NHMRC

Technical Report - Chlorate

Evaluated 2021

CDM Smith

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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
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MS	Mass Spectrometry
NHMRC	National Health and Medical Research Council

Abbreviation	Definitions
NOAEL	No Observed Adverse Effect Level
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

Document history & status

Revision	Date issued	Reviewed by	Approved by	Date approved	Revision type
Rev0	01/10/21	Maryam Moslehi	John Frangos	01/10/21	Draft
Rev1	30/11/2021	Maryam Moslehi	John Frangos	30/11/2021	Draft
Rev2	27/5/2025	Sarah Leviston	John Frangos	27/5/2025	Final
Rev3	30/6/2025	Sarah Leviston	Christian Wallis	30/6/2025	Final

Distribution of copies

Version	Date issued	Quantity	Electronic	Issued to
Rev0	01/10/21	1	pdf	Kristal Jackson
Rev1	30/11/2021	1	pdf	Hew Merrett
Rev2	27/5/2025	1	pdf	Amanda Jupp
Rev3	30/6/2025	1	pdf	Amanda Jupp

Last Saved:	30 June 2025
File Name:	Technical Report - Chlorate Rev2 NHMRC
Author:	Maryam Moslehi, Paolin Caceres Velez, John Frangos
Project Manager:	Maryam Moslehi
Client:	NHMRC
Document Title:	**Technical Report - Chlorate**
Document Version:	Rev3
Project Number:	1001098

Section 1 Technical Report Approach Overview

Table 1-1 Technical Report Sections

Section	Title	Existing guideline to review	Approach
Section 2	**Research Question**	US EPA 2006/2016, WHO 2016, Health Canada 2008, OEHHA 2002, EFSA 2015 Refer to Table 3-1	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 3	**Evidence Evaluation methods**		- Approach used to identify and retrieve existing guidance or studies: Consistent with search strategy documentation outlined in Appendix A of Research Protocol. - Process for selecting studies (i.e. application of inclusion/exclusion criteria) and list of included studies (and excluded if available): All retrieved studies are documented (consistent with PRISMA approach). Inclusion and Exclusion criteria is outlined as per PECO criteria. - Methods for data extraction and completed table of extracted data for each piece of evidence - Methods of assessing quality of existing guidance/ guidelines (i.e. use of Assessment Tool). Completed copy of Assessment tool for each guidance/guideline document. - 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 (can have different levels of information about this in each Report)
Section 4	**Results**		Summary of findings tables for each research question or section of factsheet. Easy to compare different guidelines/studies in Evaluation Report, detailed information in Technical Report
Section 5	**References**		Reference list
Appendix A	**Supplementary Information**		Additional technical detail or examples of templates used in methods to be provided as required
Appendix B	**Recent Evidence Scan**		Results of the recent evidence scan

Section 2 Research questions

The Australian Drinking Water Guidelines (ADWG) factsheets include 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. 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 2-1 below.

Table 2-1 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?

Factsheet Section	Research questions
Supporting information	
General description	Is this information current?
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 3 Evidence Evaluation – Methods & Approaches

3.1 Initial source screening – Identification of the existing guidelines

Screened guidelines are indicated in Figure 3-1. These primary sources are screened, and relevant guidelines search are conducted by content experts, Paolin Caceres Velez and Maryam Moslehi (Table 3-1).

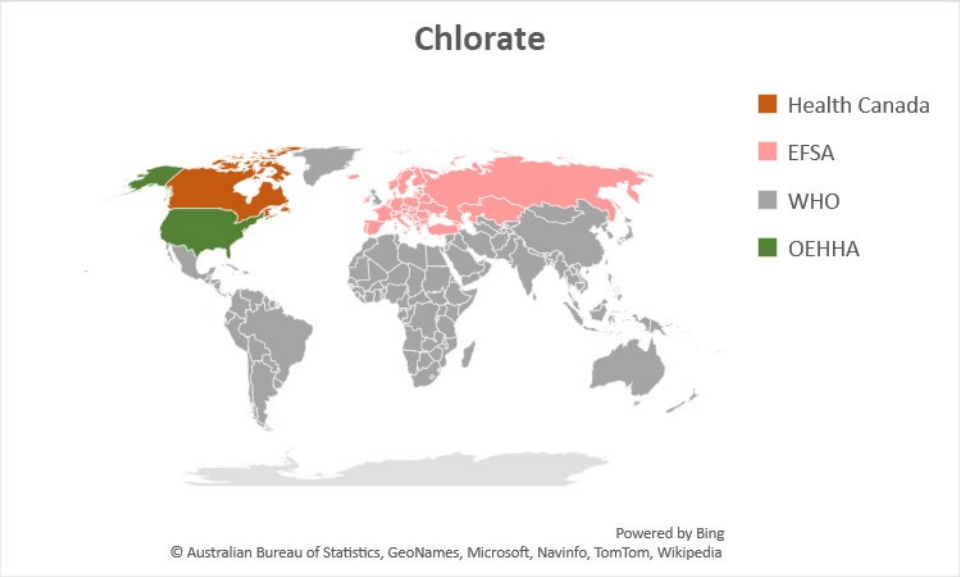


Figure 3-1 Reviewed existing guidelines

Table 3-1 Existing guidelines for chlorate in drinking water

Jurisdiction	Document title, year	Reviewer's comments
World Health Organization (WHO)	Chlorine Dioxide, Chlorite and Chlorate in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality, 2016	None.
Health Canada	Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorite and Chlorate, 2008	None.
California Office of Health and Hazard Assessment (OEHHA)	Proposed Action Level for Chlorate, 2002	Action level was established.
European Food Safety Authority (EFSA)	Scientific Opinion, Risks for public health related to the presence of chlorate in food, 2015	None.
United States Environmental Protection Agency (US EPA)	Reregistration Eligibility Decision (RED) for Inorganic Chlorates, 2006. Six-Year Review 3 Technical Support Document for Chlorate, 2016.	

3.2 Data search strategy for the existing guidelines

Data search and documentation approach is outlined in Table 3-2 below.

Table 3-2 Search strategy and selection of evidence

Search terms	Chlorate, chlorate AND drinking water, chlorate AND disinfect, chlorate AND adverse health effect, chlorate AND toxicity
Publication date	The most recent and relevant guidance documents
Language	English and German
Study Type	Primary source of guideline documents (National and International)
Inclusion and exclusion criteria	PECO (population, Exposure, Comparator and outcome)
Validation methods used	Search results are checked by senior reviewer, John Frangos
Searching methods	The most relevant primary guideline documents based on key search terms and PECO criteria
Documentation of search	Summary of the key data is recorded (based on PECO criteria)

3.3 Review of the existing guidelines against the PECO criteria

Search strategy is developed using the populations, exposure, comparators and outcomes (PECO) criteria approach. The PECO defines the objectives of the guideline review. Furthermore, the PECO informs the 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).

Table 3-3 PECO-based guideline document search strategy

Search element	Comments	Comments
Population	**Sensitive population** - Infants and children - Pregnant women - Aboriginal and Torres Strait Islander peoples - People with pre-existing health conditions identified in peer reviewed competent authority as possible renal disease - People who ingest higher than average amount of water e.g. in tropical locations or outdoor workers	Based on the mode of action, the most sensitive population is identified.
Exposure	- Lifetime exposure - Short-term exposure - Combination or reaction with substances (e.g. reaction with ozone) - Exposure through drinking, cooking, washing, skin contact - PBPK-based exposure model characteristics	Data is retrieved from the key study (ies) for guideline derivation.
Comparator	Health-based advice: - Comparison between the current guideline value and any different (higher/lower) existing values Supplementary advice: - Comparison between different water treatment options to assess incremental exposure levels and incidence results. - Comparison to no observed effects level / no exposure level	Health-based advice and supplementary information from the existing guidelines are summarised.

Search element	Comments	Comments
Outcome	The human health and aesthetic outcomes of concern from exposure to chlorate include: - Mortality - Severe human health outcomes, including incidence of life-threatening illness, disability or chronic disease with ongoing impact on quality of life. - Less severe or short-term human health outcomes, e.g. irritation. - Aesthetic outcomes, including taste, smell, colour, clarity, etc. - Other (bioanalytical assays that support health outcomes, for example results from Tox21 screening assays) Consideration regarding these outcomes will be given to: - The level of chlorate in drinking water considered to be safe or acceptable to human health over a lifetime - The level of chlorate in drinking water considered to be safe or acceptable to human health during a short-term event - The level of chlorate in drinking water considered to be acceptable in relation to aesthetic factors, including taste, smell, colour, clarity, etc.	Health adverse effects (critical health effects and other effects) are summarised and compared between the existing guidelines.

3.4 Guideline review approach

The review of the existing guideline documents includes:

- *Initial source screening*: this screening allows to limit the following search and evaluation to the guidance documents that include proposed guideline values 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 by applying a primary study 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.

3.5 Comparison between existing Drinking Water Guideline documents

A chlorate health-based guideline value was not set in the Australian Drinking Water Guidelines (ADWG) due to insufficient data. Although action to reduce the use 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 using the key parameters that are pivotal to guideline derivation (Table 3-4). As it was shown, key parameters include:

- Critical study
- Study population
- Experiment substance
- Route of exposure
- Administered dose
- Exposure duration
- Critical effects (e.g. adverse effect modelled)
- Dose adjustments
- Point of Departure (POD)
- Safety factors (interspecies, intraspecies, adequacy of database, other factors)
- All the studied health effect summary
- Mode of action

3.6 Guideline derivation and value and year of publication Quality assessment and Evaluation – Existing Guidelines

Existing guidelines containing potential health-based guideline values for possible adoption/adaptation in Australia were evaluated using an Assessment Tool provided by NHMRC and outlined in the research protocol for this review. This Tool evaluates each document against administrative and technical criteria that demonstrate transparent and robust guideline development and evidence review processes that meet NHMRC standards for guidelines. Further details on the assessment of each guideline using the Assessment Tool are provided below.

Assessments were undertaken for the following included guidelines:

- 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 assessments for each organisation (WHO, Health Canada, OEHHA, EFSA and US EPA) are provided below.

World Health Organization (WHO)

WHO 2016: Chlorine Dioxide, Chlorite and Chlorate in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. Criteria have been colour-coded as follows: 'Must-have', 'Should have' or 'May have'.			
Criteria		**Y/N/?/NA**	**Notes**
	Overall guidance/advice development process		
	Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	
	Are the administrative processes documented and publicly available?	Y	Brief details on administrative process provided in document reviewed.
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	Work is overseen by working groups with experts from different regions, details of key personnel and contributors are provided in the documents reviewed. DOI processes were not reported in document reviewed.
	Are funding sources declared?	N	Not reported.
	Was there public consultation on this work? If so, provide details.	Y	Document reviewed was available for public comment.
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	Document reviewed was internationally peer reviewed. The peer review outcomes were not made publicly available.

	Was the guidance/advice developed or updated recently? Provide details.	N	Document published in 2016.
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Not reported in document reviewed.
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	N	Not reported in document reviewed.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	Not reported in document reviewed.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	N	Not reported in document reviewed.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	Not reported in document reviewed.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Yes. Revision of previous risk assessments undertaken (e.g. EHC or CICAD monograph, IARC, JECFA) when developing the guidance.
	Can grey literature such as government reports and policy documents be included?	N	Not reported in document reviewed.
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	Not reported in document reviewed but available in other policy documents.
	Evidence search		
	Are databases and other sources of evidence specified?	N	Not reported in document reviewed.
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	N	Not reported in document reviewed.
	Is it specified what date range the literature search covers? Is there a justification?	N	Not reported in document reviewed.
	Are search terms and/or search strings specified?	N	Not reported in document reviewed.
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	N	
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	Not reported in document reviewed.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	Not reported in document reviewed.
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	Not reported in the document reviewed.
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	Y	

	Are the parameter value assumptions documented and explained?	Y	
	Are the mathematical workings/algorithms clearly documented and explained?	Y	
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	Y	
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	
	What processes are used when expert judgement is required and applied? Is the process documented and published?	N	Not reported in document reviewed.
	Is dose response modelling (e.g. BMDL) routinely used?	Y	Where data permit.
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	Y	For genotoxic carcinogens, the DWG represents an excess lifetime cancer risk of $1x10^{-5}$ for people drinking water containing the chemical at the DWG for 70 yrs.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	Y	$1x10^{-5}$.

Health Canada

Health Canada 2008: Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorite and Chlorate. Criteria have been colour-coded as follows: 'Must-have', 'Should have' or 'May have'.		
Criteria	**Y/N/?/NA**	**Notes**
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	
Are the administrative processes documented and publicly available?	Y	
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	The CDW has members from each jurisdiction in Canada, which represent the authority responsible for drinking water quality in their jurisdiction and observers. Management of interests is unclear from the document reviewed.
Are funding sources declared?	N	Not reported in document reviewed but assumed to be government funded.
Was there public consultation on this work? If so, provide details.	Y	Yes, draft technical support documents are published on the Health Canada website for public comment. Following each consultation, the document is revised and posted on the website. A summary of the comments received and how they have been addressed is available upon request.

	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	The guideline technical document is peer reviewed by external experts. The peer review outcome is available on request.
	Was the guidance/advice developed or updated recently? Provide details.	N	Published in 2008.
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Not reported in document reviewed.
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	N	Not clear from document reviewed.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	Not reported in document reviewed.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	Y	Where unpublished information is cited, it is described and recorded.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	Not reported in document reviewed.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Health Canada cites existing international agency reviews. Process for critical appraisal not reported in document reviewed.
	Can grey literature such as government reports and policy documents be included?	Y	Health Canada uses existing government reviews (e.g. toxicological reviews) as primary sources of information in technical guidance documents.
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	Policies not reported in document reviewed but justification for endpoints provided.
	Evidence search		
	Are databases and other sources of evidence specified?	N	Not reported in document reviewed.
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	N	Not reported in document reviewed.
	Is it specified what date range the literature search covers? Is there a justification?	N	Date range is not provided in document reviewed, but updates to existing technical guidelines appear to include literature published after the previous guideline was set.
	Are search terms and/or search strings specified?	N	No.
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	N	Not reported in document reviewed.
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence	N	

	(i.e. to assess and summarise the information provided in the studies)? If so, provide details.		
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	Y	
	Are the parameter value assumptions documented and explained?	Y	
	Are the mathematical workings/algorithms clearly documented and explained?	Y	
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	Y	
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	N	Not clear from document reviewed.
	What processes are used when expert judgement is required and applied? Is the process documented and published?	N	Not clear from document reviewed.
	Is dose response modelling (e.g. BMDL) routinely used?	N	Not clear from document reviewed.
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	N	Not clear from document reviewed.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	N	Not reported in document reviewed.

Office of Environmental Health and Hazard Assessment (OEHHA)

OEHHA 2002: Proposed Action Level for Chlorate. Criteria have been colour-coded as follows: 'Must-have', 'Should have' or 'May have'.		
Criteria	**Y/N/?/NA**	**Notes**
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	
Are the administrative processes documented and publicly available?	N	Not specified in document reviewed.
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	N	Not specified in document reviewed.
Are funding sources declared?	N	Not reported in document reviewed but assumed to be government funded.
Was there public consultation on this work? If so, provide details.	N	Not reported in document reviewed.
Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	N	Not reported in document reviewed.

	Was the guidance/advice developed or updated recently? Provide details.	Y	Published in 2002.
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Not reported in document reviewed.
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	N	Not reported in document reviewed.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	Not reported in document reviewed.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	N	Not reported in document reviewed.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	Not reported in document reviewed.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Yes. OEHHA reviews risk assessments performed and determinations made by US State or Federal government organisations but conducts its own risk assessment for the development of PHGs.
	Can grey literature such as government reports and policy documents be included?	Y	
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	
	Evidence search		
	Are databases and other sources of evidence specified?	N	Not reported in document reviewed.
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	N	Not reported in document reviewed.
	Is it specified what date range the literature search covers? Is there a justification?	N	Not reported in document reviewed.
	Are search terms and/or search strings specified?	N	Not reported in document reviewed
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	N	Not reported in document reviewed.
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	Not reported in document reviewed.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	Not reported in document reviewed.
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	Not reported in document reviewed.
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	Y	

	Are the parameter value assumptions documented and explained?	Y	
	Are the mathematical workings/algorithms clearly documented and explained?	Y	
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	N	
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	N	Not reported in document reviewed.
	What processes are used when expert judgement is required and applied? Is the process documented and published?	N	Not reported in document reviewed.
	Is dose response modelling (e.g. BMDL) routinely used?	Y	
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	Y	OEHHA has guidance documents that are publicly available.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	Y	The level of cancer risk used in developing PHGs is one in one million (1×10^{-6}).

European Food Safety Authority (EFSA)

EFSA 2015: Scientific Opinion on the Risks to Public Health Related to the Presence of Chlorate in Food.

Criteria have been colour-coded as follows: 'Must-have', 'Should have' or 'May have'.

Criteria	Y/N/?/NA	Notes
Overall guidance/advice development process		
Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	
Are the administrative processes documented and publicly available?	Y	
Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	The EFSA Panel on Contaminants in the Food Chain (CONTAM) undertook this work. DOI's not specified in document reviewed but are reported and made publicly available on the EFSA website.
Are funding sources declared?	N	Not reported but assumed to be funded by member states.
Was there public consultation on this work? If so, provide details.	N	Not specified in document reviewed.
Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	N	Not specified in document reviewed.
Was the guidance/advice developed or updated recently? Provide details.	N	Published in 2015.
Evidence review parameters		
Are decisions about scope, definitions and evidence review parameters documented and publicly available?	Y	Terms of reference of review provided some details of scope.

	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	Y	
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	This is not specified in document reviewed.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	N	Not specified in document reviewed.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	Y	
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	Y	Relevant risk assessments performed by other EU or international bodies can be used provided a comprehensive description of all data, processes and methods is available. The relevance of the assessment in light of more recent data is also considered.
	Can grey literature such as government reports and policy documents be included?	Y	
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	
	Evidence search		
	Are databases and other sources of evidence specified?	Y	
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	Y	
	Is it specified what date range the literature search covers? Is there a justification?	Y	
	Are search terms and/or search strings specified?	N	Not specified in document reviewed.
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	Y	
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	Y	Systematic review not undertaken for document reviewed. However, data provided by member states was evaluated to determine their quality and relevance to the assessment. This is reflected in the relative weight given to the data in the assessment and taken into account in the overall evaluation of uncertainty.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	Y	EFSA risk assessment guidance documents referenced.
	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	
	Derivation of health-based guideline values		

	Is there justification for the choice of uncertainty and safety factors?	Y	
	Are the parameter value assumptions documented and explained?	Y	
	Are the mathematical workings/algorithms clearly documented and explained?	Y	
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	N	Not reported in document reviewed.
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	N	Not reported in document reviewed.
	What processes are used when expert judgement is required and applied? Is the process documented and published?	N	Not specified in document reviewed.
	Is dose response modelling (e.g. BMDL) routinely used?	Y	
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	Y	EFSA has employed a margin of exposure (MOE) approach using a $BMDL_{10}$ for cancer incidence in animals or humans.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	Y	In general, an MOE of 10,000 or higher, if based on the $BMDL_{10}$ from an animal study, is considered to be of low concern from a public health point of view and a low priority for risk management.

United States Environmental Protection Agency (US EPA)

US EPA 2006: Reregistration Eligibility Decision (RED) for Inorganic Chlorates.

US EPA 2016: Six-Year Review 3 Technical Support Document for Chlorate.

Criteria have been colour-coded as follows: 'Must-have', 'Should have' or 'May have'.

Criteria	Y/N/?/NA	Notes
	Overall guidance/advice development process	
	Are the key stages of the organisation's advice development processes compatible with Australian processes?	Y	
	Are the administrative processes documented and publicly available?	Y	
	Was the work overseen by an expert advisory committee? Are potential conflicts of interest of committee members declared, managed and/or reported?	Y	MDBP Advisory Committee oversees 6 year review of DBPs. Board and Committee members are subject to many Federal requirements including those dealing with conflict-of-interest and ethics statutes. An evaluation of each nominee for the Committee is undertaken with regards to expertise and experience, potential conflicts of interest and bias.
	Are funding sources declared?	N	Not reported but assumed to be government funded.

	Was there public consultation on this work? If so, provide details.	N	Unclear from document reviewed, although information on public consultation provided in DBP document.
	Is the advice peer reviewed? If so, is the peer review outcome documented and/or published?	Y	Not reported in document reviewed. Details on peer review provided in DBP document.
	Was the guidance/advice developed or updated recently? Provide details.	Y	Published in 2016 alongside 6 year review of DBPs.
	Evidence review parameters		
	Are decisions about scope, definitions and evidence review parameters documented and publicly available?	N	Not clear in document reviewed.
	Is there a preference for data from studies that follow agreed international protocols or meet appropriate industry standards?	N	Not clear in document reviewed.
	Does the organisation use or undertake systematic literature review methods to identify and select data underpinning the advice? Are the methods used documented clearly?	N	Not reported in document reviewed.
	If proprietary/confidential studies or data are considered by the agency, are these appropriately described/recorded?	N	Not reported in document reviewed.
	Are inclusion/exclusion criteria used to select or exclude certain studies from the review? If so, is justification provided?	N	Not reported in document reviewed.
	Does the organisation use or adopt review findings or risk assessments from other organisations? What process was used to critically assess these external findings?	N	Not reported in document reviewed.
	Can grey literature such as government reports and policy documents be included?	Y	
	Is there documentation and justification on the selection of a toxicological endpoint for use as point of departure for health-based guideline derivation?	Y	
	Evidence search		
	Are databases and other sources of evidence specified?	Y	
	Does the literature search cover at least more than one scientific database as well as additional sources (which may include government reports and grey literature)?	Y	
	Is it specified what date range the literature search covers? Is there a justification?	Y	6 year review, cut off date specified at start of document.
	Are search terms and/or search strings specified?	N	
	Are there any other exclusion criteria for literature (e.g. publication language, publication dates)? If so, what are they and are they appropriate?	N	Not reported in document reviewed.
	Critical appraisal methods and tools		
	Is risk of bias of individual studies taken into consideration to assess internal validity? If so, what tools are used? If not, was any method used to assess study quality?	N	Not reported in document reviewed.
	Does the organisation use a systematic or some other methodological approach to synthesise the evidence (i.e. to assess and summarise the information provided in the studies)? If so, provide details.	N	Not clear from document reviewed.

	Does the organisation assess the overall certainty of the evidence and reach recommendations? If so, provide details.	N	Not clear from document reviewed.
	Derivation of health-based guideline values		
	Is there justification for the choice of uncertainty and safety factors?	Y	
	Are the parameter value assumptions documented and explained?	Y	
	Are the mathematical workings/algorithms clearly documented and explained?	Y	
	Does the organisation take into consideration non-health related matters to account for feasibility of implementing the guideline values (e.g. measurement attainability)?	Y	
	Is there documentation directing use of mechanistic, mode of action, or key events in adverse outcome pathways in deriving health-based guideline values?	Y	Cites EPA guidance documents.
	What processes are used when expert judgement is required and applied? Is the process documented and published?	N	Not reported in document reviewed.
	Is dose response modelling (e.g. BMDL) routinely used?	Y	
	What is the organisation's policy for dealing with substances for which a non-threshold mode of action may be applicable in humans? Has the policy been articulated and recorded?	Y	EPA approaches outlined in cited documents. In the absence of sufficiently, scientifically justifiable mode of action information, US EPA generally takes the default position that animal tumour findings are judged to be relevant to humans and cancer risks are assumed to conform with low dose linearity. It is noted this is a divergence from other agencies, and Australia, where a genotoxic MOA drives use of linear dose response modelling.
	If applicable: For carcinogens, what is the level of cancer risk used by the organisation to set the health-based guideline value?	Y	US EPA target cancer risk is typically 1 x 10^{-6} (1 in a million). Guideline values for 10^{-6} 10^{-5} and 10^{-4} lifetime cancer risks are provided.

Table 3-4 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)	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	Thyroid hypertrophy in adult rats	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) for increased follicular cell hypertrophy in rats.	ADI of 0 – 0.01 mg/kg bw for chlorate based on the BMDL10 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 BMD10 ($BMDL_{10}$) ranged from 1.1 to 4.4 mg/kg bw per day, expressed as chlorate. JECFA used the lowest BMDL10 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	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.	

Parameters	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015		OEHHA 2002	Health Canada 2008
				(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).			
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	
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).	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	

Parameters	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015	OEHHA 2002	Health Canada 2008
			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. 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.		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 NaClO3 and KClO3 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 ClO3 - doses, including decreased blood glutathione (at two and 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 NaClO3 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	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
				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. 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	$0.21\frac{mg}{L} = \frac{\left(0.03\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 70kg\right)}{2\frac{L}{day}} \times 0.2$ 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.* $0.7\frac{mg}{L} = \frac{\left(30\frac{\mu g}{kg}of\ body\ weight\ per\ day \times 60kg\right)}{2\frac{L}{day} \times 1000} \times 0.8$ *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.*	$0.07\frac{mg}{L} = \frac{\left(0.0012\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 60kg \times 0.8 \times 10\right)}{2\frac{L}{day} \times 4}$ 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.***	$0.8\frac{mg}{L} = \frac{\left(0.036\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 60kg\right)}{2\frac{L}{day}} \times 0.8$ 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): $= 0.2\text{ mg}/\text{L}\frac{\left(30\frac{\text{mg}}{\text{kg}}\text{of body weight per day} \times 70kg \times 0.2\right)}{2\frac{L}{day} \times 1000}$ 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).

Parameters	NHMRC 2011	US EPA 2006 & 2016	WHO 2016	EFSA 2015		OEHHA 2002	Health Canada 2008
							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: $\boldsymbol{MAC} = \frac{\left(0.03\frac{\mu g}{kg}\, of\ bw \times 70kg \times 0.8\right)}{1.5\frac{L}{day}} = \boldsymbol{1.12\frac{mg}{L}\left(rounded\ to\ 1\frac{mg}{L}\right)}$ where: - 0.03 mg/kg bw is the TDI, as calculated above, - 70 kg bw is the average body weight of an adult, - 0.80 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	0.21 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^	NA	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.

3.7 Quality assessment and Evaluation – Key studies in guidelines

Key studies refer to the studies that were used to derive guideline values in different guidance documents. Existing guidelines review indicates that:

- Key study in WHO 2016 and US EPA 2006/2016 corresponds to **NTP (2005)** toxicology and carcinogenesis studies of chlorate in rats.
- Summary of all assessments that led to WHO 2016 guideline derivation (previous and current assessments). TDI calculation by WHO is supported by the results of human volunteer studies in which repeated administration of chlorate at 36 µg/kg bw per day did not results in any adverse effects **(Lubbers et al. 1981)**.
- EFSA 2015 used the chronic TDI for perchlorate which is based on the controlled human study by **Greer et al. 2002**.
- OEHHA 2002 and Health Canada 2008 both applied the same key study, **McCauley et al. 1995** on the effects of Subchronic chlorate exposure in rats.
- No guideline value for chlorate level in drinking water in Australia was derived.

Table 3-5 and Table 3-6 evaluated the key studies introduced in the existing guidance documents. Study evaluation is a broad term encompassing interpretation of a variety of methodological features (e.g., study design, exposure measurement, study execution, data reporting).

Table 5-1 in supplementary information section (Appendix A) outlined 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". Core and prompting questions that aid selection of the appropriate domain judgement for animal and epidemiological studies are shown in Table 5-2 and Table 5-3, respectively.

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 for animal studies and human study. Overall rating (overall study confidence) is for animal and human key studies indicated below in Table 3-5 and Table 3-6, respectively. Based on the study evaluation, these key studies show high confidence (overall rating).

Table 3-5 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 – 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 3-6 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

Author, year	Evaluation parameter	Evaluation of each parameter	Overall rating	Comments/Rational
	Sensitivity Exposure measurement Sensitivity analysis	Adequate		Short exposure duration (14 days)
	Reporting quality Outcome ascertainment	Good		-

3.8 Comparison of guideline derivation and calculation

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 3-7. Different overseas agencies applied the key studies to derive the chlorate daily intake.

Table 3-7 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	

- **US EPA (2006/2016)**: The US Environmental Protection Agency (US EPA) has published a Reregistration Eligibility Decision (RED) for inorganic chlorates. A 95 % lower confidence limit for the benchmark dose response of 10% extra effect ($BMDL_{10}$) for chlorate of 0.9 mg/kg per day was calculated for increased thyroid gland follicular cell hypertrophy and follicular cell mineralisation in the National Toxicology Program (NTP) carcinogenicity study of sodium chlorate in rats (NTP, 2005). The US EPA applied an uncertainty factor of 30 (3 for interspecies and 10 for intraspecies differences) and established a chronic reference dose (RfD) of 0.03 mg/kg bw per day. The selection of the interspecies uncertainty factor of three, rather than the default factor of 10, was due to the quantitative dynamic differences between rats and humans with respect to thyroid function. The US EPA noted that the half-life of thyroid hormone thyroxine (T4) in rats is approximately 12 hours, whereas it is five to 9 days in humans. The shorter half-life in rats is likely related to a high-affinity binding globulin for T4 that is present in humans but absent in rodents. In the absence of a functional thyroid gland, a rat requires approximately 10-times more T4

than an adult human for full reconstitution. Constitutive thyroid stimulating hormone (TSH) levels are nearly 25-times higher in rats than in humans, reflecting the increased activity of the thyroid-pituitary axis in rats. An Acute Reference Dose (ARfD) was not established because effects attributable to a single dose were not seen in the available data.

The chronic NTP (2005) study was identified as the critical study for establishing a reference dose (RfD) of 0.03 mg/kg/day for chlorate (US EPA, 2006). The RfD was derived by using the Benchmark Dose (BMD) method and based on a Benchmark Dose Level (BMDL) of 28 mg/L as sodium chlorate (22 mg/L as chlorate) for increased follicular cell hypertrophy as the critical effect. The 22 mg/L concentration corresponds to a dose of 0.9 mg/kg/day for chlorate ion (US EPA, 2006). A net uncertainty factor (UF) of 30 was applied when deriving the RfD. This consisted of a UF of 10 for inter-human variability for potentially sensitive individuals in the absence of information on the variability of response in humans and a UF of 3 for interspecies uncertainty because there is increased activity of the thyroid-pituitary axis in rats (Döhler et al., 1979; McClain, 1992) modulating the applicability of the thyroid effects in rats when extrapolated to humans. A UF of 1 was assigned for LOAEL-to-NOAEL adjustment because the BMDL approach was used to set the RfD; a UF of 1 for subchronic to chronic extrapolation because a chronic study was used; and a UF of 1 for database uncertainties because the database of chlorate includes subchronic, chronic, developmental and reproductive studies.

Chlorate is able to cause haemolysis at doses greater than the RfD. Thus, persons with low red blood cell (RBC) counts, such as those with anaemia, may be particularly sensitive to sodium chlorate. However, it is not clear whether newborns are more sensitive to the haemolytic effect of chlorate than adults (CalEPA, 2002) because of age alone. Individuals co-exposed to other ions that decrease iodine uptake by the thyroid (e.g., perchlorate) or cause methemoglobinemia and low RBC counts (e.g., nitrate or nitrite) could be more sensitive to chlorate exposure (Khan et al., 2005) than the general population.

To evaluate the systems and populations exposed to chlorate in drinking water from public water systems (PWSs), monitoring data were compared to a concentration in drinking water that is termed the health reference level (HRL). The HRL is a risk-derived concentration against which to compare the occurrence data from PWSs to determine if chlorate occurs with a frequency and at levels of public health concern. HRLs are not final determinations about the level of a contaminant in drinking water that is necessary to protect any particular population and they are derived prior to development of a complete exposure assessment.

US EPA 2016 calculated a long-term non-cancer HRL of 210 µg/L for chlorate, using the RfD of 0.03 mg/kg/day for a 70-kg adult ingesting 2 L of drinking water per day and a default relative source contribution (RSC) of 20 percent (US EPA, 2014). The agency anticipates evaluating health effects related to short-term exposures as part of potential future regulatory actions.

EPA derived the HRL for chlorate using the RfD approach as follows:

$$HRL\left(\frac{mg}{L}\right) = \left(\frac{RfD \times BW}{DWI}\right) * RSC$$

Where:

RfD = Reference Dose (mg/kg/day)

BW = Body Weight for an adult, assumed to be 70 kilograms (kg); for a child, assumed to be 10 kg

DWI = Drinking Water Intake for an adult, assumed to be 2 L/day (90th percentile); for a child, assumed to be 1L/day (90th percentile)

RSC = Relative Source Contribution, or the level of exposure believed to result from drinking water when compared to other sources (e.g., food, ambient air). In the absence of a complete exposure assessment, a default RSC value is used in the calculation of the HRL. Default values are based on the Exposure Decision Tree (US EPA, 2000). 20 percent is the most conservative RSC used in the derivation of a maximum contaminant level goal (MCLG) for drinking water.

The RfD for chlorate is protective against acute alterations in thyroid homeostasis and, therefore, considered to also be protective of tumorigenicity as well as other chronic and subchronic adverse health effects discussed in the literature (Khan et al., 2005; NTP, 2005).

- **WHO 2016**: For chlorate, JECFA concluded that the most sensitive effects were changes to the thyroid gland of male rats, noting that rats are highly sensitive to the effects of agents that disrupt thyroid hormone homeostasis. A $BMDL_{10}$ (95% lower confidence limit of the BMD_{10}, for an extra 10% increase in incidence of tumours compared with the background incidence in controls) of 1.1 mg/kg bw per day was calculated for non-neoplastic effects on the thyroid of male rats in the carcinogenicity study of sodium chlorate conducted by the National Toxicology Program (NTP, 2005). 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. However, in addition to the safety factor of 10 to allow for intraspecies variability, an additional factor of 10 was required to allow for the deficiencies in the database, particularly with respect to investigation of possible neurodevelopmental effects. JECFA therefore established an acceptable daily intake (ADI) of 0–0.01 mg/kg bw for chlorate. JECFA noted that the estimated dietary exposure of 0.6 µg/kg bw per day, representing high consumers including children, was less than 10 % of the ADI and compatible with the exposure allocated to other sources within the WHO drinking water guidelines for chlorate.

  Sodium chlorite was not carcinogenic following a number of long-term studies, although these were not conducted to current standards. The International Agency for Research on Cancer concluded in 1991 that sodium chlorite was not classifiable with respect to carcinogenicity to humans. Sodium chlorite has given positive results in some, but not all, in vitro genotoxicity assays and in one of the two available in vivo mouse micronucleus assays involving intraperitoneal administration. Negative results were obtained in several in vivo assays, for induction of bone marrow micronuclei, chromosomal aberrations and sperm head abnormalities, involving oral administration of sodium chlorite to mice.

  Sodium chlorate has been tested for carcinogenicity in rats and mice under the United States National Toxicology Program; results of these studies were not available at the time WHO set the TDI for chlorate. There was no evidence of carcinogenic activity in male B6C3F1 mice and equivocal evidence in female mice based on marginally increased incidences of pancreatic islet neoplasms.

  Sodium chlorate produced positive results in some in vitro assays, but not for induction of bone marrow micronuclei or chromosomal 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. The incidence of thyroid gland follicular hypertrophy was enhanced compared with control groups at doses lower than those resulting in increased tumour incidences and was significantly greater than control in the male rats at all tested doses. Therefore, the lowest dose, equivalent to approximately 5 mg/kg bw per day, expressed as chlorate, was the LOAEL. Because a NOAEL was not identified in the study, the Committee decided to apply a 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 BMD10 values for a 10% increase in thyroid gland follicular cell hypertrophy in the male rats ranged from 1.9 to 5.9 mg/kg bw per day, expressed as chlorate. The values of the 95% lower confidence limit for the BMD ($BMDL_{10}$) ranged from 1.1 to 4.4 mg/kg bw per day, expressed as chlorate. The Committee 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.

  Based on the negative in vivo genotoxicity data and the nature of the histopathological observations, the Committee concluded that a non-genotoxic mode of action was likely for the induction of thyroid tumours by sodium chlorate. This mode of action is likely to be mediated via decreased serum thyroid hormones, leading to increased release of TSH and consequent stimulation of thyroid cell proliferation and thyroid gland growth, which can lead to thyroid tumours in rodents.

In addition to thyroid carcinogenesis, this mode of action raises concerns about possible neurodevelopmental effects, since thyroid hormone status is critical to normal brain development.

Reproductive toxicity studies have shown no adverse effects of ASC or sodium chlorite on fertility. A multigeneration study of reproduction and developmental neurotoxicity was available in which sodium chlorite was administered to rats in drinking water at a concentration of 35, 70 or 300 mg/l.

Administration of sodium chlorate to pregnant rats resulted in no maternal or developmental effects at the highest tested dose of 1000 mg/kg bw per day. Neurodevelopmental end-points were not investigated in this study, and no multigeneration study was available.

The BMD approach has been put forward as an alternative to the no observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) approach for health effects because it provides a more quantitative alternative point of departure for the first step in the dose–response assessment (International Programme on Chemical Safety, in press). The BMD approach is based on a mathematical model being fitted to the experimental data within the observable range and estimates the dose that causes a low but measurable response (the benchmark response) typically chosen at a 5% or 10% incidence above the control. The BMD lower limit (BMDL) refers to the corresponding lower limit of a one-sided 95% confidence interval on the BMD. Using the lower bound takes into account the uncertainty inherent in a given study and assures (with 95% confidence) that the chosen benchmark response is not exceeded.

- **Health Canada (2008)**: Health Canada (2008) set a TDI of 30 µg/kg bw for chlorate, with the same justification as WHO (2005). A no-observed-adverse-effect level (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). 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) resulted in a TDI of 30 µg/kg bw per day. 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). Assuming that drinking water contributes 80 % of the total exposure and a typical consumption of 2 litres (L) of water per day by a 60 kg person, the WHO proposed a provisional guideline value of 0.7 mg/L. This guideline value was designated as provisional 'because use of chlorine dioxide as a disinfectant may result in the chlorate guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection'. It was noted that a long-term study was in progress that should provide more information on the effects of chronic exposure to chlorate.
- **OEHHA (2002)**: The Office of Environmental Health Hazard Assessment (2002) set a TDI of 30 µg/kg bw for chlorate. As with Health Canada (2008), this considered a no-observed-adverse-effect level (NOAEL) of 30 mg/kg body weight (bw) per day expressed as chlorate, from a 90-day study of sodium chlorate in rats conducted by McCauley (1995). Assuming that drinking water contributes 20 % of the total exposure and a typical consumption of 2 litres (L) of water per day by a 70 kg person and an uncertainty factor of 1000, OEHHA proposed a provisional guideline value of 0.2 mg/L. The drinking water source contribution of 20% is intended to account for potential presence of disinfection byproducts such as chlorine dioxide and chlorite
- **EFSA (2015):** Panel on Contaminants in the Food Chain (CONTAM) of the European Food Safety Authority (EFSA) established:
  - Acute Reference dose: based on controlled human trial (Lubbers et al. 1981) and
  - Chronic TDI: based on TDI for perchlorate derived from Greer et al. 2002 study.

  Acute RfD: Formation of methaemoglobin is the critical acute toxic effect which was identified in cases of poisoning. Infants (and presumably the foetus) are much more sensitive than adults to intracellular methaemoglobin inducers. This is due to a relative deficiency in methaemoglobin reductase in red blood cells of newborns, because the foetal form of haemoglobin is more sensitive to reducing agents, and because the foetus

has a greater oxygen demand. A large proportion of haemoglobin in neonates and infants is in the form of foetal haemoglobin, which is more readily oxidized to methaemoglobin than adult haemoglobin (Steinberg and Benz, 1991; Mensinga et al., 2003; Sadeq et al., 2008). 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. The only controlled clinical study available is the study of Lubbers et al. (1981) who considered the impact on normal subjects (10/group) of daily ingestion of 500 mL water containing 5 mg/L sodium chlorate (equivalent to 36 µg chlorate/kg bw per day) for 12 consecutive weeks. The subjects were followed for 8 weeks following cessation of treatment. A control group received untreated water. An extensive battery of parameters was monitored to assess the biochemical and physiological response to the oral ingestion of sodium chlorate. No adverse physiological effects were identified. The NOEL was 36 µg chlorate/kg bw per day. The CONTAM Panel considers that this study can be the basis for the establishment of an ARfD. Lethal poisonings have been reported to occur at doses of approximately 50 mg chlorate/kg bw The NOEL from the controlled clinical study (Lubbers et al., 1981) is about 1 400-fold lower than the lowest lethal dose. Furthermore, it is at least 300 fold lower than the toxic level in a poisoning case (11–23 mg chlorate/kg bw/day) where induction of methaemoglobinaemia was not reported. Taking into account also that the NOEL was the highest dose tested in a study with administration daily for 12 weeks, the CONTAM Panel concluded that these differences are sufficiently large that no uncertainty factor is required for more vulnerable individuals (e.g. glucose-6-phosphate dehydrogenase-deficient individuals or hereditary methaemoglobinaemia) and establishes an ARfD of 36 µg chlorate/kg bw.

Chronic health based guideline value: based its TDI for chlorate on that for perchlorate, noting that chlorate also acts by inhibition of iodide uptake into the 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. EFSA (2015) estimated that perchlorate is about 10 times more potent than chlorate.

There are no in vivo human studies on the inhibition of iodine uptake by chlorate. However, perchlorate has a similar mode of action, and there are several observations in humans, including clinical studies and case reports from the medicinal use of perchlorate, volunteer studies and both occupational and ecological epidemiological studies on the effects of exposure to perchlorate (EFSA CONTAM Panel, 2014). Both JECFA (FAO/WHO, 2011) and 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).

In order to establish a chronic health based guidance value for chlorate, and as the toxicity of chlorate and perchlorate are both related to the inhibition of iodine uptake, the CONTAM Panel decided to use the TDI established for perchlorate and to apply an extrapolation factor for the difference in potency between chlorate and perchlorate. When comparing the NOAEL and LOAEL for thyroid follicular cell hypertrophy in rats, perchlorate is about 10 times more potent than chlorate. On this basis, the CONTAM Panel established a TDI for chlorate of 3 µg/kg bw per day, based on the TDI established for perchlorate (0.3 µg/kg bw per day) and by multiplying by a factor of 10 for the difference in potency between the two substances.

3.8.1 Critical Health Adverse Effects

Key health effects include changes in the thyroid glands (thyroid hormone homeostasis), changes in total bilirubin, iron and methaemoglobin, anaemia, Pituitary lesions (vacuolization in the cytoplasm of the pars distalis) and thyroid gland colloid depletion.

3.8.2 Other health Adverse Effects

There is some evidence of carcinogenic activities in male and female F344/N rats based on increased incidences of thyroid gland neoplasms.

Neurodevelopmental end-points were not investigated (due to absence of studies), 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.

3.8.3 Sensitive population

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.

Moreover, younger age groups of the population with mild to moderate iodine deficiency, foetuses, neonates, and individuals with low iodine intake or genetically predisposed to develop hypothyroidism are likely to be more sensitive to the effects of exposure to chlorate.

3.9 Supporting Information in factsheet – Addressing research questions

Supporting information provided in overseas guidance documents are presented in Table 3-8.

Table 3-8 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.

Section 4 Recent Evidence scan

4.1 Literature Search

The followings are the key components in the literature search process:

- Selecting databases
- Developing literature search strategy
- Documenting

4.1.1 Database selection

CDM Smith team and NHMRC committee have agreed to use the following electronic databases to conduct literature search:

- MEDLINE/PubMed/TOXLINE
- SciFinder
- Wiley (and Science Direct)

In addition to the primary databases, secondary search methods include:

- Data from government/ intergovernmental agencies [Water Research Australia (waterRA), CSIRO)]

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.

Table 4-1 Search strategy for the selected databases

Search strategy	Comments
Field of search	Medical, biology, and other life sciences journals (with coverage back to 1946) – Medical Subject Heading (MeSH) terms
Limit of publication date	2016 – present (based on the recent WHO 2016 guideline document)
Search by CASRN (and synonyms)	Yes
Refined search using Boolean operators	Yes
Key search terms	Chlorate, chlorate AND drinking water, chlorate AND disinfect, chlorate AND adverse health effect, chlorate AND toxicity
Language limit	Yes - English
Publication type	Peer reviewed, published, in press and ongoing studies
Grey literature limitation	Yes – limited to technical reports from government agencies or scientific research groups, unpublished laboratory studies conducted by industry, working papers from research groups or committees
Search for cited reference or related reference	Yes – may use as “link to similar article”.
Important note	PubMed is the primary search database as recently published articles may be in PubMed but not indexed for Medline for several weeks or months.

4.1.2 Developing literature search strategy

The efficient literature search strategy balances the needs for identification of the relevant and non-relevant studies using a process that is reproducible.

- Key studies from the existing guidelines are used to serve as a starting point that can be used as "seed" studies for literature search and screening process.
- Date of the literature search start from the date of the most recent existing guidelines.
- The search strategy may focus on updating the existing literature search and considering whether any refinements or supplemental searches are needed to address assessment needs.
- Targeted search strings are designed and incorporate supplemental searches for other informative materials such as mechanistic information (e.g., to identify studies relevant to a perturbed biological pathway that are not specific to the chemical).
- Since standard search strings are not available, literature search strategies are developed using key words related to the populations, exposure, comparators and outcomes (PECO) criteria. Development of the search strategy can include identifying relevant search terms through:
  - Review of PubMed's search
  - Extracting key word terminology from relevant reviews and a set of previously identified primary data studies that are known to be relevant to the topic ("seed" studies) and,
  - Reviewing search strategies presented in other reviews.

Table 4-2 PECO-based literature search strategy

Search element	Comments
Population	**Sensitive population** - Infants and children - Pregnant women - Aboriginal and Torres Strait Islander peoples - People with pre-existing health conditions identified in peer reviewed competent authority as possible renal disease - People who ingest higher than average amount of water e.g. in tropical locations or outdoor workers
Exposure	- Lifetime exposure - Short-term exposure - Combination or reaction with substances - Exposure through drinking, cooking, washing, skin contact - PBPK-based exposure model characteristics
Comparator	Health-based advice: - Comparison between the current guideline value and any different (higher/lower) existing values Supplementary advice: - Comparison between different water treatment options to assess incremental exposure levels and incidence results. - Comparison to no observed effects level / no exposure level

Search element	Comments
Outcome	The human health and aesthetic outcomes of concern from exposure to chlorate include: - Mortality - Severe human health outcomes, including incidence of life-threatening illness, disability or chronic disease with ongoing impact on quality of life. - Less severe or short-term human health outcomes, e.g. irritation. - Aesthetic outcomes, including taste, smell, colour, clarity, etc. - Other (bioanalytical assays that support health outcomes, for example results from Tox21 screening assays) Consideration regarding these outcomes will be given to: - The level of chlorate in drinking water considered to be safe or acceptable to human health over a lifetime - The level of chlorate in drinking water considered to be safe or acceptable to human health during a short-term event - The level of chlorate in drinking water considered to be acceptable in relation to aesthetic factors, including taste, smell, colour, clarity, etc.

- Expand the chemical-specific search terms. Specification of chemical form(s), active metabolite(s), mixtures, or valence/oxidation state (for metals) can be drawn from work in the scoping.
- Ambiguous terms including short alphanumeric sequences that could be confused with arbitrary acronyms or abbreviations are removed.
- The goal of the search is to identify primary studies as original data source of health effects pertaining to key assessment questions.
- In addition to primary studies, grey literature including technical reports from government agencies or scientific research groups, unpublished laboratory studies conducted by industry and working papers from research groups or committees are identified.

4.1.2.1 Literature search refinement

- Assessor Identifies a small set (10−20) of key validation set or test papers that the search would be expected to capture (e.g., papers identified in scoping and problem formulation). This study set can be used to test the sensitivity (error rate for missed studies) of the search.
- Develop an initial search strategy, which can be informed by how the test studies are indexed in PubMed and other databases. Test search strings in each source database.
- If one of the seed or test studies was missed, determine the reason., i.e., was the paper not in the database (or is it incorrectly indexed in the database) or because of a limitation of the search string? All the test papers that could be found in a database need to be found with the search string; if any paper is missed, the search string should be re-evaluated.
- Remove/minimise the off-topic citations from the search.
- Removing duplicates identified during literature search process
- This search strategy and database selection are conducted in a way to minimise the possibility of missing key publications. However, some publications might not be included as:
  - They have no proper indexing systems.
  - Old papers with no abstracts that might be missed in the initial screening process.
- Supplemental search strategy is used:

- Searching the reference list of primary data papers to look for citations that may have been missed during database searching.
- Additional search strategies that can be employed through a database (e.g., Web of Science) to include "forward" and "backward" searching from articles identified as key studies. Forward searching identifies articles that cite the key study, and backward searching identifies articles cited in the key study. Backward searches can be done manually by reviewing the cited references, typically in the introduction and discussion sections of a paper, for studies that were not identified in the database search. This type of searching is done on a case-by-case basis depending on factors such as whether the PECO has a targeted evidence type or health outcome focus, amount of the evidence, and use of other assessments to serve as a starting point. In general, the feasibility of conducting backward and forward searches is reduced when the PECO is broad, and the number of included studies is large.
- Searching of ToxCast/Tox21 high throughput screening data or bioinformatic databases for mechanistic evidence.
- The public, stakeholders, and technical experts may provide additional publications.
- Targeted searches focused on a specific health effect question (e.g., reproductive toxicity, cancer, pulmonary function, or even finer divisions such as autoimmunity within the broader area of immunotoxicity), a particular exposure scenario of interest (e.g., exposure during pregnancy; exposure to a specific formulation of the agent), or on potentially susceptible subpopulations and lifestages.
- Search strings to identify studies using descriptions of exposure to the agent of interest that do not include the chemical name (e.g., epidemiology studies of a broad chemical class or occupation may provide useful information).
- Targeted searches to identify absorption, distribution, metabolism, and excretion (ADME) and mechanistic studies, or studies of PBPK models; searches using the parent chemical name and CASRN alone may be too limiting for these types of data.

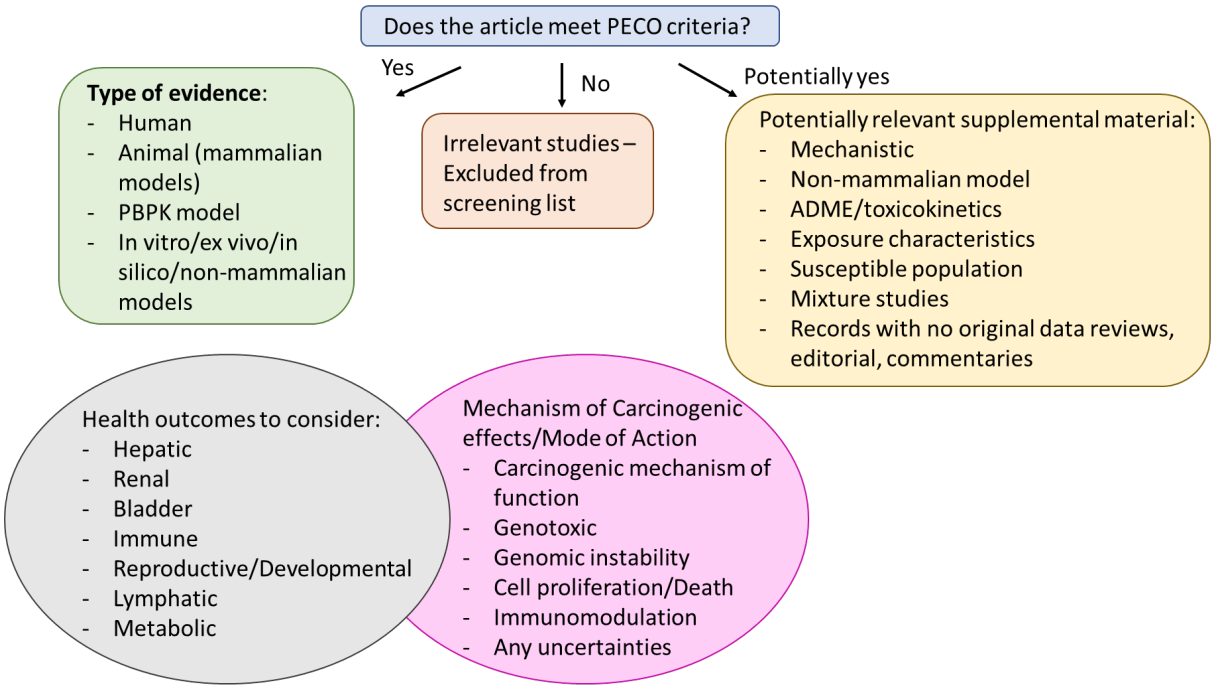
The literature search is developed by CDM Smith team in conjunction with epidemiology expert. Our team developed an inventory of the identified studies, abstracting key elements e.g., route of exposure, categorization of the exposure or outcome measures.

The literature screening process focuses on categorizing (or "tagging") studies into those that provide data that inform whether exposure to the chemical might cause toxicity (based on the PECO criteria and the supplemental tagging structure) and those that are irrelevant for the purposes of the assessment. It is important to emphasize that during the screening process neither the quality nor the results of the study are considered.

4.1.3 Inclusion and Exclusion criteria of Identified References

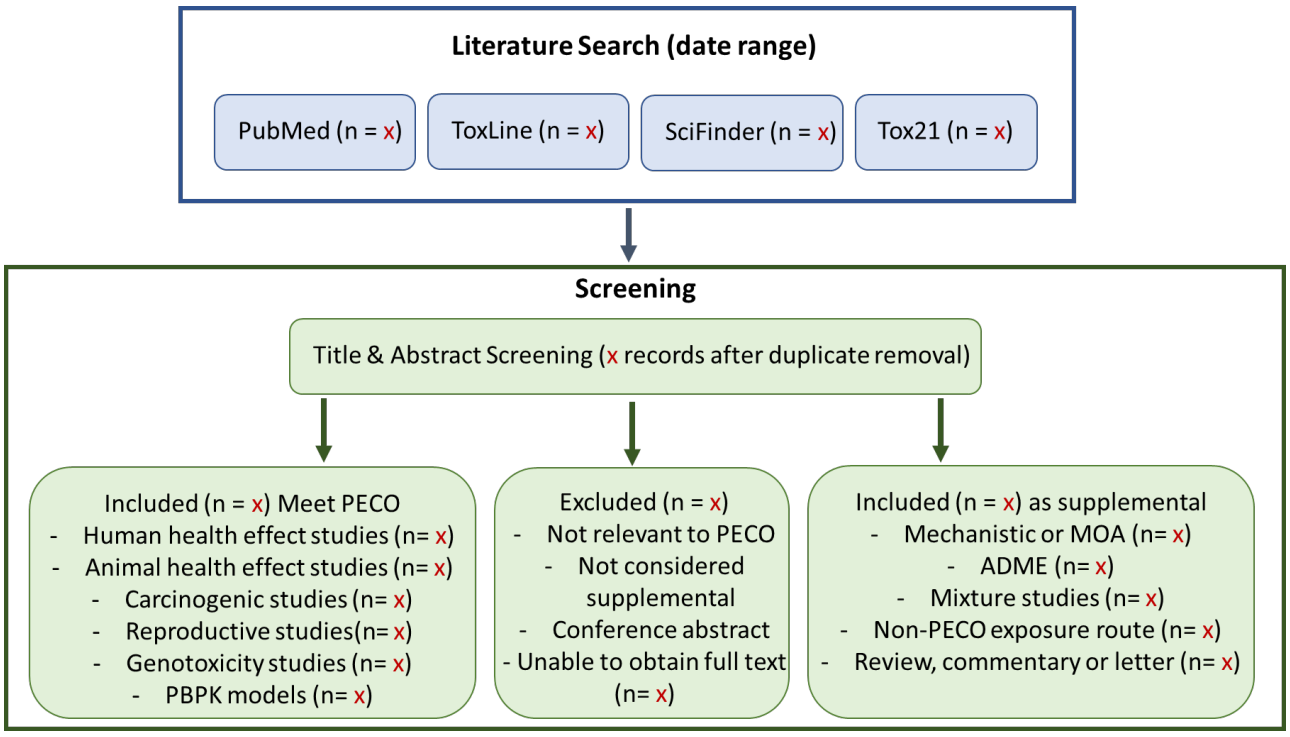
The PECO criteria are used to determine the inclusion or exclusion of identified references, focusing on capturing primary sources of health effects data. During the screening process, studies containing potentially relevant supplemental material will likely be identified and should be tagged as such 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.



Screening is done at the title and/or abstract level. All decisions (inclusion/exclusion) are listed in **Table 5-4** to **Table 5-10** in Appendix B including the list of all studies considered and categorised as included or excluded and those marked as supplemental material according to the PECO relevance.

Studies that considered as "exclude studies" are screened by the second reviewer to confirm the logic/approach.



4.2 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 4-3 below and presented in detail in Appendix B.

Table 4-3 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.

Section 5 References

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Appendix A Supplementary Information

Study Evaluation

Study Evaluation

Study evaluation, as defined herein, is a broad term encompassing interpretation of a variety of methodological features (e.g., study design, exposure measurement, study execution, data reporting). Study evaluation is analogous to other approaches that evaluate “study quality” or “utility” in that a wider set of issues are addressed in addition to risk of bias, including the rigor of study execution, study sensitivity, and reporting.

Table 5-1 outlined 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”.

Table 5-2 and Table 5-3 present core and prompting questions that aid selection of the appropriate domain judgement.

Table 5-1 Study evaluation – Domain judgement

Key study evaluation concern	Animal Studies	Epidemiological studies	Judgement			
			Good	Adequate	Deficient	Critically Deficient
Risk of bias	Selection and performance: - Allocation - Observational bias/blinding	Participant selection	Appropriate conduct and minor deficiencies not expected to influence results.	Some limitations but not likely to be severe or to have a notable impact on results.	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.	A serious flaw identified that makes the observed effects uninterpretable. Studies with a critical deficiency are considered "uninformative" overall.
	Confounding/variable control	Confounding				
	Selective reporting and attrition	Selective reporting				
Study sensitivity	Exposure methods sensitivity - Chemical administration and characterisation - Exposure timing, frequency and duration - Endpoint sensitivity	Exposure measurement	Appropriate conduct and minor deficiencies not expected to influence results.	Some limitations but not likely to be severe or to have a notable impact on results.	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.	A serious flaw identified that makes the observed effects uninterpretable. Studies with a critical deficiency are considered "uninformative" overall.
		Sensitivity analysis				
		Other sensitivity				
Reporting quality	Outcome measures and results display - Results presentation	Outcome ascertainment	Appropriate conduct and minor deficiencies not expected to influence results.	Some limitations but not likely to be severe or to have a notable impact on results.	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.	A serious flaw identified that makes the observed effects uninterpretable. Studies with a critical deficiency are considered "uninformative" overall.

Table 5-2 Animal studies evaluation – instructions to select domain judgement

Evaluation concern	Core questions	Prompting Qs for different category	Domain judgement			
			Good	Adequate	Deficient/Not reported	Critically deficient
Reporting quality	Does the study report information for evaluating the design and conduct of the study for the endpoint(s)/outcome(s) of interest? *Notes:* *Reviewers should reach out to authors to obtain missing information when studies are considered key for hazard evaluation and/or dose-response*. This domain is limited to reporting. Other aspects of the exposure methods, experimental design, and endpoint evaluation methods are evaluated using the domains related to risk of bias and study sensitivity.	Does the study report the following? **Critical information** necessary to perform study evaluation: Species, test article name, levels and duration of exposure, route (e.g., oral; inhalation), qualitative or quantitative results for at least one endpoint of interest. **Important information** for evaluating the study methods: Test animal: strain, sex, source, and general husbandry procedures. Exposure methods: source, purity, method of administration. Experimental design: frequency of exposure, animal age and life stage during exposure and at endpoint/outcome evaluation. Endpoint evaluation methods: assays or procedures used to measure the endpoints/outcomes of interest.	All critical and important information is reported or inferable for the endpoints/outcomes of interest.	All critical information is reported but some important information is missing. However, the missing information is not expected to significantly impact the study evaluation.	All critical information is reported but important information is missing that is expected to significantly reduce the ability to evaluate the study.	Study report is missing any pieces of critical information. Studies that are critically deficient for reporting are uninformative for the overall rating and not considered further for evidence synthesis and integration.

Evaluation concern	Core questions	Prompting Qs for different category	Domain judgement			
			Good	Adequate	Deficient/Not reported	Critically deficient
Risk of bias / Selection and performance bias	**Allocation** Were animals assigned to experimental groups using a method that minimizes selection bias? **Observational bias/blinding** Did the study implement measures to reduce observational bias?	For each study: Did each animal or litter have an equal chance of being assigned to any experimental group (i.e., random allocation)? Is the allocation method described? Aside from randomization, were any steps taken to balance variables across experimental groups during allocation? For each endpoint/outcome or grouping of endpoints/outcomes in a study: Does the study report blinding or other methods/procedures for reducing observational bias? If not, did the study use a design or approach for which such procedures can be inferred? What is the expected impact of failure to implement (or report implementation) of these methods/procedures on results?	Measures to reduce observational bias were described (e.g., blinding to conceal treatment groups during endpoint evaluation; consensus-based evaluations of histopathology-lesions).	Methods for reducing observational bias (e.g., blinding) can be inferred or were reported but described incompletely.	**Not reported**: Measures to reduce observational bias were not described. - (Interpreted as adequate) The potential concern for bias was mitigated based on use of automated/computer driven systems, standard laboratory kits, relatively simple, objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology. - (Interpreted as deficient) The potential impact on the results is major (e.g., outcome measures are highly subjective).	Strong evidence for observational bias that impacted the results.
Risk of bias/Confounding/ variable control	**Confounding** Are variables with the potential to confound or modify results controlled for and consistent across all experimental groups?	For each study: Are there differences across the treatment groups (e.g., coexposures, vehicle, diet, palatability, husbandry, health status) that could bias the results? f differences are identified, to what extent are they expected to impact the results?	Outside of the exposure of interest, variables that are likely to confound or modify results appear to be controlled for and consistent across experimental groups.	Some concern that variables that were likely to confound or modify results were uncontrolled or inconsistent across groups but are expected to have a minimal impact on the results.	Notable concern that potentially confounding variables were uncontrolled or inconsistent across groups and are expected to substantially impact the results.	Confounding variables were presumed to be uncontrolled or inconsistent across groups and are expected to be a primary driver of the results.
Risk of bias/Selective reporting and attrition bias	**Selective reporting and attrition** Did the study report results for all prespecified outcomes and tested animals? *Note:* *This domain does not consider the appropriateness of the analysis/results presentation. This aspect of study quality is evaluated in another domain.*	For each study: Selective reporting bias: Are all results presented for endpoints/outcomes described in the methods (see note)? Attrition bias: Are all animals accounted for in the results? If there are discrepancies, do authors provide an explanation (e.g., death or unscheduled sacrifice during the study)? If unexplained results omissions and/or attrition are identified, what is the expected impact on the interpretation of the results?	Quantitative or qualitative results were reported for all prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points. Data not reported in the primary article is available from supplemental material. If results omissions or animal attrition are identified, the authors provide an explanation, and these are not expected to impact the interpretation of the results.	Quantitative or qualitative results are reported for most prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points. Omissions and/or attrition are not explained but are not expected to significantly impact the interpretation of the results.	Quantitative or qualitative results are missing for many prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points and/or high animal attrition; omissions and/or attrition are not explained and may significantly impact the interpretation of the results.	Extensive results omission and/or animal attrition are identified and prevents comparisons of results across treatment groups.

Evaluation concern	Core questions	Prompting Qs for different category	Domain judgement			
			Good	**Adequate**	**Deficient/Not reported**	**Critically deficient**
Sensitivity/Exposure methods sensitivity	**Chemical administration and characterization** Did the study adequately characterize exposure to the chemical of interest and the exposure administration methods? *Note:* *Consideration of the appropriateness of the route of exposure is not evaluated at the individual study level. Relevance and utility of the routes of exposure are considered in the PECO criteria for study inclusion and during evidence synthesis.*	For each study: Are there concerns [specific to this chemical] regarding the source and purity and/or composition (e.g., identity and percent distribution of different isomers) of the chemical? If so, can the purity and/or composition be obtained from the supplier (e.g., as reported on the website)? Was independent analytical verification of the test article purity and composition performed? Did the authors take steps to ensure the reported exposure levels were accurate? Are there concerns about the methods used to administer the chemical (e.g., inhalation chamber type, gavage volume)? For inhalation studies: Were target concentrations confirmed using reliable analytical measurements in chamber air? For oral studies: If necessary based on consideration of chemical specific-knowledge (e.g., instability in solution; volatility) and/or exposure design (e.g., the frequency and duration of exposure), were chemical concentrations in the dosing solutions or diet analytically confirmed?	Chemical administration and characterization is complete (i.e., source, purity, and analytical verification of the test article are provided). There are no concerns about the composition, stability, or purity of the administered chemical, or the specific methods of administration. For inhalation studies, chemical concentrations in the exposure chambers are verified using reliable analytical methods.	Some uncertainties in the chemical administration and characterization are identified but these are expected to have minimal impact on interpretation of the results (e.g., source and vendor reported-purity are presented, but not independently verified; purity of the test article is suboptimal but not concerning; For inhalation studies, actual exposure concentrations are missing or verified with less reliable methods).	Uncertainties in the exposure characterization are identified and expected to substantially impact the results (e.g., source of the test article is not reported; levels of impurities are substantial or concerning; deficient administration methods, such as use of static inhalation chambers or a gavage volume considered too large for the species and/or lifestage at exposure).	Uncertainties in the exposure characterization are identified and there is reasonable certainty that the results are largely attributable to factors other than exposure to the chemical of interest (e.g., identified impurities are expected to be a primary driver of the results).
	Exposure timing, frequency and duration Was the timing, frequency, and duration of exposure sensitive for the endpoint(s)/outcome(s) of interest?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Does the exposure period include the critical window of sensitivity? Was the duration and frequency of exposure sensitive for detecting the endpoint of interest?	The duration and frequency of the exposure was sensitive, and the exposure included the critical window of sensitivity (if known).	The duration and frequency of the exposure was sensitive, and the exposure covered most of the critical window of sensitivity (if known).	The duration and/or frequency of the exposure is not sensitive and did not include most of the critical window of sensitivity (if known). These limitations are expected to bias the results towards the null.	The exposure design was not sensitive and is expected to strongly bias the results towards the null. The rationale should indicate the specific concern(s).

Evaluation concern	Core questions	Prompting Qs for different category	Domain judgement			
			Good	Adequate	Deficient/Not reported	Critically deficient
Sensitivity/Outcome measures and results display	**Endpoint sensitivity and specificity** Are the procedures sensitive and specific for evaluating the endpoint(s)/outcome(s) of interest? Note: Sample size alone is not a reason to conclude an individual study is critically deficient. Considerations related to adjustments/corrections to endpoint measurements (e.g., organ weight corrected for body weight) are addressed under results presentation.	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Are there concerns regarding the sensitivity, specificity, and/or validity of the protocols? Are there serious concerns regarding the sample size? Are there concerns regarding the timing of the endpoint assessment?	Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Examples of potential concerns include: Selection of protocols that are insensitive or nonspecific for the endpoint of interest. Evaluations did not include all treatment groups (e.g., only control and high dose). Use of unreliable methods to assess the outcome. Assessment of endpoints at inappropriate or insensitive ages, or without addressing known endpoint variation (e.g., due to circadian rhythms, oestrous cyclicity). Decreased specificity or sensitivity of the response due to the timing of endpoint evaluation, as compared to exposure (e.g., short acting depressant or irritant effects of chemicals; insensitivity due to prolonged period of non-exposure prior to testing).			
	Results presentation Are the results presented in a way that makes the data usable and transparent?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Does the level of detail allow for an informed interpretation of the results? Are the data analyzed, compared, or presented in a way that is inappropriate or misleading?	Considerations for this domain are highly variable depending on the outcomes of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Examples of potential concerns include: Nonpreferred presentation (e.g., developmental toxicity data averaged across pups in a treatment group, when litter responses are more appropriate; presentation of absolute organ-weight data when relative weights are more appropriate). Failing to present quantitative results either in tables or figures. Pooling data when responses are known or expected to differ substantially (e.g., across sexes or ages). Failing to report on or address overt toxicity when exposure levels are known or expected to be highly toxic. Lack of full presentation of the data (e.g., presentation of mean without variance data; concurrent control data are not presented).			
Overall confidence	**Overall confidence** Considering the identified strengths and limitations, what is the overall confidence rating for the endpoint(s)/outcome(s) of interest? *Note:* *Reviewers should mark studies that are rated lower than high confidence only due to low sensitivity (i.e., bias towards the null) for additional consideration during evidence*	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Were concerns (i.e., limitations or uncertainties) related to the reporting quality, risk of bias, or sensitivity identified? If yes, what is their expected impact on the overall interpretation of the reliability and validity of the study results, including (when possible) interpretations of impacts on the magnitude or direction of the reported effects?	The overall confidence rating considers the likely impact of the noted concerns (i.e., limitations or uncertainties) in reporting, bias and sensitivity on the results. A confidence rating and rationale should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study.			

Evaluation concern	Core questions	Prompting Qs for different category	Domain judgement			
			Good	Adequate	Deficient/Not reported	Critically deficient
	synthesis. If the study is otherwise well conducted and an effect is observed, the confidence may be increased.					

Table 5-3 Epidemiological studies evaluation – instruction to select domain judgement

Domain	Core question	Prompting Q for different category				Domain judgement			
						Good	Adequate	Deficient	Critically deficient
Population (participant)	Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?	**Longitudinal cohort** : Did participants volunteer for the cohort based on knowledge of exposure and/or preclinical disease symptoms? Was entry into the cohort or continuation in the cohort related to exposure and outcome?	**Occupational cohort** : Did entry into the cohort begin with the start of the exposure? Was follow-up or outcome assessment incomplete, and if so, was follow-up related to both exposure and outcome status? Could exposure produce symptoms that would result in a change in work assignment/work status ("healthy worker survivor effect")?	**Case-control study** : Were controls representative of population and time periods from which cases were drawn? Are hospital controls selected from a group whose reason for admission is independent of exposure? Could recruitment strategies, eligibility criteria, or participation rates result in differential participation relating to both disease and exposure?	**Population-based survey**: Was recruitment based on advertisement to people with knowledge of exposure, outcome, and hypothesis?	Minimal concern for selection bias based on description of recruitment process (e.g., selection of comparison population, population-based random sample selection, recruitment from sampling frame including current and previous employees). Exclusion and inclusion criteria for participants specified and would not induce bias. Participation rate is reported at all steps of study (e.g., initial enrolment, follow-up, selection into analysis sample). If rate is not high, there is appropriate rationale for why it is unlikely to be related to exposure (e.g., comparison between participants and nonparticipants or other available information indicates differential selection is not likely).	Enough of a description of the recruitment process to be comfortable that there is no serious risk of bias. Inclusion and exclusion criteria for participants specified and would not induce bias. Participation rate is incompletely reported but available information indicates participation is unlikely to be related to exposure.	Little information on recruitment process, selection strategy, sampling framework and/or participation OR aspects of these processes raises the potential for bias (e.g., healthy worker effect, survivor bias).	Aspects of the processes for recruitment, selection strategy, sampling framework, or participation result in concern that selection bias is likely to have had a large impact on effect estimates (e.g., convenience sample with no information about recruitment and selection, cases and controls are recruited from different sources with different likelihood of exposure, recruitment materials stated outcome of interest and potential participants are aware of or are concerned about specific exposures).

Domain	Core question	Prompting Q for different category					Domain judgement			
							Good	**Adequate**	**Deficient**	**Critically deficient**
Exposure	Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?	**For all**: Does the exposure measure capture the variability in exposure among the participants, considering intensity, frequency, and duration of exposure? Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably? Was the exposure measurement likely to be affected by a knowledge of the outcome? Was the exposure measurement likely to be affected by the presence of the outcome (i.e., reverse causality)?	**Case-control studies of occupational exposures**: Is exposure based on a comprehensive job history describing tasks, setting, time period, and use of specific materials?	**Biomarkers of exposure and other analytic measures of exposure**: Is a standard assay used? Is the measure valid and precise? What are the intra- and interassay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? What exposure time period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?		Valid exposure assessment methods used, which represent the etiologically relevant time period of interest. Exposure misclassification is expected to be minimal.	Valid exposure assessment methods used, which represent the etiologically relevant time period of interest. Exposure misclassification may exist but is not expected to greatly change the effect estimate.	Valid exposure assessment methods used, which represent the etiologically relevant time period of interest. Specific knowledge about the exposure and outcome raise concerns about reverse causality, but there is uncertainty whether it is influencing the effect estimate. Exposed groups are expected to contain a notable proportion of unexposed or minimally exposed individuals, the method did not capture important temporal or spatial variation, or there is other evidence of exposure misclassification that would be expected to notably change the effect estimate.	Exposure measurement does not characterize the etiologically relevant time period of exposure or is not valid. There is evidence that reverse causality is very likely to account for the observed association. Exposure measurement was not independent of outcome status.
Outcome	Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?	**For all**: Is outcome ascertainment likely to be affected by knowledge of, or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)?	**For case-control studies**: Is the comparison group without the outcome (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease?	**For mortality measures**: How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease?	**For diagnosis of disease measures**: Is the diagnosis based on standard clinical criteria? If it is based on self-report of the diagnosis, what is the validity of this measure?	**For laboratory-based measures (e.g., hormone levels):** Is a standard assay used? Does the assay have an acceptable level of interassay variability? Is the sensitivity of the assay appropriate for the outcome measure in this study population?	High certainty in the outcome definition (i.e., specificity and sensitivity), minimal concerns with respect to misclassification. Assessment instrument was validated in a population comparable to the one from which the study group was selected.	Moderate confidence that outcome definition was specific and sensitive, some uncertainty with respect to misclassification but not expected to greatly change the effect estimate. Assessment instrument was validated but not necessarily in a population comparable to the study group.	Outcome definition was not specific or sensitive. Uncertainty regarding validity of assessment instrument.	Invalid/insensitive marker of outcome. Outcome ascertainment is very likely to be affected by knowledge of, or presence of, exposure.

Domain	Core question	Prompting Q for different category		Domain judgement			
				Good	Adequate	Deficient	Critically deficient
Confounding	Is confounding of the effect of the exposure likely?	Is confounding adequately addressed by considerations in: - Participant selection (matching or restriction)? - Accurate information on potential confounders and statistical adjustment procedures? - Lack of association between confounder and outcome, or confounder and exposure in the study? - Information from other sources?	Is the assessment of confounders based on a thoughtful review of published literature, potential relationships (e.g., as can be gained through directed acyclic graphing), and minimizing potential overcontrol (e.g., inclusion of a variable on the pathway between exposure and outcome)?	Conveys strategy for identifying key confounders. This may include a priori biological considerations, published literature, causal diagrams, or statistical analyses; with recognition that not all "risk factors" are confounders. Inclusion of potential confounders in statistical models not based solely on statistical significance criteria (e.g., $p < 0.05$ from stepwise regression). Does not include variables in the models that are likely to be influential colliders or intermediates on the causal pathway. Key confounders are evaluated appropriately and considered to be unlikely sources of substantial confounding. This often will include: - Presenting the distribution of potential confounders by levels of the exposure of interest and/or the outcomes of interest (with amount of missing data noted); - Consideration that potential confounders were rare among the study population, or were expected to be poorly correlated with exposure of interest; - Consideration of the most relevant functional forms of potential confounders; - Examination of the potential impact of measurement error or missing data on confounder adjustment; - Presenting a progression of model results with adjustments for different potential confounders, if warranted.	Similar to good but may not have included all key confounders, or less detail may be available on the evaluation of confounders (e.g., sub-bullets in good). It is possible that residual confounding could explain part of the observed effect, but concern is minimal.	Does not include variables in the models that are likely to be influential colliders or intermediates on the causal pathway. And any of the following: The potential for bias to explain some of the results is high based on an inability to rule out residual confounding, such as a lack of demonstration that key confounders of the exposure-outcome relationships were considered; Descriptive information on key confounders (e.g., their relationship relative to the outcomes and exposure levels) are not presented; or Strategy of evaluating confounding is unclear or is not recommended (e.g., only based on statistical significance criteria or stepwise regression [forward or backward elimination]).	Includes variables in the models that are colliders and/or intermediates in the causal pathway, indicating that substantial bias is likely from this adjustment; or Confounding is likely present and not accounted for, indicating that all of the results were most likely due to bias.

Domain	Core question	Prompting Q for different category	Domain judgement			
			Good	**Adequate**	**Deficient**	**Critically deficient**
Analysis	Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?	Are missing outcome, exposure, and covariate data recognized, and if necessary, accounted for in the analysis? Does the analysis appropriately consider variable distributions and modeling assumptions? Does the analysis appropriately consider subgroups of interest (e.g., based on variability in exposure level or duration or susceptibility)? Is an appropriate analysis used for the study design? Is effect modification considered, based on considerations developed a priori? Does the study include additional analyses addressing potential biases or limitations (i.e., sensitivity analyses)?	Use of an optimal characterization of the outcome variable. Quantitative results presented (effect estimates and confidence limits or variability in estimates; i.e., not presented only as a p-value or "significant"/"not significant"). Descriptive information about outcome and exposure provided (where applicable). Amount of missing data noted and addressed appropriately (discussion of selection issues—missing at random vs. differential). Where applicable, for exposure, includes LOD (and percentage below the LOD), and decision to use log transformation. Includes analyses that address robustness of findings, e.g., examination of exposure-response (explicit consideration of nonlinear possibilities, quadratic, spline, or threshold/ceiling effects included, when feasible); relevant sensitivity analyses; effect modification examined based only on a priori rationale with sufficient numbers. No deficiencies in analysis evident. Discussion of some details may be absent (e.g., examination of outliers).	Same as good, except: Descriptive information about exposure provided (where applicable) but may be incomplete; might not have discussed missing data, cut-points, or shape of distribution. Includes analyses that address robustness of findings (examples in good), but some important analyses are not performed.	Does not conduct analysis using optimal characterization of the outcome variable. Descriptive information about exposure levels not provided (where applicable). Effect estimate and p-value presented, without standard error or confidence interval. Results presented as statistically "significant"/"not significant."	Results of analyses of effect modification examined without clear a priori rationale and without providing main/principal effects (e.g., presentation only of statistically significant interactions that were not hypothesis driven). Analysis methods are not appropriate for design or data of the study.

Domain	Core question	Prompting Q for different category	Domain judgement			
			Good	Adequate	Deficient	Critically deficient
Selective reporting	Is there reason to be concerned about selective reporting?	Were results provided for all the primary analyses described in the methods section? Is there appropriate justification for restricting the amount and type of results that are shown? Are only statistically significant results presented?	The results reported by study authors are consistent with the primary and secondary analyses described in a registered protocol or methods paper.	The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses.	Concerns were raised based on previous publications, a methods paper, or a registered protocol indicating that analyses were planned or conducted that were not reported, or that hypotheses originally considered to be secondary were represented as primary in the reviewed paper. Only subgroup analyses were reported suggesting that results for the entire group were omitted. Only statistically significant results were reported.	

Domain	Core question	Prompting Q for different category	Domain judgement			
			Good	Adequate	Deficient	Critically deficient
Sensitivity	Is there a concern that sensitivity of the study is not adequate to detect an effect?	Is the exposure range adequate? Was the appropriate population included? Was the length of follow-up adequate? Is the time/age of outcome ascertainment optimal given the interval of exposure and the health outcome? Are there other aspects related to risk of bias or otherwise that raise concerns about sensitivity?		The range of exposure levels provides adequate variability to evaluate primary hypotheses in study. The population was exposed to levels expected to have an impact on response. The study population was sensitive to the development of the outcomes of interest (e.g., ages, lifestage, sex). The timing of outcome ascertainment was appropriate given expected latency for outcome development (i.e., adequate follow-up interval). The study was adequately powered to observe an effect. No other concerns raised regarding study sensitivity.	Concerns were raised about the issues described for good that are expected to notably decrease the sensitivity of the study to detect associations for the outcome.	

Appendix B Recent Evidence Scan

Search Results

Database Search Results

PubMed Search Results

Table 5-4 PubMed Database Search Results – Included studies

Included Studies – Meet PECO criteria							
Human health effect	**Animal health effect (mammalian)**	**Carcinogenic**	**Reproductive**	**Genotoxicity**	**PBPK model**	**Full list of Included studies**	**Search Date**
✓						Haber, L.T.; Schoeny, R.S.; Allen, B.C. (2021). Impact of updated BMD modeling methods on perchlorate and chlorate assessments of human health hazard. 340:89-100. Toxicol Lett	8/31/2021
✓						Djam, S.; Najafi, M.; Ahmadi, S.H.; Shoeibi, S. (2020). Bottled water safety evaluations in IRAN: determination of bromide and oxyhalides (chlorite, chlorate, bromate) by ion chromatography. 18(2):609-616. J Environ Health Sci Eng	8/31/2021
✓						Rozanec, J.J.; Secin, F.P. (2020) Epidemiología, etiología, prevención del cáncer vesical [Epidemiology, etiology and prevention of bladder cancer.]. 73(10):872-878. Arch Esp Urol	9/3/2021
	✓					Vargas-Bello-Pérez, E.; Dhakal, R.; Nielsen, M.O.; Ahrné, L.; Hansen, H.H. (2020). Corrigendum to: "Short communication: Electrochemical activated drinking water effects on bovine milk production and composition, including chlorate, perchlorate, and fatty acid profile" (J. Dairy Sci. 103:1208-1214). 103(5):4892-4893. J Dairy Sci	8/31/2021
	✓					Vargas-Bello-Pérez E, Dhakal R, Nielsen MO, Ahrné L, Hansen HH. Short communication: Effects of electrochemically activated drinking water on bovine milk production and composition, including chlorate, perchlorate, and fatty acid profile. J Dairy Sci. 2020 Feb;103(2):1208-1214.	8/31/2021
	✓			✓		Ali, S.N.; Arif, H.; Khan, A.A.; Mahmood, R. (2018). Acute renal toxicity of sodium chlorate: Redox imbalance, enhanced DNA damage, metabolic alterations and inhibition of brush border membrane enzymes in rats. 33(11):1182-1194. Environ Toxicol	9/5/2021
				✓		Ali, S.N.; Ansari, F.A.; Arif, H.; Mahmood, R. (2017). Sodium chlorate induces DNA damage and DNA-protein cross-linking in rat intestine: A dose dependent study. 177:311-316. Chemosphere	9/7/2021
	✓					Ali, S.N.; Ansari, F.A.; Khan, A.A.; Mahmood, R. (2017). Sodium chlorate, a major water disinfection by-product, alters brush border membrane enzymes, carbohydrate metabolism and impairs antioxidant system of Wistar rat intestine. 32(5):1607-1616. Environ Toxicol	9/7/2021
✓						Weterings, P.J.; Loftus, C.; Lewandowski, T.A. (2016). Derivation of the critical effect size/benchmark response for the dose-response analysis of the uptake of radioactive iodine in the human thyroid. 257:38-43. Toxicol Lett.	9/7/2021
✓						Radwan, E.K.; Barakat, M.H.; Ibrahim, M.B.M. (2021). Hazardous inorganic disinfection by-products in Egypt's tap drinking water: Occurrence and human health risks assessment studies. 797:149069. Sci Total Environ	9/8/2021

Table 5-5 PubMed Database Search Results – Included as Supplemental material studies

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
✓								Spero, M.A. & Newman, D.K. (2018).Chlorate Specifically Targets Oxidant-Starved, Antibiotic-Tolerant Populations of Pseudomonas aeruginosa Biofilms. 9(5):e01400-18. mBio	8/27/2021
✓								Youngblut, M.D.; Wang, O.; Barnum, T.P.; Coates, J.D. (2016). (Per)chlorate in Biology on Earth and Beyond. 70:435-57. Annu Rev Microbiol	8/27/2021
			✓					McCarthy, W.P.; O'Callaghan, T.F.; Danahar, M.; Gleeson, D.; O'Connor, C.; Fenelon, M.A.; Tobin, J.T. (2018). Chlorate and Other Oxychlorine Contaminants Within the Dairy Supply Chain. 17(6):1561-1575. Compr Rev Food Sci Food Saf	8/27/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
			✓					Panseri, S.; Nobile, M.; Arioli, F.; Biolatti, C.; Pavlovic, R.; Chiesa, L.M. (2020). Occurrence of perchlorate, chlorate and polar herbicides in different baby food commodities. 330:127205.Food Chem	8/27/2021
✓								Ma, L.; Wen, S.; Yuan, J.; Zhang, D.; Lu, Y.L.; Zhang, Y.; Li, Y.; Cao, S. (2020). Detection of chlorite, chlorate and perchlorate in ozonated saline. 20(3):2569-2576. Exp Ther Med	8/27/2021
✓								Levanov, A.V.; Isaikina, O.Y.; Gasanova, R.B.; Uzhel, A.S.; Lunin, V.V. (2019) Kinetics of chlorate formation during ozonation of aqueous chloride solutions. 229:68-76. Chemosphere	8/27/2021
			✓					Zhang, W.; Hua, Y.; Lu, Q.; Qiu, W.; Li, Y. (2021). Determination of chlorate and perchlorate in infant formula by ultra-high performance liquid chromatography-tandem mass spectrometry. 50(4):625-632. 10.19813/j.cnki.weishengyanjiu.2021.04.015	8/31/2021
			✓					Radwa,n E.K.; Barakat, M.H.; Ibrahim, M.B.M. (2021). Hazardous inorganic disinfection by-products in Egypt's tap drinking water: Occurrence and human health risks assessment studies.797:149069. Sci Total Environ	8/31/2021
			✓					Suryanarayanan, V.; Pattanayak, D.K.; Senthil, K. R.; Kilpatrick, L.; Chopra, S.; Xu, G.; Fei, L.; Dogo-Isonagie, C.; Johansson, P. (2021). Electrochemical mineralization of iron-tannate stain on HAp and bovine enamel-A non-peroxide approach. 7(6):e07296. Heliyon	8/31/2021
			✓					Kong, Q.; Fan, M.; Yin, R.; Zhang, X.; Lei, Y.; Shang, C.; Yang, X. (2021). Micropollutant abatement and by-product formation during the co-exposure of chlorine dioxide (ClO2) and UVC radiation. 419:126424. J Hazard Mater	8/31/2021
✓								Schaberg, E.; Theocharidis, U.; May, M.; Lessmann, K.; Schroeder, T.; Faissner, A. (2021). Sulfation of Glycosaminoglycans Modulates the Cell Cycle of Embryonic Mouse Spinal Cord Neural Stem Cells. 9:643060. Front Cell Dev Biol	8/31/2021
			✓					Huang, S.; Han, D.; Wang, J.; Guo, D.; Li, J. (2021). Floral Induction of Longan (Dimocarpus longan) by Potassium Chlorate: Application, Mechanism, and Future Perspectives. 12:670587.Front Plant Sci	8/31/2021
✓								Liu, R.; Zhang, Y.; Kumar, A.; Huhn, S.; Hullinger, L.; Du, Z. (2021). Modulating tyrosine sulfation of recombinant antibodies in CHO cell culture by host selection and sodium chlorate supplementation. e2100142. Biotechnol J.	8/31/2021
			✓					Petri, E.; Virto, R. (2021). Comparison of peracetic acid and chlorine effectiveness during fresh-cut vegetables processing at industrial scale. J Food Prot. doi: 10.4315/JFP-20-448.	8/31/2021
			✓					Sanz, R. E.; Lam, S.; Smith, G.G.; Haddad, P.R.; Paull, B. (2021). Ultra-trace determination of oxyhalides in ozonated aquacultural marine waters by direct injection ion chromatography coupled with triple-quadrupole mass spectrometry. 7(4):e06885. Heliyon	8/31/2021
✓								Clark JA, Yang Y, Ramos NC, Hillhouse HW. Selective oxidation of pharmaceuticals and suppression of perchlorate formation during electrolysis of fresh human urine. Water Res. 2021 Jun 15;198:117106.	8/31/2021
						✓		Dias, J.; López, S.H.; Mol, H.; de Kok, A. (2021). Influence of different hydrophilic interaction liquid chromatography stationary phases on method performance for the determination of highly polar anionic pesticides in complex feed matrices. 44(11):2165-2176. J Sep Sci	8/31/2021
						✓		Norra, G.F.; Radjenovic, J. (2021). Removal of persistent organic contaminants from wastewater using a hybrid electrochemical-granular activated carbon (GAC) system. 415:125557. J Hazard Mater	8/31/2021
			✓			✓		Gormez, E.; Golge, O.; Kabak, B. (2021). Quantification of fosetyl-aluminium/phosphonic acid and other highly polar residues in pomegranates using Quick Polar Pesticides method involving liquid chromatography-tandem mass spectrometry measurement. 1642:462038. J Chromatogr A	8/31/2021
						✓		Sharma, S.K.; Howe, B.M.; Misra, A.K.; Rognstad, M.R.; Porter, J.N.; Acosta-Maeda, T.E.; Egan, M.J. (2021). Underwater Time-Gated Standoff Raman Sensor for In Situ Chemical Sensing. 75(6):739-746. Appl Spectrosc	8/31/2021
✓								Jackson, W.A.; Brundrett, M.; Böhlke, J.K.; Hatzinger, P.B.; Mroczkowski, S.J.; Sturchio, N.C. (2021). Isotopic composition of natural and synthetic chlorate (δ18O, Δ17O, δ37Cl, 36Cl/Cl): Methods and initial results. 274:129586. Chemosphere	8/31/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
						✓		Lin, H.; Peng, H.; Feng, X.; Li, X.; Zhao, J.; Yang, K.; Liao, J.; Cheng, D.; Liu, X.; Lv, S.; Xu, J. (2021). Huang Q. Energy-efficient for advanced oxidation of bio-treated landfill leachate effluent by reactive electrochemical membranes (REMs): Laboratory and pilot scale studies. 190:116790. Water Res	8/31/2021
			✓					Zerva I, Remmas N, Kagalou I, Melidis P, Ariantsi M, Sylaios G, Ntougias S. Effect of Chlorination on Microbiological Quality of Effluent of a Full-Scale Wastewater Treatment Plant. Life (Basel). 2021 Jan 19;11(1):68. doi: 10.3390/life11010068.	8/31/2021
✓								Lee, M.Y.et al (2021). Applications of UV/H2O2, UV/persulfate, and UV/persulfate/Cu2+ for the elimination of reverse osmosis concentrate generated from municipal wastewater reclamation treatment plant: Toxicity, transformation products, and disinfection by-products. 762:144161. Sci Total Environ	8/31/2021
✓								Kurajica, L.; Ujević, B. M.; Kinsela, A.S.; Štiglić, J.; Waite, T.D.; Capak, K.; Pavlić, Z. (2021). Effects of changing supply water quality on drinking water distribution networks: Changes in NOM optical properties, disinfection by-product formation, and Mn deposition and release. 762:144159. Sci Total Environ	8/31/2021
						✓		Yin, X.; Cui, H.; Li, S.; Niu, S. (2020). Simultaneous determination of chlorite, chlorate, perchlorate and bromate in ozonated saline by using IC-MS. 12(48):5916-5921. Anal Methods	8/31/2021
✓								Zhao, J.; Shang, C.; Zhang, X.; Yang, X.; Yin, R. (2021). The multiple roles of chlorite on the concentrations of radicals and ozone and formation of chlorate during UV photolysis of free chlorine. 190:116680. Water Res	8/31/2021
✓								Qiao, Q.; Singh, S.; Lo, S.L.; Jin, J.; Yu, Y.C.; Wang, L. (2021). Effect of current density and pH on the electrochemically generated active chloro species for the rapid mineralization of p-substituted phenol.275:129848. Chemosphere	8/31/2021
✓								Wang, J.; Wu, Y.; Bu, L.; Zhu, S.; Zhang, W.; Zhou, S.; Gao, N. (2021). Simultaneous removal of chlorite and contaminants of emerging concern under UV photolysis: Hydroxyl radicals vs. chlorate formation. 190:116708. Water Res	9/3/2021
✓								Zhang, Y.; Ji, Y.; Li, J.; Bai, J.; Chen, S.; Li, L.; Wang, J.; Zhou, T.; Jiang, P.; Guan, X.; Zhou, B. (2021) Efficient ammonia removal and toxic chlorate control by using BiVO4/WO3 heterojunction photoanode in a self-driven PEC-chlorine system. 402:123725. J Hazard Mater	9/3/2021
✓								Fang, F.; Zhang, Y.; Bai, J.; Li, J.; Mei, X.; Zhou, C.; Zhou, M.; Zhou, B. (2020). Efficient urine removal, simultaneous elimination of emerging contaminants, and control of toxic chlorate in a photoelectrocatalytic-chlorine system. 267:115605. Environ Pollut	9/3/2021
✓								Levakov, I.; Han, J.; Ronen, Z.; Dahan, O. (2021) Inhibition of perchlorate biodegradation by ferric and ferrous iron. 410:124555. J Hazard Mater	9/3/2021
						✓		Krauss, S.T.; Forbes, T.P.; Jobes, D. (2021). Inorganic oxidizer detection from propellants, pyrotechnics, and homemade explosive powders using gradient elution moving boundary electrophoresis. 42(3):279-288. Electrophoresis	9/3/2021
			✓					Lin, X.; Chen, G.; Jin, T.Z.; Wen, M.; Wu, J.; Wen, J.; Xu, Y.; An, K.;Yu, Y. (2021) Extension of shelf life of semi-dry longan pulp with gaseous chlorine dioxide generating film. 337:108938. Int J Food Microbiol	9/3/2021
						✓		Hidalgo-Ruiz, J.L.; Romero-González, R.; Martínez Vidal, J.L.; Garrido Frenich, A. (2021). Monitoring of polar pesticides and contaminants in edible oils and nuts by liquid chromatography-tandem mass spectrometry. 343:128495. Food Chem	9/3/2021
✓								Chen, T.; Yu, Z.; Xu, T.; Xiao, R.; Chu, W.; Yin, D. (2021). Formation and degradation mechanisms of CX3R-type oxidation by-products during cobalt catalyzed peroxymonosulfate oxidation: The roles of Co3+ and SO4·. 405:124243. J Hazard Mater	9/3/2021
✓								Guan, Y.H.; Chen, J.; Chen, L.J.; Jiang, X.X.; Fu, Q. (2020). Comparison of UV/H2O2, UV/PMS, and UV/PDS in Destruction of Different Reactivity Compounds and Formation of Bromate and Chlorate. 8:581198. Front Chem	9/3/2021
✓								Han, J.; Zhang, X.; Li, W.; Jiang, J. (2021). Low chlorine impurity might be beneficial in chlorine dioxide disinfection. 188:116520. Water Res	9/3/2021
✓								Zhang, R.; Klaine, S.; Alcantar, C.; Bratcher, F. (2020). Visible light generation of high-valent metal-oxo intermediates and mechanistic insights into catalytic oxidations. 212:111246. J Inorg Biochem	9/3/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
✓								Cao, N.; Yang, J. (2020). [Proficiency test for determination of chlorate in drinking water]. 49(4):630-634. Wei Sheng Yan Jiu	9/3/2021
						✓		Kurajica, L.; Ujević, M.; Novak, M.; Kinsela, A.S.; Štiglić, J.; Waite, D.T.; Capak, K. (2020). Disinfection by-products in Croatian drinking water supplies with special emphasis on the water supply network in the city of Zagreb. 276:111360. J Environ Manage	9/3/2021
✓								Li, Z.Y.; Li, X.; Tan, B.; Lv, P.L.; Zhao, H.P. NC10 bacteria promoted methane oxidation coupled to chlorate reduction. 31(4-6):319-329. Biodegradation	9/3/2021
✓								Lin, M.H.; Bulman, D.M.; Remucal, C.K.; Chaplin, B.P. (2020). Chlorinated By-product Formation during the Electrochemical Advanced Oxidation Process at Magnéli Phase Ti4O7 Electrodes. 54(19):12673-12683. Environ Sci Technol	9/3/2021
✓								Kim, T.K.; Kim, T.; Cha, Y.; Zoh, K.D. (2020). Energy-efficient erythromycin degradation using UV-LED (275 nm)/chlorine process: Radical contribution, transformation products, and toxicity evaluation. 185:116159. Water Res.	9/3/2021
							✓	Yin, Z.J.; Zhang, Y.N.; Guan, F.J.; Yu, H.; Ma, Y.J. (2020). Simultaneous separation and indirect ultraviolet detection of chlorate and perchlorate by pyridinium ionic liquids in reversed-phase liquid chromatography. 43(20):3868-3875. J Sep Sci	9/3/2021
							✓	Ma, L.; Wen, S.; Yuan, J.; Zhang, D.; Lu, Y.L.; Zhang, Y.; Li, Y.; Cao, S. (2020). Detection of chlorite, chlorate and perchlorate in ozonated saline. 20(3):2569-2576. Exp Ther Med	9/3/2021
							✓	López-Ruiz, R.; Romero-González, R.; Garrido Frenich, A. (2020). Simultaneous determination of polar pesticides in human blood serum by liquid chromatography coupled to triple quadrupole mass spectrometer. 190:113492. J Pharm Biomed Anal	9/3/2021
							✓	Torres-Rojas, F.; Muñoz, D.; Tapia, N.; Canales, C.; Vargas, I.T. (2020). Bioelectrochemical chlorate reduction by Dechloromonas agitata CKB.315:123818. Bioresour Technol.	9/3/2021
			✓					Gadelha, J.R.; Allende, A.; López-Gálvez, F.; Fernández, P.; Gil, M.I.; Egea, J.A. (2019). Chemical risks associated with ready-to-eat vegetables: quantitative analysis to estimate formation and/or accumulation of disinfection by-products during washing. 17(Suppl 2):e170913. EFSA J	9/3/2021
			✓					Panseri, S.; Nobile, M.; Arioli, F.; Biolatti, C.; Pavlovic, R.; Chiesa, L.M. (2020). Occurrence of perchlorate, chlorate and polar herbicides in different baby food commodities. 330:127205. Food Chem.	9/3/2021
							✓	Lakhian, V.; Dickson-Anderson, S.E. (2020) Reduction of bromate and chlorate contaminants in water using aqueous phase corona discharge. 255:126864. Chemosphere	9/3/2021
							✓	Absalon, D.; Matysik, M.; Woźnica, A.; Łozowski, B.; Jarosz, W.; Ulańczyk, R.; Babczyńska, A.; Pasierbiński, A. (2020). Multi-Faceted Environmental Analysis to Improve the Quality of Anthropogenic Water Reservoirs (Paprocany Reservoir Case Study). 20(9):2626. Sensors (Basel)	9/3/2021
			✓					Smith, D.J.; Scapanski, A. (2020). Distribution and Chemical Fate of [36Cl]Chlorine Dioxide Gas on Avocados, Eggs, Onions, and Sweet Potatoes. 68(17):5000-5008. J Agric Food Chem	9/3/2021
✓								Isidro, J.; Brackemeyer, D.; Sáez, C.; Llanos, J.; Lobato, J.; Cañizares, P.; Matthée ,T.; Rodrigo, M.A. (2020). How to avoid the formation of hazardous chlorates and perchlorates during electro-disinfection with diamond anodes?. 265:110566. J Environ Manage	9/3/2021
	✓							Barros, TL.; Beer, L.C.; Tellez, G.; Fuller, A.L.; Hargis, B.M.; Vuong, C.N. (2020). Research Note: Evaluation of dietary administration of sodium chlorate and sodium nitrate for Histomonas meleagridis prophylaxis in turkeys. 99(4):1983-1987. Poult Sci	9/3/2021
	✓							Barnum TP, Cheng Y, Hill KA, Lucas LN, Carlson HK, Coates JD. Identification of a parasitic symbiosis between respiratory metabolisms in the biogeochemical chlorine cycle. ISME J. 2020 May;14(5):1194-1206.	9/3/2021
							✓	Ma, X.; Li, M.; Feng, C.; He, Z. (2020). Electrochemical nitrate removal with simultaneous magnesium recovery from a mimicked RO brine assisted by in situ chloride ions. 388:122085. J Hazard Mater	9/3/2021
	✓							Nagase, H.; Katagiri, Y.; Oh-Hashi, K.; Geller, H.M.; Hirata, Y. (2020). Reduced Sulfation Enhanced Oxytosis and Ferroptosis in Mouse Hippocampal HT22 Cells. 10(1):92. Biomolecules	9/3/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
							✓	Zhou, X.; Lü, X.; Wan, J.; Guo, P.; Guo, D.; Xi, H. (2019). Determination of chlorate and perchlorate in milk power by high-performance liquid chromatography-tandem mass spectrometry. 37(10):1064-1070. Se Pu	9/3/2021
✓								Busch, M.; Simic, N.; Ahlberg, E. (2019). Exploring the mechanism of hypochlorous acid decomposition in aqueous solutions. 21(35):19342-19348. Phys Chem Chem Phys	9/3/2021
							✓	Bruzzoniti et al. (2019). Towards the revision of the drinking water directive 98/83/EC. Development of a direct injection ion chromatographic-tandem mass spectrometric method for the monitoring of 15 common and emerging disinfection by-products along the drinking water supply chain. 1605:360350. J Chromatogr A	9/3/2021
			✓					Paludetti, L.F.; Kelly, A.L.; O'Brien, B.; Gleeson, D. (2019). Monitoring residue concentrations in milk from farm and throughout a milk powder manufacturing process. 86(3):341-346. J Dairy Res	9/3/2021
	✓							Zhong, Y.; Gan, W.; Du, Y.; Huang, H.; Wu, Q.; Xiang, Y.; Shang, C.; Yang, X. (2019). Disinfection by-products and their toxicity in wastewater effluents treated by the mixing oxidant of ClO2/Cl2. 162:471-481. Water Res	9/3/2021
							✓	Constantinou, P.; Louca-Christodoulou, D.; Agapiou, A. (2019). LC-ESI-MS/MS determination of oxyhalides (chlorate, perchlorate and bromate) in food and water samples, and chlorate on household water treatment devices along with perchlorate in plants. 235:757-766. Chemosphere	9/3/2021
							✓	Melton, L.M.; Taylor, M.J.; Flynn, E.E. (2019). The utilisation of ion chromatography and tandem mass spectrometry (IC-MS/MS) for the multi-residue simultaneous determination of highly polar anionic pesticides in fruit and vegetables. 298:125028. Food Chem	9/3/2021
							✓	Wang, C.; Moore, N.; Bircher, K.; Andrews, S.; Hofmann, R. (2019). Full-scale comparison of UV/H2O2 and UV/Cl2 advanced oxidation: The degradation of micropollutant surrogates and the formation of disinfection by-products. 161:448-458. Water Res.	9/3/2021
							✓	Girenko, D.V.; Gyrenko, A.A.; Nikolenko, N.V. (2019). Potentiometric Determination of Chlorate Impurities in Hypochlorite Solutions. 2019:2360420. Int J Anal Chem	9/3/2021
							✓	Chen, J.; Li, J.; Zhang, X.; Wu, Z., Tyagi, R.D. (2020). Ultra-sonication for controlling the formation of disinfection by-products in the ClO2 pre-oxidation of water containing high concentrations of algae. 42(3):849-861. Environ Geochem Health	9/3/2021
✓								Levanov, A.V.; Isaikina, O.Y.; Gasanova, R.B.; Uzhel, A.S.; Lunin, V.V. (2019). Kinetics of chlorate formation during ozonation of aqueous chloride solutions. 229:68-76. Chemosphere	9/3/2021
							✓	Savini, S.; Bandini, M.; Sannino, A. (2019). An Improved, Rapid, and Sensitive Ultra-High-Performance Liquid Chromatography-High-Resolution Orbitrap Mass Spectrometry Analysis for the Determination of Highly Polar Pesticides and Contaminants in Processed Fruits and Vegetables. 67(9):2716-2722. J Agric Food Chem	9/3/2021
	✓							Krishnaraj, P.; Chang, Y.; Ho, T.J.; Lu, N.C.; Lin, M.D.; Chen, H.P. (2019). In vivo pro-angiogenic effects of dracorhodin perchlorate in zebrafish embryos: A novel bioactivity evaluation platform for commercial dragon blood samples. 27(1):259-265. J Food Drug Anal	9/3/2021
✓								Ye, B.; Cang, Y.; Li, J.; Zhang, X. (2019). Advantages of a ClO2/NaClO combination process for controlling the disinfection by-products (DBPs) for high algae-laden water. 41(3):1545-1557. Environ Geochem Health	9/3/2021
✓								Padhi, R.K.; Subramanian, S.; Satpathy, K.K. (2019). Formation, distribution, and speciation of DBPs (THMs, HAAs, ClO2-,andClO3-) during treatment of different source water with chlorine and chlorine dioxide. 218:540-550. Chemosphere	9/3/2021
			✓					Uzun H, Kim D, Karanfil T. Removal of wastewater and polymer derived N-nitrosodimethylamine precursors with integrated use of chlorine and chlorine dioxide. Chemosphere. 2019 Feb;216:224-233. doi: 10.1016/j.chemosphere.2018.10.088. Epub 2018 Oct 16. PMID: 30384291.	9/3/2021
✓								Rougé, V.; Allard, S.; Croué, J.P.; Von Gunten, U. (2018) In Situ Formation of Free Chlorine During ClO2 Treatment: Implications on the Formation of Disinfection By-products. 52(22):13421-13429. Environ Sci Technol	9/5/2021
	✓							Barbosa, G.O.; Augusto, T.M.; Bruni-Cardoso, A.; Carvalho, H.F. (2019). The role of SDF1 in prostate epithelial morphogenesis. 234(5):6886-6897. J Cell Physiol	9/5/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
							✓	Zapata, F.; Ortega-Ojeda, F.; García-Ruiz, C.; González-Herráez, M. (2018). Selective Monitoring of Oxyanion Mixtures by a Flow System with Raman Detection. 18(7):2196. Sensors (Basel)	9/5/2021
							✓	Isidro, J.; Llanos, J.; Sáez, C.; Brackemeyer, D.; Cañizares, P.; Matthee, T.; Rodrigo, M.A. (2018). Can CabECO® technology be used for the disinfection of highly faecal-polluted surface water? 209:346-352. Chemosphere	9/5/2021
✓								Hou, S.; Ling. L.; Dionysiou, D.D.; Wang, Y.; Huang, J.; Guo, K.; Li, X.; Fang, J. (2018). Chlorate Formation Mechanism in the Presence of Sulfate Radical, Chloride, Bromide and Natural Organic Matter. 52(11):6317-6325. Environ Sci Technol	9/5/2021
	✓							De la Peña, S.; Isela, S.R.; Zendy, O.V.; Mónica, N.M.; Irene, X.R.; Omar, A.H. (2018). Changes in trophoblasts gene expression in response to perchlorate exposition. 50:328-335. Toxicol In Vitro	9/5/2021
✓								Fang, Q.; Xu, W.; Yan, Z.; Qian, L. (2018). Effect of Potassium Chlorate on the Treatment of Domestic Sewage by Achieving Shortcut Nitrification in a Constructed Rapid Infiltration System. 15(4):670. Int J Environ Res Public Health	9/5/2021
			✓					Yüksekkaya H, Gumus M, Yucel A, Energin M, Demirci S. Ingestion of Fireworks: Rare Cause of Poisoning in Children. Pediatr Emerg Care. 2019 Mar;35(3):216-219.	9/5/2021
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		✓						Peng, L.; Dai, X.; Liu, Y.; Wei, W.; Sun, J.; Xie, G.J.; Wang, D.; Song, S.; Ni, B.J. (2018). Kinetic assessment of simultaneous removal of arsenite, chlorate and nitrate under autotrophic and mixotrophic conditions. 628-629:85-93. Sci Total Environ	9/5/2021
			✓					Banach, J.L.; van Overbeek, L.S.; Nierop, G.M.N.; van der Zouwen. P.S.; van der Fels-Klerx, H.J. (2018). Efficacy of chlorine dioxide on Escherichia coli inactivation during pilot-scale fresh-cut lettuce processing. 269:128-136. Int J Food Microbiol	9/5/2021
							✓	Shriver-Lake, L.C.; Zabetakis, D.; Dressick, W.J.; Stenger, D.A.; Trammell, S.A. (2018). Paper-Based Electrochemical Detection of Chlorate. 18(2):328. Sensors (Basel).	9/5/2021
			✓					Mastrocicco, M.; Di Giuseppe, D.; Vincenzi, F.; Colombani, N.; Castaldelli, G. (2017). Chlorate origin and fate in shallow groundwater below agricultural landscapes. 231(Pt 2):1453-1462. Environ Pollut	9/7/2021
							✓	Zapata, F.; García-Ruiz, C. (2018). The discrimination of 72 nitrate, chlorate and perchlorate salts using IR and Raman spectroscopy. 189:535-542. Spectrochim Acta A Mol Biomol Spectrosc	9/7/2021
			✓					Kim, D.; Ates, N.; Kaplan, B.S.S.; Selbes, M.; Karanfil, T. (2017). Impact of combining chlorine dioxide and chlorine on DBP formation in simulated indoor swimming pools. 58:155-162. J Environ Sci (China)	9/7/2021
✓								Jasper, J.T.; Yang, Y.; Hoffmann, M.R. (2017). Toxic By-product Formation during Electrochemical Treatment of Latrine Wastewater. 51(12):7111-7119. Environ Sci Technol	9/7/2021
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							✓	Mavroudakis, L.; Mavrakis, E.; Kouvarakis, A.; Pergantis, S.A. (2017). Determination of chlorate, perchlorate and bromate anions in water samples by microbore reversed-phase liquid chromatography coupled to sonic-spray ionization mass spectrometry. 31(11):911-918. Rapid Commun Mass Spectrom	9/7/2021
							✓	Negrel, P.; Ollivier, P.; Flehoc, C.; Hube, D. (2017). An innovative application of stable isotopes (δ2H and δ18O) for tracing pollutant plumes in groundwater. 578:495-501. Sci Total Environ	9/7/2021
✓								Ali, S.N.; Ahmad, M.K.; Mahmood, R. (2017). Sodium chlorate, a herbicide and major water disinfectant by-product, generates reactive oxygen species and induces oxidative damage in human erythrocytes. 24(2):1898-1909. Environ Sci Pollut Res Int	9/7/2021
							✓	Topcu, C. (2016). Highly selective direct determination of chlorate ions by using a newly developed potentiometric electrode based on modified smectite. 161:623-631. Talanta	9/7/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
			✓					Carlström, C.I.; Lucas, L.N.; Rohde, R.A.; Haratian, A.; Engelbrektson, A.L.; Coates, J.D. (2016). Characterization of an anaerobic marine microbial community exposed to combined fluxes of perchlorate and salinity. 100(22):9719-9732. Appl Microbiol Biotechnol	9/7/2021
			✓					Al-Otoum, F.; Al-Ghouti, M.A.; Ahmed, T.A.; Abu-Dieyeh, M.; Ali, M. (2016). Disinfection by-products of chlorine dioxide (chlorite, chlorate, and trihalomethanes): Occurrence in drinking water in Qatar. 164:649-656. Chemosphere	9/7/2021
✓								Marks, R.; Yang, T.; Westerhoff, P.; Doudrick, K. (2016). Comparative analysis of the photocatalytic reduction of drinking water oxoanions using titanium dioxide. 104:11-19. Water Res	9/7/2021
✓								Bender, K.S. Environmental (Per)chlorate Reduction: a collaborative effort in syntrophy?. 18(10):3205-3206. Environ Microbiol	9/7/2021
			✓					Kettlitz, B et al. (2016). Why chlorate occurs in potable water and processed foods: a critical assessment and challenges faced by the food industry. 33(6):968-82. Food Addit Contam Part A Chem Anal Control Expo Risk Assess	9/7/2021
✓								Qian, Y.; Guo, X.; Zhang, Y.; Peng, Y.; Sun, P.; Huang, C.H.; Niu, J.; Zhou, X.; Crittenden, J.C. (2016). Perfluorooctanoic Acid Degradation Using UV-Persulfate Process: Modeling of the Degradation and Chlorate Formation. 50(2):772-81. Environ Sci Technol	9/7/2021
							✓	Kelley JA, Ostrinskaya A, Geurtsen G, Kunz RR. Reagent approaches for improved detection of chlorate and perchlorate salts via thermal desorption and ionization. Rapid Commun Mass Spectrom. 2016 Jan 15;30(1):191-8.	9/7/2021
✓								Lin, Z.; Yao, W.; Wang, Y.; Yu, G.; Deng, S.; Huang, J.; Wang, B. (2016). Perchlorate formation during the electro-peroxone treatment of chloride-containing water: Effects of operational parameters and control strategies. 88:691-702. Water Res	9/7/2021
✓								Zhou, X.; Zhao, J.; Li, Z.; Lan, J.; Li, Y.; Yang, X.; Wang, D. (2016). Influence of ultrasound enhancement on chlorine dioxide consumption and disinfection by-products formation for secondary effluents disinfection. 28:376-381. Ultrason Sonochem	9/7/2021
							✓	Sanz, R. E.; Lam, S.; Smith, G.G.; Haddad, P.R.; Paull, B. (2021). Ultra-trace determination of oxyhalides in ozonated aquacultural marine waters by direct injection ion chromatography coupled with triple-quadrupole mass spectrometry. 7(4):e06885. Heliyon	9/8/2021
✓								Zerva, I.; Remmas, N.; Kagalou, I.; Melidis, P.; Ariantsi, M.; Sylaios, G.; Ntougias, S. (2021). Effect of Chlorination on Microbiological Quality of Effluent of a Full-Scale Wastewater Treatment Plant. 11(1):68. Life (Basel)	9/8/2021
✓								Lee et al. (2021). Applications of UV/H2O2, UV/persulfate, and UV/persulfate/Cu2+ for the elimination of reverse osmosis concentrate generated from municipal wastewater reclamation treatment plant: Toxicity, transformation products, and disinfection by-products. 762:144161. Sci Total Environ	9/8/2021

Table 5-6 PubMed Database Search Results – Excluded studies

List of excluded studies (CITATION)	Search Date
Torres-Rojas, F.; Muñoz, D.; Tapia, N.; Canales, C.; Vargas, I.T. (2020). Bioelectrochemical chlorate reduction by Dechloromonas agitata CKB. 315:123818.Bioresour Technol	8/27/2021
Wang, O. & Coates, J.D. (2017). Biotechnological Applications of Microbial (Per)chlorate Reduction. 5(4):76. Microorganisms	8/27/2021
Chen, H.W.; Xu, M.; Ma, X.W.; Tong, Z.H.; Liu, D.F. (2019). Isolation and characterization of a chlorate-reducing bacterium Ochrobactrum anthropi XM-1. 380:120873. J Hazard Mater	8/27/2021
Baptista-Pires L, Norra GF, Radjenovic J. Graphene-based sponges for electrochemical degradation of persistent organic contaminants. Water Res. 2021 Aug 2;203:117492. doi: 10.1016/j.watres.2021.117492. Epub ahead of print. PMID: 34365195.	8/31/2021
Bernabeu E, Miralles-Robledillo JM, Giani M, Valdés E, Martínez-Espinosa RM, Pire C. In Silico Analysis of the Enzymes Involved in Haloarchaeal Denitrification. Biomolecules. 2021 Jul 16;11(7):1043. doi: 10.3390/biom11071043. PMID: 34356667; PMCID: PMC8301774.	8/31/2021
Pérez-González O, Gomez-Flores R, Tamez-Guerra P. Mycelial compatibility, anastomosis, and nucleus numbers of eight Mexican Hirsutella citriformis strains isolated from Diaphorina citri. PeerJ. 2021 Apr 19;9:e11080.	8/31/2021
Shende T, Andaluri G, Suri R. Power density modulated ultrasonic degradation of perfluoroalkyl substances with and without sparging Argon. Ultrason Sonochem. 2021 Aug;76:105639. doi: 10.1016/j.ultsonch.2021.105639. Epub 2021 Jun 20. PMID: 34175810; PMCID: PMC8237577.	8/31/2021
Moon D, Jeon S, Choi JH. Crystal structure of 3,14-dimethyl-2,13-di-aza-6,17-diazo-niatri-cyclo-[16.4.0.07,12]docosane bis-(per-chlorate) from synchrotron X-ray data. Acta Crystallogr E Crystallogr Commun. 2021 Apr 23;77(Pt 5):551-554.	8/31/2021

List of excluded studies (CITATION)	Search Date
Li W, Niu Z, Zhu X. Recovery of iron by jarosite crystallization and separation of vanadium by solvent extraction with extractant 7101 from titanium white waste liquid (TWWL). Water Sci Technol. 2021 Apr;83(8):2025-2037. doi: 10.2166/wst.2021.114. PMID: 33905370.	8/31/2021
Liu D, Kounaves SP. Degradation of Amino Acids on Mars by UV Irradiation in the Presence of Chloride and Oxychlorine Salts. Astrobiology. 2021 Jul;21(7):793-801. doi: 10.1089/ast.2020.2328. Epub 2021 Mar 30. PMID: 33787313.	8/31/2021
Monteiro EV, R Queiroz JP, Faria RB. The Chlorate-Nitrous Acid-Iodine-Iodide Oscillating Reaction. ACS Omega. 2021 Mar 13;6(11):7959-7965. doi: 10.1021/acsomega.1c00933. PMID: 33778307; PMCID: PMC7992172.	8/31/2021
Yamazaki T, Kimura Y. Radiolysis-Induced Crystallization of Sodium Chloride in Acetone by Electron Beam Irradiation. Microsc Microanal. 2021 Mar 22:1-7. doi: 10.1017/S1431927621000179. Epub ahead of print. PMID: 33745494.	8/31/2021
Garcia SN, Yang X, Bereczki L, Kónya D. Aqueous Solubility of Organic Compounds for Flow Battery Applications: Symmetry and Counter Ion Design to Avoid Low-Solubility Polymorphs. Molecules. 2021 Feb 24;26(5):1203. doi: 10.3390/molecules26051203. PMID: 33668137; PMCID: PMC7956567.	8/31/2021
Xie Q, Yang J, Pan F, Cai J. Preparation of 6-carboxyl chitin and its effects on cell proliferation in vitro. Carbohydr Polym. 2021 Apr 1;257:117638. doi: 10.1016/j.carbpol.2021.117638. Epub 2021 Jan 16. PMID: 33541663.	8/31/2021
Zhang Q, Zhang X, Duan P, Jiang X, Shen H, Yan X, Xiong Z. The effect of long-term biochar amendment on N2O emissions: Experiments with N15-O18 isotopes combined with specific inhibition approaches. Sci Total Environ. 2021 May 15;769:144533. doi: 10.1016/j.scitotenv.2020.144533. Epub 2021 Jan 14. PMID: 33482542.	8/31/2021
Cui Y, Guo L, Mu Q, Cheng Q, Kang L, He Y, Tang M, Wu Q. Sleep deprivation did not enhance the success rate of chloral hydrate sedation for non-invasive procedural sedation in pediatric patients. PLoS One. 2021 Jan 12;16(1):e0245338. doi: 10.1371/journal.pone.0245338. PMID: 33434236; PMCID: PMC7802942.	8/31/2021
Kim J, Chang KS, Lee S, Jin E. Establishment of a Genome Editing Tool Using CRISPR-Cas9 in *Chlorella vulgaris* UTEX395. Int J Mol Sci. 2021 Jan 6;22(2):480. doi: 10.3390/ijms22020480. PMID: 33418923; PMCID: PMC7825080.	8/31/2021
Rao R, Liu X, Li Y, Tan X, Zhou H, Bai X, Yang X, Liu W. Bioinspired zwitterionic polyphosphoester modified porous silicon nanoparticles for efficient oral insulin delivery. Biomater Sci. 2021 Feb 9;9(3):685-699. doi: 10.1039/d0bm01772h. PMID: 33330897.	8/31/2021
Kabange, N.R.; Park, S.Y.; Lee, J.Y.; Shin, D.; Lee, S.M.; Kwon, Y.; Cha, J.K.; Cho, J.H.; Duyen, D.V.; Ko, J.M.; Lee, J.H. (2021). New Insights into the Transcriptional Regulation of Genes Involved in the Nitrogen Use Efficiency under Potassium Chlorate in Rice (Oryza sativa L.). 2021 Feb 22;22(4):2192. Int J Mol Sci	8/31/2021
Radjenovic J, Duinslaeger N, Avval SS, Chaplin BP. Facing the Challenge of Poly- and Perfluoroalkyl Substances in Water: Is Electrochemical Oxidation the Answer? Environ Sci Technol. 2020 Dec 1;54(23):14815-14829. doi: 10.1021/acs.est.0c06212. Epub 2020 Nov 15. PMID: 33191730.	9/3/2021
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Subudhi PK, Garcia RS, Coronejo S, Tapia R. Comparative Transcriptomics of Rice Genotypes with Contrasting Responses to Nitrogen Stress Reveals Genes Influencing Nitrogen Uptake through the Regulation of Root Architecture. Int J Mol Sci. 2020 Aug 11;21(16):5759. doi: 10.3390/ijms21165759. PMID: 32796695; PMCID: PMC7460981.	9/3/2021
Bellaloui N, Bruns HA, Abbas HK, Fisher DK, Mengistu A. Effects of Harvest-Aids on Seed Nutrition in Soybean under Midsouth USA Conditions. Plants (Basel). 2020 Aug 9;9(8):1007. doi: 10.3390/plants9081007. PMID: 32784886; PMCID: PMC7465667.	9/3/2021
McMahon DJ, Bowen IB, Green I, Domek M, Oberg CJ. Growth and survival characteristics of Paucilactobacillus wasatchensis WDCO4. J Dairy Sci. 2020 Oct;103(10):8771-8781. doi: 10.3168/jds.2020-18597. Epub 2020 Jul 31. PMID: 32747094.	9/3/2021
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Küblböck T, Angé G, Bikelytė G, Pokorná J, Skácel R, Klapötke TM. Guanidinium 5,5'-Azotetrazolate: A Colorful Chameleon for Halogen-Free Smoke Signals. Angew Chem Int Ed Engl. 2020 Jul 20;59(30):12326-12330. doi: 10.1002/anie.202007489. Epub 2020 Jun 25. PMID: 32519418; PMCID: PMC7383485.	9/3/2021
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Coyle DH, Wu JH, Di Tanna GL, Shahid M, Taylor F, Neal B, Trevena H. The Effects of a Supermarket-Based Intervention on the Nutritional Quality of Private-Label Foods: A Prospective Study. Nutrients. 2020 Jun 5;12(6):1692. doi: 10.3390/nu12061692. PMID: 32517118; PMCID: PMC7353040.	9/3/2021
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Habeler M, Lindner HH, Redl B. A role of heparan sulphate proteoglycan in the cellular uptake of lipocalins ß-lactoglobulin and allergen Fel d 4. Biol Chem. 2020 Aug 27;401(9):1081-1092. doi: 10.1515/hsz-2020-0132. PMID: 32229688.	9/3/2021
Gavrish SP, Shova S, Cazacu M, Dascalu M, Lampeka YD. Syntheses and crystal structures of the one-dimensional coordination polymers formed by [Ni(cyclam)]2+ cations and 1,3-bis-(3-carb-oxy-prop-yl)tetra-methyl-disiloxane anions in different degrees of deprotonation. Acta Crystallogr E Crystallogr Commun. 2020 Feb 25;76(Pt 3):446-451. doi: 10.1107/S2056989020002327. PMID: 32148892; PMCID: PMC7057376.	9/3/2021
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List of excluded studies (CITATION)	Search Date
Arzola-Alvarez C, Hume ME, Anderson RC, Latham EA, Ruiz-Barrera O, Castillo-Castillo Y, Olivas-Palacios AL, Felix-Portillo M, Armendariz-Rivas RL, Arzola-Rubio A, Ontiveros-Magadan M, Bautista-Martínez Y, Salinas-Chavira J. Influence of sodium chlorate, ferulic acid, and essential oils on Escherichia coli and porcine fecal microbiota. J Anim Sci. 2020 Mar 1;98(3):skaa059. doi: 10.1093/jas/skaa059. PMID: 32064520; PMCID: PMC7072035.	9/3/2021
Wang G, Li Y, Cai Z, Dou X. A Colorimetric Artificial Olfactory System for Airborne Improvised Explosive Identification. Adv Mater. 2020 Apr;32(14):e1907043. doi: 10.1002/adma.201907043. Epub 2020 Jan 29. PMID: 31995260.	9/3/2021
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Wiley Online Library Search Results

Table 5-7 Wiley Online Library Database Search Results – Included studies (after De-duplication)

Included Studies – Meet PECO criteria							
Human health effect	**Animal health effect (mammalian)**	**Carcinogenic**	**Reproductive**	**Genotoxicity**	**PBPK model**	**Full list of Included studies**	**Search Date**
✓						Kalankesh L.R., Rodríguez-Couto S., Zazouli M.A. Moosazadeh M., Mousavinasab S. (2019). Do disinfection by-products in drinking water have an effect on human cancer risk worldwide? A meta-analysis. Environ Qual Manage. 2019;1–15.https://doi.org/10.1002/tqem.21661	9/9/2021
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✓						2017 WHO Guidelines for Drinking Water Quality: First Addendum to the Fourth Edition. https://doi.org/10.5942/jawwa.2017.109.0087	9/9/2021

Table 5-8 Wiley Online Library Database Search Results – Included as Supplemental material studies (after De-duplication)

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
			✓					Gurudatta Singh,Anubhuti Singh,Priyanka Singh,Virendra Kumar Mishra (2021). Chapter 8: Organic Pollutants in Groundwater Resource. https://doi.org/10.1002/9781119709732.ch8	8/9/2021
							✓	Outcome of the consultation with Member States and EFSA on the basic substance application for approval of ozone to be used in plant protection as a bactericide, fungicide, insecticide, nematicide and viricide. https://doi.org/10.2903/sp.efsa.2021.EN-6659	8/9/2021
			✓					The 2019 European Union report on pesticide residues in food. https://doi.org/10.2903/j.efsa.2021.6491	8/9/2021
			✓					National summary reports on pesticide residue analysis performed in 2019. https://doi.org/10.2903/sp.efsa.2021.EN-6487	8/9/2021
			✓					Unregulated and Emerging Contaminants in Tribal Water. https://doi.org/10.1111/j.1936-704X.2020.03334.x	9/9/2021
							✓	Development and technology of rural drinking water supply in China. https://doi.org/10.1002/ird.2465	9/9/2021
✓								A review on the 40th anniversary of the first regulation of drinking water disinfection by-products. https://doi.org/10.1002/em.22378	9/9/2021

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
			✓					Unregulated Disinfection By-Products: Spatiotemporal Variation in Water Distribution Networks. https://doi.org/10.1002/9781119300762.wsts0190	9/9/2021
			✓					Inorganic Contaminants Prompt Widespread Concerns. https://doi.org/10.1002/awwa.1385	9/9/2021
			✓					National summary reports on pesticide residue analysis performed in 2017. https://doi.org/10.2903/sp.efsa.2019.EN-1666	9/9/2021
							✓	Determination of chlorine species by capillary electrophoresis – mass spectrometry. https://doi.org/10.1002/elps.201900138	9/9/2021
							✓	Monitoring UCMR Compounds in Drinking Water System Components and Treatment Chemicals. https://doi.org/10.1002/awwa.1250	9/9/2021
✓								Suppressed oxygen evolution during chlorate formation from hypochlorite in the presence of chromium(VI). https://doi.org/10.1002/jctb.5911	9/9/2021
							✓	Disinfection Processes. https://doi.org/10.2175/106143017X15023776270278	9/9/2021
							✓	Use of Sodium Thiosulfate to Quench Hypochlorite Solutions Prior to Chlorate Analysis.https://doi.org/10.5942/jawwa.2017.109.0097	9/9/2021
							✓	Disinfection By-product Occurrence at Large Water Systems After Stage 2 DBPR. https://doi.org/10.5942/jawwa.2017.109.0082	9/9/2021
			✓					Drinking Water Regulatory Priorities. https://doi.org/10.5942/jawwa.2017.109.0067	9/9/2021
✓								Chlorine Decay and Chlorate Formation in Two Water Treatment Facilities. https://doi.org/10.5942/jawwa.2017.109.0034	9/9/2021
							✓	Disinfection Processes. https://doi.org/10.2175/106143016X14696400494696	9/9/2021
			✓					Fate of Environmental Pollutants. https://doi.org/10.2175/106143016X14696400495578	9/9/2021
✓								Sodium chlorite increases production of reactive oxygen species that impair the antioxidant system and cause morphological changes in human erythrocytes.https://doi.org/10.1002/tox.22328	9/9/2021
✓								Environmental (Per)chlorate Reduction: a collaborative effort in syntrophy?.https://doi.org/10.1111/1462-2920.13275	9/9/2021
							✓	Water, 6. Treatment by Oxidation Processes.https://doi.org/10.1002/14356007.o28_o17.pub2	9/9/2021
							✓	Current to Clean Water – Electrochemical Solutions for Groundwater, Water, and Wastewater Treatment.https://doi.org/10.1002/cite.201800081	9/9/2021
			✓					Maternal residential exposure to specific agricultural pesticide active ingredients and birth defects in a 2003–2005 North Carolina birth cohort. https://doi.org/10.1002/bdr2.1448	9/9/2021

Tox21 Search Results

After de-duplication, no search results are presented as included studies for Tox21 literature screening.

Table 5-9 Tox21 Database Search Results – Included as supplemental studies (after De-duplication)

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
✓								NTP Annual Report: 2019. https://ntp.niehs.nih.gov/annualreport/2019/annualreport_508.pdf	10/9/2021

SciFinder Search Results

After de-duplication, no search results are presented as included studies for SciFinder literature screening.

Table 5-10 SciFinder Database Search Results – Included as supplemental studies (after De-duplication)

Potentially relevant supplemental material									
Mechanistic	**Non-mammalian model**	**ADME/toxicokinetics**	**Exposure characteristics**	**Human case report**	**Records with no original data reviews**	**Mixture studies**	**Methods**	**Full list (citation)**	**Search Date**
✓								A review on the electrochemical production of chlorine dioxide from chlorates and hydrogen peroxide. Sales Monteiro, Mayra Kerolly; Sales Monteiro, Mayara Maria; de Melo Henrique, Andre Miller; Llanos, Javier; Saez, Cristina; Dos Santos, Elisama Vieira; Rodrigo, Manuel Andres From Current Opinion in Electrochemistry (2021), 27, 100685.	11/9/2021
							✓	Electrochemical production and use of chlorinated oxidants for the treatment of wastewater contaminated by organic pollutants and disinfection. Scialdone, Onofrio; Proietto, Federica; Galia, Alessandro. From Current Opinion in Electrochemistry (2021), 27, 100682.	11/9/2021
			✓					Review on safety evaluation and quality control of drinking water and its impact on human health. Khan, Zeeshan. World Journal of Pharmacy and Pharmaceutical Sciences. Volume 5, Issue 03, 267-274.	9/11/2021
							✓	Research progress of control technology for by-products from chlorine dioxide inorganic disinfection. Sun, Jian; Qu, Moli. From Huanjing Kexue Yu Guanli (2017), 42(10), 67-70	14/9/2021
							✓	Treating Water by Degrading Oxyanions Using Metallic Nanostructures. Endrodi, Balazs; Simic, Nina; Wildlock, Mats; Cornell, Ann. From Electrochimica Acta (2017), 234, 108-122	14/9/2021
							✓	A review of oxyhalide disinfection by-products determination in water by ion chromatography and ion chromatography-mass spectrometry. Gilchrist, Elizabeth S.; Healy, David A.; Morris, Virginia N.; Glennon, Jeremy. Analytica Chimica Acta (2016), 942, 12-22	14/9/2021