NHMRC

Evidence Evaluation Report - Chlorate

Evaluated 2021

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Executive Summary

Background

Disinfection with hypochlorite and the conditions in which it is stored affects the degree of its degradation and formation of the disinfection by-product, chlorate. Chlorate is also a by-product of the disinfectant chlorine dioxide.

Hypochlorite has in recent years replaced chlorine gas in some water treatment plants in Australia because of safety considerations in handling liquified gases. Hypochlorite especially when stored at high temperatures can introduce chlorate as a by-product in drinking water.

Chlorine dioxide rapidly decomposes into chlorite, chlorate and chloride ions in treated water, chlorite being the predominant species. The major route of environmental exposure to chlorine dioxide, sodium chlorite and sodium chlorate is through drinking water.

No guideline value (GV) for chlorate was set in the National Health and Medical Research Council (NHMRC) Australian Drinking Water Guidelines (ADWG) after the last reviews in 1996 and 2011 due to insufficient data.

The ADWG states that given the importance of maintaining adequate disinfection of water supplies and limited options for reducing chlorate levels in supplies treated with hypochlorite, further information on the occurrence and sources of chlorate in Australian waters is needed before a guideline value can be developed.

Objectives

The objective of this review was to identify existing sources of guidance or guidelines on the impact of exposure to chlorate in drinking water on human health outcomes. The currency of the included guidelines was also assessed through a scan of recent literature to determine whether a more comprehensive review would be required. An evidence scan to inform an update to the supporting information [e.g. monitoring and treatment guidance] provided in the factsheet was also undertaken. Critical assessment of the studies identified in the evidence scan is out of scope of this review. These should be evaluated in further detail before being included in any decision-making.

Findings

Review of existing guidelines

Screening of the available guideline documents from short-listed organisations and agencies as advised by NHMRC and the Water Quality Advisory Committee resulted in the following relevant guidelines for consideration in the review for chlorate:

- World Health Organization (WHO) (2016): Chlorine Dioxide, Chlorite and Chlorate in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality.
- Health Canada (2008): Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorite and Chlorate.
- California Office of Health and Hazard Assessment (OEHHA) (2002): Proposed Action Level for Chlorate.
- European Food Safety Authority (EFSA) (2015): Scientific Opinion on the Risks to Public Health Related to the Presence of Chlorate in Food.
- United States Environmental Protection Agency (US EPA) (2006): Reregistration Eligibility Decision (RED) for Inorganic Chlorates.
- United States Environmental Protection Agency (US EPA) (2016): Six-Year Review 3 Technical Support Document for Chlorate.

The identified guidelines were found suitable to adopt/adapt based on their administrative and technical processes. However, further analysis of the toxicological basis for the available guidance values was also considered.

The existing guideline review and an analysis of key studies has shown that:

- There was overall high confidence in the studies underpinning the identified guidelines from the WHO 2016, US EPA 2006/2016, Health Canada 2008, OEHHA 2002 and EFSA 2015 based on an assessment of study quality.
- Although WHO revised the guideline value from 0.7 mg/L to 0.3 mg/L based on the 2-year NTP 2005 study (BMD was calculated by JECFA, 2008), due to considering challenges in achieving the revised value, previous provisional guideline value of 0.7 mg/L was retained. This achievability issue could also be considered by NHMRC and the Water Quality Advisory Committee during decision making.
- No guideline value on the aesthetic outcome from exposure to chlorate was established.

Decisions about the most appropriate toxicological endpoint and point of departure to use in guideline derivation are out of scope of this review. Potential guideline values if each identified overseas guideline were adapted to the Australian context have been derived for consideration (see Table 5-1). Potential adoption/adaption of the approach taken by WHO 2016 using parameters consistent with those used in the ADWG would result in a health-based guideline value for chlorate of 0.3 mg/L. Adoption/adaption of the approach taken by US EPA (2006, 2016), OEHHA (2002) and Health Canada (2008) using parameters consistent with those used in the ADWG would result in a health-based guideline value for chlorate of 0.2 mg/L.

Recent evidence scan

Applying the search strategy, refinement (based on the identified most sensitive population to chlorate and absence of neurodevelopmental studies) and inclusion/exclusion criteria, it has been shown that:

- A brief scan of recent evidence did not identify any new health endpoints or different critical studies for chlorate that had been published since the most recent review of the literature (WHO 2016).
- A published paper deriving a tolerable daily intake using an early key event in the mode of action for thyroid toxicity (inhibition of radioactive iodide uptake (RAIU) by the thyroid (Haber et al. 2021) was identified. The authors used Bayesian hierarchical modelling, a beta distribution for the RAIU endpoint and a BMR of 10% extra risk for a population having a RAIU of 8% or lower. Based on the suggested reduced total UF (4 instead of 10 to account for human variability), TDI of 0.008 mg/kg bw/day for perchlorate has been suggested as a health protective value. Consistent with the EFSA approach, the chlorate TDI can be calculated as 10x the perchlorate TDI. The resulting chlorate TDI would be 0.08 mg/kg bw/day. This approach could be considered by NHMRC and the Water Quality Advisory Committee when deriving a health-based guideline value for chlorate. Critical assessment of the studies identified in the evidence scan is out of scope of this review. These should be evaluated in further detail before being included in any decision-making.
- Australian treatment plant monitoring data for chlorate were not found through the literature search. US data with regard to chlorate control when using hypochlorite (e.g. storage) and water treatment was available. Most US treatment plants (>90%) had results less than 0.7 mg/L (WHO provisional guideline value). In particular AWWA B300 Hypochlorite Standard updated in 2018 now includes instructions on storage, use and handling of hypochlorite by water utilities to reduce chlorate concentrations.

The key challenge in maintaining a low level of chlorate in drinking water, is storage conditions of hypochlorite and chlorine dioxide in treatment plants. There are guides/standards for the control of chlorate during hypochlorite use and information available on occurrence and sources of chlorate from overseas sources showing that a majority (>90%) of treatment plants in the US can meet the provisional guideline value of 0.7 mg/L but not the updated guideline value of 0.3 mg/L (WHO, 2016). Issues around feasibility in the Australian context could also be considered by NHMRC and the Water Quality Advisory Committee during decision making.

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Key Terms and Abbreviations

Abbreviation	Definitions
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
ADWG	Australian Drinking Water Guidelines (NHMRC 2011)
APHA	American Public Health Association
ARfD	Acute Reference Dose
AWWA	American Water Works Association
BMD	Benchmark Dose
BMDL	The corresponding lower limit of a one-sided 95% confidence interval on the BMD
BMR	Benchmark Response
BW	Body Weight
CASRN	Chemical Abstracts Service Registry Number
CSIRO	The Commonwealth Scientific and Industrial Research Organisation
DBPs	Disinfection By-Products
DW	Drinking Water
DWC	Drinking Water Consumption
EFSA	European Food Safety Authority
GV	Guideline value
HPLCMS/MS	High Performance Liquid chromatography mass spectrometry/mass spectrometry
IC	Ion Chromatography
IPCS	International Program on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
Kg	Kilogram
L	Litre
LC-MS	Liquid chromatography–mass spectrometry
LOAEL	Low Observed Adverse Effect Level
LOD	Limit of Detection
LOQ	Limit of Quantification
MAC	Maximum Acceptable Concentration
MDL	Method Detection Limit
Mg	Milligram
µg	Microgram
MOA	Mode of Action
MRL	Maximum Residue Limit
MS	Mass Spectrometry
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Level

Abbreviation	Definitions
NTP	National Toxicology Program
OEHHA	California Office of Environmental Health Hazard Assessment
PBPK	Physiological based pharmacokinetic
PECO	population, exposure, comparator, outcome
POD	Point of Departure
RAIU	Radioactive iodide uptake
RfD	Reference dose
RSC	Relative Source Contribution
TDI	Tolerable Daily Intake
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
UV	Ultraviolet
WaterRA	Water Research Australia
WHO	World Health Organization

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Section 1 Evaluation Report Approach Overview

Table 1-1 Evaluation Report Sections

Section	Title	Existing guideline to review	Approach
Section 2	**Introduction and Background**	US EPA 2006/2016, WHO 2016, Health Canada 2008, OEHHA 2002, EFSA 2015	This section includes: - Definitions (key terms, outcome measures, abbreviations) - Rationale for review and - Objectives.
Section 3	**Research questions**		With regards to Questions underpinning the review and factsheet update: Health related advice and supporting information for the existing guidelines were summarised based on the agreed upon criteria outlined in research protocol final version.
Section 4	**Evidence evaluation methods**		Brief overview of the approach taken for evidence search and evaluation (detailed information is attached in Technical Report). Methods used to analyse/synthesise/summarise or compare data from different sources. Summary of findings tables directly comparing data from different sources and uncertainty. Methods used for any calculations and explanatory text for any assumptions if used
Section 5	**Results**		Summary of findings tables for each research question or section of factsheet. Easy to compare different guidelines/studies in Evaluation Report, more detailed information in Technical Report
Section 6	**Discussion**		Strengths and limitations of the studies/guidance, comparison of existing literature, a discussion of gaps in the evidence (if identified during the evaluation of the evidence) and a suggestion of areas for further research
Section 7	**Conclusion**		Summary of option/s to adopt/adapt existing guidance, including whether recent evidence indicates that a health-based guideline value needs to be comprehensively reviewed
Section 8	**Review Team**		List members of Review Team
Section 9	**Declared interests**		Documentation of the declared interest(s) of reviewers
Section 10	**Acknowledgements**		Documentation of any inputs from individuals not on the Team
Section 11	**References**		Included references

Section 2 Introduction

2.1 Background

Disinfection with hypochlorite and the conditions in which it is stored affects the degree of its degradation and formation of the disinfection by-product, chlorate (Asami, 2009). Chlorate is also a by-product of the disinfectant chlorine dioxide.

Hypochlorite has in recent years replaced chlorine gas in some water treatment plants in Australia because of safety considerations in handling liquified gases. Hypochlorite especially when stored at high temperatures can introduce chlorate as a by-product in drinking water.

Chlorine dioxide rapidly decomposes into chlorite, chlorate and chloride ions in treated water, chlorite being the predominant species. The major route of environmental exposure to chlorine dioxide, sodium chlorite and sodium chlorate is through drinking water.

With chlorine dioxide disinfection, the concentration of chlorate depends heavily on process conditions (in both chlorine dioxide generator and the water treatment plant) and applied dose of chlorine dioxide. As there is no viable option for reducing chlorate concentrations, control of chlorate concentration must rely on preventing its addition (from sodium hypochlorite) or formation (from chlorine dioxide) (WHO, 2016).

No guideline value (GV) for chlorate was set in the Australian Drinking Water Guidelines (ADWG) due to insufficient data.

Given the importance of maintaining adequate disinfection of water supplies and limited options for reducing chlorate levels in supplies treated with hypochlorite, further information on the occurrence and sources of chlorate in Australian waters is needed before a guideline value can be developed.

2.2 Objectives

The objective of this review was to identify existing sources of guidance or guidelines on the impact of exposure to chlorate in drinking water on human health outcomes. The currency of selected guidelines was also assessed through a brief scan of recent literature to determine whether a more comprehensive review would be required.

An evidence scan to inform an update to the supporting information [e.g. monitoring and treatment guidance] provided in the factsheet was also undertaken. As well as characterising guidance and guidelines for chlorate, a review of any available toxicity studies and observational studies focusing on chlorate in drinking water systems was conducted.

Section 3 Research questions

The Australian Drinking Water Guidelines (ADWG) factsheet includes two main sections of "Health-related advice" and "Supporting information". Research questions were designed and identified for health-based recommendation and supporting information for which updated evidence is sought. In order to address the research questions, PECO (population, exposure, comparator, outcome) criteria is applied (Morgan et al. 2018).

The PECO approach to question supports the conduct of a thorough review, including:

- Defining the scope of existing guidelines to potentially adopt/adapt into the ADWG
- Defining the appropriate population
- Exposure assessment over different time periods (e.g. chronic, subchronic, acute) for different routes
- Comparison between the current value (if available) and higher/lower values
- Comparison between different water treatment approaches to assess incremental exposure levels and observational study results (evidence or relative incidence)
- Comparison to no exposure to demonstrate that a particular level is below the "no observed adverse effect level"
- The human health and aesthetic outcome of concern from exposure

Thus, the PECO defines the objectives of the review or guideline. Furthermore, the PECO informs the study design or inclusion and exclusion criteria for a review, as well as facilitating the interpretation of the directness of the findings based on how well the actual research findings represent the original question (Morgan et al. 2018).

Research questions for health related advice and supporting information used in this review are shown in Table 3-1.

Table 3-1 Research questions

Factsheet Section	Research questions
Health-related advice	
Health-based guideline value	- What level of chlorate in drinking water causes adverse health effects? What is the endpoint that determines this value? - Is the proposed guideline value relevant to the Australian context? - Is there a knowledge gap from the time at which existing guideline values were developed? Does any recent literature change the guideline value? (e.g. demonstrating a new critical endpoint?)
Health considerations	- What are the key adverse health hazards from exposure to chlorate in Australian drinking water? - What is the critical human health endpoint for chlorate? - What are the justifications for choosing this endpoint?
Typical Australian water levels or exposure profile	- What are the typical levels in Australian drinking water? - Do they vary around the country or under certain conditions?
Risk summary	- What are the risks to human health from exposure to chlorate in Australian drinking water? - Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review?
Other	- Are there studies quantifying health burden (reduced or increased) due to chlorate?
Supporting information	
General description	Is this information current?

Factsheet Section	Research questions
Measurement	- Is this information current? - What are the indicators of the risks? How can we measure this exposure? - Analytical methods – current? current LODs achieved, with respect to various guideline values?
Treatment options	Is this information current?
Risk management options	- Is this information current? - What are the current practices to minimise or manage the risks identified?

Section 4 Methods – Evidence evaluation

4.1 Overview of the approach

Evidence search and evaluation approach includes:

- **Review of the existing guideline documents**:
  - Initial source screening: this screening allows to limit the following search and evaluation to the guidance documents that proposed a guideline value for chlorate in drinking water. The following guideline/guidance sources (advised by NHMRC and the Water Quality Advisory Committee) were screened:
    - World Health Organization (WHO) (including the Joint FAO/WHO Expert Committee on Food Additives [JECFA])
    - European Food Safety Authority (EFSA)
    - Health Canada
    - United States Environmental Protection Agency (US EPA)
    - US Agency for Toxic Substances and Disease Registry (ATSDR)
    - Californian Office of Health and Hazard Assessment (OEHHA)
    - Food Standards Australia New Zealand (FSANZ)
    - Australian Pesticides and Veterinary Medicines Authority (APVMA).
  - Comparison between the key parameters in the existing drinking water guidance documents: the studied parameters were selected based on PECO criteria. The key parameters include critical study that forms the basis of guideline derivation, study population, chemical of interest and applied doses, route and duration of exposure, adverse health outcomes, guideline derivation and calculations.
  - The relevant guidelines identified for inclusion in the review are assessed against an Assessment Tool provided by NHMRC: key administrative and technical criteria used to develop the guidance were assessed to determine whether the guidance is suitable for adoption/adaption in the ADWG.
  - The identified key studies in different guidance documents are assessed applying quality assessment tool and evaluation process explained in detailed in Technical Report. Briefly, study evaluation is an encompassing interpretation of a variety of methodological features (e.g., study design, exposure measurement, study execution, data reporting). It indicates the key evaluation concerns ("Domains") for animal and epidemiological studies. For each domain, four different categories of "Good", "Adequate", "Deficient" and "Critically Deficient" are introduced as "Domain Judgement". Key studies that have been used for guideline derivation in overseas guidance for chlorate in drinking water are evaluated based on the introduced domain judgment approach followed by the overall rating (overall study confidence) of "Low", "Medium" or "High Confidence".
  - Basis of guideline value derivation and calculation approaches are compared. This comparison facilitates the understanding of the differences in guideline values (based on the similar or different key studies).
  - Review of the adverse health effects introduced in key studies. The outcome review is a pivotal step as it determines the necessity for guideline value update/modification.
  - Review of the health effects introduced in guidance documents. This review helps to understand if the key adverse health effects need to be updated.
  - Identification of the knowledge gap and absence of studies for key endpoints. This step is essential for recent evidence scan and literature search refinement.

- Review of the mode of action in the defined route of exposure. This step aids better understanding of the most sensitive population as well as the most appropriate approach for guideline derivation.
- Review of the analytical methods, exposure measurement and limit of detection: this step is to compare and identify the differences between analytical approaches used by different agencies, identify the knowledge gap which determine the literature search and recent evidence scan criteria and refinement process.
- Comparison between the treatment options in the existing guidance documents: this step aids better understanding of the limitations, exposure levels and appropriate treatment options.

- **Recent evidence scan and literature search** (Literature search is limited to the peer reviewed, published, in press and ongoing studies. Abstract and conferences proceedings and studies in languages other than English are not included):
  - *Selection of databases* which is based on the agreed upon databases defined in research protocol:
    - Primary database: PubMed, ToxLine, Wiley Online Library and SciFinder
    - Secondary database: Data from government/ intergovernmental agencies [Water Research Australia (waterRA), CSIRO)]
  - *Development of literature search strategy* which balances the needs for identification of the relevant and non-relevant studies using a process that is reproducible. See Technical Report for further details.
  - *Literature search refinement*: see Technical Report for details.
  - *Inclusion and Exclusion criteria of the identified references*: The PECO criteria are used to determine the inclusion or exclusion of identified references, focusing on capturing primary sources of health effects data. During the screening process, studies containing potentially relevant supplemental material will likely be identified and should be tagged as such as they may provide useful, and sometimes critical, information.

    Although they do not meet the PECO criteria, these studies are not necessarily excluded and often meet most, but not all, of the individual “P,” “E,” “C,” “O” elements. Ultimately, they (1) may not be cited or considered in the assessment, (2) may be cited to provide context, or (3) may be carefully considered and cited in the assessment based on the results of analysing the literature inventory, refining the evaluation plan and organizing the hazard review. In many cases, these studies can be highly influential to specific assessment decisions.

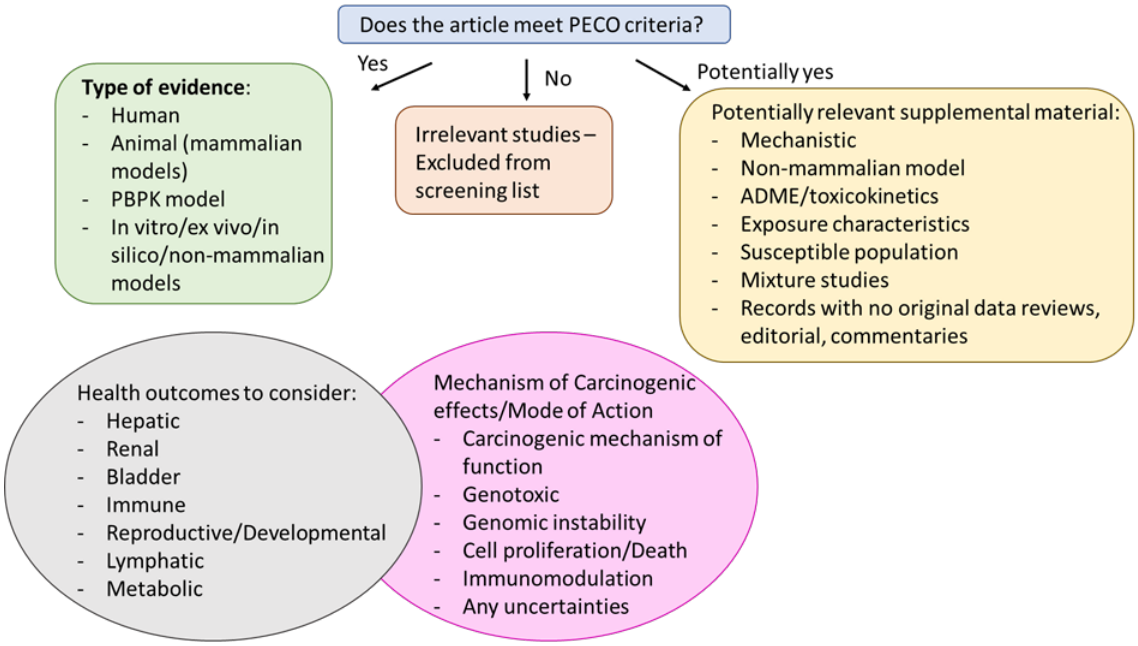

Figure 4-1 Inclusion/Exclusion criteria

Methods for guideline derivation

Following the identification and assessment of the guideline values available for THMs, HAAs and HANs from existing guidance documents, the relevant health-based guideline values were assessed to determine if the approach and toxicological basis was appropriate for the Australian context. In addition, the information extracted from the existing guidelines was used to derive potential health-based guideline values for consideration for adoption/adaption in the ADWG by NHMRC and the Water Quality Advisory Committee. Because of different properties of the individual DBPs, there are different approaches (from non-cancer or cancer endpoints) that can be used to derive appropriate drinking water guideline values. These two approaches are described below.

Non-cancer assessment – TDI approach to derive guideline value

Tolerable Daily Intake (TDI) value can be calculated by dividing the point of departure (i.e. NOAEL or BMD) with corresponding uncertainty factors (or safety factors).

Uncertainty factors and modifying factors are used to address the differences between the experimental data and the human situation, taking into account the following uncertainties in the extrapolation procedure:

- Interspecies differences,
- Intraspecies differences,
- Differences in duration of exposure,
- Issues related to dose-response,
- Quality of whole database.

Based on the point of departures from the key studies, TDI is calculated as below:

$$TDI\ (ADI\ or\ RfD) = \frac{Point\ of\ Departure\ (POD)[Modification\ if\ necessary]}{Uncertainty\ factor\ [Modifying\ Factor\ if\ necessary]}$$

Applying TDI to the assumption of human body weight, contribution of the drinking water to the total exposure and daily consumption of water, guideline value (GV) can be calculated.

$$GV\ (mg/L) = \frac{TDI\ (ADI\ or\ RfD)\ \left(\frac{mg}{kg}of\ body\ weight\ per\ day\right) * body\ weight(kg) * contribution\ of\ DW}{Daily\ water\ consumption\ (\frac{L}{day})}$$

Carcinogenicity assessment

Where chemicals are considered to be carcinogenic, cancer risk is estimated on the basis of the carcinogenesis bioassays in animal studies. Cancer potency (cancer slope factor) of the chemicals are calculated applying dose-response model or multistage-cancer model fitting described in OEHHA 2020 document.

Applying the calculated cancer slope factor (CSF) to the assumption of human body weight, daily consumption of water and the additional lifetime risk of one cancer from drinking water exposure of 10^{-6}, guideline value (GV) can be calculated.

$$GV\ (mg/L) = \frac{body\ weight(kg) \times\ 10^{-6}}{CSF\ \left(\frac{mg}{kg}of\ body\ weight\ per\ day\right))^{-1} \times Daily\ water\ consumption\ (\frac{L}{day})}$$

Section 5 Results

Applying the agreed approach for the existing guideline review and recent evidence scan, the findings are summarised in the following sections.

5.1 Existing guidelines for potential adoption/adaption

Screening of the available guideline documents from short-listed organisations and agencies as advised by NHMRC and the Water Quality Advisory Committee resulted in the following relevant guidelines for consideration in the review:

- World Health Organization (WHO) (2016): Chlorine Dioxide, Chlorite and Chlorate in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality.
- Health Canada (2008): Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorite and Chlorate.
- California Office of Health and Hazard Assessment (OEHHA) (2002): Proposed Action Level for Chlorate.
- European Food Safety Authority (EFSA) (2015): Scientific Opinion on the Risks to Public Health Related to the Presence of Chlorate in Food.
- United States Environmental Protection Agency (US EPA) (2006): Reregistration Eligibility Decision (RED) for Inorganic Chlorates.
- United States Environmental Protection Agency (US EPA) (2016): Six-Year Review 3 Technical Support Document for Chlorate.

The included guideline/guidance documents were evaluated using an Assessment Tool provided by NHMRC as outlined in the research protocol for this review. The Tool evaluated each document against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. Further details on the assessment of each guideline using the Assessment Tool are provided in the Technical Report.

The identified documents were found to be suitable to consider for adoption/adaption based on their administrative and technical processes. Further examination of the toxicological basis of the guidelines was undertaken to determine whether the guideline values were suitable for the Australian context.

5.2 Data extraction from existing guidelines

A chlorate health-based guideline value was not set in the ADWG at the time of the last review in 1996 due to insufficient data. Although action to reduce the formation of disinfection by-products is encouraged, it must not compromise disinfection as non-disinfected water poses significantly greater risk. The existing overseas drinking water guidelines for chlorate are compared below.

Table 5-1 Existing guidelines review and comparison

Parameters	NHMRC 2011	US EPA 2006/ 2016	WHO 2016	EFSA 2015		OEHHA 2002	Health Canada 2008
Study (Key/critical)	Not available (NA)	NTP (2005)		Greer et al. (2002) – based on perchlorate toxicity (chronic)	Lubbers et al. (1981) - Controlled clinical study	McCauley et al. (1995)	
Study Population	NA	50 male and 50 female F344/N rats		37 male and female volunteers	Impact on normal subjects (10/group)	Male and female Sprague-Dawley rats (10/sex/group)	
Substance	NA	Sodium chlorate		Perchlorate	Chlorate		
Route of Exposure	NA	Ingestion in drinking water					
Administered Dose	NA	0, 125, 1,000, or 2,000 mg/L sodium chlorate (equivalent to average daily doses of approximately 5, 35, and 75 mg/kg per day for male rats and 5, 45, and 95 mg/kg per day for female rats).		0.007, 0.02, 0.1, or 0.5 mg/kg-day	500 mL water containing 5 mg/L sodium chlorate (equivalent to 36 µg chlorate/kg bw/day).	3, 12 or 48 mmol/litre (equivalent to 30, 100 or 510 mg/kg of body weight per day in males and 42, 164 or 800 mg/kg of body weight per day in females, based on measured water consumption of each group)	
Exposure Duration	NA	2 years (105 to 106 weeks)		14 days	12 consecutive weeks	90-day study (subchronic)	
Critical Effects (e.g. Adverse effect) Modelled	NA	Considering all the information above, the most sensitive effects were changes to the thyroid gland of male rats. Rats are highly sensitive (more so than humans) to the effects of agents that disrupt thyroid hormone homeostasis.		Inhibition of thyroid iodine uptake Impact on RAIU and serum thyroid hormone levels of oral exposure to perchlorate	Based on the controlled clinical studies with adult volunteers, acute haematological and renal toxicity of chlorate in humans were considered as critical effects.	Pituitary lesions (vacuolization in the cytoplasm of the pars distalis) and thyroid gland colloid depletion were observed in both the mid- and high-dose groups of both sexes. A NOAEL of 30 mg/kg bw per day was identified.	
Dose adjustments	NA	Not specified					
POD (Point of departure)	NA	RfD of 0.03 mg/kg bw day for chlorate based on benchmark dose level of 28 mg/L as sodium chlorate (22 mg/L of chlorate), of which the 22 mg/L of chlorate corresponded to a dose of 0.9 mg/kg bw per day. The RfD was achieved by using the benchmark dose (BMD) and establishment of a benchmark dose level ($BMDL_{10}$) for increased follicular cell hypertrophy in rats.	ADI of 0 – 0.01 mg/kg bw for chlorate based on the $BMDL_{10}$ of 1.1 mg/kg bw per day for non-neoplastic effects on the thyroid of male rats in a carcinogenicity study. Because a NOAEL was not identified in the study, JECFA applied a benchmark dose (BMD) approach to derive a point of departure on the dose–response curve. The US EPA BMD software version 1.4.1 was used for modelling the rat thyroid gland follicular cell hypertrophy data. The calculated BMD values for a 10% increase in thyroid gland follicular cell hypertrophy in the male rats (BMD_{10}) ranged from 1.9 to 5.9 mg/kg bw per day, expressed as chlorate. The values of the lower 95% confidence limit for the BMD_{10} ($BMDL_{10}$) ranged from 1.1 to 4.4 mg/kg bw per day, expressed as chlorate. JECFA used the lowest $BMDL_{10}$ of 1.1 mg/kg bw per day, expressed as chlorate, which was derived from the model giving the best fit to the data, for its further evaluation of chlorate. For female rats, the BMD_{10} values ranged from 4.7 to 12.6 mg/kg bw per day, and the $BMDL_{10}$ values ranged from 3.0 to 6.4 mg/kg bw per day.	EFSA CONTAM Panel (2014) based the hazard characterization of perchlorate on the available human data and selected the human volunteer study of Greer et al. (2002) as the pivotal study for the dose-response assessment. They both considered the inhibition of thyroid iodine uptake as the critical effect for the dose-response assessment. The CONTAM Panel established a TDI of 0.3 µg/kg bw per day for perchlorate on basis of the reference point (RP) of 0.0012 mg/kg bw per day, based on a $BMDL_{05}$ for thyroid iodine uptake inhibition and applying an overall uncertainty factor of 4 to the RP (EFSA CONTAM Panel, 2014).	Based on the acute haematological and renal toxicity of chlorate in humans, ARfD has been established. Because of the acute haematological and renal toxicity of chlorate in humans, the NOEL was 36 µg chlorate/kg bw per day. Considering this value, an ARfD of 36 µg chlorate/kg bw was established. This ARfD covers the more vulnerable individuals (e.g. Glucose-6-phosphate dehydrogenase deficient individuals or hereditary methaemoglobinaemia).	NOAEL of 30 mg chlorate/kg-day in males and 42 mg chlorate/kg-day in females can be established (mean water consumption differed considerably between males and females): -Body weight gain was sharply curtailed in both sexes at the highest concentration. -These effects were generally paralleled by lower organ weights (except for brain and testes). -Some decreases in haemoglobin, haematocrit and red blood cell counts were observed at this same dose. -Pituitary lesions (vacuolation in the cytoplasm of the pars distalis) and thyroid gland colloid depletion were observed in both the mid- and high dose groups of both sexes.	
Interspecies	NA	3	JECFA considered that humans are likely to be less sensitive than rats to these effects and that a safety factor for interspecies variation was not required.	Not specified	Not specified	10	

Parameters	NHMRC 2011	US EPA 2006/ 2016	WHO 2016	EFSA 2015		OEHHA 2002	Health Canada 2008
Intraspecies	NA	10	10 (The rationale for selection of a tenfold uncertainty factor (as opposed to, for example, a threefold uncertainty factor) was not additionally specified by JECFA).	4 (for sensitive population)	1	10	
Adequacy of database	NA	1	Not specified.				
Other	NA	1	10 (to allow for the deficiencies in the database i.e. the absence of neurodevelopmental studies)	1	1	10 (to account for the short duration of the study)	
Composite Factor	NA	30	100	4	1	1000	
Health effect summary (other effects)	NA	In addition to the stipulated critical effect: Negative result for mutagenic effects from in-vitro and in vivo gene mutation assays. Potential effects to sensitive populations including children, based on effect of inorganic chlorate on thyroid function in rats. However, two generational reproductive studies did not show pre or post-natal effects on sensitivity or susceptibility in rats or rabbits. Haemolysis at doses greater that the RfD, may cause effect in persons with low red blood cell (RBC) counts. Several studies suggest that individuals with co-exposure to other compounds that inhibit iodine uptake by the thyroid or cause methemoglobinemia and low RBC counts may be more sensitive to chlorate that the general population.	In addition to the critical effects, other health effects include: effects on haematological parameters and on body weight gain. As is commonly seen with substances that affect thyroid function, male rats were more sensitive than females. In 90-day study, thyroid hypertrophy and decreased colloid were observed in male rats given sodium chlorate at drinking water concentrations of 1 mg/L as chlorate (equivalent to about 0.1 mg/kg bw per day as chlorate) and above. Effects including incidence and severity of follicular cell hyperplasia were dose related and more consistently observed at chlorate doses of 75 mg/kg bw per day and above. Regarding carcinogenicity and mutagenicity, sodium chlorate produced positive results in some in vitro assays, but not for induction of bone marrow micronuclei or chromosome aberrations following oral administration to mice. There was some evidence of carcinogenic activity in male and female F344/N rats based on increased incidences of thyroid gland neoplasms. Administration of sodium chlorate to pregnant rats resulted in no maternal or developmental effects at the highest dose tested (1000 mg/kg bw per day). Due to the absence of studies, neurodevelopmental end-points were not investigated and no multigeneration study was available. WHO considered that the thyroid carcinogenesis raises concerns about possible neurodevelopmental effects, as thyroid hormone status is critical to normal brain development. WHO accounted for this within the uncertainty factors.	In addition to the critical studies, Other human health effect studies showed that: A 29-year-old man who had ingested about 20 g sodium chlorate (equivalent to 230 mg chlorate/kg bw) who became cyanotic, had a severe drop in haemoglobin, and methaemoglobin and methaemoalbumin were detected in his plasma. A case of severe sodium chlorate poisoning was also observed within 5 hours after suicidal ingestion of 150–200 g sodium chlorate (117–156 mg chlorate/kg bw) (Knight et al. 1967). Methaemoglobinaemia was the early symptom of the intoxication. 14 cases of sodium chlorate poisoning, with ingested amounts (1–2 g to 300 g) known in 12 of the cases. The patient who had ingested the lowest amount (1–2 g, which corresponds to 11–23 mg chlorate/kg bw) survived. Methaemoglobinaemia was seen in 13 of the 14 patients. Persons with pre-existing blood conditions, especially anaemia, or those with kidney diseases, might be more sensitive. Persons with genetic diseases such as hereditary methaemoglobinaemia and glucose-6-phosphate dehydrogenase deficiency (which increases the haemolytic susceptibility of humans to oxidizing agents), and other persons who may be unusually susceptible to oxidants may also be at greater risk than the general population.		In addition to the critical study, other health effect studies showed that: In 90-day study, significant biological changes (reduction in organ and body weights, and haematological effects) in male and female rats exposed to mean doses of 100 and 158 mg/kg-day chlorate in drinking water, respectively. The Department of Health Services' proposed action level of 0.5 mg/L (500 µg/L) for chlorate is derived from a subchronic study in which Sprague-Dawley rats were administered 0, 10, 100 or 1,000 mg/kg-day sodium chlorate by gavage for 90 days (15/sex/group). The most significant finding was anaemia, especially in female rats, which exhibited lower blood cell counts, haematocrit and haemoglobin levels than controls. A slight decrease ($p<0.05$) in adrenal weight was found for high-dose animals when compared to controls. Although not statistically significantly different from control values, there was also a trend toward a decrease in the adrenal to body weight ratio for high-dose animals, with males more affected than females. A NOAEL of 100 mg/kg-day sodium chlorate (or 78 mg/kg-day chlorate) was derived from this study. The proposed action level calculation included an uncertainty factor of 1,000. - A 25-week study reported a significant reduction in body weights, and significant increases in kidney weights in male rats exposed to mean doses of 654-686 mg/kg-day sodium or potassium chlorate in drinking water for 25 weeks (range 445-535 mg/kg-day chlorate). - A subchronic oral toxicity study of sodium chlorate in beagle dogs reported some emesis (one female dog only during the first three weeks of dosing), along with a notation from a range-finding study that doses of 360 mg/kg-day were emetic. DPR reported a NOEL of 60 mg/kg-day for this study. - A 90-day study reported anaemia, especially in female rats, which exhibited slightly lower blood cell counts, haematocrit and haemoglobin levels. The dose of 100 mg/kg-day was identified as a no-observed effect level (NOEL) for sodium chlorate (or 78 mg/kg-day chlorate) from this study. - Administration of 1 percent potassium or sodium chlorate (mean consumption of $NaClO_3$ and $KClO_3$ ranged between 654 and 686 mg/kg-day) in the drinking water of male F344 rats for 25 weeks resulted in a significant decrease in mean body weights relative to the controls. Relative kidney weights of the group dosed with potassium chlorate were significantly increased compared with the control group, which may indicate some renal toxicity. - Male Sprague-Dawley rats (usually four animals per group) were exposed to relatively low concentrations of these chemicals in drinking water for up to 11 months. Several different effects were reported at both ClO_3 - doses, including decreased blood glutathione (at two and	

Parameters	NHMRC 2011	US EPA 2006/ 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
			Other in vivo studies on nephrotoxicity, immune function and sperm quality indicated that such effects would not be critical to the safety assessment. With regard to human studies, WHO stated that no clear treatment related effects on blood, urine analysis or physical examination were observed at 0.036 mg/kg bw per day of chlorate. The absence of detrimental physiological responses within the limits of the study demonstrated the relative safety of oral ingestion of chlorate. Considering all the information above, WHO concluded that the most sensitive effects were changes to the thyroid gland of male rats. Rats are highly sensitive (more so than humans) to the effects of agents that disrupt thyroid hormone homeostasis. WHO considered that humans are likely to be less sensitive than rats to these effects and that a safety factor for interspecies variation was not required.		nine months), decreased osmotic fragility of erythrocytes (increasing with time), inhibition of incorporation of tritiated thymidine into nuclei in rat testes (determined at three months only), decreased RBC count and haematocrit (at nine months), and decreased body weight throughout treatments. It should be noted that the reported LOAEL of 1.5 mg/kg-day for chlorate for these studies is far lower than reported in any other toxicity studies. - Little data exist on the carcinogenic potential of any of the chlorates in either humans or experimental animals. No lifetime cancer bioassays have been identified for chlorates. the results of the tests can be considered as mostly negative, with little indication of carcinogenic potential. - Data No reproductive studies were found for chlorate in humans. - High chlorate levels were found in the testes of rats after oral administration of potassium chlorate, but it is not known if chlorate can affect male fertility. The chlorates in general induce extracellular methemoglobinemia following initial lysis of erythrocytes. As such, Hazardous Substances Data Bank (HSDB, 2001) lists sodium chlorate as a Class A (unconfirmed human reproductive hazard) for reproductive hazard because it is unclear whether extracellular methemoglobin induction following erythrocyte lysis carries the same theoretical foetal risk as does intracellular methemoglobin induction. Potassium chlorate, on the other hand, is listed in Class E (known not to affect animal reproduction but no human data) for reproductive hazard. - A small number of subjects with glucose-6-phosphate dehydrogenase deficiencies which might make them more susceptible to oxidative stress caused by the chlorine disinfectants was exposed to the same dose of chlorite daily for 12 weeks. Some statistically significant trends in biochemical or physiological parameters (albumin/globulin ratio, thyroid hormone levels, mean corpuscular haemoglobin, and methemoglobin values) were observed, but were judged to be of no clinical significance. Chlorite and chlorate can be expected to have similar biochemical effects, but do not appear to be absorbed and distributed in the same fashion and are not interconvertible in vivo, according to the data from rat studies.	
Aesthetic outcome	NA	Not specified	Not specified.	Not specified.	Not specified.	
Mode of Action	NA	In accordance with EPA policy (EPA 1998), sodium chlorate was 'not likely to be carcinogenic to humans at doses that do not alter thyroid hormone homeostasis'. As such an non-threshold mode of action was considered, where the RfD was considered to be protective of cancer.	Based on the negative in vivo genotoxicity data and the nature of the histopathological observations, JECFA concluded that a non-genotoxic mode of action was likely for the induction of thyroid tumours by sodium chlorate.	Most of the potential acute adverse health effects of exposure towards $NaClO_3$ are associated with blood oxidation. The primary mechanism of chlorate toxicity is rupture of the red blood cell membranes with intravascular haemolysis. Steffen and Wetzel (1993) proposed that subsequent to initial formation of methaemoglobin, chlorate inactivates glucose-6-phosphate dehydrogenase and glyceraldehyde phosphate dehydrogenase and thus interrupts the capacity of the erythrocyte to generate nicotinamide adenine dinucleotide phosphate (NADPH), which is also a cofactor required for methaemoglobin reductase. Without cellular NADPH a cascade of protein denaturation and a crosslinking of erythrocyte membrane proteins occurs, finally resulting in erythrocyte haemolysis. Chlorate is chemically similar to perchlorate, which is a well-known thyroid gland toxicant and chemical oxidant. Chlorate inhibits the active transport of iodine from the blood to the follicular cells of the thyroid via the sodium iodine symporter (NIS). This can result in decreased serum thyroid hormones, increased release of TSH and consequent stimulation of thyroid cell proliferation and thyroid gland growth (ATSDR, 2008). It is unlikely that chlorate induces thyroid gland follicular cell tumours through a direct genotoxic mode of action. Nevertheless, chlorate might cause oxidative damage. Chlorate-induced methaemoglobin formation is most likely caused by an autocatalytic reaction. Subsequently, chlorate disturbs the capacity of the erythrocyte to form nicotinamide adenine dinucleotid phosphate (NADPH), resulting in a cascade of protein denaturation, crosslinking of membrane proteins and finally haemolysis.	The primary mechanism of chlorate toxicity is rupture of the red blood cell membranes with intravascular haemolysis. The formation of methemoglobin is secondary to lysis of red blood cells and is caused by autooxidation of the free haemoglobin. The formation of methemoglobin from free haemoglobin is irreversible and may cause life-threatening effects. (Within the red blood cells, methemoglobin is rapidly reduced by methemoglobin reductase, but this activity is lost with cell lysis). Potassium chlorate is also a relatively powerful irreversible inhibitor of catalase.	

Parameters	NHMRC 2011	US EPA 2006/ 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
				Chlorate-induced renal failure appears to be secondary to haemolysis. Like perchlorate, the chlorate ion is a competitive inhibitor of iodine uptake via the sodium iodine symporter (NIS) in the thyroid resulting in decreased serum thyroid hormones T4 and T3 and increased release of TSH. Persistent stimulation of the thyroid gland by elevated levels of TSH results in increases in thyroid gland size and weight, decreased colloid, hypertrophy and hyperplasia of thyroid follicle cells and thyroid tumours in rats.		
Malignancy	NA	Not specified				
Guideline Derivation Method, variables and calculation	NA	$0.21\frac{mg}{L} = \frac{\left(0.03\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 70kg \times 0.2\right)}{2\frac{L}{day}}$ A chronic non-threshold health reference level (HRL) of 0.21 mg/L was derive, based on the RfD of 0.03 mg/kg bw per day, an adult body weight of 70 kg, a 2 L per day drinking water consumption rate and a default RfD contribution from drinking water pathways of 20%.	$0.3\frac{mg}{L} = \frac{\left(1.1\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 60kg \times 0.8\right)}{2\frac{L}{day} \times 100}$ Using the upper bound of the BMDL of 1.1 mg/kg bw, a typical human body weight of 60 kg, the assumption that drinking water contributes 80% (default ceiling value based on drinking water as the predominant source of exposure) of the total exposure and a typical consumption of 2 L of water per day, a health-based value of 0.3 mg/L (rounded figure) could be calculated. Control of storage conditions is most difficult in small, resource-limited water supplies, and so the potential for the health-based value to be exceeded is also greater under these circumstances. *In view of the above considerations, the previous provisional guideline value of 0.7 mg/L is retained.* $0.7\frac{mg}{L} = \frac{\left(30\frac{\mu g}{kg}of\ body\ weight\ per\ day \times 60kg \times 0.8\right)}{2\frac{L}{day} \times 1000}$ *Application of an uncertainty factor of 1000 to this NOAEL (10 each for inter- and intraspecies variation and 10 for the short duration of the study) gives a TDI of 30 µg/kg of body weight. This TDI is also supported by the human volunteer studies.*	$0.07\frac{mg}{L} = \frac{\left(0.0012\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 60kg\right)}{\times\ 0.8 \times\ 10\ 2\frac{L}{day} \times 4}$ Chronic: A tolerable daily intake (TDI) of 3 µg chlorate/kg body weight (bw) was set by read across from a TDI of 0.3 µg/kg bw derived for this effect for perchlorate, multiplied by a factor of 10 to account for the lower potency of chlorate.	$0.8\frac{mg}{L} = \frac{\left(0.036\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 60kg\right)}{\times\ 0.8\ 2\frac{L}{day}}$ Acute: Formation of methaemoglobin was identified as the critical acute effect of chlorate. An acute reference dose (ARfD) of 36 µg chlorate/kg bw was derived from a no-observed effect-level for chlorate in a controlled clinical study.	Protective concentration (C): $= 0.2\ \text{mg/L} \frac{\left(30\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 70kg\right)}{\times\ 0.2\ 2\frac{L}{day} \times 1000}$ Where: NOAEL = 30 mg/Kg-day (pituitary gland vacuolization and thyroid gland colloid depletion), BW = 70kg (adult body weight), RSC = 0.2 (relative source contribution), UF = 1000 (uncertainty factor), DWC = 2L/day (adult drinking water consumption). The relative source contribution of 0.2 is intended to acknowledge potential co-exposures to the related drinking water disinfection by-products chlorite and chlorine dioxide, which have toxic effects similar to chlorate. Due to differences in water consumption, male rats were consistently exposed to a lower dose than were females in this study. The health-protective levels for chlorate would be 210 and 290 µg/L (ppb) for males and females, respectively.	In addition, in human volunteers, a chlorate dose of 0.036 mg/kg bw per day for 12 weeks did not result in any adverse effects (Lubbers et al., 1981). Although the database for chlorate is less extensive than that for chlorite, a well-conducted 90-day study in rats was available, which identified a NOAEL of 30 mg/kg bw per day based on thyroid gland colloid depletion at the next higher dose of 100 mg/kg bw per day (McCauley et al., 1995). A TDI for chlorate can therefore be derived as follows: $\boldsymbol{TDI} = \frac{\left(30\frac{\mu g}{kg}of\ body\ weight\ per\ day\right)}{1000}$ $= 0.03mg/Kg\ bw$ where: - 30 mg/kg bw per day is the NOAEL based on thyroid gland colloid depletion in a 90-day study in rats, - 1000 is the uncertainty factor (×10 for interspecies variation; ×10 for intraspecies variation; ×10 to account for the short duration of the study). This TDI is consistent with results from human volunteer studies. Because chlorate is classified in Group VIB, the MAC for chlorate in drinking water is calculated from the TDI as follows:

Parameters	NHMRC 2011	US EPA 2006/ 2016	WHO 2016	EFSA 2015		OEHHA 2002	Health Canada 2008
							$\boldsymbol{MAC} = \frac{\left(0.03\frac{\mu g}{kg} of\ bw\ \times\ 70kg\right)}{1.5\frac{L}{day}} \times 0.8$ $= \mathbf{1.12}\frac{\boldsymbol{mg}}{\boldsymbol{L}}\left(\boldsymbol{rounded\ to}\ \mathbf{1}\frac{\boldsymbol{mg}}{\boldsymbol{L}}\right)$ where: - 0.03 mg/kg bw is the TDI, as calculated above, - 70 kg bw is the average body weight of an adult, - 0.8 is the proportion of total daily intake allocated to drinking water (as drinking water is the major source of exposure), - 1.5 L/day is the average daily consumption of drinking water for an adult.
Guideline value	NA	0.2 mg/L	0.7 mg/L	0.07 mg/L (Based on perchlorate TDI)	0.8	0.2 mg/L	MAC: 1 mg/L.
Endorsed (Year)	NA	2016	2016	2015		2002	2008
Potential Australian health-based guideline value if adopted/ adapted ^		Based on RFD of 0.03 mg/kg bw/day, 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.2 mg/L** = 0.03 x 70 x 0.2/ 2	Based on NOAEL with UF 1000 derived ADI of 0.03 mg/kg bw, 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.2 mg/L** = 0.03 x 70 x 0.2/ 2 Based on the BMDL of 1.1 mg/kg bw and UF of 100, 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.08 mg/L** = 1.1 x 70 x 0.2/ 2 x 100	Based on perchlorate RFD of 0.0003 mg/kg bw/day (multiplied by a factor of 10 to account for the lower potency of chlorate) (0.003), 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.02 mg/L** = 0.003 x 70 x 0.2/ 2 Based on chlorate RFD of 0.036 mg/kg bw/day, 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.25 mg/L** = 0.036 x 70 x 0.2/ 2		Based on TDI of 0.03 mg/kg bw/day, 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.2 mg/L** = 0.03 x 70 x 0.2/ 2	Based on TDI of 0.03 mg/kg bw/day, 70 kg body weight, 2 L per day drinking water consumption and a 20% allocation of RfD to drinking water. **0.2 mg/L** = 0.03 x 70 x 0.2/ 2

^ For non-carcinogenic endpoints a 20% allocation of TDI has been retained consistent with other jurisdictions (US EPA 2006, US EPA 2016, OEHHA 2002)), noting that there are commercial/industrial uses listed based on a high-level review of Inventory Multi-tiered Assessment and Prioritisation (IMAP) risk assessment that may attribute to background exposure. IMAP assessment available at IMAP_1820 - IMAP Assessment - 03 July 2015.pdf.

5.3 Analysis of key studies in guidance documents

Key studies that have been used for guideline derivation in overseas guidance for chlorate in drinking water were evaluated based on the introduced domain judgment approach. Overall rating (overall study confidence) is for these key studies are indicated in Table 5-2 and Table 5-3 below. Based on the study evaluation, these key studies show high confidence (overall rating).

Table 5-2 Evaluation of the two key animal studies

Author, year	Evaluation parameter	Evaluation of each parameter	Overall rating	Comments
NTP 2005 (used in WHO 2016, US EPA 2006/2016)	**Risk of bias** Selection and performance (allocation, observational bias/blinding) Confounding/variable control Selective reporting and attrition	Good	High confidence	- Chronic study, using a suitable cohort of male and female rats (50 per sex per dose group). Drinking water exposure relevant to derivation of drinking water standards. -
	Sensitivity Exposure methods (chemical administration and characterisation, exposure timing, frequency and duration, endpoint)	Good		
	Reporting quality Outcome measures and Results presentation	Good		
McCauley et al. (1995) (used in OEHHA 2002, Health Canada 2008)	**Risk of bias** Selection and performance (allocation, observational bias/blinding) Confounding/variable control Selective reporting and attrition	Good	High Confidence	Subchronic not chronic study Subchronic not chronic study – 90 days. Male and female cohort, with 10 per sex per dose group. Drinking water exposure relevant to derivation of drinking water standards.
	Sensitivity Exposure methods (chemical administration and characterisation, exposure timing, frequency and duration, endpoint)	Adequate		
	Reporting quality Outcome measures and Results presentation	Good		

Table 5-3 Evaluation of a key controlled clinical study

Author, year	Evaluation parameter	Evaluation of each parameter	Overall rating	Comments/Rational
Lubbers et al. (1981) (used in WHO 2016)	**Risk of bias** Participant selection Confounding Selective reporting	Adequate	Medium to high confidence	Only male volunteers.
	Sensitivity Exposure measurement Sensitivity analysis	Adequate		Sensitivity (exposure range): Dose levels (what's the basis of highest applied dose?) = 300 fold lower than the reported lethal poisoning (50 mg/kg bw)
	Reporting quality Outcome ascertainment	Good		-
Greer et al. (2002) (used in EFSA 2015)	**Risk of bias** Participant selection Confounding Selective reporting	Good	High confidence	Both male and female volunteers
	Sensitivity Exposure measurement Sensitivity analysis	Adequate		Short exposure duration (14 days)
	Reporting quality Outcome ascertainment	Good		-

5.4 Comparison between guideline derivation approach in guidance documents

Tolerable Daily Intake (TDI) value can be calculated by dividing the point of departure (i.e. NOAEL or BMD) with corresponding uncertainty factors (or safety factors).

Uncertainty factors and modifying factors are used to address the differences between the experimental data and the human situation, taking into account the following uncertainties in the extrapolation procedure:

- Interspecies differences,
- Intraspecies differences,
- Differences in duration of exposure,
- Issues related to dose-response,
- Quality of whole database.

Based on the point of departures from the key studies, TDI is calculated as below:

$$TDI\ (ADI\ or\ RfD) = \frac{Point\ of\ Departure\ (POD)[Modification\ if\ necessary]}{Uncertainty\ factor\ [Modifying\ Factor\ if\ necessary]}$$

Applying TDI to the assumption of human body weight, contribution of the drinking water to the total exposure and daily consumption of water, guideline value (GV) can be calculated.

$$GV\ (mg/L) = \frac{TDI\ (ADI\ or\ RfD)\ \left(\frac{mg}{kg}of\ body\ weight\ per\ day\right) * body\ weight(kg) * contribution\ of\ DW}{Daily\ water\ consumption\ (\frac{L}{day})}$$

Summary of the applied parameters and assumptions in guideline derivation based on the tolerable daily intake, TDI (or acceptable daily intake (ADI) or reference dose (RfD)) is shown in Table 5-4 below.

Table 5-4 Guideline derivation – Basis and key parameters

Agency	US EPA (2006/ 2016)	WHO (2016)	Health Canada (2008)	OEHHA (2002)	EFSA (2015)	
Key study	NTP (2005)	NTP (2005)	McCauley (1995)	McCauley (1995)	Acute: Lubbers (1981)	Chronic: Greer et al. (2002) – perchlorate study
POD (mg/kg bw/day)	$BMDL_{10}$: 1.1	$BMDL_{10}$: 1.1	NOAEL: 30	NOAEL: 30	NOAEL: 0.036	$BMDL_{05}$ (Reference point for perchlorate): 0.0012
Interspecies	3	1	10	10	1	
Intraspecies	10	10	10	10	1	
Other safety factors	1	10 (database deficiency)	10 (short duration)	10 (short duration)	1	4
TDI, ADI, RfD mg/kg bw/day	0.03	0.011	0.03	0.03	0.036	0.003 (chlorate TDI = 10X perchlorate TDI of 0.0003)
Human body weight (kg)	70	60	70	70	60	
Drinking water contribution to total exposure	0.2	0.8	0.8	0.2	0.8	
Water consumption (L/day)	2	2	1.5	2	2	
Guideline value (mg/L)	Health reference level: 0.2	Health-based: 0.3	Maximum acceptable concentration (MAC): 1 (rounded)	Health protective level: 0.2	0.8	0.07
Provisional health-based guideline value	-	0.7	-	-	0.7	

Potential Australian health-based guideline value if TDI, ADI, RfD adopted (see also Table 5-1)	0.1 mg/L	0.04 mg/L (rounded)	0.1 mg/L	0.1 mg/L	0.12 mg/L	0.001 mg/L

5.5 Addressing research questions for guidance documents

Research questions for health-related advice and supporting information are addressed using information extracted from the existing guidance documents and presented in the Table 5-5.

Table 5-5 Health-related advice and supporting information review and comparison

Factsheet	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
	Health-related advice					
Level of chemical in drinking water that causes adverse health effects	Data are insufficient to set a guideline value in drinking water.	High doses of chlorate might interfere with thyroid function (>30 mg/kg).	High doses of chlorate might interfere with thyroid function (>30 mg/kg).	High doses of chlorate might interfere with thyroid function (>30 mg/kg).	High doses of chlorate can also interfere with thyroid function (>30 mg/kg).	High doses of chlorate can also interfere with thyroid function (>30 mg/kg).
Knowledge gap from the time of development of the existing guideline	Few data are available on chlorate levels in Australian water supplies.	Monitoring data was collected at water treatment plans servicing over 100,000 people. So exposure concentrations and risk characterisation may not be representative of smaller (or all) wastewater treatment systems in the US. Fluctuations in concentrations are not likely to be captured due to quarterly sampling requitements.	- This guideline value is designated as provisional. - Limited information on the adverse effects of chronic exposure to chlorate. - Absence of information on neurodevelopmental studies.	Assessment of the chronic and acute (if applicable) human health risks as the consequence of the presence of chlorate in in drinking water, with attention to sensitive population (i.e. children, pregnant women, iodine deficient people).	- Lack of a cancer bioassay and the potential for extra sensitivity of neonates and newborns to chlorates. - There is a paucity of data concerning postnatal reproductive/developmental effects in animals and humans, and no multi-generation reproductive study exists for these compounds.	- The chronic and carcinogenicity studies, and the developmental and reproductive studies do not provide sufficient information to derive a guideline for chlorate. - In addition, in human volunteers, highest dose does not show any adverse effects.
	Typical Australian exposure levels					
Typical levels of chemical in Australian drinking water	Not specified. Few data are available on chlorate levels in Australia water supplies. Further information on the occurrence and sources of chlorate in Australian waters is needed before a guideline value can be developed.	For systems using hypochlorite maximum chlorate concentrations were 502 µg/L. For systems using chlorine dioxide (or a mixture with hypochlorite) the maximum concentration was 691 µg/L. The 90th percentiles were 239 µg/L (hypochlorite), 264 µg/L (chlorine dioxide) and 242 µg/L (mixture of hypochlorite and chlorine dioxide).	Not specified per country. Chlorate concentrations above 1 mg/l have been reported when hypochlorite was used, but such high concentrations would be unusual unless hypochlorite is stored under adverse conditions. A 1996 Information Collection Rule survey of chlorate in disinfected drinking water in the USA reported that in water treatment plants using hypochlorite, the median chlorate concentration was 99 µg/L, the 90th percentile concentration was 239 µg/L and the maximum concentration was 502 µg/L (US EPA, 2006). Chlorate concentrations above 1 mg/L have been reported when hypochlorite was used (Stanford et al., 2011), but such high concentrations would be unusual unless hypochlorite is stored under adverse conditions (see Section 4.2 for more information). In water treatment plants using chlorine dioxide, the median chlorate concentration was 129 µg/L, the 90th percentile concentration was 264 µg/L and the maximum concentration was 691 µg/L (US EPA, 2006).	Not specified.	Not specified.	Treatment plants using chlorine dioxide as primary disinfectant should not exceed a maximum feed dose of 1.2 mg/L, which will ensure that the chlorite and chlorate guidelines can be met, and that consumers are not exposed to concentrations of chlorine dioxide that could pose health risks. The maximum levels of chlorate in the distribution system usually occur in the end locations.
Do they vary around the country or under certain conditions (e.g. brominated water, desalination etc)	Not specified.	The formation of chlorate can depend on disinfection processes including chemicals (hypochlorite or chlorine dioxide), processes and storage.	Use of chlorine dioxide as a disinfectant may result in the chlorite and chlorate guideline values being exceeded. The formation of chlorate ion in a hypochlorite solution is influenced by storage conditions.	Not specified.	Not specified.	The formation of chlorate ion in a hypochlorite solution is influenced by storage conditions such as pH, temperature, length of time in storage, presence of ultraviolet light, concentration of solution and presence of transition metals (Gordon et al., 1995). In order to control this persistent by-product, it is important to minimize its formation

Factsheet	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
						during the chlorine dioxide generation process and/or to remove the chlorite ion before adding secondary disinfection with chlorine (Gallagher et al., 1994).
	Risk summary					
Risks to human health from exposure to the chemical in Australian drinking water	The primary concern with chlorate is oxidative stress resulting in changes in red blood cells. This endpoint is seen in laboratory animals and, by analogy with chlorate, in humans exposed to high doses in poisoning incidents.	Adverse effects of exposure from chronic and subchronic exposure are to the thyroid and blood. Persons with low red blood cell counts/anaemia may be more susceptible to chlorate.	A chlorate dose of 36 µg/kg bw per day for 12 weeks did not result in any adverse effects in human volunteers. High doses of chlorate could also interfere with thyroid function.	- Chronic dietary exposure to chlorate is of potential concern in particular for the high consumers in the younger age groups of the population with mild to moderate iodine deficiency. -The information on the toxic effects of chlorate in humans comes from reports on cases of poisoning after oral intake. Sodium chlorate typically induces local irritation of the gastrointestinal mucous membranes in humans after acute exposure, which has not been reported in studies with laboratory rodents performed with comparable doses.	High doses of chlorate could also interfere with thyroid function.	A chlorate dose of 36 µg/kg bw per day for 12 weeks did not result in any adverse effects in human volunteers. High doses of chlorate could also interfere with thyroid function. As sodium chlorate is used as a herbicide, several cases of chlorate poisoning in humans have been reported.
	General description					
Date of general description information publication	Endorsed in 2011. The last version of the Australian Drinking Water Guidelines was Updated in March 2021 (Version 3.6).	RED for inorganic chlorates dated July 2006. 3-year review endorsed in 2016 (US EPA 2016).	WHO (2016). Chlorine dioxide, chlorate and chlorite in drinking water.	EFSA Journal 2015;13(6):4135.	Office of Environmental Health Hazard Assessment, 2002.	Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Chlorite and Chlorate. 2008.
	Measurement					
Risk indicators	High doses of chlorate can also interfere with thyroid function.	High doses of chlorate can also interfere with thyroid function.	High doses of chlorate can also interfere with thyroid function.	High doses of chlorate can also interfere with thyroid function.	High doses of chlorate can also interfere with thyroid function.	High doses of chlorate can also interfere with thyroid function.
Exposure measurements*		Chlorate data was available in the US from two main sources (Information Collection Rule (ICR) and America Water Works Association Research Foundation (AwwaRF)). Chlorate monitoring was required for water treatment plants using chlorine dioxide or hypochlorite solutions for treatment, where chlorate is a disinfection byproduct. For systems using hypochlorite maximum chlorate concentrations were 502 µg/L. For systems using chlorine dioxide (or a mixture with hypochlorite) the maximum concentration was 691 µg/L. The 90th percentiles were 239 µg/L (hypochlorite), 264 µg/L (chlorine dioxide) and 242 µg/L (mixture of hypochlorite and chlorine dioxide). Maximum concentrations were below the chronic population adjusted dose (cPAD) for all age groups except infants less than a year old. (<1 year old). The 90th percentile and median concentrations were below cPAD for	In section 2 (Environmental Levels and Human Exposure): Water: In water treatment plants using chlorine dioxide, the median chlorate concentration was 129 µg/L, the 90th percentile concentration was 264 µg/L and the maximum concentration was 691 µg/L (US EPA, 2006). More details page 3 and 4. Food: chlorate may occur in foods because of the uses of chlorine dioxide, sodium chlorate or sodium chlorite in flour processing (US EPA, 1983; CMA, 1989; USFDA, 1990). More details page 3 and 4.	Residues of chlorate in **food** and **drinking water**: Data indicated that chlorate residues are present at levels that frequently exceed the default MRL of 0,01 mg/kg and that the levels vary depending on the source and the product. It follows from those findings that even if good practices are used, it is currently not possible to achieve levels of chlorate residues compliant with the current MRL of 0,01 mg/kg. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R0749&from=EN / P07 -Default MRL value of 0.01 mg/kg is applicable to all food products listed in Annex I of that Regulation. For chlorate no specific MRLs were set, thus the default MRL is applicable. EFSA Journal 2015 / P13.	Not specified.	The major route of environmental exposure to chlorite and chlorate is through drinking water. Chlorite and chlorate ions are often found in drinking water where chlorine dioxide is used in the treatment process. It is the generation technology and, to a lesser degree, the generator “tuning” that will determine the types and quantities of by-products or unreacted precursors, such as chlorite, chlorate and perchlorate (ClO_4^-) ions, that may be found in the final chlorine dioxide feed (Gordon, 2001). Formation of chlorate ion in water may also occur through the photolytic decomposition of pre-existing chlorine dioxide and chlorite by sunlight and fluorescent lighting (Griese et al., 1992). The concentrations of chlorine dioxide, chlorite and chlorate ions were measured in 8 systems in Quebec (Aranda-Rodriguez et al., 2004; Health Canada, 2005) in winter and summer 2003. More details in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Chlorite and Chlorate/P6.

Factsheet	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
		all age groups. ICR data also reported chlorate in untreated water likely to be the result of agriculture or other uses of sodium chlorate.				
Analytical methods, date of publication	Method 4500, chlorine. In: Standard Methods for the examination of water and wastewater, 21st Edition (APHA, 2005a). Method 4500, chlorine dioxide. In: Standard Methods for the examination of water and wastewater, 21st Edition (APHA, 2005b).	- EPA 300.0 – Determination of Inorganic Anions by Ion Chromatography - EPA 300.1 – Determination of Inorganic Anions in Drinking Water by Ion Chromatography - EPA Method 317.0 Determination of Inorganic Oxyhalide Disinfection By-Products in Drinking Water Using Ion Chromatography with the Addition of a Post column Reagent for Trace Bromate Analysis. - EPA Method 326.0, Revision 1.0, Determination of Inorganic Oxyhalide Disinfection By-Products in Drinking Water Using Ion Chromatography Incorporating the Addition of a Suppressor Acidified Post column Reagent for Trace Bromate Analysis.	Guidance document (WHO, 2016), Table 3, page 10: - Amperometric (Standard Method 4500-ClO2-E, APHA, AWWA & WEF (1998)) - Ion chromatograph/ conductivity (US EPA Method 300.0 (1993B Revision 2.2), US EPA (1999)) - Ion chromatograph/ conductivity (US EPA Method 300.1 (1997E Revision 1.0), US EPA (1998)) - Ion chromatograph/ conductivity and ultraviolet/visible detectors (US EPA Method 317.0 (Revision 2.0*), US EPA (2001)) - Ultraviolet/visible spectrophotometric Lissamine Green B (US EPA Method 327.0 (Revision 1.0*), US EPA (2003)) - Flow injection analysis – iodometric (Novatek (1991))	- High performance liquid chromatography (HPLC) was the separation method selected for almost all samples that provided information on the analytical method used. - Ion chromatography with suppressed conductivity detection. - Other option for detections were tandem mass spectrometry (MS/MS) electrical conductivity detection (ECD) and mass spectrometry detection (MS). In complex matrices of animal origin, liquid chromatography-mass spectrometry (LC-MS) utilising a Cl18O3 - internal standard has been demonstrated to be applicable to quantify chlorate at low levels. EFSA Journal 2015 / P58.	Not specified.	Ion chromatograph/ Conductivity and Flow injection analysis — iodometric. For more details see Appendix A: Analytical methods for chlorite and chlorate in drinking water. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Chlorite and Chlorate/ P37.
Limit of detection	Not specified.	MRL = 20 µg/L.	The limits of detection for the methods are generally below 0.1 mg/L. MDLs as low as 0.45 µg/l for chlorite and 0.78 µg/l for chlorate (IC with conductivity detection); 78 µg/l for chlorine dioxide (UV/visible. spectrophotometric method); 20 µg/l for Flow injection analysis.	HPLCMS/MS: LOQ of 2 µg/kg in the analysis of Fruit and fruit products. EFSA Journal 2015 / P16.	Not specified.	MDLs: 0.78 µg/L for IC with conductivity detection; and 20 µg/L for Flow injection analysis
	Treatment options					
Treatment option	Endorsed 2011. Chlorine dioxide can be removed from drinking water by the addition of reducing agents such as sodium bisulfite (although some studies indicate that the chlorate concentration increases as a result), by exposure to sunlight, or by the use of granular activated carbon.	- Reduction of disinfection demand. Can include pre-treatment of water to lower disinfection dose with powdered activated carbon (PAC) or removal or organic material using granular activated carbon (GAC). - Modification of disinfection practices - Removal of chlorate. Gonce and Voudrias (1994) showed limited success with GAC. Westerhoff and Johnson (2001) showed slow improvement in groundwater with zero valent iron, likely to removed up to 30% chlorate with	WHO, 2016 Currently, there is no readily available and low-cost treatment available to remove chlorate ion once it has been formed in drinking water. Although anion exchange and reverse osmosis are possible technologies for the removal of chlorate (Alfredo et al., 2015), they are high-cost treatment options. Granular activated carbon is generally not effective, as chlorate is reversibly adsorbed on granular carbon (Gonce & Voudrias, 1994).	Not specified.	Not specified.	Currently, there is no known practical and economical treatment available to remove chlorate ion once it has been formed in drinking water. As much as 35% of the chlorate found in a distribution system can be attributed to the performance (tuning) of the chlorine dioxide generator. If chlorite ion is present in water and is not removed, it will react with any applied free chlorine to produce chlorate and chloride ions. To control this persistent by-product, it is important to minimize its formation during the chlorine dioxide generation process and/or to remove the chlorite ion before adding secondary disinfection with chlorine (Gallagher et al., 1994).

Factsheet	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
		20 minute contact time at 28 degree Celsius. - Sivasubramanian (2015) showed limited success due to inhibitory effects of nitrate with reducing agents and UV light sources. No practical methods to remove chlorate, prevention likely to be the most practical method to reduce exposure.				
	Risk management					
Is it current practices to minimise or manage the risks identified?	Chlorate levels can be minimised by restricting storage times for hypochlorite solution (7 days maximum storage is recommended) and storing the solution under cool dark conditions. No data are available on taste and odour thresholds for chlorite and chlorate.	Best management practices (BMP) introduced to help reduce exposure to chlorate. BMPs include - Production modification and operational changes. - Materials substitution. - Purchase of high quality hypochlorite and careful storage and use (with optimal pH, temperature and light). - High efficiency in the operation of chlorine dioxide generators - Reducing chlorite ions prior to the addition of free chlorine.	When using hypochlorite, the following control approach is recommended to minimize formation of chlorite and chlorate: - purchase fresh solutions that are of an appropriate quality, - store them in a cool place and out of direct sunlight, and - use the hypochlorite as soon as possible after purchase (e.g. within a month, if possible). - Further, new hypochlorite solutions should not be added to containers containing old hypochlorite solutions, as this will accelerate chlorate formation. As there is no low-cost option for reducing concentrations of chlorate once it is formed, control of chlorate concentration must rely on preventing its addition (from sodium hypochlorite) or formation (from chlorine dioxide).	Where possible, without compromising disinfection, shall strive for a lower value (lower that guideline value). This parameter shall be measured only if such disinfection methods are used. EFSA Journal 2015 / P8.	An action level for chlorate is needed because of concerns about its presence in Southern California in water associated with hazardous waste clean-up activities that may find its way into drinking water supplies. The origin of the chlorate in the raw water samples is unclear.	Exposure to chlorate may also be linked to the use of hypochlorite solutions as a source of chlorine in municipal treatment plants. This exposure can be reduced through appropriate storage/use of hypochlorite solutions at the treatment plant. The maximum levels of chlorite and chlorate in the distribution system usually occur in the mid-system and end locations, respectively. A minimum quarterly monitoring of chlorite and chlorate is recommended, ideally at representative locations for chlorite and chlorate in the distribution system. For systems using hypochlorite solutions, levels of chlorate should be monitored in the treated water at the plant. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Chlorite and Chlorate. P2.

* Korn et al. (2002) developed empirical equations to model the disappearance of chlorine dioxide and the formation of chlorite and chlorate. The models were validated against measurements of these species from water systems.

5.6 Recent evidence scan results

Applying the search strategy, refinement and inclusion/exclusion criteria, list of "included", "excluded" and "potentially relevant supporting information" results are summarised in Table 5-6 below and presented in detail in Appendix B of the Technical Report (CDM Smith 2025).

Table 5-6 Recent evidence scan results

Database		PubMed	Wiley Online Library	Tox21	SciFinder
Scanning result (for each key search term)	Chlorate	296	899	5	36
	Chlorate AND drinking water	29	213	141	36
	Chlorate AND disinfect	51	171	9	36
	Chlorate AND adverse health effect	1	142	16	36
	Chlorate AND toxicity	38	434	369	36
	Sodium Chlorate	57	884	3	5
Number of "Included" studies	Human health effect	5	4*+3	-	-
	Animal health effect	4	4*	-	-
	Carcinogenic	-	-	-	-
	Reproductive	-	-	-	-
	Genotoxicity	2	2*	-	-
	PBPK models	-	-	-	-
Number of "Included as supplemental" studies	Mechanistic	40	5*	1*	1*
	Non-mammalian effect	8	-	-	-
	ADME/Toxicokinetics	1	-	-	-
	Exposure characteristics	28	10*	-	1*
	Human case report	-	-	-	-
	Records with no original data review, editorial	1	-	-	-
	Mixture studies	13	-	-	-
	Methods	27	10	-	4
Excluded studies		168[#]	855	368	25

*after de-duplication

#Excluded studies from PubMed database are listed in Appendix B of the Technical Report (CDM Smith 2025).

The evidence scan highlighted that:

- Weterings et al. (2016) proposed a benchmark response (BMR) for perchlorate based on the iodine uptake inhibition:
  - This approach was different from the chemical-induced thyroid function investigation by measuring serum levels of thyroid-related hormones. Instead, it focused on iodine uptake inhibition, an upstream event that by itself is not necessarily adverse. Establishing the extent of uptake inhibition that can be considered de

minimis, the chosen benchmark response (BMR), is therefore critical. The BMR values selected by two international advisory bodies were 5% and 50%, a difference that had correspondingly large impacts on the estimated risks and health-based guidance values that were established. Potential treatment-related inhibition of thyroidal iodine uptake is usually determined by comparing thyroidal uptake of radioactive iodine (RAIU) during treatment with a single pre-treatment RAIU value. In the present study it is demonstrated that the physiological intra-individual variation in iodine uptake is much larger than 5%. Consequently, in-treatment RAIU values, expressed as a percentage of the pre-treatment value, have an inherent variation, that needs to be considered when conducting dose-response analyses. Based on statistical and biological considerations, a BMR of 20% is proposed for benchmark dose analysis of human thyroidal iodine uptake data, to take the inherent variation in relative RAIU data into account. They concluded that the inherent variability of the dataset should be taken into account when conducting benchmark dose analysis with secondary RAIU data from studies without a concurrent control group. In view of the normal intra-individual variability, a critical effect size (BMR) of 20% is considered most appropriate for benchmark dose analysis of these data. In the case of perchlorate, using PROAST benchmark dose analysis software (see supplementary documentation), the resulting $BMDL_{20}$ is 16.6 mg/kg bw/day. Applying the assessment factor of 4, derived by the EFSA CONTAM panel to allow for interhuman differences in toxicokinetics (EFSA, 2014), leads to a TDI for perchlorate of 4 mg/kg bw/day. The TDI for chlorate, established by EFSA (EFSA, 2015a), is derived from the TDI for perchlorate and consequently may also need to be re-considered.

- Haber et al. (2021) proposed a new point of departure (POD) and tolerable daily intake (TDI) for perchlorate and chlorate based on the benchmark response (BMR) as a point value of 8% radioactive iodide uptake (RAIU) by the thyroid (rather than a change in RAIU) based on descriptions in the medical literature that RAIU below this value (8%) is considered abnormal:
  - **POD**: Because a definition of the BMR based on the mean response would correspond to about 50% of the population with a response below the BMR at the benchmark dose, a hybrid definition of the BMR was applied. Novel modelling code was developed using the same underlying mathematical expressions as used by US EPA but implementing a Bayesian hierarchical approach. That is, the BMD was defined as the dose at which it was estimated that there would be a 10% extra risk in the population of having RAIU of 8% or lower. **The resulting point of departure based on the BMDL was 0.03 mg/kg-day.**
  - **TDI**: RAIU measurements are not recommended for the sensitive population consisting of pregnant women presumably because conducting the test would require exposing the foetus to radioactivity. Quantitative information is also lacking to relate the RAIU perchlorate dose-response for the average population to that for iodine-deficient populations. Thus, key uncertainties are:
    - Response of the sensitive populations (pregnant women and iodine-deficient people),
    - The degree to which the relatively small sample size of the groups in the medical study that established a BMR captured overall human variability (Greer et al. 2002). People over 46 are another potentially sensitive population, but the test population did include people through age 57.
    - It is also noted that EFSA (2014) expressed concern about the potential impact of chronic adaptive changes to compensate for the lower thyroid iodide uptake. However, it was noted that there were no effects on thyroid hormones at 0.1 mg/kg-day in the Greer et al. (2002) study (at about 3x the BMDL).
    - Consideration of the appropriate total uncertainty factor (UF) should also take into account that RAIU is an early key event, that the RAIU of 8% is above the bottom range of normal reported by IOM (2001), and that the use of the hybrid approach adds additional conservatism. Based on these considerations and the conservatisms in the current assessment, it has been suggested that a reduced total UF is likely to be appropriate. Although an argument could also be made for a total UF of 10, to account for human variability (including the combined impact of pregnancy and iodine deficiency) and the effect of prolonged exposure is that this additional conservatism is needed. Amitai et al. (2007)

found no effect on T4 levels in newborns born to iodine-sufficient mothers consuming "very high" levels of perchlorate in drinking water, up to 340 mg/L perchlorate (calculated to correspond to 0.0097 mg/kg-day).

- Although there are limitations to their calculation, this result is consistent with our conclusion that a total UF of 4 is adequate and the resulting TDI of 0.008 mg/kg-day would be health-protective. Consistent with the approach of EFSA (2015), the chlorate TDI could be calculated as 10x the perchlorate TDI. The resulting chlorate TDI would be 0.08 mg/kg-day. In comparison the existing guidelines have PODs of between 0.036 to 30 mg/kg bw/day. The EFSA POD of 0.036 mg/kg bw/day is the lowest POD identified.

- Alfredo et al. (2015) provides a summary of the chlorate monitoring data collected from two sampling campaigns:
  - the US EPA Information Collection Rule (ICR) promulgated in 1996. ICR monitoring occurred between July 1997 and December 1998. Sampling occurred at 296 public water systems. All systems used chlorine dioxide or hypochlorite and the monitoring occurred both at the treatment plant influent and effluent.
  - Unregulated contaminant monitoring rule (UCMR 3) during 2013-2014. The UCMR 3 data is from the distribution system entry point and other monitoring samples as of July 2014 (the program ended in 2015).

  The summary of the ICR and UCMR 3 data is provided in Table 5-7 below. The results show that there are very few systems (5% and 7% of ICR and UCMR 3 systems respectively) with results that exceed 700 µg/L (i.e. WHO Drinking water guideline).

Table 5-7 Summary of ICR and UCMR 3 data

Monitoring Results	ICR Data* *Number (%)*	UCMR 3 Data† *Number (%)*
Samples	897	25,533
Systems	82	2,648‡
Samples > MRL§	747 (83)	14,356 (56)
Systems > MRL§	80 (98)	1,781 (67)
Samples > 210 µg/L	135 (15)	3,671 (14)
Systems > 210 µg/L	31 (38)	857 (32)
Samples > 700 µg/L	17 (21)	344 (1.3)
Systems > 700 µg/L	4 (5)	174 (7)
Samples > 840 µg/L	12 (1)	203 (0.8)
Systems > 840 µg/L	4 (5)	118 (4)

ICR—Information Collection Rule, MRL—maximum reporting level, UCMR 3—third round of Unregulated Contaminant Monitoring Regulation

*Finished water samples only

†Distribution system entry point and other monitoring samples as of July 2014

‡Represents 55–60% of the systems expected to report data under the UCMR 3

§20-µg/L MRL in both databases

Systems were evaluated using the utility's maximum reported concentration.

- AWWA B300 Hypochlorite Standard (AWWA, 2018) include the following instructions for hypochlorite solutions to control chlorate concentrations. These include:
  - Dilute hypochlorite solutions on delivery. Dilute a 15% solution by a factor of 2, which decreases perchlorate formation by a factor of 7.
  - Reduce storage temperature. Each 5 degree reduction in temperature reduces the rate of decomposition by a factor of 2.
  - Control pH between 11 and 13. Below pH 11, chlorate formation increases. Above pH 13, perchlorate formation increases. On-site generators typically are between 9-10 and the solutions should be used within one to two days.
  - Control the concentration of metal ions. Purchase filtered hypochlorite solutions and use low metal ion concentration feed water for on-site generators. Use fresh hypochlorite solutions when possible.

Section 6 Discussion

6.1 Evaluation of potential guideline values to adopt/adapt

Following the identification of relevant existing guidelines in overseas and Australian documents:

- The available Australian guideline values and their basis of derivation were compared against the existing overseas documents.
- The most recently updated guideline documents (based on the latest key studies and supporting information) were evaluated for their suitability to adopt/adapt based on their guideline development processes and evidence methods.
- Different guideline values for potential adoption/adaption in the ADWG were derived from existing guidance values from other jurisdictions for consideration by NHMRC and the Water Quality Advisory Committee.

The available guidance from the identified existing guidelines were found suitable to adopt/adapt based on their administrative and technical processes. However, further analysis of the toxicological basis for the guideline values was considered (see Section 5.3).

- Although a WHO provisional guideline value of 0.7 mg/L was mentioned in the 1996 review of the ADWG chlorate factsheet (most recently endorsed in 2011), no guideline value was established in the ADWG. The data available at the time was considered insufficient in order to set a guideline value for chlorate in Australian drinking water supplies.
- WHO (2016) adopted the point of departure (BMD) calculated by JECFA (2008) based on LOAEL from NTP 2005 study. Modelling was applied for the rat thyroid gland follicular cell hypertrophy data. The calculated BMD values for a 10% increase in thyroid gland follicular cell hypertrophy in the male rats (BMD_{10}) ranged from 1.9 to 5.9 mg/kg bw per day, expressed as chlorate. The values of the lower 95% confidence limit for the BMD_{10} ($BMDL_{10}$) ranged from 1.1 to 4.4 mg/kg bw per day, expressed as chlorate**.** JECFA used the lowest $BMDL_{10}$ of 1.1 mg/kg bw per day, expressed as chlorate, which was derived from the model giving the best fit to the data, for its further evaluation of chlorate. For female rats, the BMD_{10} values ranged from 4.7 to 12.6 mg/kg bw per day, and the $BMDL_{10}$ values ranged from 3.0 to 6.4 mg/kg bw per day.

  Although derived guideline based on the $BMDL_{10}$ of 1.1 mg/kg is 0.3 mg/L, challenges in chlorine storage condition make it difficult to maintain the chlorate level of less than 0.3 mg/L. Therefore, WHO retained the previous provisional guideline value of 0.7 mg/L that was based on NOAEL of 30 mg/kg body weight (bw) per day expressed as chlorate, from a 90-day study of sodium chlorate in rats, in which thyroid gland colloid depletion was reported at the next higher dose of 100 mg/kg bw per day (McCauley et al., 1995). WHO noted that this TDI was supported by the results of human volunteer studies, in which repeated administration of chlorate at 36 µg/kg bw per day did not result in any adverse effects (including blood and urine analysis, electrocardiograms and physical examination, e.g. blood pressure, respiration rate, pulse and temperature) (Lubbers et al., 1981).
- US EPA (2006 & 2016) adopted RfD of 0.03 mg/kg bw day, using the same study as WHO (2016). The RfD was calculated using a $BMDL_{10}$ dose level of 28 mg/L as sodium chlorate (22 mg/L of chlorate), which to a dose of 0.9 mg/kg bw per day. An uncertainty factor of 30 was applied to calculate an RfD of 0.03 mg/kg bw per day. The critical effect for the ($BMDL_{10}$) for increased follicular cell hypertrophy in rats. In accordance with EPA policy (EPA 1998), sodium chlorate was 'not likely to be carcinogenic to humans at doses that do not alter thyroid hormone homeostasis'. As such an non-threshold approach was considered to be protective of cancer.
- OEHHA (2002) and Health Canada (2008) guideline value derivations were based on McCauley et al., 1995 animal study.
- EFSA (2015) based its TDI for chlorate on that for perchlorate (applying Greer et al. 2002 study on perchlorate), noting that chlorate also acts by inhibition of iodide uptake into thyroid, but that the human database on

chlorate is much more limited. EFSA did not consider the toxicity studies of chlorate in rats to be relevant for deriving a human exposure limit, due to differences in thyroid hormone physiology; EFSA did, however, consider the rodent data useful for a comparative analysis of the potency of perchlorate and chlorate. In contrast, WHO (2016) developed an ADI for chlorate based on nonneoplastic changes in the thyroid of male rats in a chronic study. The documentation noted that rats are more sensitive than humans to effects on thyroid hormone homeostasis, but WHO (2016) chose a rat study as the basis for the assessment. A similar approach was used by the US EPA (2016) in developing an RfD for chlorate in the context of a pesticide assessment and by OEHHA (2002) and Health Canada (2008) in developing TDI.

- In addition to derivation of chronic health-based guideline value based on Greer et al. (2002) study of perchlorate toxicity in controlled human study, acute reference dose of 0.36 mg/kg bw/day was established based on the observed effects on no effects at the highest dose applied (controlled clinical study by Lubbers et al. 1981 on adult volunteers).
- Guideline values differ due to the different assumptions and policies. The main differences were:
  - Proportion of total daily intake attributable to the consumption of water: WHO, EFSA and Health Canada applied drinking water contribution of 80% whereas OEHHA and US EPA applied 20%.
  - Adult body weight: WHO and EFSA applied the adult body weight of 60 kg whereas OEHHA, US EPA and Health Canada applied body weight of 70 kg.
- Uncertainty factors (UFs) are applied based on the key study (McCauley 1995) qualities and uncertainties:
  - UF of 10 for intraspecies differences
  - UF of 10 for interspecies differences
  - Factor of 10 for short duration (90 days) of study and database deficiency:
    - Short study duration (90-day study) and
    - Database deficiency which includes the absence of neurodevelopmental studies
- It is of note that JECFA (2008) considered that humans are likely to be less sensitive than rats to thyroid effects and that an uncertainty factor for interspecies variation was not required.
- The identified mode of action includes:
  - Non-genotoxic mode of action for the induction of thyroid tumours.
  - Rupture of the red blood cell membranes with intravascular haemolysis: that subsequent to initial formation of methaemoglobin, chlorate inactivates glucose-6-phosphate dehydrogenase and glyceraldehyde phosphate dehydrogenase and thus interrupts the capacity of the erythrocyte to generate nicotinamide adenine dinucleotide phosphate (NADPH), which is also a cofactor required for methaemoglobin reductase. Without cellular NADPH a cascade of protein denaturation and a crosslinking of erythrocyte membrane proteins occurs, finally resulting in erythrocyte haemolysis.
- Based on the identified mode of action, sensitive population are people with pre-existing blood conditions, especially anaemia, or those with kidney diseases, might be more sensitive. Persons with genetic diseases such as hereditary methaemoglobinaemia and glucose-6-phosphate dehydrogenase deficiency (which increases the haemolytic susceptibility of humans to oxidizing agents), and other persons who may be unusually susceptible to oxidants may also be at greater risk than the general population.

Decisions about the most appropriate toxicological endpoint and point of departure to use in guideline derivation are out of scope of this review. Potential guideline values if each identified overseas guideline were adapted to the Australian context have been derived for consideration (Table 5-1). Adoption/adaption of the WHO (2016) approach using parameters consistent with the ADWG would result in the following guideline derivation for consideration by NHMRC and the Water Quality Advisory Committee:

Chlorate:

$$0.3 \text{ mg/L} = \frac{0.011\frac{mg}{kg} \times 70\ kg \times 0.8}{\frac{2L}{d}}$$

Where:

- 0.011 mg/kg bodyweight per day is the values of the lower 95% confidence limit for the BMD_{10} (lowest $BMDL_{10}$) based on LOAEL from 2-year carcinogenicity study in rats (NTP 2005). Applying the safety factor of 100 (10 for intraspecies and 10 for database deficiency), TDI of 0.011 mg/kg bw/day can be used to derive chlorate guideline value.
- 0.8 is the proportion of total daily intake attributable to the consumption of water.
- 70 kg is the average weight of an adult.
- 2 L/day is the average amount of water consumed by an adult.

Adoption/adaption of the US EPA (2006, 2016), Health Canda (2008) and OEHHA (2002) reference dose using parameters consistent with the ADWG would result in the following guideline derivation for consideration by NHMRC and the Water Quality Advisory Committee:

$$0.2 \text{ mg/L} = \frac{0.03\frac{mg}{kg} \times 70\ kg \times 0.2}{\frac{2L}{d}}$$

Where:

- 0.03 mg/kg bodyweight per day from studies reviewed by US EPA (2006, 2016), OEHHA (2002) and Health Canada (2008).
- 0.2 is the proportion of total daily intake attributable to the consumption of water.
- 70 kg is the average weight of an adult.
- 2 L/day is the average amount of water consumed by an adult.

6.2 Recent evidence – results and comparison

Based on the identified most sensitive population to chlorate, refined recent evidence scan approach was developed and scanning results have highlighted the new modelling approach to measure benchmark response which results in higher TDI value of 0.08 mg/kg bw/day compared to the previously calculated TDI of 0.01 mg/kg bw/day in JECFA 2008 and WHO 2016 and TDI of 0.03 mg/kg bw/day in Health Canada 2008, OEHHA 2002, US EPA 2006, US EPA 2016.

This new approach proposed in Haber et al. (2021) study stated that:

- The BMR approach used by Haber team reflects the preference by US EPA (2012) and an acceptable approach by EFSA (2017). This approach was also strongly preferred by international consensus (IPCS, 2020).
- Based on the available information on the normal range in thyroid responses, they defined the BMR as a point value, based on the lower end of the clinically normal range published in the medical literature. Specifically, BMR was defined as RAIU of <80% for a 24 h measurement based on UCLA Health 2020 and MedLine Plus 2020, both of which described the normal range for the RAIU at 24 h as 8-25%.
- Defining the BMR based on an abnormal response raises an additional issue for practical application. If the BMR is simply defined as 8% RAIU, and the dose is computed at which the dose-response model predicts RAIU equal

to 8%, that means that, at that BMD, the average RAIU would be 8%. In population terms, that translates to approximately 50% of the population having an RAIU below 8% (i.e., 50% in the abnormal range). This is clearly a much higher proportion of the population with an abnormal response than would be used when modelling a dichotomous (yes/no) response. To avoid this issue, "hybrid" approach is used for defining the BMR (Crump, 1995). The hybrid approach calculates extra risk for continuous endpoints, based on a distribution of the continuous response (in this case, the Beta distribution), and either a cut-point separating normal from abnormal (in this case, the 8% response), or a specified proportion of abnormal responses in the control population. This approach allows to define a BMD at which it was estimated that there would be a 10% extra risk in the population of having RAIU of 8% or lower.

This proposed approach by Haber et al. (2021) highlighted the importance of derivation approach and applied modelling which best suited to the available data. This approach could be considered by NHMRC and the Water Quality Advisory Committee when deriving a health-based guideline value for chlorate.

6.3 Knowledge gaps and suggestions for further research

The following knowledge gaps have been identified during the review process:

- The key endpoint reported was changes in thyroid gland function including thyroid gland follicular cell hypertrophy increase and thyroid gland colloid depletion. Since thyroid hormone status plays critical role in normal brain development and due to the absence of neurodevelopmental studies and endpoints, further investigation of the impact of chlorate on neurodevelopment would be required.
- Based on the Haber et al. (2021) study, consideration of the benchmark response (BMR) as start point based on abnormal range of thyroid function is better suited to the available data on the impact of (per)chlorate on thyroid function. As such, further investigation of the modelling approach would be required to derive the most relevant point of departure.
- Moreover, no clear treatment related effects of chlorate on humans were reported. Based on the absence of any detrimental physiological responses, relative safety of oral ingestion of chlorate has been suggested. However, further epidemiological studies would be required to determine the impact of chlorate on human health.

Further research in these areas would be helpful to develop an accurate risk assessment of chlorate in drinking water.

6.4 Strength and limitations

Based on the key studies quality assessments the following areas of uncertainty should be considered:

- The short duration of the McCauley 1995 study might limit the certainty of the thyroid glands function. The NTP 2005 study (2-year study) showed that severity of follicular cell hyperplasia was dose related and more consistently observed at chlorate doses of 75 mg/kg bw per day and above.
- In the controlled clinical study (Lubbers et al. (1981)) and NTP 2005 2-year study, no adverse health effects were reported. This uncertainty in point of departure might result in the overly conservative guideline value selection.
- In the WHO 2016 guidance, JECFA considered that humans are likely to be less sensitive than rats to thyroid effects and as such animal study is likely to be conservative experimental model for guideline derivation.

Section 7 Conclusion

Screening of the available guideline documents from short-listed organisations and agencies as advised by NHMRC and the Water Quality Advisory Committee resulted in the following relevant guidelines for consideration in the review for chlorate:

- World Health Organization (WHO) (2016): Chlorine Dioxide, Chlorite and Chlorate in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality.
- Health Canada (2008): Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorite and Chlorate.
- California Office of Health and Hazard Assessment (OEHHA) (2002): Proposed Action Level for Chlorate.
- European Food Safety Authority (EFSA) (2015): Scientific Opinion on the Risks to Public Health Related to the Presence of Chlorate in Food.
- United States Environmental Protection Agency (US EPA) (2006): Reregistration Eligibility Decision (RED) for Inorganic Chlorates.
- United States Environmental Protection Agency (US EPA) (2016): Six-Year Review 3 Technical Support Document for Chlorate.

The identified guidelines were found suitable to adopt/adapt based on their administrative and technical processes. However, further analysis of the toxicological basis for the available guidance values was also considered.

Based on the existing guideline review and an analysis of the underpinning key studies it was determined that:

- McCauley 1995 (90-day) study was used as the key study for derivation of guideline values in WHO 2016, Health Canada (2008), OEHHA (2002) and EFSA (2015). There was overall high confidence in this study and others used in the identified guidelines based on an assessment of study quality.
- Although WHO 2016 revised the guideline value from 0.7 mg/L to 0.3 mg/L based on the 2-year NTP 2005 study (BMD was calculated by JECFA, 2008), due to considering challenges in achieving the revised value, previous provisional guideline value of 0.7 mg/L was retained. This achievability issue could also be considered by NHMRC and the Water Quality Advisory Committee during decision making.
- No guideline value on the aesthetic outcome from exposure to chlorate was established.

Decisions about the most appropriate toxicological endpoint and point of departure to use in guideline derivation are out of scope of this review. Potential guideline values if each identified overseas guideline were adapted to the Australian context have been derived for consideration (Table 5-1). However, potential adoption/adaption of the approach taken by WHO 2016 using parameters consistent with those used in the ADWG would result in a health-based guideline value for chlorate of 0.3 mg/L. Adoption/adaption of the approach taken by US EPA (2006, 2016), OEHHA (2002) and Health Canada (2008) using parameters consistent with those used in the ADWG would result in a health-based guideline value for chlorate of 0.2 mg/L.

The recent evidence scan identified that:

- No new sensitive health endpoint or different critical study for chlorate appeared to have been published since the most recent review of the literature (WHO 2016).
- A published paper by Haber et al. (2021) deriving a tolerable daily intake using an early key event in the mode of action for thyroid toxicity (inhibition of radioactive iodide uptake (RAIU) by the thyroid was identified and could be considered by NHMRC and the Water Quality Advisory Committee when deriving a health-based guideline value for chlorate. The authors used Bayesian hierarchical modelling, a beta distribution for the RAIU endpoint and a BMR of 10% extra risk for a population having a RAIU of 8% or lower. Based on the suggested reduced total UF (4 instead of 10 to account for human variability), TDI of

0.008 mg/kg bw/day for perchlorate has been suggested as a health protective value. Consistent with the EFSA approach, the chlorate TDI can be calculated as 10x the perchlorate TDI. The resulting chlorate TDI would be 0.08 mg/kg bw/day. Critical assessment of the studies identified in the evidence scan is out of scope of this review. These should be evaluated in further detail before being included in any decision-making.

- Australian treatment plant monitoring data for chlorate were not found by the literature search. US data with regard to chlorate control when using hypochlorite (e.g. storage) and water treatment is available. Most US treatment plants (>90%) had results less than 700 µg/L (WHO provisional guideline value). In particular AWWA B300 Hypochlorite Standard updated in 2018 now includes instructions on storage, use and handling of hypochlorite by water utilities to reduce chlorate concentration.

The key challenge in maintaining a low level of chlorate in drinking water is storage condition of hypochlorite and chlorine dioxide in treatment plants. There are guides/standards for the control of chlorate during hypochlorite use and information available on occurrence and sources of chlorate from overseas sources showing that a majority (> 90%) of treatment plants in the US can meet the provisional guideline value of 0.7 mg/L but not the updated guideline value of 0.3 mg/L (WHO, 2016). Issues around feasibility in the Australian context could also be considered by NHMRC and the Water Quality Advisory Committee during decision making.

Section 8 Review Team

Name	Role	Qualification	Experience
John Frangos	Senior Reviewer	MSc Toxicology, DABT, FACTRA	25+ years of experience in toxicology and risk assessment and regulatory advice to industry and government bodies (including GV development and health impacts of environmental exposure.
Dr Paolin Rocio Caceres Velez	Reviewer	PhD Ecotoxicology / Nanotoxicology	5 years of experience in ecotoxicity risk assessment
Dr Maryam Moslehi	Reviewer	PhD Molecular Biochemistry/Health Science	3 years of experience in risk assessment and literature review

Section 9 Declaration of interests

None.

Section 10 Acknowledgments

None.

Section 11 References

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