considered it unlikely that dietary exposure to Ni results in cancer in humans.</p>
	Identified sensitive sub-populations	<p>Chronic exposure: The foetus might be particularly sensitive towards the adverse effects of Ni because it lacks effective means for eliminating excessive Ni.</p> <p>Acute exposure: Ni-sensitised individuals.</p>
	Any non-health-based considerations?	No
Exposure considerations	Principal routes of exposure in general population	Diet and to a lesser extent from drinking water.
	Levels in drinking water supplies (include location)	Ni concentrations in waters across Europe were generally below 10 µg/L.
	Any special considerations to exposure levels (e.g. higher in drought?)	No

Agency Report Reference: *EFSA (2015a). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.*

Agency Report Reference: *EFSA (2015b). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.*

Agency Report Reference: *EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.*

	<p>Typical exposure in general population (include units for intakes &amp; location)</p>	<p>Mean dietary acute exposure in the young population ('Infants', 'Toddlers', 'Other children' and 'Adolescents') ranged from 3.4 (95 % CI = 3.1–3.7) µg/kg b.w. in one survey for 'Adolescents' to 14.3 (95 % CI = 13.2–15.5) µg/kg b.w. in one survey for 'Toddlers'. The 95th percentile ranged 8.6 (95 % CI = 8.0–9.1) µg/kg b.w. in one survey for 'Adolescents' to 35.0 (95 % CI = 26.8–47.2) µg/kg b.w. in one survey for 'Toddlers'. The acute exposure to Ni in the adult population ('Adults', 'Elderly' and 'Very elderly') was lower than that observed in the young population. Mean dietary acute exposure ranged from 2.5 (95 % CI = 2.2–2.9) µg/kg b.w. in one survey for 'Elderly' to 4.9 (95 % CI = 4.6–5.5) µg/kg b.w. in one survey for 'Adults'. The 95th percentile ranged from 5.5 (95 % CI = 5.1–6.0) µg/kg b.w. in one survey for 'Elderly' to 11.8 (95 % CI = 10.6–13.8) µg/kg b.w. in one survey for 'Adults'. Average acute exposure estimations did not differ much from those calculated for the chronic exposure.</p>
<p>Risk Summary</p>	<p>Any risks to human health from drinking water identified in agency document?</p>	<p>No however the CONTAM Panel concluded that, at the current levels of acute dietary exposure to Ni, there is a concern that Ni-sensitised individuals may develop eczematous flare-up skin reactions.</p>
	<p>Any emerging risks identified?</p>	<p>Chronic exposure: The mean chronic dietary exposure to Ni, across the different dietary surveys and age classes, ranging from 2.0 (minimum LB, 'Elderly') to 13.1 µg Ni/kg b.w. per day (maximum UB, 'Toddlers') is close to the TDI or above it particularly when considering the young age classes (e.g. 'Infants', 'Other children', 'Toddlers' and 'Adolescents').</p> <p>Acute exposure: All the MOEs calculated from these exposure levels are considerably below 10 for all age groups both for the estimated mean and 95th percentile exposure levels.</p>

Agency Report Reference: *EFSA (2015a). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.*

Agency Report Reference: *EFSA (2015b). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.*

Agency Report Reference: *EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.*

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SLI (2000b). An oral (gavage) two-generation reproduction toxicity study in Sprague-Dawley rats with nickel sulfate hexahydrate. Final Report. Volume 1 of 3. Spencerville, OH: Springborn Laboratories, Inc. SLI Study No. 3472.4. Unpublished study. *As cited in EFSA 2015b.*

## EFSA 2020 a, b

Agency Report Reference: *EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.*

Agency Report Reference: *EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.*

General Information	Date of data extraction	16/11/2021
	Authors	Individual authors are not acknowledged.
	Publication date	30 September 2020 (Approved date).
	Literature search timeframe	<ul style="list-style-type: none"> <li>Literature search for supporting information. Last 5 years for toxicokinetic, all years for occurrence of nanoparticles and migration from food contact materials</li> <li>Literature search for hazard identification and characterisation: Limited to between 01/01/2013 and 25/06/2019</li> </ul>
	Publication type	Agency Review
	Peer reviewed?	Yes.
	Country of origin	Not stated (Europe).
	Source of funding	European Union

Agency Report Reference: *EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.*

Agency Report Reference: *EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.*

	Possible conflicts of interest	Not stated. At least once every year, and in any case within 45 calendar days following any change in his/her interests, experts (and other staff of EFSA) submit a declaration of interest (DoI) to EFSA (EFSA 2018b). DoI's are made publically available on the EFSA website (EFSA 2006). The detailed approach to managing potential conflicts of interest is described in EFSA (2017b, 2018b).
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	Chronic exposure: Oral tolerable daily intake Acute exposure: Lowest-observed-adverse-effect-level (LOAEL) for an MOE approach
	Exposure timeframe	Chronic exposure: BMDL10 Acute exposure: LOAEL
	Critical health endpoint(s) – oral exposure	Chronic exposure: An increased incidence of post-implantation loss in rats was identified as the critical effect for the risk characterisation of chronic oral exposure. Acute Exposure: Eczematous flare-up reactions in the skin elicited in Ni -sensitised humans.
	Justification provided by agency for critical endpoint	Chronic exposure: 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 $\geq 1.3$ mg/kg bw per day. Acute exposure: A condition known as systemic contact dermatitis, was identified as the critical effect for the risk characterisation of acute oral exposure.
	Critical study(ies) underpinning point of departure	Chronic exposure: Two-generation reproductive toxicity study (RTI 1988a,b, SLI 2000b; Smith et al., 1993) Acute exposure: Oral Ni challenge in humans by Gawkrödger et al. (1986) and dose-response study by Jensen et al. (2003) also in humans. The "Contam Panel" combined data from both these studies.
	Species for critical study(ies)	Chronic exposure: Rat Acute exposure: Ni -sensitised humans
	Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc)	Chronic exposure: BMDL10 Acute exposure: LOAEL
	Point of departure value (include units)	Chronic exposure: A BMDL10 of 1.3 mg Ni/kg body weight (bw) per day was selected as the reference point Acute exposure: A LOAEL of 4.3 $\mu$ g Ni/kg bw was selected as the reference point
Uncertainty factor(s) & rationale	Chronic exposure: 100 to account for interspecies differences and human variability Acute exposure: A margin of exposure (MOE) of 30 was considered indicative of a low health concern.	

Agency Report Reference: *EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.*

Agency Report Reference: *EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.*

	The derivation:	<p>Chronic exposure: the BMDL10 of 1.3 mg Ni/kg/day and an uncertainty factor of 100 was used to derive a TDI of 13 µg/kg/day.</p> <p>Acute exposure: Not relevant. The LOAEL was used in a margin of exposure (MOE) approach for the acute risk assessment.</p>
	Guideline value (include units)	<p>Chronic exposure: A TDI of 13 µg/kg/day.</p> <p>Acute exposure: A LOAEL of 4.3 µg Ni/kg bw and MOE approach (target MOE of 30).</p>
	Mode of action for critical health endpoint	<p>Chronic exposure: The mode of action appears to involve reactive oxygen species (ROS), at least in part mediated by Ni complexation with protamine 2 which is expressed in sperm chromatin. Humans express both protamine 2 and protamine 1 at appreciable levels in sperm (43% protamine 2) and therefore may be more similar in this respect to the mouse (67–72% protamine 2 in various mouse species) than to the rat which expresses very little protamine 2 (2–5% in Norwegian rats). Thus, on the basis of protamine 2 expression levels, it appears that the susceptibility of humans to infertility might be more similar to that of the mouse rather than to that of the rat, although the relative level of antioxidant defence in sperm will undoubtedly also be a major determinant of susceptibility. There is also a possible interference with calcium ion channels. <i>In vitro</i>, Leydig cell toxicity and reduced testosterone production is related to increased ROS and there is evidence of altered extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) signalling which appears to inhibit testosterone synthetase.</p> <p>Acute exposure: Reduced interleukin (IL)-10 levels were noted in the desensitised individuals, indicating a role for IL-10 in the regulation of Ni -specific responses after oral uptake of Ni in Ni -sensitised individuals.</p> <p>Gingival fibroblasts may be involved in the induction of oral tolerance through Ni -induced alteration in nuclear factor kappa B (NF-κB) and hypoxia-inducible factor 1-alpha (HIF-1α) regulation. Increased IL1-b, chemokine ligand 20 and vascular endothelial growth factor protein levels, as well as decreased IL-10 levels, which predispose an individual to an inflammatory reaction in the skin due to Ni, seem to be inhibited in gingival/oral tissue.</p>
	Genotoxic oral carcinogen?	<p>No tumours have been observed in the carcinogenicity studies in experimental animals after oral administration of soluble Ni compounds. It is unlikely that dietary exposure to Ni results in cancer in humans.</p> <p>Ni and Ni compounds have been classified by the IARC as carcinogenic to humans (Group 1) causing cancers of the lung, nasal cavity and paranasal sinuses after inhalation.</p>
	Identified sensitive sub-populations	<p>Chronic exposure: Not stated.</p> <p>Acute exposure: Ni-sensitised individuals.</p>

Agency Report Reference: *EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.*

Agency Report Reference: *EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.*

	Any non-health-based considerations?	No
Exposure considerations	Principal routes of exposure in general population	Dietary exposure (food and drinking water).
	Levels in drinking water supplies (include location)	Total Ni concentrations in ground water and water from drinking water sources/supplies may range from less than 1 µg/L up to few tens of µg/L, although cases of a high Ni occurrence (up to hundreds of µg/L) have also been reported. (Location not specified). Across European countries, Ni in drinking water has a lower bound mean of 2 µg/kg and upper bound mean of 3 µg/kg (17,831 results).
	Any special considerations to exposure levels (e.g. higher in drought?)	Certain food groups are considered as main contributors to dietary exposure - high mean levels of Ni were reported for 'Legumes, nuts and oilseeds' (~ 2,000 µg/kg), certain types of chocolate (cocoa) products (3,800 µg/kg), and 'Cocoa beans and cocoa products' (9,500 µg/kg)
	Typical exposure in general population (include units for intakes & location)	In 2015, dietary exposure assessments in European countries showed that mean adult exposure ranged from 90 to 361 µg/day. Assuming a body weight of 70 kg, this range corresponds to 1.3–5.2 µg/kg bw per day. The Panel also assessed chronic and acute dietary exposure using occurrence data submitted to EFSA. Mean chronic dietary exposure to Ni, across the different dietary surveys and age classes, ranged from 2.0 to 13.1 µg/kg bw per day (minimum LB–maximum UB). The 95th percentile dietary exposure ranged from 3.6 to 20.1 µg/kg bw per day (minimum LB–maximum UB). The highest chronic dietary exposure to Ni was observed for toddlers and other children. The main contributors were 'Grain and grain-based products', 'Non-alcoholic beverages (except milk-based beverages)', 'Sugar and confectionery', 'Legumes, nuts and oilseeds', and 'Vegetables and vegetable products (including fungi)'.
Risk Summary	Any risks to human health from drinking water identified in agency document?	No. The contribution of 'Drinking water' [to Ni intake] was very small.
	Any emerging risks identified?	Chronic exposure: The CONTAM Panel concluded that the 95th percentile chronic dietary exposure to Ni may raise a health concern for the young age groups. The CONTAM Panel noted that the critical effect for the TDI, post-implantation loss, is not a relevant effect for young age groups. Acute Exposure: The MOE values when using the 95th percentile UB acute dietary exposure range from 0.1 to 0.8 across dietary surveys and age classes. These MOE values raise a health concern for Ni -sensitised individuals.

Agency Report Reference: *EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.*

Agency Report Reference: *EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.*

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Jensen, C.S., Menne, T., Lisby, S., Kristiansen, J. and Veien, N.K. (2003). Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Dermatitis*, 49, 124–132. *As cited in EFSA 2015b.*

RTI (Research Triangle Institute), 1988a. Two-generation reproduction and fertility study of nickel chloride administered to CD rats in the drinking water: Fertility and reproductive performance of the P generation. Final study report (II of III). Research Triangle Park, NC: Office of Solid Waste Management, US Environmental Protection Agency. Unpublished report. *As cited in EFSA 2020a.*

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## OEHHA 2001

Agency Report Reference: OEHHA (2001). Public Health Goals for Chemicals in Drinking Water – Nickel. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.		
General Information	Date of data extraction	17/11/2021
	Authors	David Ting
	Publication date	August 2001
	Literature search timeframe	Not stated <i>per se</i> . However, bibliography contains cited references back to the year 1955 and up to the year 2000.
	Publication type	Agency review
	Peer reviewed?	Yes Primary reviewers: Frank Mycroft. Final reviewers: Anna Fan, George Alexeeff, Robert Howd.
	Country of origin	United States (California)
	Source of funding	Not stated, however appears to be the Government of California.
	Possible conflicts of interest	Not stated in this document.
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	Drinking water guideline (i.e. Public Health Goal or PHG)
	Exposure timeframe	Chronic
	Critical health endpoint(s) – oral exposure	Increased perinatal mortality (or early pup mortality). A number of studies indicated that oral exposure of Ni could aggravate Ni dermatitis in people who are sensitive to Ni.
	Justification provided by agency for critical endpoint	OEHHA concluded that the 1.12 mg/kg-day dose in the Springborn Laboratory (SLI 2000b) study represents the highest NOAEL which is lower than the lowest relevant LOAEL, and therefore selected it as the critical endpoint for risk assessment. It results in the lowest reference value when excluding other studies.  Other studies were excluded due to small sample sizes or the human subjects in the studies were in a state of fasting before and after the Ni exposures and represented an extremely sensitive subpopulation.  Studies reported by Nielsen et al. (1999) and Cronin et al. (1980) are not chosen for the development of the PHG because the human subjects in the studies were in a state of fasting before and after the nickel exposures and represented an extremely sensitive subpopulation. Furthermore, there were only five subjects per each dose group in the study reported by Cronin et al. (1980).
	Critical study(ies) underpinning point of departure	The PHG is based on three reproduction toxicity studies in rats (Smith et al., 1993, Springborn Laboratory 2000a, 2000b).
	Species for critical study(ies)	Rat
	Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc)	NOAEL

<b>Agency Report Reference: OEHHA (2001). Public Health Goals for Chemicals in Drinking Water – Nickel. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.</b>	
Point of departure value (include units)	<p>OEHHA identified the oral dose of 1.12 mg Ni/kg-d as the appropriate NOAEL value, from the lower dose-range in the Springborn Laboratory (2000b) study.</p> <p>LOAELs of 8.6 and 12 µg Ni/kg were identified for acute effects (dermatitis) in nickel-sensitised women.</p>
Uncertainty factor(s) & rationale	<p>An overall uncertainty factor of 1,000 was used in the development of the PHG. The uncertainty factor includes factors of ten for inter-species extrapolation and intra-species variability, and an additional factor of ten to account for the potential carcinogenicity of soluble Ni by the oral route.</p> <p>For acute effects an uncertainty factor of 10 for LOAEL to NOAEL was selected.</p>
The derivation:	<p>The PHG was calculated by assuming a relative source contribution of 30 percent, a water consumption rate of 2 L/day, and an adult body weight of 70 kg.</p> <p>Guideline value (µg/L) =</p> $[1,120 \mu\text{g/kg bw/day} \times 70\text{kg} \times 0.3] \div [1,000 \times 2 \text{ L/day}] = 11.8 \mu\text{g/L}$ <p>The PHG for Ni was therefore determined to be 12 µg Ni/L (12 ppb) (rounded).</p> <p>A PHG for acute effects was not derived.</p>
Guideline value (include units)	<p>0.012 mg/L (12 µg/L or 12 ppb) for soluble Ni compounds in drinking water</p>
Mode of action for critical health endpoint	<p>A mode of action for the critical endpoint was not provided.</p> <p>A mode of action was specified for genotoxicity: A number of hypotheses have been proposed about the mechanisms that can explain the observed genotoxicity and transformation potential of soluble Ni compounds. These include; i) that soluble Ni compounds affected cell growth by selectively blocking the S-phase of the cell cycle, ii) most of the genotoxic characteristics of Ni<sup>2+</sup> including DNA strand breaks, DNA-protein cross-links, and chromosomal damage could be explained by the ability of Ni<sup>2+</sup> to generate oxygen free radicals or iii) while Ni<sup>2+</sup> in the presence of inorganic ligands is resistant to oxidation, Ni<sup>2+</sup> chelated with peptides has been shown to be able to catalyze reduction-oxidation reactions.</p>

Agency Report Reference: OEHHA (2001). Public Health Goals for Chemicals in Drinking Water – Nickel. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.		
	Genotoxic oral carcinogen?	<p>If soluble Ni absorbed through the oral route were carcinogenic, its potency is likely to be lower than that estimated from occupational studies of inhalation exposures.</p> <p>All four oral rodent cancer bioassays reported in the literature failed to show that soluble Ni is an oral carcinogen. The Ni doses used in one of the studies (Ambrose et al., 1976) were close to or exceeded the maximally tolerated dose.</p> <p>Several researchers found that certain amino acids, peptides, and proteins are excellent chelators of Ni ion and even at physiological concentrations can significantly inhibit cellular uptake of Ni ion. This phenomenon may reduce the carcinogenic potential of soluble Ni absorbed through the gastrointestinal tract.</p> <p>Nonetheless, an uncertainty factor of 10 was used in the derivation of the PHG to account for the potential carcinogenicity of soluble Ni by the oral route.</p>
	Identified sensitive sub-populations	Individuals allergic to Ni are the sensitive sub-population
	Any non-health-based considerations?	No.
Exposure considerations	Principal routes of exposure in general population	Not stated <i>per se</i> but focus is on food and water.
	Levels in drinking water supplies (include location)	Denmark: up to 490 µg/L US: Maximum of 957 µg/L in “first draw” drinking water California (US): 540 µg/L (maximum), 26.1 µg/L (average), and 17.9 µg/L (median). The detection limit for the purposes of reporting for nickel is 10 µg/L (10 ppb).
	Any special considerations to exposure levels (e.g. higher in drought?)	Elevated Ni levels may exist in drinking water as a result of the corrosion of Ni -containing alloys used as valves and other components in the water distribution system as well as from Ni -plated faucets. Some food sources such as chocolate, nuts, beans, peas, and grains are relatively rich in Ni. Stainless-steel kitchen utensils have been shown to release Ni into acid solutions, especially during boiling. The amount of Ni released depends on the composition of the utensil, the pH of the food, and the duration of contact. It has been estimated that the contribution of kitchen utensils to the oral intake of Ni can be as much as 1 mg/day.
	Typical exposure in general population (include units for intakes & location)	<ul style="list-style-type: none"> <li>US: 168±11 µg/day.</li> <li>Denmark: 150 µg/day (as high as 900 µg/day with certain foods with high Ni content).</li> <li>Switzerland: 73±9 µg/day (in a restaurant) and 142±20 µg/day (in a military canteen)</li> <li>United Kingdom (1981-84): 140-150 µg/day.</li> </ul>

Agency Report Reference: <i>OEHHA (2001). Public Health Goals for Chemicals in Drinking Water – Nickel. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.</i>		
Risk Summary	Any risks to human health from drinking water identified in agency document?	Yes. Current levels of Ni in drinking water are commonly higher than the PHG value. However, at the PHG level of 12 µg/L, assuming a water consumption rate of 2 L/day, the estimated intake dose from water would be 24 µg/day. Assuming a dietary intake dose of approximately 200 µg/day the contribution of water to total intake of Ni would be about 11 percent.
	Any emerging risks identified?	No. The PHG is also believed to be protective of persons who are allergic to Ni. In two human studies, it was demonstrated that oral administration of Ni could aggravate hand eczema in people sensitised towards Ni. The human NOAELs derived from these studies ranged from 0.86 to 1.2 µg Ni/kg. These values are considerably higher than the estimated Ni dose associated with the consumption of soluble Ni in drinking water at the PHG level (24 µg/day or 0.34µg/kg/day).
<b>References:</b> Ambrose, A.M., Larson, P.S., Borzelleca, J.F., et al. 1976. Long term toxicologic assessment of nickel in rats and dogs. <i>J Food Sci Technol</i> 13:181-187. <i>As cited in OEHHA (2001).</i>  SLI (2000a). A one-generation reproduction range-finding study in rats with nickel sulfate hexahydrate. Spencerville, OH: Springborn Laboratories, Inc. SLI Study No. 3472.3. Unpublished study. <i>As cited in OEHHA 2001.</i>  SLI (2000b). An oral (gavage) two-generation reproduction toxicity study in Sprague-Dawley rats with nickel sulfate hexahydrate. Final Report. Volume 1 of 3. Spencerville, OH: Springborn Laboratories, Inc. SLI Study No. 3472.4. Unpublished study. <i>As cited in OEHHA 2001.</i>  Smith, M.K., George, E.L., Stober, J.A., Feng, H.A. and Kimmel, G.L. (1993). Perinatal toxicity associated with nickel chloride exposure. <i>Environmental Research</i> , 61, 200–211. <i>As cited in OEHHA 2001.</i>		

## WHO 2007, 2021

Agency Report Reference: <i>WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.</i>		
Agency Report Reference: <i>WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.</i>		
General Information	Date of data extraction	17/11/2021
	Authors	2007: J.K. Fawell 2021: Not stated.
	Publication date	2007: 2007 (07.08) 2021: 25 May 2021 (Draft document)
	Literature search timeframe	Although not stated <i>per se</i> , bibliographies cite literature in the following timeframes: 2007 = 1972 – 2004, 2021 = 1972 - 2019
	Publication type	2007 & 2021: Agency reviews

<p>Agency Report Reference: <i>WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.</i></p> <p>Agency Report Reference: <i>WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.</i></p>		
	Peer reviewed?	<p>2007: Yes, it has gone through a peer review process by individuals from various countries. The draft text was discussed at the Working Group Meeting for the second addendum to the third edition of the GDWQ, held on 15–19 May 2006. The final version of the document takes into consideration comments from both peer reviewers and the public.</p> <p>2021: Yes. The document is draft for public review.</p>
	Country of origin	2007 & 2021: Not specified (World Health Organisation - concerted effort).
	Source of funding	2007 & 2021: Not specified; likely WHO
	Possible conflicts of interest	2007 & 2021: Not stated.
Health considerations	Guideline value type (e.g. oral TRV, drinking water guideline)	2007 & 2021: Drinking water guideline (DWG)
	Exposure timeframe	2007 & 2021: Chronic
	Critical human health endpoint	<p>2007 &amp; 2021: Post-implantation/perinatal lethality.</p> <p>2021: The critical effect for the risk characterisation of chronic oral exposure to Ni is reproductive and developmental toxicity.</p>
	Justification provided by agency for critical endpoint	<p>2007: It was a well conducted two-generation study on rats, a NOAEL of 1.1 mg of Ni per kg of body weight per day was identified for all the end-points studied, including the variable of post-implantation/perinatal lethality (SLI, 2000; EU, 2008).</p> <p>2021: The reassessment takes into account improved science and methods, including a meta-analysis of epidemiological data and an updated BMD approach that enabled an improved determination of a POD for chronic oral exposure. The reassessment also identified weaknesses in the original study used to derive a guideline value (Nielsen et al., 1999, WHO, 2005) (latter reference not cited in WHO 2021 bibliography). Although this study no longer forms the basis for the guideline value, the guideline value remains the same.</p>
	Critical study(ies) underpinning point of departure	2007 & 2021: Two-generation study in rats (SLI, 2000; EU, 2004).
	Species for critical study(ies)	2007 & 2021: Rats
	Point of departure type (e.g. NOAEL, LOAEL, BMDL10, etc)	<p>2007: NOAEL</p> <p>2021: BMDL10</p>
	Point of departure value (include units)	<p>2007: 1.1 mg of Ni per kg of body weight per day. For acute effects, a LOAEL of 0.012 mg/kg was established after provocation of fasted patients (highly sensitised population) with an empty stomach.</p> <p>2021: The resulting BMDL10 for post-implantation loss of 1.3 mg /kg bw per day for the F0 and F1 data of the two-generation study was selected as a point of departure. A LOAEL of 4.3 µg nickel/kg bw was identified for acute effects (SCD) in Ni sensitised people..</p>
	Uncertainty factor(s) & rationale	2007 & 2021: An uncertainty factor of 100 (10 to account for interspecies variation and 10 to account for intraspecies variation)

Agency Report Reference: *WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.*

Agency Report Reference: *WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.*

	Guidance Value	2007: A TDI of 11 µg/kg of body weight 2021: A TDI of 13 µg/kg bw/day. A LOAEL of 4.3 µg nickel/kg bw was selected as a reference point for acute effects and MOE evaluation.
	The derivation	2007: A health-based value of 70 µg/litre (rounded from 66 µg/litre) could be determined from this TDI by assuming a 60-kg adult drinking 2 litres of water per day and allocating 20% of the TDI to drinking-water. Guideline value (µg/L) = $[11 \mu\text{g/kg bw/day} \times 60\text{kg} \times 0.2] \div [2 \text{ L/day}] = 70 \mu\text{g/L}$ (rounded from 66 µg/L). 2021: The health-based value of 80 µg/L (13 µg/kg bw/day × 60 kg bw, with water consumption of 2 L/day) is protective of chronic systemic toxicity. Guideline value (µg/L) = $[13 \mu\text{g/kg bw/day} \times 60 \text{ kg bw} \times 0.2] \div [2 \text{ L/day}] = 78 \mu\text{g/L}$ (rounded from 80 µg/L).
	Guideline value (include units)	2007 & 2021: 70 µg/litre. Note in 2021 the reassessment of the risk posed by Ni in drinking-water [was used to support] maintaining the guideline value of 70 µg/L
	Mode of action for critical health endpoint	2007 & 2021: Not stated for chronic effects (from oral exposure).
	Genotoxic carcinogen?	2007 & 2021: There is a lack of evidence of a carcinogenic risk from oral exposure to Ni.
	Identified sensitive sub-populations	2007 & 2021: Not stated although Ni sensitised individuals are discussed.
	Any non-health based considerations?	2007 & 2021: No.
Exposure considerations	Principal routes of exposure in general population	2007 & 2021: Food is the dominant source of Ni exposure in the non-smoking, non-occupationally exposed population.

<p>Agency Report Reference: <i>WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.</i></p> <p>Agency Report Reference: <i>WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.</i></p>		
	Levels in drinking water supplies (include location)	<p>2007:</p> <ul style="list-style-type: none"> <li>• Europe: Generally &lt;10 µg/litre.</li> <li>• Denmark and Finland &lt;1 µg/litre.</li> <li>• Canada: below the detection limit of 2 µg/litre (median), 69 µg/litre (Maximum).</li> <li>• USA: 90% of all samples (n = 2503) contained ≤10 µg/litre, ≤20 µg/litre (97% of samples).</li> <li>• Other: 100–2500 µg/litre (in polluted areas and areas in which natural Ni was mobilised).</li> </ul> <p>2021</p> <ul style="list-style-type: none"> <li>• England and Wales, median and 97.5th percentile concentrations for Ni in drinking-water 1.36 (median) and 4.63 µg/L (97,5<sup>th</sup> percentile) (or only 0.003 and 0.009 mg/day assuming a drinking-water intake rate of 2 L per day. Based on earlier data, water generally contributes 0.005–0.025 mg daily (i.e. 2–11% of the total daily oral intake of Ni).</li> </ul>
	Any special considerations to exposure levels (e.g. higher in drought?)	<p>2007 &amp; 2021: The primary source of Ni in drinking-water is leaching from metals in contact with drinking-water, such as pipes and fittings.</p> <p>2007: As nuts and beans are important sources of protein for vegetarians, this population group can be expected to have a markedly higher intake of Ni than that reported in other studies. The Ni intake of eight volunteers ingesting normal diets averaged 0.13 mg/day (range 0.06–0.26 mg/day), compared with 0.07 mg/day (range 0.02–0.14 mg/day) when diets containing low Ni levels were consumed. When food rich in Ni was ingested, the daily intake was 0.25 mg/day (range 0.07–0.48 mg/day). A duplicate-diet study of vegetarians in the United Kingdom indicated an average dietary intake of Ni of 0.17 mg/day.</p>
	Typical exposure in general population (include units for intakes & location)	<p>2007: Intake from different environmental media:</p> <ul style="list-style-type: none"> <li>• Air: It has been estimated that non-occupational exposure via inhalation is 0.2–1.0 µg/day in urban areas and 0.1–0.4 µg/day in rural areas. The mainstream smoke of one cigarette contains about 0.04–0.58 µg of Ni.</li> <li>• Food: Daily dietary intakes of Ni were 0.14–0.15 mg in the United Kingdom in 1981–1984, 0.082 mg in Sweden in 1987, 0.16 mg (mean; 95% fractile, 0.27 mg) in Denmark, and 0.16 mg in the USA.</li> <li>• Water generally contributes 0.005–0.025 mg daily (i.e., 2–11% of the total daily oral intake of Ni)</li> </ul> <p>There is a great deal of concordance between the different studies of dietary intake, with the overall assessment that diet provides less than 0.2 mg/day.</p>

Agency Report Reference: *WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.*

Agency Report Reference: *WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.*

Risk Summary	Any risks to human health from drinking water identified in agency document?	2007 & 2021: No. The acute exposure from a glass of tap water (c.a. 200 ml) was 0.26 µg/kg bw and the MOE is about 16. Considering that the systemic contact dermatitis elicited in the Jensen et al. (2003) study was associated with a bolus exposure with higher concentration of Ni under fasted conditions, in contrast to the intermittent nature of a normal drinking-water exposure scenario, the MOE value for the acute scenario will be of low health concern. Daily drinking of the water at the chronic health-based value concentration (80 µg/L) of Ni therefore does not raise a significant acute nor long term health concern.
	Any emerging risks identified?	2007 & 2021: No.

#### References:

EU (2004) Nickel sulphate risk assessment. Draft, May 2004. Prepared by the Danish Environmental Protection Agency for the European Union (EU).

EU (2008). European Union risk assessment report: nickel and nickel compounds. Luxembourg: European Union (EU). *As cited in WHO 2021.*

Jensen, C.S., Menne, T., Lisby, S., Kristiansen, J. and Veien, N.K. (2003). Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Dermatitis*, 49, 124–132. *As cited in WHO 2021.*

Nielsen, G.D., Søderberg, U., Jørgensen, P.J., Templeton, D.M., Rasmussen, S.N., Andersen, K.E., et al. (1999). Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity. *Toxicol Appl Pharmacol.* 154(1):67–75. *As cited in WHO 2021.*

SLI (Springborn Laboratories, Inc.) (2000) An oral (gavage) two-generation reproduction toxicity study in Sprague–Dawley rats with nickel sulphate hexahydrate. Prepared by SLI, Spencerville, Ohio, for Nickel Producers Environmental Research Association, Durham, North Carolina (Study No. 3472.2).; *As cited in WHO 2021.*

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

## Exposure-Related Information for Nickel

## FSANZ 2008

Agency Report Reference: <i>FSANZ (2008). 22nd Australian Total Diet Study. August 2008. Food Standards Australia New Zealand (FSANZ).</i>		
General Information	Date of data extraction	19/11/2021
	Authors	Not stated
	Publication date	August 2008
	Publication type	Agency review
	Country of origin	Australia
	Description	Contains relevant information on Ni tolerable intake in Australian diets (may or may not be relevant for context). No guidance / guideline values derived in this document.
Exposure considerations	Principal routes of exposure in general population	Ni is a trace metal, which is widespread in soil, water and air due to both natural and human processes. Small quantities of Ni are present in food by virtue of its absorption and metabolism by plants and microorganisms. While Ni can be absorbed via inhalation and through the skin, food is the dominant source of exposure for the general population, with water generally being a minor contributor to total intake.
	Findings	<ul style="list-style-type: none"> <li>In humans, Ni is poorly absorbed from the gastrointestinal tract. It was determined that absorbed Ni was less-than 1% of the dose ingested in food. In contrast, an approximately 30-fold higher absorption occurred when the same dose of Ni was ingested via drinking water. Similar findings have been reported in laboratory animals. It is known that Ni absorption can be affected by intake of other foods such as milk, tea, coffee and orange juice.</li> <li>Major contributors to dietary intake of Ni were bread, cake, peanut butter, cereal, chocolate and tea.</li> <li>Oral exposure to Ni has been shown to cause hypersensitivity (e.g. in the form of hand eczema) in people previously sensitised via the dermal route to metallic Ni or Ni salts with oral doses as low as 500 µg/day causing a positive response in sensitive individuals.</li> <li>Up to the age of 7-8, boys and girls had similar intakes. A divergence appeared during adolescence and led to different levels in adulthood, with men consuming an average of around 150 µg/day and women only around 115 µg/day. Adult intakes in Australia seem to be higher than in the US where adult intakes have been estimated to fall in the range 79-105 µg/day, but lower than Canada where studies report that adults consume between 207-406 µg/day.</li> </ul>

## ICON Water 2019, 2020

Agency Report Reference: *ICON Water (2019). Drinking Water Quality Report 2018-19. ICON Water. Canberra.*

*ICON Water (2020). Drinking Water Quality Report 2019-20. ICON Water. Canberra.*

General Information	Date of data extraction	10/11/2021
	Authors	Not stated
	Publication date	2019-2020
	Publication type	Drinking Water Corporation report.
	Description	No guidance value derived in this document <i>per se</i> but contains relevant information on Ni exposure levels in Australian drinking water supply system (may or may not be relevant for context).
	Findings <sup>1</sup>	Australian Drinking Water Guideline): 0.02 mg/L Minimum: <0.001 mg/L Maximum: 0.003 mg/L Mean: <0.001 mg/L 95 <sup>th</sup> percentile: <0.001 mg/L
<sup>1</sup> Summary data for all drinking water quality zones in the supply system		

## Melbourne Water 2021

Agency Report Reference: *Melbourne Water (2021). Testing Water Quality. Melbourne Water.*

General Information	Date of data extraction	10/11/2021
	Authors	Not stated
	Publication date	2021
	Publication type	Drinking Water testing report.
	Description	No guidance value derived in this document <i>per se</i> but contains relevant information on Ni exposure levels in Australian drinking water supply system (may or may not be relevant for context).
	Findings <sup>1</sup>	Australian Drinking Water Guideline: 0.02 mg/L Mean: <0.001 mg/L
<sup>1</sup> Summary data for all drinking water quality zones in the supply system		

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

Agency Report Reference: <i>See bibliography</i>		
General Information	Date of data extraction	10/11/2021
	Authors	Not stated.
	Publication date	2005-2020
	Publication type	Drinking Water Corporation report.
	Description	No guidance value derived in this document <i>per se</i> but contains relevant information on Ni exposure levels in Australian drinking water supply system (may or may not be relevant for context).
	Findings <sup>1</sup>	Australian Drinking Water Guideline: 0.02 mg/L Range of means: 0.001 – 0.015 mg/L
<sup>1</sup> Summary data for all drinking water quality zones in the supply system		

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

Agency Report Reference: <i>See bibliography</i>		
General Information	Date of data extraction	10/11/2021
	Authors	Not stated.
	Publication date	2021
	Publication type	Drinking Water report.
	Description	No guidance value derived in this document <i>per se</i> but contains relevant information on Ni exposure levels in Australian drinking water supply system (may or may not be relevant for context).
	Findings <sup>1</sup>	Australian Drinking Water Guideline: 0.02 mg/L Mean: <0.001 mg/L
<sup>1</sup> Summary data for all drinking water quality zones in the supply system		

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

Agency Report Reference: <i>See bibliography</i>		
General Information	Date of data extraction	11/11/2021
	Authors	Jes Temby, Luc Richard, Frances Smith, Ailsa Sypkes, Michael Brewster
	Publication date	2014-2020
	Publication type	Drinking Water Corporation report.
	Description	No guidance value derived in this document <i>per se</i> but contains relevant information on Ni exposure levels in Australian drinking water supply system (may or may not be relevant for context).

Agency Report Reference: <i>See bibliography</i>		
	Findings <sup>1</sup>	Australian Drinking Water Guideline (health): 0.02 mg/L Mean range: <0.0005 – 0.003 mg/L Minimum range: <0.0005 – 0.0007 mg/L Maximum range: 0.0005 – 0.007 (0.0226) mg/L <sup>(2)</sup>
<p><sup>1</sup>Summary data for all drinking water quality zones in the supply system</p> <p><sup>2</sup>04/05/2015 During this reporting period samples exceeded the ADWG health limit for Ni at Rosebery drinking water system. Total Ni 0.0226 mg/L. Seen as a one off result, not representative of water in the system. Weekly flushing and weekly sampling of the reticulation failed to detect any other occurrences.</p>		

## Chapman et al. 2008

Agency Report Reference: <i>Chapman H, Cartwright T, Huston R, and O'Toole (2008). Water quality and health risks from urban rainwater tanks. Research Report 42. Cooperative Research Centre for Water Quality and Treatment. CRC for Water Quality and Treatment 2008.</i>		
General Information	Date of data extraction	11/11/2021
	Authors	Heather Chapman, Tony Cartwright, 2, Rob Huston, and Joanne O'Toole
	Publication date	2008
	Publication type	Research report No 42.
	Description	No guidance value derived in this document <i>per se</i> but contains relevant information on Ni exposure levels in Australian drinking water supply system (may or may not be relevant for context).
	Findings	Total detected: 18 Total tested: 69 Mean: 0.002 mg/L Minimum: 0.0005 mg/L Maximum: 0.005 mg/L ADWG Limit: 0.02 mg/L

**APPENDIX C**

Existing guideline/guidance assessment tables



## Criteria for assessing existing guidance or guidelines

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

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

### EFSA 2015 a, b, c

**Agency Report Reference: EFSA (2015a). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.**

**Agency Report Reference: EFSA (2015a). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.**

**Agency Report Reference: EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.**

Criteria	Y/N/?/NA	Notes
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	Yes (EFSA 2009).
Are the administrative processes documented and publicly available?	Y	Yes. Documented in various different guidance documentation (e.g. EFSA 2009, 2017a, 2018a, 2019d).
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Yes. EFSA sets up a Working Group of experts to carry out the risk assessment. The Working Group typically comprises members of the EFSA Panel plus additional scientists from specialist fields (EFSA 2019c). A Scientific Committee of EFSA has the task of supporting the work of the Panels. EFSA's Director of Science appoints a group of high level external scientists to audit the quality of experts that have applied to be members of scientific Panels or Committees (EFSA 2006).
Are funding sources declared?	N	Not stated.

Criteria	Y/N/?/NA	Notes
Was there public consultation on this work? If so, provide details.	Y	Yes, EFSA often holds public consultations on a case-by-case basis for draft outputs and consider comments received in the revised document (EFSA 2019c). All comments received during the public consultation process are published together with a report outlining EFSA's response to the points raised (EFSA 2017c).
Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	According to a preliminary implementation plan written in 2015 (EFSA 2015d), an external peer review system is likely to have been put in place in the last few years. In 2007, a proposal document was published for various levels of peer review (EFSA 2007). Examples of technical documents consulted for this report contain acknowledgment of the peer reviewer, but peer review comments do not appear to be publicly available (EFSA 2016b). In other cases, e.g. EFSA (2018c), a separate document with expert peer review comments has been made publicly available. Within its regulatory remit, EFSA itself performs an independent scientific peer review of the pesticide assessment reports produced by designated EU rapporteur Member states (EFSA 2015e).
Was the guidance/advice developed or updated recently? Provide details.	Y	A new updated document was released recently
Evidence review parameters		
Are decisions about scope, definitions and evidence review parameters documented and publicly available?	Y	Yes. (Refer to EFSA 2015c).
Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	Y	Yes (EFSA 2009).
Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	Y	Yes (EFSA 2009, 2010a, 2012d). There is EFSA guidance available on how and when systematic reviews can/should be undertaken (EFSA 2010a, 2012d). Although a particular question may be identified as being answerable using a systematic review, it does not necessarily follow that a systematic review would be worthwhile or practically feasible (EFSA 2010a). Cost, timing, resource requirements, and the need for integrating conflicting results are all factors.
If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	Yes (EFSA 2009). Proprietary studies are only considered when EFSA undertakes risk assessments under its regulatory remit, e.g. for pesticides.
Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	Y	

Criteria	Y/N/?/NA	Notes
Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	NA	
Can grey literature such as government reports and policy documents be included?	Y	Yes. However, personal communications are cited only in specific instances where the information provided is highly pertinent to the issue in question and fulfils scientific criteria (EFSA 2009).
Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	-
<b>Evidence search</b>		
Are databases and other sources of evidence specified?	Y	Yes (EFSA 2009). All references also cited in bibliography.
Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	Y	Yes. Guidance is provided in EFSA (2010a).
Is it specified what date range the literature search covers? Is there a justification?	Y	Yes. (Refer to EFSA 2015c).
Are search terms and/or search strings specified?	Y	Yes (refer to EFSA 2015c)
Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	Y	Yes (refer to EFSA 2015c)
<b>Critical appraisal methods and tools</b>		
Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	Y	Data from all sources is evaluated to determine their quality and relevance to the assessment. This is reflected in the relative weight given to the data in the assessment and taken into account in the overall evaluation of uncertainty (EFSA 2009). When a systematic review is deemed feasible and desirable, EFSA (2010a) provides guidance on how to assess methodological & reporting quality of studies.
Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	Y	
Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	Y	
<b>Derivation of health-based guideline values</b>		
Is there justification for the choice of uncertainty and safety factors?	Y	Yes. (refer to EFSA 2015b)
Are the parameter value assumptions documented and explained?	Y	Yes. Default values are provided in EFSA (2012b), but deviations from defaults are explained in individual assessments.

Criteria	Y/N/?/NA	Notes
Are the mathematical workings/algorithms clearly documented and explained?	Y	Yes, as exhibited in example risk assessments (EFSA 2008, 2010b, 2018c, 2018d, 2018e).
Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	NA	No, non-health related matters do not appear to be considered in guideline development. Recorded as 'not applicable'.
Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	Yes (EFSA 2017f).
What processes are used when expert judgement is required and applied? Is the process documented and published?	Y	EFSA (2014) provides guidance on this matter. Guidance on conducting weight of evidence assessments is also provided (EFSA 2017g).
Is dose response modelling (e.g. BMDL) routinely used?	Y	Yes if data permits, after it was recommended for use by EFSA in 2009 and re-affirmed for its relevance in 2017 (EFSA 2012, 2017e).
What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	Y	Yes (EFSA 2012). Until 2005, the advice given by EFSA was to reduce exposures to such substances to a level that is as low as reasonably achievable (ALARA principle). Since then, EFSA has employed a margin of exposure (MOE) approach using a BMDL10 for cancer incidence in animals or humans.
If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	NA	-
<p><b>Summary:</b>  Total # of 'Must-Have' criteria met (or not applicable): 19/20 = 95 %  Total # of 'Should-Have' criteria met (or not applicable): 10/10 = 100%  Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100%</p>		

**References:**

EFSA (2006). Transparency in risk assessment carried out by EFSA: guidance document on procedural aspects. Prepared by a working group consisting of members of the Scientific Committee and various EFSA Departments, European Food Safety Authority. EFSA Journal 2006; 353: 1-16.

EFSA (2007). Scientific advice by the Scientific Committee (Question No EFSA-Q-2007-060) adopted by written procedure on 3 August 2007. Proposal for a review system for EFSA's scientific activities. European Food Safety Authority. The EFSA Journal 2007. 526: 1-15.

EFSA (2008). Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. Scientific opinion of the Panel on Contaminants in the Food Chain. European Food Safety Authority. Question No EFSA-Q-2004-163. EFSA Journal 653: 1-131. <http://www.efsa.europa.eu/en/efsajournal/doc/653.pdf>.

EFSA (2009). Transparency in risk assessment - scientific aspects. Guidance of the Scientific Committee on Transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles. Question No EFSA-Q-2005-050Ba. European Food Safety Authority. EFSA Journal 2009; 1051: 1-22.

EFSA (2010a). Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Guidance for those carrying out systematic reviews. European Food Safety Authority. EFSA Journal 2010; 8(6): 1637.

EFSA (2010b). Scientific opinion on lead in food. EFSA Panel on Contaminants in the Food Chain, European Food Safety Authority. EFSA Journal 2010. 8(4): 1570.

EFSA (2012b). Scientific opinion. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. European Food Safety Authority. The EFSA Journal. 10(3): 2579. <http://www.efsa.europa.eu/en/search/doc/2579.pdf>.

EFSA (2012c). Scientific opinion. Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Scientific Committee, European Food Safety Authority. The EFSA Journal 2012. 10(3): 2578.

EFSA (2012d). External scientific report: Implementation of systematic reviews in EFSA scientific outputs workflow (CFT/EFSA/AMU/2010/01). European Food Safety Authority. Supporting publications. 2012. EN-367.

EFSA (2014). Guidance of EFSA. Guidance on expert knowledge elicitation in food and feed safety risk assessment. European Food Safety Authority. The EFSA Journal 2014. 12(6): 3734.

EFSA (2015d). Preliminary implementation plan transformation to an "Open EFSA". European Food Safety Authority. 27 March 2015. [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/openefsapreliminaryimplementationplan150327.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/openefsapreliminaryimplementationplan150327.pdf).

EFSA (2015e). Decision of the Executive Director of the European Food Safety Authority concerning pesticides risk assessment peer review. European Food Safety Authority. [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/eddecisionppr.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/eddecisionppr.pdf).

EFSA (2016b). Review of proposed MRLs, safety evaluation of products obtained from animals treated with zilpaterol and evaluation of the effects of zilpaterol on animal health and welfare. European Food Safety Authority. EFSA Journal 2016. 14(9): 4579.

EFSA (2017a). Guidance on risk assessment of substances present in food intended for infants below 16 weeks of age. European Food Safety Authority. Adopted 26 April 2017. EFSA Journal 2017; 15(5):4849. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4849>.

EFSA (2017f). Guidance on the assessment of the biological relevance of data in scientific assessments. EFSA Scientific Committee, European Food Safety Authority. EFSA Journal 2017. 15(8): 4970.

EFSA (2017c). Decision of the Management Board of the European Food Safety Authority concerning the establishment and operations of the Scientific Committee, Scientific Panels and of their Working Groups. European Food Safety Authority. Decision No.: mb17033-a4. Effective date: 01/06/2017. <http://www.efsa.europa.eu/sites/default/files/paneloperation170601.pdf>.

EFSA (2017g). Guidance on the use of the weight of evidence approach in scientific assessments. EFSA Scientific Committee, European Food Safety Authority. EFSA Journal 2017. 15(8): 4971.

EFSA (2018a). Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health. European Food Safety Authority. Adopted 29 May 2018. EFSA Journal 2018; 16(7):5327. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5327>.

EFSA (2018c). Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. European Food Safety Authority. EFSA Journal. 16(5): 5194.

EFSA (2018d). Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. European Food Safety Authority. EFSA Journal. 16(11): 5333.

EFSA (2018e). Update of the Scientific Opinion on opium alkaloids in poppy seeds. European Food Safety Authority. EFSA Journal 2018. 16(5): 5243.

EFSA (2019a). Chemical contaminants (webpage). European Food Safety Authority. No date on webpage.. <http://www.efsa.europa.eu/en/topics/topic/chemical-contaminants>

EFSA (2019c). Working practices (webpage). European Food Safety Authority. No date on webpage. <http://www.efsa.europa.eu/en/howwework/workingpractices>

Criteria	Y/N/?/NA	Notes
EFSA (2019d). Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. European Food Safety Authority. Adopted 20 February 2019. EFSA Journal 2019; 17(3):5634. <a href="https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5634">https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5634</a> .		

## EFSA 2020 a, b

**EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.**

**EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.**

Criteria	Y/N/?/NA	Notes
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	Yes (EFSA 2009).
Are the administrative processes documented and publicly available?	Y	Yes (refer to EFSA 2020b). Documented in various different guidance documentation (e.g. EFSA 2009, 2017a, 2018a, 2019d).
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Yes (refer to EFSA 2020b). EFSA sets up a Working Group of experts to carry out the risk assessment. The Working Group typically comprises members of the EFSA Panel plus additional scientists from specialist fields (EFSA 2019c). A Scientific Committee of EFSA has the task of supporting the work of the Panels. EFSA's Director of Science appoints a group of high level external scientists to audit the quality of experts that have applied to be members of scientific Panels or Committees (EFSA 2006).
Are funding sources declared?	N	Not stated.
Was there public consultation on this work? If so, provide details.	Y	Yes (refer to EFSA 2020b). EFSA often holds public consultations on a case-by-case basis for draft outputs and consider comments received in the revised document (EFSA 2019c). All comments received during the public consultation process are published together with a report outlining EFSA's response to the points raised (EFSA 2017c).

Criteria	Y/N/?/NA	Notes
<p>Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?</p>	Y	<p>Yes (refer to EFSA 2020b). According to a preliminary implementation plan written in 2015 (EFSA 2015a), an external peer review system is likely to have been put in place in the last few years. In 2007, a proposal document was published for various levels of peer review (EFSA 2007). Examples of technical documents consulted for this report contain acknowledgment of the peer reviewer, but peer review comments do not appear to be publicly available (EFSA 2019e, 2016b). In other cases, e.g. EFSA (2018c), a separate document with expert peer review comments has been made publicly available. Within its regulatory remit, EFSA itself performs an independent scientific peer review of the pesticide assessment reports produced by designated EU rapporteur Member states (EFSA 2015b).</p>
<p>Was the guidance/advice developed or updated recently? Provide details.</p>	NA	-
Evidence review parameters		
<p>Are decisions about scope, definitions and evidence review parameters documented and publicly available?</p>	Y	Yes (refer to EFSA 2020b). (Also refer to EFSA 2020b).
<p>Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?</p>	Y	Yes (EFSA 2009).
<p>Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?</p>	Y	<p>Yes (refer to EFSA 2020b). Also refer to EFSA 2009, 2010a, 2012d. There is EFSA guidance available on how and when systematic reviews can/should be undertaken (EFSA 2010a, 2012d). Although a particular question may be identified as being answerable using a systematic review, it does not necessarily follow that a systematic review would be worthwhile or practically feasible (EFSA 2010a). Cost, timing, resource requirements, and the need for integrating conflicting results are all factors.</p>
<p>If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?</p>	Y	Yes (EFSA 2009). Proprietary studies are only considered when EFSA undertakes risk assessments under its regulatory remit, e.g. for pesticides.
<p>Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?</p>	Y	If there are, these are specified when appropriate (EFSA 2010a).
<p>Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?</p>	Y	Reference is made to other organisations evaluations (refer to EFSA 2020a)
<p>Can grey literature such as government reports and policy documents be included?</p>	Y	Yes. However, personal communications are cited only in specific instances where the information provided is highly pertinent to the issue in question and fulfils scientific criteria (EFSA 2009).

Criteria	Y/N/?/NA	Notes
Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	Yes (refer to EFSA 2020a)
Evidence search		
Are databases and other sources of evidence specified?	Y	Yes (EFSA 2009). All references also cited in bibliography.
Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	Y	Yes. Guidance is provided in EFSA (2010a).
Is it specified what date range the literature search covers? Is there a justification?	Y	Yes. A literature search has been performed under the current mandate in order to locate new information since the publication of the previous Opinion. The new information has been evaluated in the current Opinion. (Refer to EFSA 2020a). Also refer to EFSA 2010a.
Are search terms and/or search strings specified?	Y	
Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	Y	
Critical appraisal methods and tools		
Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	Y	Data from all sources is evaluated to determine their quality and relevance to the assessment. This is reflected in the relative weight given to the data in the assessment and taken into account in the overall evaluation of uncertainty (EFSA 2009). When a systematic review is deemed feasible and desirable, EFSA (2010a) provides guidance on how to assess methodological & reporting quality of studies.
Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	Y	
Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	Y	
Derivation of health-based guideline values		
Is there justification for the choice of uncertainty and safety factors?	Y	Yes. (refer to EFSA 2020a)
Are the parameter value assumptions documented and explained?	Y	Yes. Default values are provided in EFSA (2012b), but deviations from defaults are explained in individual assessments.
Are the mathematical workings/algorithms clearly documented and explained?	Y	Yes, as exhibited in example risk assessments (EFSA 2008, 2010b, 2018c, 2018d, 2018e).
Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	NA	No, non-health related matters do not appear to be considered in guideline development. Recorded as 'not applicable'.
Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	Yes (EFSA 2017f). Judgement is referred to in EFSA responses to stakeholder comments (EFSA 2020b)

Criteria	Y/N/?/NA	Notes
What processes are used when expert judgement is required and applied? Is the process documented and published?	Y	EFSA (2014) provides guidance on this matter. Guidance on conducting weight of evidence assessments is also provided (EFSA 2017g).
Is dose response modelling (e.g. BMDL) routinely used?	Y	Yes if data permits, after it was recommended for use by EFSA in 2009 and re-affirmed for its relevance in 2017 (EFSA 2012, 2017e).
What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	Y	Yes (EFSA 2012). Until 2005, the advice given by EFSA was to reduce exposures to such substances to a level that is as low as reasonably achievable (ALARA principle). Since then, EFSA has employed a margin of exposure (MOE) approach using a BMDL10 for cancer incidence in animals or humans.
If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	NA	-
<p><b>Summary:</b>  Total # of 'Must-Have' criteria met (or not applicable): 19/20 = 95 %  Total # of 'Should-Have' criteria met (or not applicable): 10/10 = 100%  Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100%</p>		

**References:**

EFSA (2006). Transparency in risk assessment carried out by EFSA: guidance document on procedural aspects. Prepared by a working group consisting of members of the Scientific Committee and various EFSA Departments, European Food Safety Authority. EFSA Journal 2006; 353: 1-16.

EFSA (2007). Scientific advice by the Scientific Committee (Question No EFSA-Q-2007-060) adopted by written procedure on 3 August 2007. Proposal for a review system for EFSA's scientific activities. European Food Safety Authority. The EFSA Journal 2007. 526: 1-15.

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EFSA (2009). Transparency in risk assessment - scientific aspects. Guidance of the Scientific Committee on Transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles. Question No EFSA-Q-2005-050Ba. European Food Safety Authority. EFSA Journal 2009; 1051: 1-22.

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EFSA (2010b). Scientific opinion on lead in food. EFSA Panel on Contaminants in the Food Chain, European Food Safety Authority. EFSA Journal 2010. 8(4): 1570.

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EFSA (2016b). Review of proposed MRLs, safety evaluation of products obtained from animals treated with zilpaterol and evaluation of the effects of zilpaterol on animal health and welfare. European Food Safety Authority. EFSA Journal 2016. 14(9): 4579.

EFSA (2017a). Guidance on risk assessment of substances present in food intended for infants below 16 weeks of age. European Food Safety Authority. Adopted 26 April 2017. EFSA Journal 2017; 15(5):4849. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4849>.

Criteria	Y/N/?/NA	Notes
EFSA (2017c). Decision of the Management Board of the European Food Safety Authority concerning the establishment and operations of the Scientific Committee, Scientific Panels and of their Working Groups. European Food Safety Authority. Decision No.: mb17033-a4. Effective date: 01/06/2017. <a href="http://www.efsa.europa.eu/sites/default/files/paneloperation170601.pdf">http://www.efsa.europa.eu/sites/default/files/paneloperation170601.pdf</a> .		
EFSA (2017e). Update: use of the benchmark dose approach in risk assessment. EFSA Scientific Committee, European Food Safety Authority. EFSA Journal 2017. 15(1): 4658.		
EFSA (2017g). Guidance on the use of the weight of evidence approach in scientific assessments. EFSA Scientific Committee, European Food Safety Authority. EFSA Journal 2017. 15(8): 4971.		
EFSA (2018c). Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. European Food Safety Authority. EFSA Journal. 16(5): 5194.		
EFSA (2018d). Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. European Food Safety Authority. EFSA Journal. 16(11): 5333.		
EFSA (2018e). Update of the Scientific Opinion on opium alkaloids in poppy seeds. European Food Safety Authority. EFSA Journal 2018. 16(5): 5243.		
EFSA (2019c). Working practices (webpage). European Food Safety Authority. No date on webpage. <a href="http://www.efsa.europa.eu/en/howwework/workingpractices">http://www.efsa.europa.eu/en/howwework/workingpractices</a> .		
EFSA (2019d). Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. European Food Safety Authority. Adopted 20 February 2019. EFSA Journal 2019; 17(3):5634. <a href="https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5634">https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5634</a> .		

## OEHHA 2001

**Agency Report Reference: OEHHA (2001). Public Health Goals for Chemicals in Drinking Water – Nickel. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.**

Criteria	Y/N/?/NA	Notes
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	The process for OEHHA Public Health Goal (PHG) development is: <ul style="list-style-type: none"> <li>• Literature search/review.</li> <li>• Critical endpoint/study selection.</li> <li>• Dose-response analysis.</li> <li>• Exposure assessment.</li> <li>• Risk characterisation.</li> <li>• Calculation of health-protective concentration for contaminant in drinking water.</li> </ul> These stages of the risk assessment framework are compatible with the Australian risk assessment process.
Are the administrative processes documented and publicly available?	Y	A preface has been provided with the document that outlines the administrative processes for preparing the technical document.
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	?	Not a committee <i>per se</i> however the PHG technical support document for Ni was discussed at the PHG workshop held on November 5, 1999, or as revised following the workshop (OEHHA 2001b). Although not stated, potential conflicts of interest are managed through the University of California contract as part of the process for acquiring peer reviewers. OEHHA is not involved in the selection of peer reviewers.
Are funding sources declared?	N	Funding sources are not declared in the report.
Was there public consultation on this work? If so, provide details.	Y	Not stated in the document. The first drafts of the documents were posted on the OEHHA Web site on October 8, 1999, and the second drafts have been posted on the OEHHA Web site since February 11, 2000. In addition, a one-day public workshop was held on November 5, 1999, at the auditorium in the Elihu Harris Building, 1515 Clay Street, Oakland, California to discuss the scientific basis and recommendations in the draft documents (OEHHA 2001b).
Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	Yes. OEHHA thanked the U.S. Environmental Protection Agency (Office of Water; National Center for Environmental Assessment) and faculty members of the University of California for their peer reviews of the PHG document, and acknowledged comments were received from other interested parties. Comments were also received from industry (OEHHA 2001b).

Criteria	Y/N/?/NA	Notes
Was the guidance/advice developed or updated recently? Provide details.	NA	-
Evidence review parameters		
Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Not clear from the document reviewed.
Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	NA	No, all valid studies are considered.
Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	?	For this review, the literature searches undertaken are not detailed so it is not known if the review has been undertaken systematically. PHG scientists have typically undertaken literature searches. Review of the information has been based on expert scientific judgment. However OEHHA is increasingly incorporating more systematic/methodological processes (e.g., evidence mapping) for selection of key studies.
If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	Yes. PHG technical support documents provide summaries of studies but not raw data. Nonetheless, companies and other entities are informed that any information submitted to OEHHA will become public information.
Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	Not detailed in document.
Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	NA	-
Can grey literature such as government reports and policy documents be included?	Y	Yes, but its role in the risk assessment would depend on the quality of the data.
Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	-
Evidence search		
Are databases and other sources of evidence specified?	Y (1/2)	Databases not specified, but all references also cited in bibliography.
Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	NA	Not stated.
Is it specified what date range the literature search covers? Is there a justification?	N	However, the bibliography lists references up to the year 2000.
Are search terms and/or search strings specified?	N	Not stated.
Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	NA	-

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

Criteria	Y/N/?/NA	Notes
<p><b>Summary:</b>            Total # of 'Must-Have' criteria met (or not applicable): 12.5/20 = 63 %            Total # of 'Should-Have' criteria met (or not applicable): 6.5/10 = 65%            Total # of 'May-Have' criteria met (or not applicable): 1/2 = 50%</p>		
<p><b>References:</b>            OEHHA (2001b). Responses to Major Comments on Technical Support Document. Public Health Goal for Nickel In Drinking Water. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.</p> <p>OEHHA (2006c). Second Public Comment Period for the Proposed Public Health Goals for Cadmium, Glyphosate, N-Nitrosodimethylamine, and Water-Soluble Polychlorinated Biphenyls (PCBs) in Drinking Water. [Accessed 27/07/2021]. <a href="https://oehha.ca.gov/water/public-health-goal/second-public-comment-period-proposed-public-health-goals-cadmium">https://oehha.ca.gov/water/public-health-goal/second-public-comment-period-proposed-public-health-goals-cadmium</a></p>		

## WHO 2007, 2021

**WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.**

**WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.**

Criteria	Y/N/?/NA	Notes
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	-
Are the administrative processes documented and publicly available?	Y	Yes. Documented in various different guidance documentation (WHO 1987, 1990, 1994, 1999, 2006, 2009, 2017).
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Yes. By the Drinking-Water Quality Committee (DWQC) (WHO 2009). All 6 WHO regional offices participated in the process of the latest revision, in consultation with Member States (WHO 2017).

Criteria	Y/N/?/NA	Notes
Are funding sources declared?	Y	Although funding sources are not declared in the document, it is likely funded by the WHO.
Was there public consultation on this work? If so, provide details.	Y	The front matter of the text indicates the final version of the document takes into consideration comments from both peer reviewers and the public.
Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	The DWGs per se are the collective product of many experts and therefore the advice is internationally peer reviewed (WHO 2009). The peer review outcomes are not made publicly available, however they are retained by the WHO Secretariat (WHO 2009).
Was the guidance/advice developed or updated recently? Provide details.	Y	A draft document (WHO 2021) has been released for public consultation.
Evidence review parameters		
Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Not specified.
Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	NA	All valid studies appear to be considered. Validity appears to be determined by expert judgement.
Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	Unclear in this document.
If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	Unpublished proprietary data are referenced as such in reference lists, and where they form pivotal information they are described in detail.
Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	Not specified.
Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	NA	-
Can grey literature such as government reports and policy documents be included?	Y	Yes, where reviews are 'recognised of high quality' (WHO 2017).
Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	-
Evidence search		
Are databases and other sources of evidence specified?	Y (1/2)	Although the bibliography provides references for all literature consulted, the databases consulted for the literature review are not listed in the agency reviews.

Criteria	Y/N/?/NA	Notes
Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	NA	Unable to be ascertained from the information in the documents.
Is it specified what date range the literature search covers? Is there a justification?	N	Literature search details are not specified, however the dates of publications in the bibliography of the draft report (WHO 2021) cite reports between the years 1971 to 2020.
Are search terms and/or search strings specified?	N	Literature search details are not specified.
Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	NA	Literature search details are not specified.
<b>Critical appraisal methods and tools</b>		
Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	No information given regarding whether risk of bias assessment was undertaken for individual studies. However, the shortcomings of some studies (where identified by the authors) have been provided in the text.
Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	Not specified
Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	Not specified
<b>Derivation of health-based guideline values</b>		
Is there justification for the choice of uncertainty and safety factors?	Y	-
Are the parameter value assumptions documented and explained?	Y	-
Are the mathematical workings/algorithms clearly documented and explained?	Y (1/2)	They can be inferred from what is known about WHO drinking water guideline development.
Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	Y	For Ni, non-health related matters do not appear to be relevant (as there is no characteristic odour or taste associated with Ni in drinking water).
Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	Guidance documentation is not cited. However, guidance document does exist (FAO/WHO 2009, WHO 2005, 2007).
What processes are used when expert judgement is required and applied? Is the process documented and published?	N	Unclear from documentation consulted.
Is dose response modelling (e.g. BMDL) routinely used?	Y	Yes, where data permit and where a BMDL would provide greater confidence in the point of departure (WHO 2009). BMDL was used for Ni.

Criteria	Y/N/?/NA	Notes
<p>What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?</p>	NA	<p>For genotoxic carcinogens, the DWG represents an excess lifetime cancer risk of <math>1 \times 10^{-5}</math> for people drinking water containing the chemical at the DWG for 70 yrs (WHO 2009). Compounds shown to be a carcinogen are evaluated on a case-by-case basis, where evidence of genotoxicity &amp; human relevance is considered to determine correct approach for risk assessment (WHO 2009). Not done for Ni as not identified to be an oral genotoxic carcinogen.</p>
<p>If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?</p>	NA	-
<p><b>Summary:</b>            Total # of 'Must-Have' criteria met (or not applicable): 15/20 = 75%            Total # of 'Should-Have' criteria met (or not applicable): 6/10 = 60%            Total # of 'May-Have' criteria met (or not applicable): 2/2 = 100%</p>		

**References:**

FAO/WHO (2009). Environmental Health Criteria 240: Principles and methods for the risk assessment of chemicals in food. Chapter 5: Dose-response assessment and derivation of health-based guidance values. Geneva: A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. [http://www.inchem.org/documents/ehc/ehc/ehc240\\_chapter5.pdf](http://www.inchem.org/documents/ehc/ehc/ehc240_chapter5.pdf).

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

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

WHO (1987). Environmental Health Criteria 70: Principles for the safety assessment of food additives and contaminants in food. International Programme on Chemical Safety, World Health Organization, Geneva. <http://www.inchem.org/documents/ehc/ehc/ehc70.htm>.

WHO (1990). Environmental Health Criteria 104: Principles for the toxicological assessment of pesticides residues in food. International Programme on Chemical Safety, World Health Organization, Geneva. <http://www.inchem.org/documents/ehc/ehc/ehc104.htm>.

WHO (1994). EHC 170: Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits. International Programme on Chemical Safety, World Health Organisation: Geneva.

WHO (1999). Environmental Health Criteria 210: Principles for the assessment of risks to human health from exposure to chemicals. Geneva: World Health Organization. <http://www.inchem.org/documents/ehc/ehc/ehc210.htm>.

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

WHO (2006). Environmental Health Criteria 237: Principles for evaluating health risks in children associated with exposure to chemicals. World Health Organization, Geneva. <http://www.who.int/ipcs/publications/ehc/ehc237.pdf>.

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

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

Criteria	Y/N/?/NA	Notes
WHO (2017). Guidelines for drinking-water quality. Fourth edition incorporating the first Addendum. World Health Organization. Geneva. <a href="https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=8A179F96A66DD2F070E785831CAB3180?sequence=1">https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=8A179F96A66DD2F070E785831CAB3180?sequence=1</a>		

# APPENDIX D

Data extraction tables – Supporting Information in Factsheet

## Supporting Information in Nickel Factsheet

## ATSDR 2005

Agency Report Reference: <i>ATSDR (2005). Toxicological Profile for Nickel. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. August 2005.</i>		
General Description	Uses	Ni is primarily used in alloys because it imparts to a product such desirable properties as corrosion resistance, heat resistance, hardness, and strength. Ni alloys are often divided into categories depending on the primary metal with which they are alloyed and their Ni content. Copper- Ni alloys (e.g., Monel alloys) are used for industrial plumbing, marine equipment, petrochemical equipment, heat exchangers, pumps, and electrodes for welding. Coinage metal contains 75% copper and 25% Ni. Ni -chromium alloys (e.g., Nichrome) are used for heating elements. Ni -iron-chromium alloys (e.g., Inconel) provide strength and corrosion resistance over a wide temperature range.
	Sources in drinking water	The most probable route of exposure from hazardous waste sites would be from consumption of contaminated drinking water. There is no information linking this source of Ni contamination in groundwater to levels of Ni in drinking water that would be of concern (>50 µg/L).
	Other	-
Treatment of drinking water	Treatment technology	Ni may be removed by chemical precipitation or coagulation treatment in publicly owned treatment works.
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	The most common methods used to detect Ni in environmental samples are AAS, either flame or graphite furnace, ICP-AES, or ICP-MS. Ni in water and waste water samples can be analysed using ASTM Test Methods D1976 (ICP-AES) and D5673 (ICP-MS) or EPA Test Methods 249.1 (atomic absorption, direct aspiration), 249.2 (atomic absorption, furnace technique), 200.7 (ICP-AES), 200.8 (ICP-MS), 1638 (ICP-MS), and 200.12 (atomic absorption, graphite furnace technique), or a direct current plasma atomic emission spectrophotometric method.
	Limit of determination/ Limit of Reporting (LOR)	<ul style="list-style-type: none"> <li>Water: 0.2µg/L (AAS) or 0.082µg/L (ICP-OES)</li> <li>Drinking water: 4 (ICP-AES) - 15µg/L (ICP-MS)</li> <li>Water/wastewater: 0.04 - 40µg/L (AAS or ICP)</li> </ul>
	Other	Concentrations of Ni in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on Ni levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

**Agency Report Reference: ATSDR (2005). Toxicological Profile for Nickel. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. August 2005.**

Additional information	Any additional non-health related information considered important?	-
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## EFSA 2005

**Agency Report Reference: EFSA (2005). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Nickel. European Food Safety Authority (EFSA). The EFSA Journal (2005) 146, 1-21.**

General Description	Uses	Not discussed. Ni is essential for the catalytic activity of some plant and bacterial enzymes. It is said to influence iron absorption and metabolism and the haemopoietic process. However, biochemical functions of Ni have not been demonstrated in humans and higher animals.
	Sources in drinking water	Naturally found in the environment (leaching from soils etc.), pipes and fittings and emissions from industrial sites.
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Not stated.
	Limit of determination/ Limit of Reporting (LOR)	Not stated.
	Other	-
Additional information	Any additional non-health related information considered important?	-

## EFSA 2015a, b, c

**Agency Report Reference: EFSA (2015a). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.**

**Agency Report Reference: EFSA (2015b). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.**

**Agency Report Reference: EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.**

General Description	Uses	<p>Ni is primarily an alloy metal, and its main utilisation (61 %) is in the many varieties of Ni steels and Ni cast irons. The metal is used (26 %) in many industrial and consumer products such as AlNiCo magnets (typically 8–12 % Al, 15–26 % Ni, 5–24 % Co, ≤ 6 % Cu, ≤ 1 % Ti, and Fe to 100 %), coinage, rechargeable batteries, electric guitar strings, microphone capsules, and special alloys. Coinage may have a very high Ni content, close to 100 %. Ni foam or mesh is used for electrodes in alkaline fuel cells, while the metal itself or its alloys are frequently used as catalysts for hydrogenation reactions. Ni is also employed for electroplating (13 %) and other uses, namely in pigments and colours for ceramics and glassware, for Ni brasses and bronzes, in marine anti-fouling agents, and for alloys with aluminium, cobalt, chromium, copper, gold, lead, silver, and titanium. In particular, Ni may be present in white gold and in inexpensive alloys for fashion or junk jewellery (including piercing).</p> <p>Ni plating to strengthen metal against corrosion and wear as well as to improve its appearance was developed in the 1800s – quite before the development of commercial chrome plating – and has been used widely since the second half of the 19th century.</p>
	Sources in drinking water	<ul style="list-style-type: none"> <li>• Ni is a naturally occurring element due to a variety of processes; it is present in all compartments of the environment and ubiquitous in the biosphere.</li> <li>• Ni enters ambient waters primarily as Ni-containing particulate matter carried by rainwater and through the degradation/dissolution of primary bedrock materials and soils.</li> <li>• The main anthropogenic sources of Ni in water are primary Ni production, metallurgical processes, combustion and incineration of fossil fuels, chemical and catalyst production, and discharges of industrial and municipal wastes.</li> </ul>
	Other	Ni concentrations in surface marine waters were found to be sensitive to salinity and phosphorus concentration.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	--
	Other	-

**Agency Report Reference: EFSA (2015a). Scientific Opinion on the risks to animal and public health and the environment related to the presence of nickel in feed. European Food Safety Authority (EFSA). EFSA Journal 2015;13(4):4074.**

**Agency Report Reference: EFSA (2015b). Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2015;13(2):4002.**

**Agency Report Reference: EFSA (2015c). Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. European Food Safety Authority (EFSA). Supporting Publications 2015:EN-478.**

Measurement	Analytical method	The most common methods used to detect Ni in food and water samples, with or without preconcentration or separation steps, are atomic absorption spectrometry (AAS), either flame or graphite furnace (FAAS, GFAAS), inductively coupled plasma optical/atomic emission or mass spectrometry (ICP-OES/ICP-AES or ICP-MS), followed by spectrophotometric techniques (ultra-violet (UV)-visible absorption, photodiode array
	Limit of determination/ Limit of Reporting (LOR)	In water samples, the limit of detection (LOD) ranged from 0.05 µg/L to 1.05 µg/L depending on the pre-concentration and the detection techniques used. Analytical techniques with a LOD > 2 µg/L do not comply with Council Directive 98/83/EC.
	Other	-
Additional information	Any additional non-health related information considered important?	-

## EFSA 2020 a, b

**Agency Report Reference: EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.**

**EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.**

General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	--
Measurement	Analytical method	Flame or graphite furnace with atomic absorption spectrometry (F- or GF-AAS), and, increasingly, inductively coupled plasma-optical/atomic emission spectrometry (ICP-OES/ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS) are the most common analytical techniques suitable for the determination of total Ni in foods and drinking water.
	Limit of determination/ Limit of Reporting (LOR)	The limits of detection (LODs) in water samples range from 0.05 to 1.0 µg/L depending on the analytical techniques used.
	Other	-

**Agency Report Reference: EFSA (2020a). Update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Journal 2020;18(11):6268.**  
**EFSA (2020b). Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water. European Food Safety Authority (EFSA). EFSA Supporting publication 2020:EN-1940.**

Additional information	Any additional non-health related information considered important?	-
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**OEHHA 2001**

**Agency Report Reference: OEHHA (2001). Public Health Goals for Chemicals in Drinking Water – Nickel. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. August 2001.**

General Description	Uses	Ni is a natural occurring element; it is neither created nor destroyed by human activities. It is a commercially important metal because of its hardness, strength, and resistance to corrosion. Ni production can be referred to as either primary or secondary depending on the source of the raw material. Primary Ni is produced by the mining and smelting of Ni ores. More than 80 percent of all Ni is used in its metallic form, principally as Ni -alloys.
	Sources in drinking water	Ni enters groundwater and surface water by dissolution of rocks and soils, from atmospheric fallout, from biological decays and from waste disposal.
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	The detection limit for the purposes of reporting for Ni is 10 µg/L (10 ppb).
	Other	-
Additional information	Any additional non-health related information considered important?	-

**WHO 2007, 2021**

**Agency Report Reference: WHO (2007). Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organisation.**  
**WHO (2021). Nickel in drinking water. Background document for development of WHO Guidelines for drinking-water quality. Version for public review. 25 May 2021.**

General Description	Uses	Ni is used mainly in the production of stainless steels, non-ferrous alloys and super alloys. Other uses of Ni and Ni salts are in electroplating, as catalysts, in Ni–cadmium batteries, in coins, in welding products, and in certain pigments and electronic products. It is estimated that 8% of Ni is used for household appliances. Ni is also incorporated in some food supplements, which can contain several micrograms of Ni per tablet.
	Sources in drinking water	The primary source of Ni in drinking-water is leaching from metals that are in contact with drinking-water, such as in pipes and fittings. Ni enters ambient waters primarily as Ni -containing particulate matter carried by rainwater and through the degradation/dissolution of Ni -containing rocks and soils. The main anthropogenic sources of Ni in water are primarily Ni production, metallurgical processes, combustion and incineration of fossil fuels, chemical and catalyst production, and discharges of industrial and municipal wastes.
	Other	-
Treatment of drinking water	Treatment technology	Conventional surface water treatment, comprising chemical coagulation, sedimentation and filtration, can achieve 35–80% removal of Ni, depending on a number of factors including the coagulant dosage, the age of the activated carbon and pH . Better Ni removal may occur with waters containing high concentrations of humic substances; for waters low in solids, addition of powdered activated carbon can improve Ni removal. Increasing pH and the presence of high turbidity both favour Ni removal. The optimum pH for removal on activated carbon was reported to be pH 8. However, other studies have reported that Ni is rather poorly adsorbed on activated carbon.
	Effectiveness	
	Any special conditions?	-
	Other	-
Measurement	Analytical method	The two most commonly used analytical methods for Ni in water are atomic absorption spectrometry and inductively coupled plasma atomic emission spectrometry.
	Limit of determination/ Limit of Reporting (LOR)	Flame atomic absorption spectrometry is suitable in the range of 0.1–10 mg/L (ISO, 1986, reaffirmed in 2017). Inductively coupled plasma atomic emission spectrometry can be used for the determination of Ni with a limit of detection of about 10 µg/L.
	Other	-
Additional information	Any additional non-health related information considered important?	No.

## FSANZ 2008

Agency Report Reference: <i>FSANZ (2008). 22th Australian Total Diet Study. August 2008. Food Standards Australia New Zealand (FSANZ).</i>		
General Description	Uses	Not stated.
	Sources in drinking water	Not stated.
	Other	<ul style="list-style-type: none"> <li>Ni is an essential nutrient for certain microorganisms and is incorporated into several Ni-containing enzymes.</li> <li>A specific biological function for Ni has not yet been established in humans.</li> </ul>
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	Food samples: Inductively coupled plasma mass spectrometry (ICP-MS)
	Limit of determination	Soil: 0.01 mg/kg, Liquid: 0.001 mg/kg
	Other	-
Additional information	Any additional non-health related information considered important?	-

## ICON Water 2019, 2020

Agency Report Reference: <i>ICON Water (2019). Drinking Water Quality Report 2018-19. ICON Water. Canberra.</i>		
<i>ICON Water (2020). Drinking Water Quality Report 2019-20. ICON Water. Canberra.</i>		
General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	<1µg/L
	Other	-

Agency Report Reference: *ICON Water (2019). Drinking Water Quality Report 2018-19. ICON Water. Canberra.*

*ICON Water (2020). Drinking Water Quality Report 2019-20. ICON Water. Canberra.*

Additional information	Any additional non-health related information considered important?	-
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## Melbourne Water 2021

Agency Report Reference: *Melbourne Water (2021). Testing Water Quality. Melbourne Water.*

General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	<0.001mg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

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

Agency Report Reference: *See bibliography*

General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-

Agency Report Reference: <i>See bibliography</i>		
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	<0.002mg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

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

Agency Report Reference: <i>See bibliography</i>		
General Description	Uses	-
	Sources in drinking water	-
	Other	-
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	<0.001mg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

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

Agency Report Reference: <i>See bibliography</i>		
General Description	Uses	-
	Sources in drinking water	-
	Other	-
	Treatment technology	-

Agency Report Reference: <i>See bibliography</i>		
Treatment of drinking water	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	<0.0001mg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

## Chapman et al. 2008

Agency Report Reference: <i>Chapman H, Cartwright T, Huston R, and O'Toole (2008). Water quality and health risks from urban rainwater tanks. Research Report 42. Cooperative Research Centre for Water Quality and Treatment. CRC for Water Quality and Treatment 2008.</i>		
General Description	Uses	-
	Sources in drinking water	-
	Other	Compared to rainwater, when sampling the hot water tap Ni and lead have a large increase in incidence of detection and chromium a minor increase. All but one of the hot water systems sampled is supplied by the rainwater tank, so the increase can be directly compared to the incidence of detection in rainwater. Thus, after rainwater passes through the hot water system it is more likely to contain higher concentrations of chromium, lead and Ni than before.
Treatment of drinking water	Treatment technology	-
	Effectiveness	-
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination/ Limit of Reporting (LOR)	<0.004mg/L
	Other	-
Additional information	Any additional non-health related information considered important?	-

## Barloková et al 2021

*Barloková, D., Ilavský, J., Marton, M., Kunstek, M. (2019). Removal of Heavy Metals in Drinking Water by Iron-based Sorption Materials. IOP Conf. Ser.: Earth Environ. Sci. 362 (2019) 012109*

General Description	Uses	-
	Sources in drinking water	Heavy metals are a naturally occurring compound that is found in the environment. The sources of heavy metals in natural water may originate from geochemical reactions, uncontrolled industrial waste discharges, agricultural use of pesticides containing heavy metals, or chemical warfare.
	Other	-
Treatment of drinking water	Treatment technology	Sorption properties of granular iron-based sorption materials (CFH12, CFH18, Bayoxide E33, GEH) in removal of Ni from drinking water. Adsorption on a suitable adsorption material is the most frequently used methods in water treatment. In terms of plant operation, filtration (sorption) process represents a simple, effective and economical friendly method of heavy metals removal namely for the possibility of using a large scale of substances with a sorption ability – sorbents. Oxides, oxyhydroxides and hydroxide containing iron are among the most frequently used sorbents of the heavy metal removal.
	Effectiveness	According to the model tests (concentration of nickel in raw water of about 50 µg/L, filtration rate 5.8 m/h, concentration Ni 20 µg/L at the outlet of media, pH 7.0) the adsorption capacity of nickel for Bayoxide E33 was set to 198 µg/g, for CFH18 107.5 µg/g, GEH 97.5 µg/g and CFH12 38.1 µg/g. The limit of 20 µg/L of Ni was exceeded after 4808 BV for Bayoxide E33, 1409 BV for CFH12, 3007 BV for CFH18 and 3218 BV for GEH.  The concentration of nickel in raw water was in the range from 48.5 to 51.1 µg/L, Bayoxide E33 is the most suitable for nickel removal as compared to other tested sorption materials.
	Any special conditions?	-
	Other	The quality of the treated water (pH, silica, phosphorus, fluorides, sulphates, total mineralization, iron and manganese, organic matter, etc.), redox conditions, the valency of metal and filtration conditions has the impacts on heavy metal removing efficiency.
Measurement	Analytical method	ICP-MS
	Limit of determination	The detection limit for these metals by ICP-MS was 2 µg/L.
	Other	-
Additional information	Any additional non-health related information considered important?	-

## Khan et al 2021

**Khan, F.S.A., Mubarak, N.M., Tan, Y.H., Khalid, M., Karri, R.R., Walvekar, R., Mazari, S.A. (2021). A comprehensive review on magnetic carbon nanotubes and carbon nanotube-based buckypaper for removal of heavy metals and dyes. Journal of Hazardous Materials, 413 (2021), 125375.**

General Description	Uses	Computer components, electroplating, surgical and dental prostheses, nickel cadmium batteries, arc-welding, pigments, glass moulds, ceramics, pigments
	Sources in drinking water	Increase in the world population, unpremeditated industrialization, urbanization, agricultural events, and excessive chemical usage have tremendously increased environmental pollution by introducing toxic contaminants
	Other	-
Treatment of drinking water	Treatment technology	One route to the removal of these pollutants is the utilization of magnetic carbon nanotubes (CNT) as adsorbents. Magnetic carbon nanotubes hold remarkable properties such as surface-volume ratio, higher surface area, convenient separation methods, etc. The suitable characteristics of magnetic carbon nanotubes have led them to an extensive search for their utilization in water purification.
	Effectiveness	Removal of nickel (Ni (II)) elevated around 25% as the ionic strength of solution increased from 0.01 ~1 M Cl <sup>-</sup> because of the contribution of inner-sphere surface complexation. pH affects the performance and removal of heavy metals
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-
	Limit of determination	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

## Kurdiumov et al 2020

**Kurdiumov, V.R., Timofeev, K.L., Maltsev, G.I., LEBED, A.B. (2020). Sorption of nickel (II) and manganese (II) ions from aqueous solutions. Journal of Mining Institute. 2020. Vol. 242, p. 209-217. DOI: 10.31897/PMI.2020.2.209**

General Description	Uses	-
	Sources in drinking water	Ni ions are one of the most typical impurities of mine water at the non-ferrous metal deposits, they are present due to the leaching of copper-nickel ores, manganites, pyrolusite by groundwater. Ni in mine water at a depth of 100-300m (at 1.5mg/L) is affecting the state of nearby natural reservoirs and drinking water sources.
	Other	-

**Kurdiumov, V.R., Timofeev, K.L., Maltsev, G.I., LEBED, A.B. (2020). Sorption of nickel (II) and manganese (II) ions from aqueous solutions. Journal of Mining Institute. 2020. Vol. 242, p. 209-217. DOI: 10.31897/PMI.2020.2.209**

Treatment of drinking water	Treatment technology	Sorption by mineral and synthetic materials is one of the most promising treatment technologies due to the high degree of metal extraction and the absence of secondary contamination of the treated water compared to traditional methods of treatment. Studies have shown that the best extraction of non-ferrous metals is provided by weakly acidic macroporous cation exchange resins with chelate groups of iminodiacetic acid.
	Effectiveness	In bicomponent systems, the extraction of Ni ions increases from 59 to 78 % (static exchange capacity or SEC – from 307 to 429 mmol/L)
	Any special conditions?	SEC increases with increased temperature and pH
	Other	-
Measurement	Analytical method	Atomic absorption spectrophotometer
	Limit of determination	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

## Nujić et al 2020

**Nujić, M. and Habuda-Stanić, M. (2018). Chapter 15 Toxic Metal Ions in Drinking Water and Effective Removal Using Graphene Oxide Nanocomposite. In A New Generation Material Graphene: Applications in Water Technology (pp. 373-395). Cham: Springer International Publishing.**

General Description	Uses	-
	Sources in drinking water	-
	Other	Ni is one of the most common toxic metal ions in water.
Treatment of drinking water	Treatment technology	Different treatment technologies such as coagulation, chemical precipitation, ion-exchange and filtration have been employed for pollutant removal from water, but adsorption is still one of the most suitable technologies for heavy metal ions removal (such as Ni). Recent studies show that graphene oxide (GO), functionalized GO and their composites can efficiently remove heavy metal ions from water. Ethylenediaminetetraacetic acid (EDTA) / GO (EDTA-GO) are effective adsorbents for the removal of Ni in water.
	Effectiveness	Chitosan/ graphene oxide (GO) nanocomposite, Chitosan/iron oxide and silica from rice husk ash/GO (RHA-SiO <sub>2</sub> /GO) adsorbents showed good adsorption properties for Ni ions with capacities of 72.04, 57.86 and 256 mg/g respectively.
	Any special conditions?	-
	Other	-
Measurement	Analytical method	-

**Nujić, M. and Habuda-Stanić, M. (2018). Chapter 15 Toxic Metal Ions in Drinking Water and Effective Removal Using Graphene Oxide Nanocomposite. In A New Generation Material Graphene: Applications in Water Technology (pp. 373-395). Cham: Springer International Publishing.**

	Limit of determination	-
	Other	-
Additional information	Any additional non-health related information considered important?	-

# APPENDIX E

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



### **Recent Health-Based Studies for Nickel**

No health-based studies which would potentially alter the conclusions of the evaluation were found in the evidence scan conducted. Since no studies passed the content screening stage, there were no studies deemed relevant to include in this data extraction step.

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