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Canada

Draft Screening Assessment

Acids and Bases Group

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment on 22 substances referred to collectively under the Chemicals Management Plan as the Acids and Bases Group. These 22 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns. Two other substances were determined to be of low concern through other approaches, and decisions for these substances are provided in separate reports.[1] The Chemical Abstracts Service Registry Numbers (CAS RN[2]), their *Domestic Substances List* (DSL) names and their common names are listed in the table below.

Substances in the Acids and Bases Group

Subgroup	**CAS RN**	**DSL name (molecular formula)**	**Common name**
Ammonia	5470-11-1[a, b]	Hydroxylamine, hydrochloride (ClH_4NO)	Hydroxylammonium chloride
Free available chlorine, chlorate and chlorite	7681-52-9[b]	Hypochlorous acid, sodium salt ($NaClO$)	Sodium hypochlorite
Free available chlorine, chlorate and chlorite	7775-09-9[b]	Chloric acid, sodium salt ($NaClO_3$)	Sodium chlorate
Free available chlorine, chlorate and chlorite	7778-54-3[b]	Hypochlorous acid, calcium salt ($CaCl_2O_2$)	Calcium hypochlorite
Free available chlorine, chlorate and chlorite	7782-50-5[b]	Chlorine (Cl_2)	Chlorine
Free available chlorine, chlorate and chlorite	10049-04-4[b]	Chlorine dioxide (ClO_2)	Chlorine dioxide

[1] Conclusions for substances bearing CAS RNs 18917-89-0 and 68442-82-0 are provided in the Rapid Screening of Substances with Limited General Population Exposure Screening Assessment.

[2] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

Subgroup	CAS RN	DSL name (molecular formula)	Common name
Hydrogen and hydroxide	1310-58-3	Potassium hydroxide (KOH)	Potassium hydroxide
Hydrogen and hydroxide	1310-73-2	Sodium hydroxide (NaOH)	Sodium hydroxide
Hydrogen and hydroxide	1312-76-1	Silicic acid, potassium salt (K_2SiO_3)	Potassium silicate
Hydrogen and hydroxide	1344-09-8	Silicic acid, sodium salt ($HNaSiO_3$)	Sodium silicate
Hydrogen and hydroxide	7647-01-0	Hydrochloric acid (HCl)	Hydrochloric acid
Hydrogen and hydroxide	7664-93-9	Sulphuric acid (H_2SO_4)	Sulphuric acid
Hydrogen and hydroxide	12136-45-7	Potassium oxide (K_2O)	Potassium oxide
Nitrate and nitrite	7631-99-4	Nitric acid sodium salt ($NaNO_3$)	Sodium nitrate
Nitrate and nitrite	7632-00-0	Nitrous acid, sodium salt ($NaNO_2$)	Sodium nitrite
Nitrate and nitrite	7697-37-2	Nitric acid (HNO_3)	Nitric acid
Nitrate and nitrite	7757-79-1	Nitric acid potassium salt (KNO_3)	Potassium nitrate
Nitrate and nitrite	10124-37-5	Nitric acid, calcium salt ($Ca(NO_3)_2$)	Calcium nitrate
Phosphate	1314-56-3	Phosphorus oxide (P_2O_5)	Diphosphorus pentoxide
Phosphate	7664-38-2	Phosphoric acid (H_3PO_4)	Phosphoric acid
Sulphite	7631-90-5	Sulfurous acid, monosodium salt ($HNaSO_3$)	Sodium bisulfite
Sulphite	7681-57-4	Disulphurous acid, disodium salt ($Na_2O_5S_2$)	Sodium metabisulfite

[a] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other human health concerns.
[b] These substances were considered only from a human health perspective in this assessment.

Seven substances in the Acids and Bases Group—chlorine, hydrochloric acid, sulphuric acid, sodium nitrate, potassium nitrate, calcium nitrate and nitric acid—are known to be naturally occurring in the environment. Further, the water dissociation products of most of the 22 substances in this group are ubiquitous and naturally present in aquatic environments.

In Canada, the 22 substances are generally used as paint and coating additives; intermediates; plant nutrients; pesticides; process regulators; and as agents for redox

reactions, corrosion inhibition, anti-scaling, plating, surface treating, filler, cleaning, disinfecting, bleaching and petroleum-refining. Some of these substances may also be found in drugs, including natural health products (NHPs), cosmetics, dyes, or in explosives; or used as food additives or as a component in the manufacture of food packaging materials.

The 22 substances readily react and transform in aqueous solutions. For the purpose of this screening assessment, they were categorized into six subgroups based on their primary water dissociation products: (1) ammonia, (2) free available chlorine, chlorate and chlorite (FACCC), (3) sulphite, (4) hydrogen and hydroxide, (5) phosphate, and (6) nitrate and nitrite.

Based upon their physical-chemical properties, environmental fate and behaviour, and reported uses, the six substances in the ammonia and FACCC subgroups are considered to have been addressed previously for ecological concerns through the Priority Substances List assessment reports for “Ammonia in the Aquatic Environment”, “Effluents from Pulp Mills using Bleaching”, “Chlorinated Wastewater Effluents”, and “Inorganic Chloramines”. Given these previous assessments and ongoing regulatory activities, these six substances were not considered further from an ecological perspective in this assessment; however, a conclusion for potential harm to human health was not determined at the time. Therefore, these substances were considered only from a human health perspective in this assessment.

The ecological risks of the remaining 16 substances in the Acids and Bases Group were characterized using a qualitative or quantitative approach. Exposure profiling and hazard characterization were based on domestic and international reports as well as scientific literature. Canadian import, manufacture and release data reported by industrial facilities were also analyzed to help characterize the potential for exposure in Canada.

The ecological hazard potential of substances in the hydrogen and hydroxide, and phosphate subgroups, and one substance in the nitrate and nitrite subgroup (nitric acid), is associated with changes in water pH, rather than direct toxicological effects. Information collected on the pH of municipal wastewater treatment system effluents, the main source of potential environmental exposure for these substances, indicate that their pH is within the Canadian Water Quality Guideline (CWQG) for freshwater (pH 6.5-9). Therefore, there is low potential for these substances to cause ecological harm through adjustment of pH in the receiving environment. The remaining four substances in the nitrate and nitrite subgroup and the sulphite subgroup are not anticipated to cause ecological harm based on characterization of hazard and exposure potential.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from 16 substances in the Acids and Bases Group. It is proposed to conclude that these 16 substances do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or

long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

With respect to human health, hydroxylammonium chloride was evaluated as part of the Rapid Screening of Substances with Limited General Population Exposure. Based on this approach, exposure of the general population to hydroxylammonium chloride was considered to be negligible and therefore this substance is considered to be of low concern for human health at current levels of exposure.

Three subgroups (sulphite, hydrogen and hydroxide, and phosphate) were considered in the Science Approach Document for Substances with Low Human Health Hazard Potential. The Low Human Health Hazard Potential approach is used to identify substances with low inherent repeated-dose toxicity. This hazard-based approach considers a number of metrics, including the effects noted in animal and human toxicity studies, and the relevant route(s) of exposure of the substance, to determine if health effects of the substance are limited or unlikely. On the basis of the results presented in that approach document, these 11 substances are considered to be of low concern for human health. Three substances in the FACCC subgroup were also evaluated using the Low Human Health Hazard Potential Approach and are considered to be of low concern for human health based on their low human health hazard potential.

For chlorine, a three day inhalation exposure study in humans and a one-year inhalation study in monkeys were selected for risk characterization. A comparison of estimated levels of exposure from outdoor air and critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases.

A two-generation reproductive study in rats was selected for risk characterization of oral exposure to chlorine dioxide. For the inhalation route, a subchronic inhalation study in rats was selected for risk characterization of repeated exposure to chlorine dioxide. Canadians may be exposed to chlorine dioxide through environmental media such as drinking water and air, as well as products available to consumers, including non-prescription drugs and odour control products. A comparison of estimated levels of exposure from outdoor air and products available to consumers and critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases.

A two-year carcinogenicity study in rats was selected for risk characterization of chronic oral exposure to sodium chlorate. A subchronic study in rats was selected for risk characterization of subchronic oral exposure to sodium chlorate. Exposure to sodium chlorate may occur from drinking water and from cosmetics and cleaning products. A comparison of estimated levels of exposure to the general population and critical effect levels results in margins of exposure that are adequate to account for uncertainties in the health effects and exposure databases.

Acceptable daily intake (ADI) values derived by the European Food Safety Authority were used as a reference dose for risk characterization for the substances in the nitrate and nitrite subgroup. Nitrate and nitrite occur naturally in environmental media, are permitted food additives, may be used as components in the manufacture of food packaging materials, or as components in incidental additives used in food processing establishments, and may also be found in products available to consumers such as cosmetics, cleaning products and NHPs. Exposure estimates presented in comparison to the ADIs did not result in any exceedances and are therefore considered to be of low risk to human health.

Considering all the information presented in this draft screening assessment, it is proposed to conclude that the 22 substances in the Acids and Bases Group do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Six of the 22 substances in the Acids and Bases Group (hydroxylammonium chloride, sodium hypochlorite, sodium chlorate, calcium hypochlorite, chlorine, and chlorine dioxide) were previously addressed by Environment Canada under the Priority Substances Assessment Program; however, a conclusion for potential harm to human health was not determined. As these substances were not re-assessed from an ecological perspective, the conclusion for these six substances is limited to the criteria under paragraph 64(*c*) of CEPA.

It is therefore proposed to conclude that 16 substances in the Acids and Bases Group (sodium bisulfite, sodium metabisulfite, potassium hydroxide, sodium hydroxide, potassium silicate, sodium silicate, hydrochloric acid, sulphuric acid, potassium oxide, diphosphorus pentoxide, phosphoric acid, sodium nitrate, sodium nitrite, nitric acid, potassium nitrate, and calcium nitrate) do not meet any of the criteria set out in section 64 of CEPA. In addition, it is proposed to conclude that the other six substances in the Acids and Bases Group (hydroxylammonium chloride, sodium hypochlorite, sodium chlorate, calcium hypochlorite, chlorine, and chlorine dioxide) do not meet the criteria under paragraph 64(*c*) of CEPA.

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1. Introduction

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment on 22 of 24 substances, referred to collectively as the Acids and Bases Group, to determine whether these substances present or may present a risk to the environment or to human health. These 22 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

The other two substances (CAS RNs 18917-89-0, magnesium, bis(2-hydroxybenzoato-O1,O2)-, (T-4)-; and 68442-82-0, calcium, carbonate dimethylhexanoate complexes) were considered in the Ecological Risk Classification of Organic Substances Science Approach Document ECCC 2016a) and via the approach applied in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a), and were identified as being of low concern to both human health and the environment. As such, they are not addressed further in this report. Decisions for these substances are provided in the Rapid Screening of Substances with Limited General Population Exposure Screening Assessment (ECCC, HC 2018a).

The 22 substances in this assessment readily react and transform in aqueous solutions. For the purpose of this screening assessment they were categorized into six subgroups based on their primary water dissociation products: (1) ammonia, (2) free available chlorine, chlorate and chlorite (FACCC), (3) sulphite, (4) hydrogen and hydroxide, (5) phosphate, and (6) nitrate and nitrite.

Based on their physical-chemical properties, environmental fate and behaviour, and reported uses, the six substances in the ammonia and FACCC subgroups are considered to have been addressed within the ecological scope of previous assessments and ongoing regulatory activities. These substances are not considered further from an ecological perspective in this assessment. Therefore, the focus of this assessment for these substances is on human health.

The ecological risks of the remaining 16 substances in the Acids and Bases Group were characterized using a qualitative or quantitative approach. Exposure profiling and hazard characterization were based on domestic and international reports as well as scientific literature. Canadian import, manufacture and release data were also analyzed to help characterize the potential for exposure in Canada. Indirect lines of evidence, which include existing regulatory measures and classification of hazard or fate characteristics completed by other agencies, were also considered when available. Exposure resulting from fertilizer and pesticide uses of these substances are outside the scope of this assessment and are regulated under the *Pest Control Products Act* (Canada 2002b) and the *Fertilizer Act* (Canada 1985). This assessment focusses on direct ecotoxicological effects of the substances in the Acids and Bases Group. While certain substances in the group (e.g., phosphates and nitrates) are nutrients for primary

producers and other microorganisms, and can stimulate biomass growth in certain aquatic environments, eutrophication and its associated secondary ecological effects (e.g. oxygen depletion) are not in the scope of this assessment. Eutrophication is a complex phenomenon that can occur even in unpolluted waters (CCME 2004). A detailed examination of nutrients and their impacts on the Canadian environment has been documented previously by Chambers et al. (2001). Several initiatives have studied excess nutrients in fresh water (Environment Canada 2007; Environment Canada 2013b; ECCC 2017a,b; Government of Canada [modified 2017]; Government of Canada [modified 2021]).

The human health risks of the substances in this assessment were characterized using three approaches. The ammonia subgroup (containing one substance) was addressed using the approach applied in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a). Three subgroups (sulphite, hydrogen and hydroxide, and phosphate), comprising 13 substances, were addressed using the Low Human Health Hazard Potential Approach (Health Canada [modified 2017]). The remaining two subgroups (free available chlorine, chlorate and chlorite; and nitrate and nitrite) containing eight substances were assessed using a combination of the Low Human Health Hazard Potential Approach and quantitative approaches.

Some of the substances in the Acids and Bases Group have been reviewed by national and international organizations. Nitrate and nitrite have been evaluated by the International Agency for Research on Cancer (IARC) Monographs Programme, the European Food Safety Authority (EFSA), the United States Environmental Protection Agency (U.S. EPA), the United States (U.S.) Department of Health and Human Services, the European Commission (EU) Scientific Committee on Food (SCF), the World Health Organization (WHO), the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA), the Organisation for Economic Co-operation and Development (OECD), and the Canadian Council of Ministers of the Environment (CCME) (IARC 2010; EFSA 2017a, 2017b; U.S. EPA Revised 1991; ASTDR 2017; SCF 1997; WHO 2011; Health Canada 2013; JECFA 2003; OECD 2005, 2008b; ATSDR 2017; CCME 2012). Nitrate and nitrite have also been evaluated by Health Canada's drinking water quality program (Health Canada 2013). The free available chlorine, chlorate and chlorite subgroup has been evaluated by the European Union (EU), the EC, the OECD, the U.S. EPA, the WHO, Environment and Climate Change Canada, Health Canada's Water and Air Quality Bureau, and the Ontario Ministry of the Environment (ON MOE) (U.S. EPA 2006a, 2006b; EU 2007a, 2007b, 2009; WHO 2016; Health Canada 2008a, 2009; OECD 2004a, 2006b; EC, HC 1991, 1993, 2001b; ON MOE 2007a). These assessments were used to inform the ecological and human health risk assessment presented in this report.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to December 2020. Empirical data from key studies as well as results from models were used to

reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external review. Comments on the technical portions relevant to the environment were received from Geoff Granville at GCGranville Consulting Group. Comments on the technical portions relevant to human health were received from Dr. Joseph Caruso (Wayne State University, United States), Dr. Judy LaKind (University of Maryland School of Medicine, U.S.), and Dr. Shahid Parvez (Indiana University Fairbanks School of Public Health, U.S.). The health portion of this assessment is based on the approach applied in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a) and the Substances with Low Human Health Hazard Potential Approach (ECCC, HC 2018b) which were each subject to a 60-day public comment period. Additionally, the Substances with Low Human Health Hazard Potential Approach was subject to external peer review. While external comments were taken into consideration, the final content and outcome of this screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution[3]. This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

2. Identity of substances

The subgroup, CAS RN, *Domestic Substances List* (DSL) name, molecular formula and common name for the 22 substances in the Acids and Bases Group are presented in **Error! Not a valid bookmark self-reference.**.

Table 2-1. Substance identities

[3] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

Subgroup	CAS RN	DSL name (molecular formula)	Common name
Ammonia	5470-11-1	Hydroxylamine, hydrochloride (ClH_4NO)	Hydroxylammonium chloride
Free available chlorine, chlorate and chlorite	7681-52-9	Hypochlorous acid, sodium salt (NaClO)	Sodium hypochlorite
Free available chlorine, chlorate and chlorite	7775-09-9	Chloric acid, sodium salt ($NaClO_3$)	Sodium chlorate
Free available chlorine, chlorate and chlorite	7778-54-3	Hypochlorous acid, calcium salt ($CaCl_2O_2$)	Calcium hypochlorite
Free available chlorine, chlorate and chlorite	7782-50-5	Chlorine (Cl_2)	Chlorine
Free available chlorine, chlorate and chlorite	10049-04-4	Chlorine dioxide (ClO_2)	Chlorine dioxide
Sulphite	7631-90-5	Sulfurous acid, monosodium salt ($HNaSO_3$)	Sodium bisulfite
Sulphite	7681-57-4	Disulphurous acid, disodium salt ($Na_2O_5S_2$)	Sodium metabisulfite
Hydrogen and hydroxide	1310-58-3	Potassium hydroxide (KOH)	Potassium hydroxide
Hydrogen and hydroxide	1310-73-2	Sodium hydroxide (NaOH)	Sodium hydroxide
Hydrogen and hydroxide	1312-76-1	Silicic acid, potassium salt (K_2SiO_3)	Potassium silicate
Hydrogen and hydroxide	1344-09-8	Silicic acid, sodium salt ($HNaSiO_3$)	Sodium silicate
Hydrogen and hydroxide	7647-01-0	Hydrochloric acid (HCl)	Hydrochloric acid
Hydrogen and hydroxide	7664-93-9	Sulphuric acid (H_2SO_4)	Sulphuric acid
Hydrogen and hydroxide	12136-45-7	Potassium oxide (K_2O)	Potassium oxide
Phosphate	1314-56-3	Phosphorus oxide (P_2O_5)	Diphosphorus pentoxide
Phosphate	7664-38-2	Phosphoric acid (H_3PO_4)	Phosphoric acid
Nitrate and nitrite	7631-99-4	Nitric acid sodium salt ($NaNO_3$)	Sodium nitrate

Subgroup	CAS RN	DSL name (molecular formula)	Common name
Nitrate and nitrite	7632-00-0	Nitrous acid, sodium salt ($NaNO_2$)	Sodium nitrite
Nitrate and nitrite	7697-37-2	Nitric acid (HNO_3)	Nitric acid
Nitrate and nitrite	7757-79-1	Nitric acid potassium salt (KNO_3)	Potassium nitrate
Nitrate and nitrite	10124-37-5	Nitric acid, calcium salt ($Ca(NO_3)_2$)	Calcium nitrate

3. Ammonia subgroup

3.1 Sources and uses

Hydroxylammonium chloride

Hydroxylammonium chloride is not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2008, less than 1 tonne of hydroxylammonium chloride were imported by Canadian companies[4] (Environment Canada 2009; ECCC, HC 2021). There was no manufacturing above the reporting threshold of 100 kg. According to the North American Industry Classification System codes reported, these organizations were from the chemical product manufacturing and scientific research and development services sectors. This substance was reported as being used for distribution and laboratory purposes. Sources and uses resulting in exposure to the general population from this substance have not been further characterized as exposure to the general population has previously been determined to be low (ECCC, HC 2018a).

3.2 Environmental fate and behaviour

Information on the fate and behaviour of hydroxylammonium chloride was primarily obtained through a read-across approach using information for an analogue, bis(hydroxylammonium)sulphate, presented in a screening initial data set (SIDS) report (OECD 2008a).

[4] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2009) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

Based on the negligible vapour pressure for bis(hydroxylammonium)sulphate (Table B-1, Appendix B), hydroxylammonium chloride is not expected to partition to air from aquatic and terrestrial environments.

In aqueous solutions, hydroxylammonium chloride is expected to dissolve (Table B-1, Appendix B) and dissociate completely to ultimately generate ammonia (NH_3) and nitrogen (N_2) (OECD 2008a). Ammonia is highly water-soluble. In surface waters, ammonia generally exists in equilibrium with ammonium (NH_4^+), its ionized and less toxic form (EC, HC 2001a; CCME 2010). The predominant species at equilibrium depends on the pH and temperature of the solution; in more alkaline solutions the formation of ammonia is favoured. Given its complete dissociation in water and very low potential to adsorb onto organic matter (OECD 2008a), hydroxylammonium chloride is not expected to persist in water and soil.

3.3 Potential to cause ecological harm

Hydroxylammonium chloride is expected to dissociate completely in water to ultimately generate ammonia, which has been characterized in a previous assessment report for "Ammonia in the Aquatic Environment" (EC, HC 2001a). That assessment examined the ecological impact of unionized (NH_3) and ionized (NH_4^+; also known as ammonium) ammonia in the environment and found that ammonia in the aquatic environment has the potential to cause ecological harm. As additional exposure sources of concern have not been identified, hydroxylammonium chloride will not be assessed further for its potential ecological risk at this time and will be addressed by risk management measures that are being or have been developed for ammonia dissolved in water (Canada, Dept. of the Environment 2004; Environment Canada 2002).

3.4 Potential to cause harm to human health

Hydroxylammonium chloride was considered in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a), which was used to determine if the substance(s) required further assessment on the basis of the potential for direct and indirect exposures to the general population. The potential for direct exposure was evaluated on the basis of considerations such as evidence of the substance being present in a product used by the general population. The potential for indirect exposure was adopted from the general approach reported in the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances (Health Canada 2016). On the basis of the evaluation of both direct and indirect exposures conducted as part of the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a), exposure of the general population to hydroxylammonium chloride was considered to be negligible and therefore this substance is considered to be of low concern for human health at current levels of exposure.

4. Free available chlorine, chlorate and chlorite subgroup

4.1 Sources and uses

Sodium hypochlorite

Sodium hypochlorite is not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, between 10 000 tonnes to 100 000 tonnes of sodium hypochlorite were reported to be imported and manufactured by companies from the basic chemical manufacturing sector, and the soap, cleaning compound and toilet preparation manufacturing sector[5] (Environment Canada 2013a). Thirteen other sectors—including the pulp, paper and paperboard mills sector—reported less than 10 000 tonnes (each) of sodium hypochlorite to the survey (ECCC, HC 2021). This substance was reported to be used as a bleaching agent, processing aid, redox agent, biocide, water treatment agent, paint and coating additive, intermediate, multifunctional (more than 1 code reported), and for other uses claimed confidential (ECCC, HC 2021). Given that the Low Human Health Hazard Potential Approach is being used to assess this substance, further characterization of sources and uses resulting in exposure to the general population was not undertaken.

Calcium hypochlorite

Calcium hypochlorite is not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, between 10 tonnes to 100 tonnes of calcium hypochlorite were reported to be imported into Canada by the following sectors: other chemical product manufacturing, and chemical (except agricultural) and allied product merchant wholesalers[6] (Environment Canada 2013a). The main uses reported were for bleaching and multifunctional purposes, including redox reactions and pest control. Given that the Low Human Health Hazard Potential Approach is being used to assess this substance, further characterization of sources and uses resulting in exposure to the general population was not undertaken.

Chlorine

[5] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

[6] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

Chlorine is a naturally occurring substance. According to information submitted in response to a CEPA section 71 survey, between 10 000 tonnes to 100 000 tonnes and 1 000 tonnes to 10 000 tonnes of chlorine were manufactured and imported, respectively for the reporting year of 2011[7]. Reporting sectors included basic chemical manufacturers; pulp, paper and paperboard mills; and the resin, synthetic rubber, and artificial and synthetic fibres and filaments manufacturing sector (Environment Canada 2013a). The basic chemical manufacturers reported function codes associated with industrial applications (e.g., metal extraction and refining), multifunctional applications (e.g., chemical synthesis, oxidizing, plasticizing, and processing), and incidental production (e.g., as a by-product, impurity or contaminant).

Between 2012 and 2016, releases of chlorine (excluding spills) reported to the National Pollutant Release Inventory (NPRI) were mostly to the atmospheric compartment, with annual release ranging from 156 tonnes to 338 tonnes (NPRI 2012-2016). The top sectors reporting direct discharges of chlorine to water were pulp, paper and paperboard mills (384 tonnes total); oil and gas extraction (94 tonnes total); and water, sewage and other systems (51 tonnes total) (ECCC, HC 2021; NPRI 2012-2016).

Chlorine may be found in drugs including natural health products (NHPs), as a permitted food additive, as a component in the manufacture of food packaging materials, and as a component in incidental additives[8] used in food processing establishments (personal communication, email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 3, 2018; unreferenced; email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated January 22, 2019; unreferenced; personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 9, 2018; unreferenced). It is on the Cosmetic Ingredient Hotlist and described on that list as prohibited for use in cosmetic products (Health Canada [modified 2018]).

Chlorine dioxide

Chlorine dioxide is not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, chlorine dioxide

[7] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

[8] While not defined under the *Food and Drugs Act* (FDA), incidental additives may be regarded, for administrative purposes, as those substances which are used in food processing plants and which may potentially become adventitious residues in foods.

was reported to be manufactured by Canadian companies in the chemical manufacturing[9] (1 000 tonnes to 10 000 tonnes) and pulp and paper (100 000 tonnes to 1 000 000 tonnes) sectors (Environment Canada 2013a). Releases of chlorine dioxide were predominantly to the atmospheric compartment as reported to the NPRI between 2012 and 2016 (NPRI 2012-2016; ECCC, HC 2021). Annual releases of chlorine dioxide to the air ranged from 293 tonnes to 407 tonnes. One pulp and paper facility reported releasing less than a total of 1 tonne to water between 2012 and 2016 (ECCC, HC 2021). Chlorine dioxide is mainly used as a bleaching agent in the pulp and paper sector. Chlorine dioxide is a permitted food additive, may be used as a component in the manufacture of food packaging materials and as a component in incidental additives used in food processing establishments, as a medicinal or non-medicinal ingredient in non-prescription drugs including disinfectants and a moisturizing lubricant eye drop, as well as in products available to consumers, such as odour control products (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada, dated June 9, 2018; unreferenced; personal communication, email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 8, 2019; unreferenced; personal communication, emails from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 9, 2019 and March 20, 2019; unreferenced; SDS 2013).

Sodium chlorate

Sodium chlorate is not known to occur naturally. Sodium chlorate was not included in a survey issued pursuant to a CEPA section 71 notice. Data collected from the Canada Border Services Agency (CBSA) reported between 1 000 tonnes to 10 000 tonnes of sodium chlorate imported into Canada on an average annual basis between 2010 and 2013 (CBSA 2016). Companies in the basic chemical manufacturing and chemical wholesalers sectors accounted for 98% of this quantity. Additional data obtained from the Canadian International Merchandise Trade (CIMT) database (1997-) show that approximately 10 384 tonnes of sodium chlorate were imported into Canada in 2017. In 2018, Canada was reported as the world's largest producer of sodium chlorate, followed by the U.S. (CEH 2018). Bommaraju and O'Brien (2015) suggest that over 95% of the sodium chlorate produced globally is used to generate chlorine dioxide for pulp bleaching. In 2002, approximately 99% of the sodium chlorate produced in North America, which equated to roughly 600 000 tonnes in Canada, was used by the pulp

[9] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

and paper sector to generate chlorine dioxide for pulp bleaching (Mendiratta and Duncan 2003).

Sodium chlorate may be used as a component in the manufacture of food packaging materials, as a component in an incidental additive used in food processing establishments, as a food processing aid[10], as an active ingredient in pesticides, or as a non-medicinal ingredient in non-prescription drugs such as disinfectants (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 9, 2018; unreferenced; email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 3, 2018; unreferenced). On the basis of notifications submitted to Health Canada, it may be found in a limited number of cosmetic products (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 17, 2018; unreferenced).

4.2 Environmental fate and behaviour

Chlorine, calcium hypochlorite and sodium hypochlorite

The environmental fate and behaviour of chlorine, calcium hypochlorite and sodium hypochlorite were examined in several reports (OECD 2004a; EU 2007a, 2007b; ATSDR 2010).

Chlorine is a gas with a vapour pressure of approximately 5 085 mmHg at 20˚C (ECHA 2007-; EU 2007a) and an atmospheric half-life of minutes to several hours depending on the time of day (EU 2007a; ATSDR 2010). This indicates that chlorine will likely not persist in air due to photolysis. Calcium hypochlorite exists as a powder and has negligible vapour pressure at room temperature (OECD 2004a), whereas sodium hypochlorite typically exists as an aqueous solution and has a vapour pressure of 13 mmHg to 15 mmHg at 20˚C (EU 2007b). Based on this information, calcium hypochlorite is not expected to partition to air, whereas sodium hypochlorite solutions can be semi-volatile at room temperature.

Chlorine, calcium hypochlorite and sodium hypochlorite readily react with water to yield free available chlorine (FAC) (EC, HC 1993, 2001b; CCME 1999; OECD 2004a; EU

[10] While “food processing aid” is not defined under Canada’s *Food and Drugs Act* (FDA), substances which are used for a technical effect during food manufacture, processing or distribution may be considered food processing aids when such use does not affect the intrinsic characteristics of the food and results in no or negligible residues of the substance or its by-products in or on the finished food. As with other substances used in food manufacture, processing and distribution, the use of food processing aids must not result in a violation of the safety provisions set out under section 4 of the FDA

2007a, 2007b; ATSDR 2010). These three substances are not expected to bioaccumulate in organisms because they are highly reactive in water and so unavailable for uptake by organisms (OECD 2004a; EU 2007a, 2007b; ATSDR 2010).

FAC, also known as free residual chlorine (FRC), refers to dissolved chlorine gas (Cl_2), hypochlorous acid (HClO) and the hypochlorite ion (ClO^-) in solution. Along with combined residual chlorine (CRC), which consists of organic and inorganic chloramines, FAC and CRC are collectively referred to as total residual chlorine (TRC) (EC, HC 1993, 2001b; CCME 1999; OECD 2004a; ATSDR 2010). In water, all three FAC species coexist in equilibrium (WHO 2003). However, the prevalent form of FAC depends on the pH of the solution: the hypochlorite ion dominates at pH greater than approximately 7.5, whereas hypochlorous acid is the main form at pH below 7.5, and molecular chlorine is the main species in very acidic solutions (EC, HC 1993; OECD 2004a; EU 2007b). In the presence of organic or inorganic nitrogen, FAC reacts to generate CRC. Other by-products that can be formed via different reactions with FAC include trihalomethanes, bromoamines, and bromochloramines (EC, HC 1993; CCME 1999; EU 2007a, 2007b). The degradation rate of reactive chlorine is positively correlated with temperature, pH, light intensity, organic carbon, and organic nitrogen content in water, all of which are site-specific (CCME 1999). Inorganic chloramines and FAC are not considered persistent in water, although the former has a longer half-life in surface waters ranging from 1 minute to 23 days depending on site-specific environmental conditions (EC, HC 2001b). In static tests where 0.2 mg/L to 1.0 mg/L of available chlorine were added to water, the half-life of FAC in the presence of raw sewage was observed to be 140 minutes (Olivieri et al. 1986). The EU (2007a, 2007b) reported a half-life of less than 120 minutes for both hypochlorous acid and the hypochlorite ion in clean aqueous test media, where reduction and photolysis were observed to be important degradation processes. Hypochlorous acid is not expected to volatilize from water based on its low air-water partition coefficient of 4×10^{-5} (EU 2007b).

Chlorine dioxide and sodium chlorate

The fate and behaviour of chlorine dioxide, sodium chlorate and their dissociation products were reviewed by multiple organizations, including the British Columbia Ministry of Environment (BC MOE 2002), the Agency for Toxic Substances and Disease Registry (ATSDR 2004), ON MOE (2007a), Health Canada (2008a, 2008b), the WHO (2016) and the U.S. EPA (2016).

Chlorine dioxide is a gas with a vapour pressure of approximately 760 mmHg at 20˚C (HSDB 1983c- ; ATSDR 2004; ON MOE 2007a) and an atmospheric lifetime (i.e., the amount of time it takes to reduce the concentration of the substance to 1/e or 37% of its original value) estimated to be less than 1 minute under sunlight (ON MOE 2007a). This suggests that chlorine dioxide will not persist in air due to photolysis. The vapour pressure of sodium chlorate is negligible at room temperature (Health Canada 2008b; U.S. EPA 2016), and therefore it will not partition to air.

According to the ATSDR (2004) and the WHO (2016), chlorine dioxide is stable in pure neutral water if it is stored in a sealed container that is protected from sunlight. In alkaline solutions, up to 70% of the chlorine dioxide hydrolyzes to form chlorite ions while the remaining fraction transforms into chlorate ions (ATSDR 2004; Health Canada 2008a; WHO 2016). The half-life of chlorine dioxide in water (at 5 mg/L to 10 mg/L in a basic solution) ranges from 20 minutes to 180 minutes (ATSDR 2004). As a strong oxidant, chlorine dioxide can rapidly react with other substances (e.g., iron, manganese, copper, and sulphide) in solution to produce compounds such as insoluble oxides, hydroxides and sulphate (ATSDR 2004). However, unlike chlorine, chlorine dioxide does not form trihalomethanes (BC MOE 2002; ATSDR 2004; U.S. EPA 2016). Sodium chlorate readily dissolves and dissociates in water to release sodium and chlorate ions (Health Canada 2008b; U.S. EPA 2016). Given their high reactivity, chlorine dioxide and sodium chlorate are not expected to bioaccumulate (ATSDR 2004; U.S. EPA 2016); this is supported by their low octanol-water partition coefficients (log K_{ow}) of -3.22 and -7.18, respectively (Health Canada 2008a).

Chlorate and chlorite ions are well-known to be disinfection by-products of chlorine dioxide. It is important to note that chlorine dioxide and chlorite can react with free available chlorine to form chlorate (BC MOE 2002; Health Canada 2008a). According to Health Canada (2008a) and the WHO (2016), the chlorate ion is very persistent in water. Although chlorite has low particulate adsorption capacity, the ion reacts with some metals, such as iron and manganese (ATSDR 2004). Reports have also shown that chlorate and chlorite ions undergo microbial reduction in anaerobic environments, such as anoxic groundwater, soils and sediments (ATSDR 2004; U.S. EPA 2006a).

4.3 Potential to cause ecological harm

Based on the physical-chemical properties, environmental fate and behaviour, and reported uses of chlorine, chlorine dioxide, sodium hypochlorite, sodium chlorate and calcium hypochlorite, these substances are considered to have been characterized in the previous assessment reports for “Effluents from Pulp Mills using Bleaching” (EC, HC 1991), “Chlorinated Wastewater Effluents ” (EC, HC 1993), and “Inorganic Chloramines” (EC, HC 2001b). These assessments examined the environmental impact of chlorine-containing substances when used for disinfection, biofouling control and pulp bleaching in the Canadian environment. These assessments found that effluents from pulp mills using bleaching, chlorinated wastewater effluents, and inorganic chloramines have the potential to cause ecological harm.

As additional exposure sources of concern have not been identified, these substances will not be assessed further for their potential ecological risk at this time and will be addressed by risk management measures that are being or have been developed for effluents from pulp mills using bleaching, chlorinated wastewater effluents, and inorganic chloramines (Environment Canada 2002; Environment Canada 2012).

4.4 Potential to cause harm to human health

4.4.1 Health effects assessment

Free available chlorine (sodium hypochlorite, calcium hypochlorite, chorine)

Calcium hypochlorite and sodium hypochlorite are considered to be of low concern to human health by the oral route of exposure according to the Low Human Health Hazard Potential Approach (Appendix C; Health Canada [modified 2017]).

Studies assessing oral toxicity to chlorine in water are considered to be equivalent to studies assessing the oral toxicity of hypochlorous acid and/or hypochlorite (EU 2007a; Health Canada 2009). Therefore, chlorine is considered to be of low concern to human health via the oral route based on the results of the Low Human Health Hazard Potential Approach for calcium and sodium hypochlorite. In addition, Health Canada's drinking water quality program did not consider it necessary to establish a guideline for chlorine in drinking water, based on its low toxicity at concentration found in drinking water as a result of treatment (Health Canada 2009). Chlorine is in gaseous form at room temperature and pressure, thus exposure will be primarily via inhalation (EU 2007a). Based on the information presented above, this section will focus only on health effects of chlorine via the inhalation route of exposure. The EU and the U.S. EPA have reviewed chlorine (EU 2007a; EU 2017; U.S. EPA 1999). These existing assessments were used to inform the assessment of health effects of chlorine via the inhalation route. A literature search was conducted for the period of January 2016 to May 2019, which encompasses the year prior to the most recent assessment on chlorine. The results from this literature search do not impact the inhalation hazard characterization from previous assessments (i.e., not suggesting different critical endpoints or lower points of departure).

Toxicokinetics

Upon inhalation, chlorine gas reacts with surface material and tissue of the respiratory tract. Chlorine is a strong oxidizing agent; therefore, it causes disruption to cellular proteins upon contact (EU 2007a). Chlorine gas is moderately soluble in epithelial lining fluid of the lung, resulting in the generation of FAC (EU 2007a).

Acute health effects

Exposure of rats to chlorine gas via inhalation was found to result in a 60-minute LC_{50} of 448 ppm (1.3 mg/L) (Zwart and Woutersen 1988). Inhalation of chlorine gas at concentrations higher than 1 000 ppm (3 000 mg/m^3) may be lethal to humans after approximately 10 minutes of exposure (EU 2007a).

Symptoms of acute chlorine exposure in humans include nausea, vomiting with syncope and coma, convulsions and cyanosis. Symptoms start within 10 minutes of exposure and dysfunction is cleared within 1 to 3 months (EU 2007a). Exposure to high

concentrations of chlorine may also lead to irritant-induced asthma (White and Martin 2010). The most common cause of death by chlorine exposure in humans is pulmonary edema. Other causes of death related to acute exposure to high concentrations of chlorine gas include bronchoconstriction, shock, immediate respiratory arrest and cardiac complications (EU 2007a).

Repeated-dose health effects

No systemic effects were observed in repeated-dose inhalation exposure studies in rats, mice or monkeys up to 9 ppm (27 mg/m^3) (EU 2007a). Effects are localized to the upper respiratory tract at concentrations below 9 ppm (27 mg/m^3) and exhibit an increase in incidence and/or severity with increasing chlorine concentration (EU 2007a).

Repeated exposure to low concentrations of chlorine via inhalation in humans is not expected to lead to effects other than irritation (EU 2007a). A 3-day voluntary human exposure study showed no effects at 0.5 ppm (1.5 mg/m^3) (Schins et al. 2000). This is consistent with the no-observed adverse effect concentration (NOAEC) of 0.5 ppm (1.5 mg/m^3) reported in a one-year inhalation study in monkeys (Klonne et al. 1987).

Carcinogenicity studies are available in rats and mice for the inhalation route; however, genotoxicity tests are generally performed in an aqueous medium, and were tested using sodium hypochlorite solutions (EU 2007a, 2007b). The EU (2007a) and Health Canada (2009) assessments determined that chlorine is not genotoxic. Chlorine is not expected to be carcinogenic via the inhalation route (EU 2007a, 2007b; Wolf et al. 1995). There are no available data for developmental or reproductive toxicity of chlorine via the inhalation route (EU 2007a).

Chlorine dioxide (CAS RN 10049-04-4)

Several organizations and jurisdictions have reviewed chlorine dioxide and/or chlorite (ATSDR 2004; WHO 2002, 2016; ON MOE 2007a; U.S. EPA 2006a; IARC 1991; Health Canada 2008a). These existing assessments were used to inform the health effects section of this assessment. A literature search was conducted for the period of January 2015 to May 2019, which encompasses the year prior to the most recent assessment on chlorine dioxide and chlorite. Additional information was identified from the recent literature which resulted in the selection of an additional point of departure for acute inhalation toxicity which was not identified in existing international assessments.

Chlorine dioxide is fairly unstable and is rapidly reduced to chlorite upon ingestion. Accordingly, Health Canada (2008a) established a drinking water guideline for chlorite and chlorate, but not for chlorine dioxide. In water, chlorine dioxide forms approximately 70% chlorite and 30% chlorate (Section 4.2). In addition, there is interconversion between chlorine dioxide and chlorite both in water and the human gut (ATSDR 2004; OECD 2006b). Therefore, in the current assessment, studies using chlorite is used to assess oral toxicity to chlorine dioxide. Inhalation toxicity will be assessed using toxicity information on chlorine dioxide itself.

Toxicokinetics

Upon ingestion, chlorine dioxide and chlorite are rapidly absorbed into systemic circulation from the gastrointestinal tract and widely distributed throughout the body, with highest concentrations in the plasma (WHO 2016; U.S. EPA 2006d; ATSDR 2004; Health Canada 2008a). Peak plasma concentrations are reached at 1 hour for chlorine dioxide, and at 2 hours for chlorite (Health Canada 2008a; Abdel-Rahman et al. 1982). Dermal absorption of chlorine dioxide is expected to be low (Scatina et al. 1983, 1984; EU 2007a). In the body, chlorine dioxide is converted to chloride ions, chlorite and, to a lesser extent, chlorate. Both chlorite and chlorate dissociate into chloride ions. Chlorine dioxide and chlorite are primarily excreted via the urine with smaller amounts excreted in the faeces (30 and 40% of the administered dose, respectively) (WHO 2016; U.S. EPA 2006d; ATSDR 2004; Health Canada 2008a). The half-life of chlorine dioxide is 44 hours (Health Canada 2008a; Abdel-Rahman et al. 1982, 1984).

Acute health effects

The acute oral toxicity of chlorine dioxide in experimental animals is low, with a median lethal dose (LD_{50}) above 10 000 mg/kg in mice. Chlorite is highly acutely toxic in rats, with acute oral LD_{50} values ranging from 79 to 133 mg/kg (ATSDR 2004). Symptoms of acute human exposure to chlorine dioxide generally involve irritation of the eyes, nose and respiratory tract, and may also include chest pain, coughing, bloody nose, and sputum. Short-term exposure to high levels of chlorine dioxide may result in pulmonary edema (ON MOE 2007a).

Repeated-dose health effects

Neurotoxicity after oral administration of chlorine dioxide and sodium chlorite has been observed in developmental toxicity studies in rats. In a two-generation reproduction study (Gill et al. 2000), sodium chlorite was administered to rats (F_0 and F_1 generations) at 0, 35, 70 or 300 ppm in their drinking water. Neurobehavioural effects (lowered auditory startle amplitude, decreased brain weight and decreased exploratory activity) were observed in F_1 and F_2 generations at 70 and 300 ppm. A no-observed adverse effect level (NOAEL) of 2.9 mg/kg bw/day was established (Gill et al. 2000). The WHO (2016) and Health Canada (2008a) used this study to derive guideline values for chlorite in drinking water (0.7 mg/L and 1 mg/L, respectively). In addition, a developmental toxicity study in rats administered chlorine dioxide in drinking water showed a decrease in locomotor activities in pups weaned at the 14 mg/kg bw/day dose level (Orme et al. 1985). No effects were observed at 3 mg/kg bw/day.

A subchronic inhalation study exposed rats to chlorine dioxide vapours (5 hours/day, 5 days/week) at 1 ppm (2.8 mg/m^3) for 2 months. The chlorine dioxide-exposed rats exhibited respiratory effects that included peribronchiolar edema and vascular congestion in lungs (Paulet and Desbrousses 1972). A lowest-observed adverse effect concentration (LOAEC) of 1 ppm (2.8 mg/m^3) was identified. This LOAEC was used to derive the Ontario Air Quality Criteria for chlorine dioxide (ON MOE 2007a) and the U.S.

EPA reference concentration (RfC) for chlorine dioxide. In the current assessment, this RfC was converted to a continuous exposure concentration by adjusting for the number of hours per day (5/24) as well as the number of days per week (5/7) the animals were exposed to chlorine dioxide. The resulting continuous air concentration at the LOAEC was calculated to be 0.42 mg/m^3.

In a short-term inhalation study, rats were exposed to 0, 5, 10 or 15 ppm of chlorine dioxide gas (15 minutes of exposure 3 or 4 times per day) for 1 month. Rats exposed to chlorine dioxide concentrations above 5 ppm (14 mg/m^3) exhibited nasal, bronchial, and alveolar inflammation. A NOAEC of 5 ppm (14 mg/m^3) was identified (Paulet and Desbrousses 1974).

The currently available evidence suggests that chlorine dioxide is not mutagenic. Both positive and negative results have been reported in *in vitro* (bacterial) assays (WHO 2016; Health Canada 2008a; U.S. EPA 2006a; ON MOE 2007a). Available data from *in vivo* mammalian studies (the mouse micronucleus assay, the bone marrow chromosomal aberration assay, and the mouse sperm-head abnormality assay) indicates that chlorine dioxide is not mutagenic (Health Canada 2008a; ON MOE 2007a).

The carcinogenicity of chlorine dioxide has not been determined due to inadequate data for evaluation of carcinogenicity in humans and animals (Health Canada 2008a).

Sodium chlorate (CAS RN 7775-09-9)

Several international organizations have reviewed sodium chlorate (U.S. EPA 2006b; OECD 2006a; WHO 2016; JECFA 2008;). Sodium chlorate was also reviewed by Health Canada (Health Canada 2008a and 2008b). These existing assessments were used to inform the health effects section of this assessment. A literature search was conducted for the period of January 2015 to May 2019, which encompasses the year prior to the most recent assessment on sodium chlorate. The results from this literature search do not impact the risk characterization from previous assessments (i.e., not suggesting different critical endpoints or lower points of departure).

Toxicokinetics

Upon ingestion, chlorate is rapidly absorbed into systemic circulation from the gastrointestinal tract and widely distributed throughout the body, with highest concentrations in the plasma (WHO 2016; U.S. EPA, 2006d; ATSDR 2004; Health Canada 2008a). Peak plasma concentrations of chlorate are reached at 1 hour (Health Canada 2008a; Abdel-Rahman et al. 1982). Dermal absorption of chlorate is expected to be low (Scatina et al. 1983, 1984; EU 2007a). In the body, chlorate dissociates into chloride ions. Chlorate is primarily excreted via the urine (38% of the administered dose), with smaller amounts excreted in the faeces (WHO 2016; U.S. EPA 2006d; ATSDR 2004; Health Canada 2008a). Chlorate has a biphasic half-life of 6 and 36.5 hours (Health Canada 2008a; Abdel-Rahman et al. 1982, 1984).

Acute health effects

The acute oral toxicity of sodium chlorate in experimental animals is low, with a LD_{50} above 5 000 mg/kg in rats (U.S. EPA 2006b). Incident reports show that ingestion of toxic doses of sodium chlorate by humans produces gastritis, hemolysis, methaemoglobinemia, hemoglobinurea, late toxic nephritis, and acute renal failure (U.S. EPA 2006b). Doses exceeding 100 mg/kg are generally fatal to humans (U.S. EPA 2006b).

Repeated-dose health effects

Subchronic and chronic exposure to sodium chlorate competitively inhibits iodide uptake by thyroid follicular cells, resulting in decreased serum levels of thyroid hormones triiodothyronine and thyroxine and increased thyroid stimulating hormone (U.S. EPA 2006c; OECD 2006a; WHO 2016). Consequently, exposure to sodium chlorate can cause changes in thyroid follicular cell histology, such as colloid depletion, hypertrophy, and the incidence and severity of hyperplasia (WHO 2016). In addition, there is evidence from a 2-year carcinogenicity study that exposure to 2 000 mg/L sodium chlorate in drinking water causes thyroid tumours in rodents (NTP 2005). Based on the nature of the histopathological observations, the mechanism of action for thyroid tumour induction by sodium chlorate is likely due to disruption in thyroid hormone homeostasis (JECFA 2008), as described above. This is in agreement with conclusions by the U.S. EPA (2006b), which classified sodium chlorate as not likely to be carcinogenic to humans at doses that do not alter thyroid hormone homeostasis.

The U.S. EPA, the WHO and JECFA all derived guideline values based on the most sensitive endpoint from a 2-year carcinogenicity study (i.e., thyroid gland follicular cell hypertrophy in male rats) in which sodium chlorate was administered in drinking water (NTP 2005). No lowest-observed adverse effect level (LOAEL) could be identified because increase in thyroid gland follicular gland hypertrophy occurred at all doses tested. The U.S. EPA (2006b) derived a chronic reference dose based on a benchmark dose lower bound (BMDL) of 0.9 mg/kg bw/day (NTP 2005). JECFA (2008) established an acceptable daily intake (ADI) of 0 to 0.01 mg/kg bw/day using a BMDL of 1.1 mg/kg bw/day and WHO (2016) based their drinking water guideline (of 0.3 mg/L) on the ADI derived by JECFA.

Sodium chlorate was negative in most bacterial gene mutation assays and in several cytogenetics tests (i.e., hypoxanthine phosphorybosyl transferase assay in Chinese hamster ovaries, micronucleus assay, chromosomal aberration test, mouse sperm head abnormality assay) (U.S. EPA 2006b; JECFA 2008). However, DNA strand breaks and DNA protein cross-linking through the production of reactive oxygen species were observed in rats administered sodium chlorate (Ali et al. 2017a, 2017b).

Health Canada (2008a) based their drinking water guideline for chlorate (maximum acceptable concentration of 1 mg/L) on a 90-day repeated-dose drinking water study in rats (McCauley et al. 1995). A NOAEL of 30 mg/kg bw/day, based on thyroid gland

colloid depletion at the next higher dose of 100 mg/kg bw/day, was used to derive the guideline value (Health Canada 2008a).

No neurotoxic effects were observed in acute and subchronic studies with sodium chlorate (U.S. EPA 2006b). No information was available on inhalation or dermal toxicity of chlorate (U.S. EPA 2006b).

4.4.2 Exposure assessment

Free available chlorine (sodium hypochlorite, calcium hypochlorite, chlorine)

In water, chlorine forms an equilibrium with hypochlorite and hypochlorous acid, and exposure to these substances via the oral route is considered to be of low concern to human health (see the Health Effects section, Appendix C). Based on its physical-chemical properties, the hypochlorite ion will not volatize from solutions, and hypochlorous acid has a very low volatility (EU 2007b). Therefore, only exposure to chlorine via the inhalation route will be considered in the following section.

Chlorine gas (Cl_2) is not found naturally in the environment; although the chloride ion (Cl^-) is present from many naturally occurring salts (Health Canada 2009). Canadians may be exposed to chlorine gas through releases to air from industrial facilities. Between the years 2012 and 2016, annual atmospheric releases of chlorine ranged up to 338 tonnes (ECCC, HC 2021). Chlorine gas is volatile and susceptible to photolysis; the estimated half-life is in the order of minutes to several hours depending on the time of day (see section 4.2, ATSDR 2010; EU 2007a). Monitoring studies may measure a combination of chlorine and hypochlorous acid or chlorine alone, depending on the analytical techniques used. There is no Canadian monitoring data available for chlorine gas. Concentrations of chlorine gas in the U.S. were in the range of 2.6×10^{-6} to 2.9×10^{-3} µg/m^3 as measured by Faxon and colleagues (2015). Older monitoring studies reported higher concentrations of chlorine (0.03 to 0.43 µg/m^3) and of hypochlorous acid (< 0.08 to 0.73 µg/m^3) in coastal sites (EU 2007a). A median chloride ion concentration of 0.0331 µg/m^3 was measured in samples collected at 96 sites across the U.S. between 2010 and 2019 (CASTNET 2016). However, it is worth noting that the chloride ion has many natural sources, particularly seawater, such that measured concentrations are a combination of natural and man-made sources.

Chlorine is used in various industrial sectors. No products available to consumers containing chlorine were identified that would result in inhalation exposure to the general population.

Chlorine dioxide

Chlorine dioxide is not present naturally in the environment, but exposure to the general population can occur through industrial releases and use as a disinfectant. Chlorine dioxide is primarily used as a bleaching agent for the pulp and paper industry and the majority of releases of chlorine dioxide to air are from the pulp and paper facilities

(Environment Canada 2013a; NPRI 2012-2016). Annual releases of chlorine dioxide to air between 2012 and 2016 from facilities in Canada were up to 338 tonnes per year (ECCC, HC 2021). Chloride dioxide is highly reactive and the estimated atmospheric lifetime ranges from seconds to one hour, as it rapidly degrades under sunlight into oxygen and chlorine (WHO 2002; ON MOE 2007a; ATSDR 2010). In conditions of no sunlight, it may last as long as 40 to 80 hours (ECCC, HC 2021). Typically, chlorine dioxide will exist only in the immediate vicinity of where it is produced or used, although average concentrations of 0.2 to 17 µg/m^3 over 30-minute periods have been measured in air beyond the fence line of wood pulp bleaching operations in Ontario (ON MOE 2007a). The majority of the 30-minute measurements of air concentrations beyond the fence line were less than 1.0 µg/m^3.

Chlorine dioxide is used as a disinfectant in drinking water treatment plants as an alternative to chlorine. In water, chlorine dioxide readily dissociates into chlorite and chlorate ions. Health Canada has evaluated the effects of chlorine dioxide, chlorite and chlorate in drinking water (Health Canada 2008a). It was determined that a guideline value for chlorine dioxide was not necessary due to its rapid dissociation into chlorite and chlorate. However, a maximum feed dose of 1.2 mg/L is still recommended to ensure concentrations of chlorine dioxide or its by-products do not reach a level of concern for Canadians. Maximum acceptable concentrations (MAC) for chlorite and chlorate are both 1 mg/L and are considered to be protective of exposure to chlorine dioxide. Average concentrations at a water treatment plant in Quebec were 0.29 to 0.45 mg/L for chlorite and 0.12 to 0.22 mg/L for chlorate, both below the MAC of 1 mg/L. Average concentrations of chlorine dioxide ranged at a much lower concentration, from 0.03 to 0.09 mg/L (Health Canada 2008a).

In Canada, chlorine dioxide is a food additive permitted for use as a bleaching agent in a limited number of foods as prescribed in the *List of Permitted Bleaching, Maturing or Dough Conditioning Agents,* incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. It is also a component of some processing aid formulations that are used for antimicrobial treatment. As a result of its technical function in foods, levels of chlorine dioxide present in or on foods are quickly diminished through chemical reactions, and residues remaining on food from its use as a permitted food additive or as a processing aid are expected to be low (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada, dated 24 March 2019; unreferenced). Chlorine dioxide may be used as a component in the manufacture of food packaging materials and as a component in incidental additives used in food processing establishments such that there would be no potential for direct food contact; therefore dietary exposure form these uses is not expected (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 25 2019; unreferenced).

Chlorine dioxide is also found in a limited number of products available to consumers. It is present as a non-medicinal ingredient in one non-prescription drug, a moisturizing lubricant eye drop, at a concentration of 0.05 mg/mL (personal communication, email

from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 8, 2019; unreferenced; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2019; unreferenced). The intake estimate is presented in Table 4-1.

Chlorine dioxide is also used in odour control products to eliminate undesirable odours, for example, to eliminate human scent during hunting. A spray product intended for this use was identified containing 1% chlorine dioxide (SDS 2013). Although both dermal and inhalation exposure are expected from use of this product, the inhalation route is the predominate route of exposure given the high vapour pressure of chlorine dioxide and the low relative bioavailability of chlorine dioxide via the dermal route. A relative bioavailable fraction of 0.001 was determined based on two studies that examined the pharmacokinetics of chlorine dioxide through the oral and dermal routes (Scatina et al. 1983, 1984) (see Appendix E, Table E-2 for details). Given the low oral and dermal bioavailability, a quantitative assessment was conducted for the inhalation route only. The instantaneous release model from ConsExpo was used to estimate exposure (ConsExpo Web [modified 2019]) and a time-weighted average (TWA) concentration was calculated. The released mass was estimated based on the amount of product needed to cover the head and hands (approximately 1 g; U.S. EPA 2012) and resulted in an estimated air concentration of 0.015 mg/m^3. It is possible to have additional inhalation exposure following application from evaporation of chlorine dioxide from the surface of the skin; however, the instantaneous model assumes the total amount applied is immediately available for inhalation. Therefore, the assessment was considered sufficiently conservative to account for any potential additional inhalation exposure following application. Details are provided in Appendix E and the exposure estimate is presented in Table 4-1.

Table 4-1 Estimated exposures to chlorine dioxide from ambient air and products available to consumers

Exposure scenario (duration)	Age group	Route of exposure	Air concentration (mg/m^3)	Systemic exposure (mg/kg bw/day)
Ambient air (daily)[a]	NA[b]	Inhalation	0.00035	NA
Moisturizing lubricant eye drop (daily)[c]	Adult	Ophthalmic	NA	5.41 x 10^{-5}
Hunting spray (per event)[d]	Adult	Inhalation	0.015	NA

Abbreviations: NA, Not Applicable

[a] TWA was derived based on a 30-minute average concentration of 0.017 mg/m^3, adjusted to a continuous exposure of 24 hours.

[b] Age groups are not applicable to air concentrations.

[c] It was assumed that a consumer would apply 4 drops per use (2 drops per eye), up to twice daily (personal judgement; ECCC, HC 2019). The size of the drop was based on the maximum capacity of the conjunctival sac of 10 µL (Farkouh et al. 2016).

[d] TWA was derived for mean event concentration of 0.9 mg/m^3 over 5 minutes, adjusted to a TWA of 5 hours to match the study duration.

Sodium chlorate

No release data on sodium chlorate to environmental media was available; however, it has been estimated that up to 95% of sodium chlorate produced globally is used for the production of chlorine dioxide. Therefore, industrial releases of sodium chlorate to the environment are expected to be low.

The general population may be exposed to the chlorate ion in water as a result of the use of chlorine dioxide as a drinking water disinfectant. Details regarding exposure to chlorate from drinking water are described above in the exposure assessment for chlorine dioxide.

Sodium chlorate may be used as a component in the manufacture of food packaging materials and as a component in incidental additives used in food processing establishments; however, there is no potential for direct food contact, therefore dietary exposure is not expected.

Based on notifications to Health Canada, sodium chlorate is found in a limited number of cosmetics, at concentrations of 0.3 to 1% (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 17, 2018; unreferenced). Dermal exposure to cosmetics was estimated based on the use of bubble bath liquid for all ages. Exposure estimates were highest in teens (14 to 18 years old). This estimate of exposure is provided in Table 4-2.

Sodium chlorate is found as a non-medicinal ingredient in a disinfectant product at a concentration of 0.43% (personal communication, email from the Therapeutic Products Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada, dated January 25, 2019; unreferenced). This cleaning product is a concentrated solution, used primarily for bleaching purposes, but may also be used to disinfect or sanitize almost any surface in the home. Given the high probability of multiple use patterns, exposure was estimated based on three sentinel scenarios which are expected to be representative of the highest or most frequent exposures: cleaning a kitchen countertop, hand-washing laundry and cleaning a floor. Estimates of exposure to both the undiluted product during mixing and exposure to the diluted concentration during application were derived for each scenario. Exposure was estimated using the ConsExpo model (ConsExpo Web [modified 2019]) and the U.S. EPA Residential Standard Operating Procedures (U.S. EPA 2012). Details on the models and inputs used are presented in Appendix E.

In the first scenario, exposure from sanitizing or disinfecting a kitchen countertop was estimated, assuming that a consumer may prepare a “ready-to-use” solution for use in a trigger spray bottle. Dermal exposure via spills is assumed to occur during direct pouring of the undiluted product into a trigger spray bottle. Once the diluted spray

solution is prepared (i.e., water is added to the concentrated product), inhalation and dermal exposure to the dilute concentration is estimated during spraying of the countertop. Though sodium chlorate is non-volatile, it is assumed that the use of a trigger spray could generate respirable aerosol particles and thus result in inhalation exposure. Dermal exposure also occurs during wiping of the countertop.

In the second scenario, exposure from hand-washing laundry in a diluted solution of bleach was estimated for dermal exposure to the hands and forearms. Dermal exposure was estimated in two parts: spills during pouring of the concentrated solution and exposure to the diluted solution during washing. Pouring was assumed to use a cap to measure the concentrated solution before mixing it into the larger tub. Dermal exposure was also estimated during hanging of the laundry, which assumes a residual amount of solution remains in the laundry.

In the final scenario, exposure from cleaning a floor was used to estimate exposure while cleaning large surface areas, as well as post-application exposure to children. Dermal exposure to the user was estimated in two parts: spills during direct pouring of the concentrated solution, as well as exposure to the diluted solution during the cleaning of the floor. Dermal exposure and hand-to-mouth contact was estimated post-application for a child crawling on the floor. A mopping exposure study conducted for the U.S. EPA showed that for substances with low vapour pressure ($< 10^{-4}$ mmHg) and scenarios with low potential for aerosol formation (such as cleaning a floor), monitored inhalation exposure was very low (< 0.5 µg/m^3). Therefore, though inhalation exposure may be possible from cleaning activities such as mopping, inhalation exposure is expected to be limited and this scenario is expected to be protective of any potential inhalation exposure from cleaning a floor.

Table 4-2 presents the air concentration and exposure from the use of products containing sodium chlorate in sentinel scenarios. Among sentinel scenarios, exposure was highest for adults during floor cleaning. Exposures during other cleaning scenarios such as cleaning walls, sinks, showers, toilets, etc., are expected to be less than the sentinel scenarios presented.

Exposure to sodium chlorate from products available to consumers was evaluated through the relevant routes of exposure which include oral, inhalation and dermal. Inhalation and oral absorption were assumed to be 100%, while available data were used for the dermal route to present more refined estimates of systemic exposure. Based on a dermal absorption *in vitro* study (ECHA 2007a), the dermal absorption of sodium chlorate ranged from 0.5 to 1.9% in human skin (including residues from the stratum corneum) from a dermal loading of 0.15 to 5 mg/cm^2. There is an inverse relationship between the dermal load and the percentage absorbed. Given that the dermal loading in the scenarios described below (Table 4-2) is much lower than the lowest amount used in the study, it was considered appropriate to use the measured absorption values of 0.5 to 1.9% to support a higher default percentage absorption. A value of 10% dermal absorption was selected for sodium chlorate.

Table 4-2. Estimated exposure to sodium chlorate from the use of products

Product scenario[a] (duration)	Age group	Route of exposure	Systemic exposure (mg/kg bw[b])
Cleaning kitchen counters (daily)	Adult	Dermal and inhalation	0.00314
Hand-washing laundry (per event – 1/week)	Adult	Dermal	0.0043
Cleaning floors (per event – 3/week)	Adult	Dermal	0.00409
Crawling on floors –post application exposure (daily)	Toddler (1 year old)	Dermal and oral	0.0027
Bubble bath (per event – 2 to 3/week)	Teen (14 to 18 year olds)	Dermal	0.0004

Abbreviations: NA, Not Applicable

[a] Dermal exposure estimates were adjusted for 10% dermal absorption.

[b] Exposure for "daily" scenarios is estimated on a mg/kg bw/day basis; exposure for "per event" scenarios is estimated on a mg/kg bw/event basis.

4.4.3 Risk Characterization

Free available chlorine (sodium hypochlorite, calcium hypochlorite, chlorine)

Sodium hypochlorite and calcium hypochlorite were assessed using the Low Human Health Hazard Approach (Appendix C; Health Canada [modified 2017]). The available information, including conclusions from international organizations indicates that sodium hypochlorite and calcium hypochlorite are negative for carcinogenicity, mutagenicity and reproductive/developmental toxicity. No adverse effects in repeated-dose studies were observed up to 14.4 mg/kg bw/day via the oral route of exposure. As such, quantitative exposure estimates for sodium hypochlorite and calcium hypochlorite were not derived and the risk to human health is considered to be low.

Studies assessing oral toxicity to chlorine in water are considered to be equivalent to studies assessing the oral toxicity of hypochlorous acid and/or hypochlorite (EU 2007a; Health Canada 2009). Therefore, no oral exposure estimates to chlorine were quantified and the risk to human health via the oral route is considered to be low. There is potential for the general population to be exposed to chlorine via inhalation. Potential health effects from exposure to chlorine were identified via the inhalation route of exposure. No irritation was observed in a 3-day voluntary human exposure study after exposure to 1.5 mg/m^3 (Schins et al. 2000). This is supported by a NOAEC of 1.5 mg/m^3 reported in a one-year inhalation study in monkeys (Klonne et al. 1987) based on respiratory irritation at the next dose level (3.9 mg/m^3).

Releases of chlorine to air from industrial processes may result in potential inhalation exposure for Canadians. Measured data in the U.S. suggests chlorine gas may be present in the range of 2.6×10^{-5} to 0.43 µg/m^3. Chlorine is not expected to be found in other environmental media and there were no products available to consumers identified containing chlorine that would result in inhalation exposure. Risk characterization of chlorine was determined by comparing the highest measured air concentration (0.43 µg/m^3) to the critical health effect identified above (presented in Table 4-3).

Table 4-3 Relevant exposure and hazard values for determination of risk for chlorine

Scenario (duration)	Exposure (mg/m^3)	Critical health effect	Effect level (mg/m^3)	MOE
Ambient air (daily)	0.00043	Respiratory tract irritation	1.5	3488

Abbreviations: MOE, Margin of Exposure

The margins of exposure (MOE) were considered to be adequate to address any uncertainties in the exposure and health effects databases.

Chlorine dioxide

Chlorine dioxide was reviewed by the WHO (2016), Health Canada (2008a) and the U.S. EPA (2006a). Chlorine dioxide breaks down to chlorite, and to a lesser extent, chlorate, in the body upon ingestion and the oral health effect endpoint is based on chlorite information. Neurobehavioural effects were observed in a two-generation reproduction study in rats exposed to sodium chlorite (Gill et al. 2000). Based on the results of this study, an oral NOAEL of 2.9 mg/kg bw/day was established. All international organizations listed above used this NOAEL for deriving drinking water guideline values or for risk characterization and this NOAEL was selected for risk characterization in this assessment.

For continuous exposure to chlorine dioxide from levels in ambient air, a LOAEC of 2.8 mg/m^3 was selected from a subchronic inhalation study, which reported peribronchiolar edema and vascular congestion in lungs of chlorine dioxide-exposed rats. This value was converted to a continuous exposure concentration of 0.42 mg/m^3. The endpoint for intermittent exposure to inhalation exposure to chlorine dioxide is 14 mg/m^3, based on the absence of respiratory effect in rats exposed to that concentration for 15 minutes 2 or 4 times per day for 1 month (Paulet and Desbrousses 1974).

It was considered appropriate to compare air concentrations rather than systemic exposure estimates because effects due to inhalation of chlorine dioxide are primarily localized to the route of exposure.

The main route of exposure to chlorine dioxide for Canadians is through drinking water from its use as a disinfectant. This source of exposure has been addressed by Health Canada's drinking water quality program and is expected to be of low risk to human health (Health Canada 2008a).

Releases of chlorine dioxide to air from industrial processes may result in potential inhalation exposure for Canadians. Though chlorine dioxide is highly volatile and degrades under sunlight, it has been measured near industrial facilities where it is released. Measurements ranged from 0.2 to 17 µg/m^3 beyond the fence line of wood pulp bleaching operations in Ontario, and the majority of the measurements were below 1 µg/m^3 (ON MOE 2007a). The upper range of the measured air concentrations was chosen to represent the level of chlorine dioxide in air, to which the general population can potentially be exposed.

Canadians can be exposed to chlorine dioxide through products available to consumers. Exposure to chlorine dioxide may occur through use of products such as an moisturizing lubricant eye drop or odour control products. The exposure from the odour control spray is considered to be conservative as application generally takes place outdoors and the substance is expected to dissipate more rapidly than estimated, due to environmental conditions such as air flow and sunlight, which are not taken into account in the model. The exposure estimates, health effects and MOEs are presented below in Table 4-4.

Table 4-4. Relevant exposure and hazard values for chlorine dioxide, as well as MOEs, for determination of risk

Scenario (duration)	Exposure estimate	Critical health effect endpoint[a]	Critical effect level	MOE
Ambient air (daily)	0.00035 mg/m^3	Respiratory effects (LOAEC)	0.42 mg/m^3	1200
Ophthalmic exposure via moisturizing lubricant eye drop (daily)	5.41 x 10^{-5} mg/kg bw/day	Neurodevelopmental effects via oral route (NOAEL)	2.9 mg/kg bw/day	53604
Inhalation exposure via hunting spray (per event)	0.015 mg/m^3 (TWA)[b]	Respiratory effects (NOAEC)	14 mg/m^3	933

Abbreviations: MOE, Margin of Exposure

[a] Inhalation endpoints were chosen on the basis of frequency of exposure (chronic exposure = continuous exposure inhalation study (Paulet and Desbrousses 1972; per event exposure = intermittent exposure inhalation study (Paulet and Desbrousses 1974).

[b] TWA concentration was derived for 5 hours based on a mean event concentration of 0.9 mg/m^3 over 5 minutes exposure time [TWA (mg/m^3) = mean event concentration (mg/m^3) * exposure time (hour) / 5 hours].

The MOEs are considered to be adequate to address any uncertainties in the exposure and health effects databases.

Sodium chlorate

Sodium chlorate has been reviewed by the WHO (2016), the JECFA (2008), the U.S. EPA (2006b), and Health Canada (2008a, 2008b). The WHO (2016), the JECFA (2008), and the U.S. EPA (2006b) selected a 2-year carcinogenicity study in male rats to derive their chronic point of departure (NTP 2005). In particular, thyroid gland follicular cell hypertrophy was selected as the most sensitive endpoint. All administered doses caused an effect; therefore, benchmark dose modelling was used to derive an effect level. A BMDL of 0.9 mg/kg bw/day derived by the U.S. EPA (2006b) was selected for chronic risk characterization for sodium chlorate. For intermittent exposures to sodium chlorate (i.e., less than 1 event/week), a subchronic study was considered to be more appropriate for risk characterization than a chronic study because it is expected that sodium chlorate can be eliminated from the body between exposure events. Health Canada (2008a) and the U.S. EPA (2006b) selected a NOAEL of 30 mg/kg bw/day from a 90-day repeated-dose drinking water study in rats, based on thyroid gland colloid depletion at the next higher dose of 100 mg/kg bw/day (McCauley et al. 1995). This study was selected for subchronic risk characterization of sodium chlorate.

Canadians may be exposed to sodium chlorate through products available to consumers and through drinking water. Levels measured in drinking water were found to be lower than the Health Canada (2008a) MAC, as well as the WHO drinking water guideline. Chlorate in drinking water is therefore considered to be of low risk to Canadians. Exposure to sodium chlorate may result from the use of disinfecting bleach and cosmetics. Concentrated bleach disinfectants may be used in a variety of ways; therefore, the sentinel scenarios presented below are expected to be protective of exposure from other cleaning scenarios. Exposure to sodium chlorate may also result from the use of cosmetics such as bubble bath products. The exposure estimates, health effects and MOEs are presented in Table 4-5.

Table 4-5 Relevant exposure and hazard values for sodium chlorate, as well as MOEs, for determination of risk

Exposure scenario (duration)[a]	Exposure (mg/kg bw/day)	Critical health effect endpoint[b]	Critical effect level (mg/kg bw/day)	MOE
Dermal and inhalation exposure via cleaning kitchen counter (daily)	0.0031	Thyroid effects (BMDL)	0.9	286
Dermal exposure via hand-washing laundry (per event)	0.0043	Thyroid effects (NOAEL)	30	6911
Dermal exposure via cleaning floor (daily)	0.0018	Thyroid effects (BMDL)	0.9	499

Dermal and oral post-application exposure from cleaning floor (daily)	0.0027	Thyroid effects (BMDL)	0.9	339
Dermal exposure from bubble bath (daily)	0.0002	Thyroid effects (BMDL)	0.9	5439

Abbreviations: MOE, Margin of Exposure
[a] A dermal absorption value of 10% was applied to scenarios resulting in dermal exposure to sodium chlorate.
[b] Endpoints were chosen on the basis of frequency of exposure (frequency more than 1/week = 2-year carcinogenicity study; frequency less than or equal to 1/week = 90 day subchronic study)

The MOEs are considered to be adequate to address any uncertainties in the exposure and health effects databases.

5. Sulphite subgroup

5.1 Sources and uses

Sodium metabisulfite and sodium bisulfite

Sodium metabisulfite and sodium bisulfite are not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, between 1 000 tonnes to 10 000 tonnes of sodium metabisulfite and 1 000 tonnes to 10 000 tonnes of sodium bisulfite were reported to be manufactured and/or imported in Canada[11] (Environment Canada 2013a). The top sectors that imported and manufactured these two substances were basic chemical manufacturing, chemical (except agricultural) and allied product merchant wholesalers, and other chemical product manufacturing. These substances were mostly used for redox control, photo processing, laboratory work, and multifunctional purposes (e.g., process control, cleaning and degreasing, enhancing paints and coatings).

5.2 Environmental fate and behaviour

Data on the fate and behaviour of sodium bisulfite are limited. Thus, information for sodium bisulfite was obtained by a read-across approach using OECD (2001a, 2008c) and National Institute of Chemical Safety (NICS 2014) assessments conducted on the analogue substances sodium metabisulfite and sodium sulfite.

Based on their negligible vapour pressure, sodium metabisulfite and sodium bisulfite are not expected to volatilize to the atmosphere (OECD 2001a, 2008c; NICS 2014).

[11] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

Sodium metabisulfite reacts with water to produce sodium bisulfite and sulphur dioxide, both of which dissociate further to form bisulfite (HSO_3^-) and sulphite (SO_3^{2-}) ions. Given that sodium metabisulfite and sodium bisulfite are expected to completely dissociate in water, they should not persist in water, soils and sediments (OECD 2001a, 2008c; NICS 2014). According to the OECD (2001a; 2008c) and NICS (2014), sodium metabisulfite will not bioaccumulate, suggesting that sodium bisulfite will likely not bioaccumulate either.

Sulphite is the predominant species in slightly basic solutions, bisulfite is the prevalent form in slightly acidic solutions, and sulphur dioxide is the main form in very acidic solutions (Halevy et al. 2007; Jarvis 2014). In deionized water and rainwater, sulphite is oxidized to sulphate, where the half-lives of sulphite are approximately 77 hours and 10 hours, respectively (Tsunogai 1971; OECD 2008c). Sulphite ions in surface water are catalytically oxidized by oxygen or microbes to sulphate ions (OECD 2008c). In the presence of some metal cations (e.g., iron, calcium, magnesium, manganese, and copper), the oxidation rate is significantly accelerated (Tsunogai 1971; OECD 2008c). Sulphite and bisulfite ions have not been observed to adsorb onto soil or sediment particles (NICS 2014).

5.3 Potential to cause ecological harm

The predicted no-effect concentration (PNEC) for sodium metabisulfite has been reported to be 1 mg/L (NICS 2014). The PNEC was based on the long-term no observed effect concentration (10 mg/L) for *Daphnia magna* and an assessment factor of 10. A PNEC for the sulfite ion was derived from the same study and calculated to be 0.84 mg/L (NICS 2014). According to Tsunogai (1971) and the OECD (2008c), the sulphite ion is short-lived in the environment, especially in the presence of metals. Results of various ecotoxicological studies have also shown that the sulphite ion induces fish and aquatic invertebrate mortality by reducing the pH level and oxygen availability in the aqueous media (Ryon et al. 2002; Basu and Dorner 2010; NICS 2014).

As described in Section 5.1 of this report, sodium metabisulfite and sodium bisulfite are mainly used as laboratory substances and redox agents by chemical manufacturing and distribution companies. These uses would result in transformation of the substance to a less reactive form. It is unlikely that the substances would be released directly to the environment in significant quantities. Excess sulphite in wastewater effluent may lead to lower oxygen availability; however, various effluent regulations have set limits for appropriate oxygen demand levels (Canada 2012).

Given their environmental instability and relatively low ecotoxicity, sodium metabisulfite and sodium bisulfite are expected to have low potential to cause ecological harm in Canada. The OECD (2008c) and NICS (2014) also found sodium sulfite (an analogue) and sodium metabisulfite to be of low concern for the environment.

5.4 Potential to cause harm to human health

Both substances from the sulphite subgroup were considered using the Low Human Health Hazard Potential Approach (see Appendix A; Health Canada [modified 2017]). Details with regard to data and considerations for the substances in the sulphite subgroup are presented in the Science Approach Document for Substances with Low Human Health Hazard Potential (Health Canada [modified 2017]). On the basis of these results, sodium metabisulfite and sodium bisulfite were considered to be of low concern for human health.

6. Hydrogen and hydroxide subgroup

6.1 Sources and uses

Potassium oxide, sodium silicate and potassium silicate

Potassium silicate and sodium silicate are naturally occurring compounds; however potassium oxide is not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, between 100 tonnes to 1 000 tonnes of potassium oxide, 100 000 tonnes to 1 000 000 tonnes of sodium silicate, and 10 000 tonnes to 100 000 tonnes of potassium silicate were reported to be manufactured and imported in Canada[12] (Environment Canada 2013a). The top sectors importing and manufacturing these three substances were basic chemical manufacturing; other chemical product manufacturing; chemical (except agricultural) and allied product merchant wholesalers; soap, cleaning compound and toilet preparation manufacturing; petroleum and coal manufacturing; paint, coating and adhesive manufacturing; and other undisclosed sectors. Potassium oxide, sodium silicate, and potassium silicate were mainly used in industrial, corrosion inhibition and anti-scaling, and absorbent processes (Environment Canada 2013a).

Hydrochloric acid and sulphuric acid

Hydrochloric acid and sulphuric acid are naturally occurring compounds. They may be present in volcanic gases at various concentrations depending on the location and composition of the volcano (HSDB 1983a- ,1983b- ,1983f-). Hydrochloric acid is also a major component of gastric juices in organisms (HSDB 1983a-), and sulphuric acid is also produced via oxidation by certain bacterial microbes (HSDB 1983f-).Based on CBSA (2016) data, the average annual import quantity in Canada between the year 2010 and 2013 for hydrochloric acid and sulphuric acid was between 10 000 tonnes to 100 000 tonnes (for each substance). Information obtained from the CIMT (1997-)

[12] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

database suggests that 45 036 tonnes and 95 518 tonnes of hydrochloric acid and sulphuric acid, respectively, were imported into Canada in 2017. Three sectors accounted for 95% of the total hydrochloric acid imported into Canada: soap, cleaning compound and toilet preparation manufacturing; basic chemical manufacturing; and chemical wholesalers (CBSA 2016). For sulphuric acid, roughly 92% of the total quantity reported to the CBSA (2016) database was imported by three sectors; the petroleum product wholesaler-distributors; oil and gas extraction; and chemical wholesalers. Both of these strong acids are widely used in various applications, including petroleum production and refining, descaling, ore processing, industrial cleaning, pH adjustment, and manufacturing of fertilizers, chemicals, explosives, and batteries (HSDB 1983a- ,1983f-). Sulphuric acid may also be used in the electricity sector for treatment of makeup water at power plants where steam production is required to generate electricity (personal communication, email from the Risk Management section, Environment and Climate Change Canada to the Ecological Assessment Division, Environment and Climate Change Canada, dated April 7, 2020).

Potassium hydroxide and sodium hydroxide

Potassium hydroxide and sodium hydroxide are not known to occur naturally. On an average annual basis, between 10 000 tonnes to 100 000 tonnes of solid and aqueous potassium hydroxide were imported into Canada between 2010-2013, while 100 000 tonnes to 1 000 000 tonnes of solid and aqueous sodium hydroxide were imported into Canada within the same period (CBSA 2016). In 2017, 35 602 tonnes and 397 350 tonnes of potassium hydroxide and sodium hydroxide, respectively, were imported into Canada (CIMT 1997-). Chemical wholesalers and pesticide, fertilizer, and basic chemical manufacturers collectively accounted for 92% of the total potassium hydroxide imported into Canada between 2010 and 2013 (CBSA 2016). During this three-year period, 90% of the total sodium hydroxide reported to the CBSA database was collectively imported by the following sectors: basic chemical manufacturers; chemical wholesalers; and pulp, paper and paperboard mills (CBSA 2016). As strong bases, potassium and sodium hydroxide have been used for many functions, such as cleaning, bleaching, pH adjustment; and manufacturing chemicals, fertilizers, and pesticides (HSDB 1983m- ,1983n-).

6.2 Environmental fate and behaviour

The fate and behaviour of potassium oxide, sodium silicate, potassium silicate, hydrochloric acid, sulphuric acid, potassium hydroxide, and sodium hydroxide are discussed in reports published by the OECD (2001b, 2001c, 2002a, 2002b, 2004b), the Human and Environmental Risk Assessment (HERA) initiative (HERA 2005), the U.S. EPA (2007), and other agencies (ATSDR 1998; Library of Parliament 1998; ON MOE 2007c). Fate information for potassium oxide was also obtained from the European Chemicals Agency's Registered Substances Database (ECHA 2007-).

Hydrochloric acid, the aqueous form of gaseous hydrogen chloride, is highly volatile with a vapour pressure of approximately 32 000 mmHg to 35 000 mmHg (at 20 ^{o}C to

25ºC) (OECD 2002a; ECHA 2007-). In the atmosphere, hydrogen chloride reacts with hydroxyl radicals to form free chloride radicals, where the estimated half-life for this reaction is 11 days (OECD 2002a). However, this free radical reaction does not occur in the presence of moisture because of the substance's high water solubility. Sulphuric acid has a vapour pressure that is less than 10^{-3} mmHg at 20 ˚C to 25˚C (OECD 2001c; Table B-1, Appendix B), and sulphuric acid particles have an average tropospheric half-life between 3.5 days to 10 days (ON MOE 2007c). Both hydrochloric and sulphuric acid can be removed from air via dry and wet deposition (Reuss and Johnson 1986; OECD 2001c, 2002a), and sulphuric acid is a major component of acid precipitation (ATSDR 1998; Library of Parliament 1998; OECD 2001c; ON MOE 2007c). Nonetheless, hydrochloric acid and sulphuric acid may persist in air for days. Given that potassium hydroxide, sodium hydroxide, potassium oxide, potassium silicate and sodium silicate all have negligible vapour pressure, they are not expected to partition to air and thus are not of concern in the atmospheric compartment (OECD 2001b, 2002b, 2004b; HERA 2005; ECHA 2007-).

The substances in the hydrogen and hydroxide subgroup readily dissociate in water to form hydrogen, hydroxide, sulphate, chloride, potassium, or sodium ions (OECD 2001b, 2001c, 2002a, 2002b; ECHA 2007-). Anhydrous forms of sodium silicate and potassium silicate dissolve slowly under ambient conditions, whereas solutions—including those that are spray-dried—are miscible with water and release sodium or potassium cations, hydroxide anions and silicic acids (OECD 2004b; HERA 2005; U.S. EPA 2007). These dissociation products are ubiquitous in the environment, and some (e.g., sodium, potassium, sulphate, and chloride ions) are even considered major freshwater ions because of their abundance (Gorham 1961). Since the substances in this subgroup readily transform in water, they are not expected to persist in aquatic and terrestrial environments nor are they expected to bioaccumulate in organisms.

6.3 Potential to cause ecological harm

Data reported to the NPRI between 2012 to2016 show that hydrochloric acid was released to surface waters by pulp and paper facilities, and sulphuric acid was discharged to surface waters by meat product manufacturing, power generation and chemical manufacturing facilities (ECCC, HC 2021; NPRI 2012-2016). Although releases of sulphuric acid to air (3619 tonnes to 7144 tonnes) may raise concerns about acidic precipitation, these quantities are negligible in comparison to air releases of precursors to sulphuric acid (i.e., sulphur dioxide, which is listed on Schedule 1 of CEPA).

According to the OECD (2001b, 2001c, 2002a, 2002b, 2004b), HERA initiative (HERA 2005), U.S. EPA (2007), and ON MOE (2007c), the primary ecotoxicological hazard of the seven substances in the hydrogen and hydroxide subgroup is driven by pH-related effects, rather than from direct effects of the substance (U.S. EPA 2007). The pH of Canadian municipal wastewater treatment system effluents were surveyed in the National Survey of Wastewater Treatment Plants for the year 2000 (CWWA 2001). All facilities reported pH levels within the CWQG for fresh water (pH = 6.5 to9) (CCME

2021). Additionally, monitoring of pH levels from 2010 to 2019 at certain wastewater treatment systems across Canada show an annual pH average of 7.35, with the lowest measured pH of 6.32 and the highest measured pH of 8.73 (personal communication, email from the Wastewater Science Unit, Environment and Climate Change Canada to the Ecological Assessment Division, Environment and Climate Change Canada, dated January 7, 2020).

Most reported uses of these substances are expected to discharge to wastewater treatment systems. Based on typical pH levels in final wastewater effluent, the potential for the seven substances in the hydrogen and hydroxide subgroup to cause ecological harm in Canada is expected to be low.

6.4 Potential to cause harm to human health

All seven substances from the hydrogen and hydroxide subgroup were considered using the Low Human Health Hazard Potential Approach (see Appendix A, Table A-2; Health Canada [modified 2017]). Details with regard to data and considerations for the hydrogen and hydroxide subgroup are presented in the Science Approach Document for Substances with Low Human Health Hazard Potential (Health Canada [modified 2017]). On the basis of these results, these seven substances were considered to be of low concern for human health.

7. Phosphate subgroup

7.1 Sources and uses

Phosphoric acid and diphosphorus pentoxide

Phosphoric acid and diphosphorus pentoxide are not known to occur naturally. According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, between 100 000 tonnes to 1 000 000 tonnes of phosphoric acid were reported to be manufactured and imported into Canada while 100 tonnes to 1 000 tonnes of diphosphorus pentoxide were imported in the same year[13] (Environment Canada 2013a). Based on the quantities, the top sectors reporting the two substances were: pesticide, fertilizer and other agricultural chemical manufacturing; basic chemical manufacturing; chemical (except agricultural) and allied product merchant wholesalers; and paint, coating and adhesive manufacturing. Phosphoric acid and diphosphorus pentoxide were mainly used in agricultural, intermediary, paint and coating enhancement, and other applications, such as process control, cleaning and

[13] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

degreasing, corrosion inhibition and anti-scaling, surface activation, and adhesion and sealing.

7.2 Environmental fate and behaviour

Although the ON MOE (2007b) and the OECD (2009) assessed phosphoric acid, fate and behaviour data for both phosphoric acid and diphosphorus pentoxide are limited.

In the atmosphere, phosphoric acid can be found in aerosol particles and water droplets despite its low vapour pressure (0.03 mmHg at 20˚C, see Table B-1, Appendix B). The average tropospheric half-life of particles is estimated to be between 3.5 days to 10 days (ON MOE 2007b); and thus, phosphoric acid may be considered persistent in air. However, according to Krassován et al. (2015), the atmospheric compartment does not play a significant role in the biogeochemical cycling of phosphorus since emissions of related gaseous compounds are low.

In water, diphosphorus pentoxide rapidly hydrolyzes to form phosphoric acid (ECHA 2007-). Phosphoric acid is a tribasic acid, in which the first hydrogen ion is strongly ionizing, the second is moderately weak, and the third is very weak (pK_{a1}=2.15, pK_{a2}=7.09, pK_{a3}=12.32) (OECD 2009).

Phosphorus exists in aquatic environments in three forms: inorganic phosphorus, particulate organic phosphorus and dissolved organic phosphorus (CCME 2004). Phosphate has high adsorption capacity to soils and sediments, in particular those with high iron oxides and calcium carbonate content; and hence, lacks mobility in terrestrial and aquatic environments (CCME 2004; ON MOE 2007b; Rivett et al. 2008). According to Ator et al. (2011), total phosphorus (TP) concentrations are higher in surface waters that drain areas with frequent rainfall and poorly-drained soils. These conditions promote soil erosion and reduce the potential for infiltration, thereby increasing phosphate concentrations in surface waters via runoff (Ator et al. 2011). In low-turbidity waters, such as lakes and wetlands, sediment deposition is an important process that removes phosphate from the water column (Blevins 2004). However, Blevin (2004) notes that changes in temperature, pH, turbidity, oxygen levels and the saturation of the sediments can all remobilize phosphate.

7.3 Potential to cause ecological harm

Between 2012 and 2016, annual releases of TP reported to the NPRI was predominately to surface waters, with a range of 5226 tonnes to 5353 tonnes (NPRI 2012-2016). Quantities of release to land and air were secondary compared to releases to surface waters. Water, sewage and other systems, and pulp, paper and paperboard mills were the top sectors directly discharging TP to surface waters (ECCC, HC 2021; NPRI 2012-2016).

According to the ON MOE (2007b) and the OECD (2009), the ecotoxicity of phosphoric acid and diphosphorus pentoxide is related to pH-driven effects. However, pH at

municipal wastewater treatment systems have been shown to fall within the CWQG for fresh water (pH= 6.5 to9) (CCME 2021; see section 6.3 for further information). Furthermore, both of these substances dissociate in water to release the phosphate ion, which is non-toxic to aquatic organisms (CCME 2004) and is an essential macronutrient that is required by all living organisms for its key role in metabolic processes (Brinch-Pedersen et al. 2002; CCME 2004).

Given the low potential to induce pH-driven effects, phosphoric acid and diphosphorus pentoxide are anticipated to have low potential to cause ecological harm in Canada. The OECD (2009) also concluded that phosphoric acid is of low priority for further ecological work, in part because of its low hazard.

7.4 Potential to cause harm to human health

Both substances from the phosphate subgroup were considered using the Low Human Health Hazard Potential Approach (see Appendix A, Table A-2; Health Canada [modified 2017]). Details with regard to data and considerations for the phosphate subgroup are presented in the Science Approach Document for Substances with Low Human Health Hazard Potential (Health Canada [modified 2017]). On the basis of these results, these two substances were considered to be of low concern for human health.

8. Nitrate and nitrite subgroup

8.1 Sources and Uses

Nitric acid, calcium nitrate, potassium nitrate, and sodium nitrate

Nitric acid, calcium nitrate, potassium nitrate, and sodium nitrate are naturally occurring compounds. Sodium nitrate and calcium nitrate can be found in caves or ore deposits in specific regions around the world (Broughton 1971; Duncan 1997; Urbansky et al. 2000). Nitrogen oxides derived from lightning and biogenic sources can form nitric acid in atmospheric vapours (Lazrus and Gandrud 1974; Schumann and Huntrieser 2007; Stewart et al. 2008). According to information submitted in response to a CEPA section 71 survey, for the reporting year of 2011, between 100 000 tonnes to 1 000 000 tonnes of nitric acid, calcium nitrate and sodium nitrate were manufactured and imported in Canada, with the majority attributed to nitric acid[14] (Environment Canada 2013a). Import quantities for potassium nitrate reported to the CBSA indicate an average annual import quantity of 1 000 tonnes to 10 000 tonnes between 2010 and 2013 (CBSA 2015), and in 2017, 12 218 tonnes of potassium nitrate were imported into Canada (CIMT 1997-). The largest quantities were mainly reported by the following sectors: pesticide, fertilizer

[14] Values reflect quantities reported in response to a CEPA section 71 survey (Environment Canada 2013a) and are available in the supporting document (ECCC, HC 2021). See survey for specific inclusions and exclusions (schedules 2 and 3).

and other agricultural chemical manufacturing; other chemical product manufacturing; oil and gas extraction; non-residential building construction; chemical (except agricultural) and allied product merchant wholesalers; basic chemical manufacturing; and paint, coating and adhesive manufacturing (CBSA 2015; Environment Canada 2013). Nitric acid, calcium nitrate, and sodium nitrate were reported to be mainly used for agricultural (non-pesticidal), process and redox control, and intermediary purposes (Environment Canada 2013a), whereas potassium nitrate is used for manufacturing fertilizers and explosives (HSDB 1983k- ; NRC [modified 2019]).

Nitric acid, calcium nitrate, potassium nitrate and sodium nitrate are permitted food additives, and may be used as components in the manufacture of food packaging materials, or as components in incidental additives used in food processing establishments (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 9, 2018; unreferenced). Sodium nitrate, potassium nitrate, and nitric acid may be found as medicinal or non-medicinal ingredient in drugs including NHPs (personal communication, email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 3, 2018; unreferenced; email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated January 22, 2019; unreferenced). On the basis of notifications to Health Canada, sodium nitrate and potassium nitrate may also be found in cosmetics (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 17, 2018; unreferenced). Other products available to consumers containing sodium nitrate include cleaning products, lawn fertilizers, and adhesive/sealant products. Nitric acid, calcium nitrate, potassium nitrate and sodium nitrate may also be used in pesticides (personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 5, 2018; unreferenced).

Sodium nitrite

Sodium nitrite is not known to naturally occur; however, nitrite ions are ubiquitous in the environment. Between 2010 and 2013, an average annual import quantity of 1 000 tonnes to 10 000 tonnes of sodium nitrite was reported to the CBSA (2015). According to data obtained from the CIMT (1997-) database, approximately 5 650 tonnes of “HS 283410 Nitrites, of metals”, which includes sodium nitrite, were imported into Canada in 2017. Between 2010 and 2013, the chemical, machinery, equipment and supplies wholesalers accounted for roughly 94% of the total sodium nitrite imported (CBSA 2015). Sodium nitrite is mainly used for food preservation, chemical manufacturing and corrosion inhibition (HSDB 1983j-; CFIA [modified 2018]).

Sodium nitrite is a permitted food additive, and may be used as a component in the manufacture of food packaging materials, or as a component in incidental additives used in food processing establishments (personal communication, email from the Food

Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 9, 2018; unreferenced). Sodium nitrite may be used in pesticides and as a medicinal or non-medicinal ingredient in drugs including NHPs (personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 5, 2018; unreferenced, email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated May 3, 2018; unreferenced; email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated January 22, 2019; unreferenced). Sodium nitrite may also be found in other products available to consumers such as cleaning products, paint and/or primers, and automobile care products (leak sealant, engine coolant and tire cleaning products).

8.2 Environmental fate and behaviour

Numerous reports (U.S. EPA 1991; OECD 2005, 2007, 2008b; WHO 2011; CCME 2012; Health Canada 2013; ATSDR 2017) have examined the fate and behaviour of the five substances in the nitrate and nitrite subgroup, including their primary water dissociation products, i.e., nitrate and nitrite ions.

In the atmosphere, nitrogen oxides can react with water vapour or hydroxyl radicals to form nitric acid (vapour pressure of 47 mmHg and water solubility greater than 500 g/L at 20˚C, see Table B-1, Appendix B), which can be removed via dry and wet deposition (CCME 2012; WHO 2011). Sodium nitrite, sodium nitrate, potassium nitrate and calcium nitrate all have negligible vapour pressure (OECD 2005, 2007; Table B-1, Appendix B); and thus, are not expected to partition to the atmosphere.

In water, sodium nitrite rapidly dissociates to release sodium and nitrite ions (OECD 2005), while nitric acid, sodium nitrate, potassium nitrate and calcium nitrate will dissolve and release nitrate ions and metal cations (OECD 2007; ATSDR 2017). Bioaccumulation is not expected for sodium nitrite, nitric acid, potassium nitrate, sodium nitrate and calcium nitrate because they readily dissociate into ions in aqueous solutions (OECD 2005, 2007, 2008b).

Nitrite is the reduced and less stable form of nitrate; and thus, the latter species is typically more prevalent in the environment (Chambers et al. 2001; WHO 2011; CCME 2012; ATSDR 2017). In the environment, nitrite may be transformed to nitrate through microbially mediated nitrification. Subsequently, microbes are able to convert nitrate to gaseous nitrogen through denitrification in anaerobic environments, such as waterlogged soils. In most inland and coastal environments, denitrification results in net losses of nitrate when compared to gains through nitrogen fixation (CCME 2012). In terrestrial environments, adsorption of nitrate onto soils and sediments is unlikely to occur unless the materials have considerable anion exchange capacity; these types of soils and sediments are rare in non-tropical regions. Based on this, groundwater leaching and surface runoff are considered important transport processes for the nitrate

ion in Canadian ecosystems (CCME 2012). The CCME (2012) also notes that the fate processes of nitrate and nitrite are largely governed by pH, temperature and oxygen availability. Nitrate and nitrite ions have been observed to accumulate in some fish and plants (Margiocco et al. 1983; OECD 2008b; CCME 2012; ATSDR 2017).

8.3 Potential to cause ecological harm

8.3.1 Ecological effects assessment

While the ecotoxicological effects of nitric acid are mostly pH-related, the effects of the other four substances (i.e., sodium nitrite, sodium nitrate, calcium nitrate and potassium nitrate) in this subgroup are mainly attributed to their dissociation products: nitrite (NO_2^-) or nitrate (NO_3^-) (OECD 2005, 2008b; ATSDR 2017). For nitrate, the CCME (2012) developed a long-term freshwater guideline value of 13 mg NO_3^-/L (3 mg NO_3^- - N/L), using species sensitivity distributions for low- and no-effect endpoints of fish, amphibians, and invertebrates. For nitrite, the CCME developed a long-term freshwater guideline value of 0.197 mg NO_2-/L using chronic aquatic fish data (CCME 1987). The nitrite ion is considerably more toxic than the nitrate ion, although it is less stable (and thus less prevalent) in the environment compared to nitrate (WHO 2011; CCME 2012; Health Canada 2013; ATSDR 2017). According to the CCME (2012), aquatic plants in aerobic environments depend on nitrate as their principal source of nitrogen.

8.3.2 Ecological exposure assessment

An analysis of 2016 and 2017 NPRI data show that the top sectors reporting direct discharges of the nitrate ion, based on annual average effluent concentrations, were water, sewage and other systems; metal ore mining; and meat packaging (NPRI 2012-2016). Reported annual averages of nitrate ion concentrations in effluent were used to calculate preliminary predicted environmental concentrations (PEC) by adding a dilution factor of 10 to account for dilution of the effluent in the receiving environment. This analysis indicated two facilities released nitrate at levels of potential concern. The first facility is a meat processing facility located in High River, Alberta and discharges into a restored wetland designed to treat wastewater from both an industrial and municipal wastewater system (Sosiak 1994). A study examining the nutrient flux within the wetland over a three-year period (2012-2015) reported average total nitrogen concentrations in the wastewater effluent to be 61 mg/L (Zhu 2019). The average total nitrogen concentration measured downstream of the wetland (Little Bow River) over this same time period was reported to be 2.55 mg N/L. The lower nitrogen concentration in the receiving environment may be attributed to factors such as dilution, plant uptake, and nitrification – denitrification (Vymazej 2007). The second facility is involved in mineral mining and is subject to the *Metal and Diamond Mining Effluent Regulations* and submits water quality monitoring data under the environmental effects monitoring provisions (Canada 2002a). According to surface water quality monitoring data sampled for 2015 to 2016 and 2018 to 2019, the maximum surface water concentration of nitrate at the site is reported to be 6.82 mg NO_3^-/L.

The CCME (2012) notes that runoff from agricultural sources (e.g., cropland and feedlots) and urban sources (e.g., lawns, landfills, vehicular exhaust, and storm sewer overflows) are the greatest sources of nitrate input into surface waters. This trend was also observed in groundwater and surface waters in England (Rivett et al. 2008) and the U.S. (Puckett et al. 2011). The CCME (2012) also notes that all forms of inorganic ammonia or ammonium in surface waters can transform into nitrate via nitrification; and thus, contribute to the overall surface water nitrate concentrations.

Between 2012 and 2016, 2 facilities in the motor vehicle manufacturing sector and the iron and steel mills and ferro-alloy manufacturing sector reported direct releases of sodium nitrite to surface waters (57.5 tonnes released over the 4 years). The PECs were determined using the reported release quantities to water, effluent flow rate of the municipal wastewater system, and an assumption of year-round operating days. A wastewater removal rate of 0% was assumed, which may be a conservative assumption considering nitrite can readily oxidize (Chambers et al. 2001). The PEC for sodium nitrite (adjusted to reflect the concentration of the nitrite ion) for the first facility ranged from 0.002 to 0.003 mg NO_2^-/L and the PEC for the second facility ranged from 0.09 to 0.12 mg NO_2^-/L.

Between 2012 and 2016, release of nitric acid was mainly to the atmospheric compartment (100 tonnes) (ECCC, HC 2021; NPRI 2012-2016).

8.3.3 Characterization of ecological risk

The aquatic toxicity of nitric acid is mostly pH-driven. As current pH levels in wastewater treatment system effluent is within or near the CWQG for freshwater (pH = 6.5 to 9;(see Section 6.3 for further information), the potential to cause ecological harm from this substance is considered to be low. Although releases of nitric acid to the atmospheric compartment (100 tonnes) may raise concerns about acidic precipitation, these quantities are negligible in comparison to air releases of nitric acid precursors (a total of 586 342 tonnes of the precursor nitrogen oxides was reported to be released to air in 2016) (NPRI 2012-2016). Nitrogen oxides is listed on Schedule 1 of CEPA and is being risk managed.

To characterize the risk from the remaining substances in the nitrate and nitrite subgroup (calcium nitrate, sodium nitrate, potassium nitrate, and sodium nitrite), exposure estimates were compared to chronic toxicity information for aquatic environments to determine whether there is potential for ecological harm in Canada.

With respect to the 3 nitrate substances, measured concentration of total nitrogen in the receiving environment at the first facility investigated, a meat processing facility (see Section 8.3.2) (2.55 mg N/L) is below the PNEC (3 mg NO_3^- - N/L). The PEC for total nitrogen incorporates concentrations of nitrogen from substances other than the nitrate ion and therefore may be conservative. This indicates low potential for harm to the

aquatic environment at this site. Measured concentration of nitrate at the second facility, a mineral mine (6.82 mg NO_3^-/L) is also below the PNEC (13 mg NO_3^-/L), indicating there is low potential for harm to the aquatic environment at this site.

Similarly, for sodium nitrite, the highest calculated concentration of nitrite (0.12 mg/L) is below the chronic toxicity guideline value of 0.197 mg/L (CCME 1987), indicating there is low potential for harm to the aquatic environment from this substance.

Based on the characterization of both hazard and exposure, the five substances in the nitrate and nitrite subgroup are anticipated to have low potential to cause ecological harm in Canada.

8.4 Potential to cause harm to human health

8.4.1 Health effects assessment

Nitrate and nitrite are interconverted within the body via oxidation-reduction reactions; therefore, it is difficult to assess their human health effects in isolation. The cations (sodium, potassium and calcium) are expected to enter normal homeostatic processes, and the health effects assessment is focussed on the nitrate and nitrite ion, which are expected to determine the toxicity of the substances.

Several international organizations have reviewed nitrate and nitrite (JECFA 1996, 2003; IARC 2010; U.S. EPA Revised 1991, 2018; WHO 2016; EFSA 2008, 2017a, 2017b; ATSDR 2017). Nitrate and nitrite were also reviewed by Health Canada (Health Canada 2013). These existing assessments were used to inform the health effects section for this assessment. A literature search was conducted on literature published from 2016 to May 2019, which encompasses the year prior to the most recent assessment on nitrate and nitrite. The results from this literature search do not impact the risk characterization from previous assessments (i.e., not suggesting different critical endpoints or lower points of departure).

Toxicokinetics

Nitrate and nitrite that passes through the small intestine is rapidly and near completely absorbed into systemic circulation, with a bioavailability of at least 92%. Less than 2% of dietary nitrate intake reaches the terminal ileum (Health Canada 2013; WHO 2016). Peak plasma levels of nitrate and nitrite are reached 40 minutes to 60 minutes after consumption of a high-nitrate diet (Pannala et al. 2003), suggesting quick absorption into systemic circulation. Dermal absorption of nitrite has been shown not to occur in product formulations with neutral or basic pH. However, acidified-nitrite solutions can penetrate the dermal barrier and enter systemic circulation (Opländer et al. 2012).

Once absorbed, nitrate and nitrite are rapidly distributed throughout the tissues. Within systemic circulation, nitrite can be reoxidized by haemoglobin by a coupled-reaction, which produces nitrate and methaemoglobin (Health Canada 2013; WHO 2016; EFSA

2017b; ATSDR 2017). Nitrate and nitrite are both produced endogenously, primarily through the reduction of L-arginine to nitric oxide. Nitric oxide is rapidly oxidized to nitrite in the presence of oxygen and ceruloplasmin (ASTDR 2017).

In addition, plasma nitrate is selectively transported to salivary glands by the sodium/iodide symporter (Health Canada 2013; WHO 2016; EFSA 2017b; ATSDR 2017). Consequently, nitrate is found in high concentrations in the saliva (EFSA 2017b). This symporter is also active in mammary glands, resulting in nitrate distribution to breast milk (Health Canada 2013; WHO 2016).

The majority of plasma nitrate is excreted unchanged in the urine (60-75%) (Health Canada 2013; WHO 2016; EFSA 2017b; ASTDR 2017). The amount of nitrite excreted in the urine is essentially negligible (0.02%) because nearly all nitrite is oxidized to nitrate by haemoglobin in the blood (WHO 2016; EFSA 2017a; EFSA 2017b). Some nitrate is excreted in breast milk and perspiration and negligible amounts are excreted in the faeces (<1%) (Health Canada 2013; ASTDR 2017). The biological half-life of plasma nitrate and nitrite are 5 hours to 6 hours and 20 minutes to 30 minutes, respectively (ASTDR 2017), suggesting that both nitrate and nitrite are cleared from systemic circulation in less than 48 hours.

Acute Health Effects

The acute oral toxicity of nitrate in experimental animals is generally low, with LD_{50} above 3100 mg/kg bw/day. Nitrite is highly acutely toxic in experimental animals, with an LD_{50} of 120 mg/kg bw/day (Health Canada 2013).

For nitrate, human oral lethal doses range from 67 mg/kg bw to 833 mg/kg bw. For nitrite, the estimated oral lethal dose for humans ranges from 33 mg/kg bw to 250 mg/kg bw. The lower doses apply to children, the elderly and people with a deficiency in reduced nicotinamide adenine dinucleotide-cytochrome b5-methaemoglobin reductase (Health Canada 2013).

Repeated-Dose Health Effects

Health Canada (2013) derived a drinking water guideline for nitrate (MAC of 45 mg/L) based on the absence of adverse health effects (methaemoglobinemia and thyroid effects) below 45 mg/L (5.9 mg/kg bw/day). While no single key study was used to derive the guideline value, a weight of evidence approach was used based on the results of epidemiological studies. This MAC is protective of bottle-fed infants, which are considered to be the most sensitive subpopulation.

The Health Canada (2013) drinking water guideline for nitrite (MAC = 3 mg/L = 0.39 mg/kg bw/day) was based on the MAC for nitrate of 45 mg/L (i.e., converting 45 mg/L for nitrate to corresponding molar concentration for nitrite and multiplying by a factor of 0.1 to account for the estimated conversion of nitrate to nitrite). The WHO (2016) also

derived a drinking water guideline for nitrite using an approach that was consistent with Health Canada (2013).

The EFSA (2017a) ADI for nitrite was based on a 14-week repeated-dose drinking water study in rats (NTP 2001). Increase in methaemoglobin was selected as the most relevant effect for nitrite exposure. No LOAEL could be identified because the increase in methaemoglobin levels occurred at all doses tested. The BMDL for increase in methaemoglobin determined from this data was 9.63 mg sodium nitrite/kg bw/day. The resulting ADI was 0.07 mg nitrite/kg bw/day. The benchmark response of 5% was selected (with adjustments for within-group variation) (EFSA 2017a). Background levels of methaemoglobin are typically between 1 to 3% of total blood haemoglobin concentration (Goldsmith et al. 1976), and clinical methaemoglobinemia is generally indicated at methaemoglobin levels >10% of total haemoglobin (ATSDR 2017). A 5% increase in methaemoglobin levels over the background is considered to have limited clinical significance and this BMDL is considered to be conservative.

A range of ADIs for nitrate was derived using the ADI for nitrite (0.07 mg/kg bw/day) and the overall conversion of nitrate to nitrite in the mouth (1 to 9%) (EFSA 2017a). This resulted in an estimated range of 1.05 mg/kg bw/day to 9.4 mg/kg bw/day for nitrate. The previous ADI established by SCF (1997) and JECFA (2003) (i.e., 3.7 mg/kg bw/day) falls within the range calculated by EFSA (2017b); therefore, EFSA retained the ADI for nitrate of 3.7 mg/kg bw/day. Note that while the JECFA (2003) ADIs for nitrite and nitrate had the same numerical values as EFSA, they were based on non-cancer effects on the heart and lung in a 2-year study in rats.

The ADIs developed by EFSA (2017a, 2017b) for nitrite (0.07 mg/kg bw/day) and nitrate (3.7 mg /kg bw/day) are more conservative than MACs generated by Health Canada (2013). Therefore, the EFSA ADIs were selected as suitable guidance values for risk characterization of exposure to nitrite and nitrate.

At higher exposure levels studies in humans exposed to nitrate in drinking water at concentrations above 50 mg/L show an increase in thyroid volume and thyroperoxidase levels as well as increased incidence of goitre (Health Canada 2013; WHO 2016). In rats, exposure to sodium nitrate concentrations of 50 mg/L (equivalent to 36.45 mg/L as nitrate ion) and above for 30 weeks increased the weight of the thyroid. IARC (2010) has assessed the carcinogenicity of ingested nitrates and nitrites in humans. Overall, IARC (2010) concluded that ingested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans (group 2A). The strongest associations between nitrite intake and cancer were recorded in individuals with high nitrite and low vitamin C intake, a combination which promotes the endogenous formation of N-nitroso compounds (IARC 2010).

Health Canada (2013) concluded that there is no clear evidence of carcinogenicity from nitrate or nitrite *per se* in humans. This conclusion was supported by WHO (2016). Health Canada (2013) quantified the cancer risk that may exist under conditions of endogenous nitrosation of ingested nitrate. Estimated lifetime excess cancer risk from

the endogenous formation of N-nitrosodimethylamine (NDMA), an N-nitroso compound, was based on the exposure to nitrate in drinking water at a level equivalent to the MAC (45 mg/L = 5.9 mg/kg bw/day). The estimated lifetime excess cancer risk was estimated to be $6.5x10^{-6}$, which is in the range of risk considered by Health Canada to be essentially negligible ($1x10^{-6}$ to $1x10^{-5}$). EFSA (2017a) applied the same model as Health Canada (2013) to estimate the amount of endogenous NDMA formation using the nitrite ADI (0.07 mg/kg bw/day) and nitrate ADI (3.7 mg/kg bw/day). EFSA (2017a) derived MOEs of $4.2x10^{5}$ and $3.2x10^{4}$ for nitrite and nitrate, respectively, which are above the MOE considered by EFSA to be low concern for genotoxic and carcinogenic substances (i.e., an MOE of 10 000). Overall, it has been concluded that nitrate and nitrite are not genotoxic (EFSA 2017a; EFSA 2017b; Health Canada 2013; WHO 2016). However, there is evidence of genotoxicity if nitrate and nitrite are co-administered with nitrosatable compounds (Health Canada 2013; WHO 2016).

Health Canada (2013) and WHO (2016) concluded that nitrate and nitrite do not cause concern for reproductive and developmental toxicity (NTP 1990; NTP 2001; Globus and Samuel 1978; Shimada 1989). No information was available on dermal or inhalation toxicity of nitrate or nitrite (Health Canada 2013; ATSDR 2017).

8.4.2 Exposure assessment

Four substances (sodium nitrate, nitric acid, potassium nitrate and calcium nitrate) are assessed on the basis of the nitrate ion and the fifth substance (sodium nitrite) is assessed on the basis of the nitrite ion. The cations of these 5 substances are not expected to play a role in their overall health effects; and therefore, the assessment is focused on the nitrate and nitrite anions.

Environmental media and food

Nitrate and nitrite are both ubiquitously present in the environment. Nitrite is less common due to its instability at environmentally relevant conditions. Nitrate is produced by oxidation of nitrogen by microorganisms in plants, soil and water. Nitrate and nitrite are also present as a result of anthropogenic sources such as agricultural runoff, wastewater treatment, and discharges from industrial processes (Health Canada 2013).

Food

Nitrate and nitrite occur naturally in a wide variety of foods; vegetables are cited as the main source of dietary nitrate due to their potential to accumulate nitrate (Gangolli 1994; EFSA 2017b). Green leafy vegetables contain notably high levels of nitrate, though wide variations in nitrate levels have been found depending on the type of vegetable, its source, and conditions of transport, storage and processing (EFSA 2017b). Nitrite is present in vegetables and other foods in lower amounts than nitrate; however, endogenous conversion via metabolism of dietary nitrate is a significant source of nitrite in humans (EFSA 2008). Based on the secretion rates of nitrate (20–25%) into the saliva and the range of nitrate to nitrite conversion rates in the mouth (5–36%), the

EFSA estimated the range for the overall conversion of dietary nitrate to nitrite to be between 1 and 9% (EFSA 2017b).

Potassium and sodium salts of nitrate and nitrite are food additives permitted for use as preservatives in a variety of foods as prescribed in the *List of Permitted Preservatives*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act* (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada, dated 24 March 2019; unreferenced). The addition of a minimum of 100 ppm of nitrate or nitrite is required in 'cured' foods sold in Canada (CFIA [modified 2018]).

Canadian dietary exposure to nitrate and nitrite was estimated based on their natural occurrence in foods and based on their permitted uses as food additives. Exposure to nitrate and nitrite from its natural occurrence in foods was estimated by multiplying the consumption rate obtained from the Canadian Community Health Survey (CCHS) of various food groups by the amount of nitrate and nitrite measured in those foods Most of the data on levels in food were from the Canadian Total Diet Study (TDS; 2000-2001), when available (more details are available in Appendix D). Dietary exposure to nitrate and nitrite from their permitted food additive uses were estimated by considering the food categories permitted to contain these preservatives in Canada. Infants less than 6 months of age were not considered to consume foods that contained nitrate or nitrite as a permitted food additive. Mean intake estimates from the permitted food additive use ranged from 0.02 to 0.06 mg/kg bw/day for nitrate, and from 0.01 to 0.05 mg/kg bw/day for nitrite (Appendix D, Table D-1, Table D-2). The endogenous conversion of nitrate to nitrite in the body also contributed significantly to the total exposure of nitrite. The portion of nitrite that comes from the conversion of dietary nitrate was calculated by assuming a nitrate to nitrite conversion in saliva of 9% (upper end of the range estimated by EFSA). This was added to the estimate of direct dietary exposure to nitrite, to estimate the total nitrite dietary exposure.

Drinking Water

The most common sources of nitrate and nitrite in water are both natural and anthropogenic, including agricultural activities, wastewater treatment, industrial releases and contamination with animal / human waste. Nitrate and nitrite concentrations from Canadian drinking water treatment plants were measured in a national survey from 2009 to 2010; 130 treated and raw water samples were analyzed. Nitrate was detected in 42% of treated drinking water samples, with an average of 3.8 mg/L and a maximum of 20 mg/L. Nitrite was detected in only 7% of treated drinking water samples, with an average of 0.05 mg/L and a maximum of 0.3 mg/L. Generally, nitrate concentrations in well water are higher than in surface water supplies due to the minimal plant uptake and the lack of organic carbon needed for denitrification (Health Canada 2013). Individual studies and monitoring programs have measured nitrate concentrations in well water across Canada (Health Canada 2013). In Manitoba, 12.5% of raw well water samples exceeded the MAC (from 2002-2008) compared with 1.2% of surface water samples; however, none of the samples exceeded the MAC in later years (from 2009-2011). In

British Columbia 60% of well water samples from the Fraser Valley exceeded the MAC in a 1972 study (Health Canada 2013). In a more recent 2005 study from British Columbia, only 10 of 25 wells contained nitrate above the MAC (Health Canada 2013). Shallow wells and wells in agricultural areas are particularly susceptible to nitrate contamination (Health Canada 2013). Data from the remaining provinces and territories collected from 2000 to 2009 indicate that nitrate was not detected at levels above 3.2 mg/L (Health Canada 2013). Given that nitrate concentrations in well water exceeded the MAC in only a few provinces, and that concentrations have been declining in recent studies, the average concentrations across Canada of nitrate and nitrite in treated drinking water samples were used to determine the daily intake estimates for the general population. Intake estimates ranged from 67 µg/kg bw/day to 319 µg/kg bw/day for nitrate and from 1 µg/kg bw/day to 4 µg/kg bw/day for nitrite (Table D-4 and Table D-5, Appendix D). Intake was highest in the 6- to 11-month old age groups and lowest in adults (19 years and older).

Soil and dust

Nitrate and nitrite in soil are a nitrogen-containing source of food for plants and microorganisms. Measurements of nitrate in soil were not available; however, residual levels of nitrogen in agricultural lands were estimated from 1981 to 2006, every 5 years, based on nitrogen input and output (Drury et al. 2011). Amounts ranged from 2.8 kg N/ha to 63.3 kg N/ha across different ecozones in Canada, while the net Canadian residual nitrogen levels increased from 9.3 kg N/ha in 1981 up to 25 kg N/ha in 2001 and decreased slightly to 17.8 kg N/ha in 2006. After harvest, most of the residual nitrogen is in the form of nitrate, with some ammonia and trace amounts of nitrite (Drury et al. 2011). It was conservatively assumed that potentially all of the nitrogen in soil could be in the form of nitrate and a nitrate concentration of 35 mg/kg was derived based on the residual levels of nitrogen (see Table D-3, Appendix D). Measurements of nitrate in dust were not available; therefore, the estimated concentration of nitrate in soil was used as a surrogate for dust concentration.

Combined intake of nitrate from soil and dust using the estimated concentration of 35 mg/kg resulted in estimates of exposure ranging from 0.002 µg/kg bw/day to 0.14 µg/kg bw/day across all age groups (Table D-4, Appendix D). Estimates were highest in the 1-year old age group and lowest in adults. Toddlers and young children typically have higher intake estimates due to hand-mouth contact and accidental ingestion of soil and/or dust. This is considered to be a conservative estimate because it is assuming 100% of residual nitrogen is present as nitrate, and agricultural lands are not likely to be the main source of exposure to the general population. In addition, agricultural lands received added nitrogen each year in the form of fertilizer and therefore the estimated concentration from these lands will be higher than the natural background occurrence. Given that only trace amounts of residual nitrogen would be in the form of nitrite, intake of nitrite from soil or dust is expected to be minimal.

Air

Nitrogen-containing compounds are present in the air primarily due to anthropogenic releases. Atmospheric nitrate may undergo deposition onto surface water or may deposit on land, where it migrates into surface water (Health Canada 2013). Annual releases to air of some nitrogen-containing compounds (nitrate ion, sodium nitrite and nitric acid) ranged from <1 tonne to 21 tonnes (ECCC, HC 2021). Levels of nitrate in air are generally below 1 µg/m^3, as measured across Canada, the Netherlands and a network of Pacific islands. The average annual air concentration measured in 50 locations across Canada was 0.88 µg/m^3 (Health Canada 2013). Measurements of atmospheric nitrate in the U.S. are similar with an average concentration of less than 1 µg/m^3 (CASTNET [modified 2016]). The average annual air concentration of 0.88 µg/m^3 was used to estimate Canadians' exposure to nitrate from air. Exposure to nitrate from air ranged from 0.18 µg/kg bw/day to 0.64 µg/kg bw/day and was highest in the 1-year old age group and lowest in adults (19+) (Table D-4, Appendix D). Measurements of nitrite in air were not available.

Overall

Combined intake of nitrate and nitrite from food and environmental media (soil, dust, air, and drinking water) for the general population aged 6 months and older ranged from 0.1 mg/kg bw/day to 0.35 mg/kg bw/day for nitrate and from 0.01 mg/kg bw/day to 0.05 mg/kg bw/day for nitrite. The highest exposed age group was the 6 to 11 months old infants for nitrate and 2 to 3 year olds for nitrite (Appendix D, Table D-4, Table D-5).

Naturally occurring background concentrations of nitrate and nitrite in food contribute over 92% of total daily intake from environmental media and food in Canadians over 6 months of age and over 97% in Canadians over 1 year. The contribution from use of nitrate and nitrite as a permitted food additive was less than 2% of total intake from food for the general population age 6 months and older, thus use as permitted food additives is considered to be minor in comparison to the natural presence of these substances in foods. The endogenous conversion of nitrate to nitrite in the body also contributed significantly to the total exposure of nitrite. In comparison to intake of nitrite from food and drinking water, intake from other environmental media (soil, dust, air, and drinking water) contributed very little to total daily nitrite intake (less than 1% for all age groups).

It is known that dietary nitrate and nitrite can lead to the formation of potentially carcinogenic *N*-nitroso compounds, such as *N*-nitrosamines and *N*-nitrosamides, through reactions with available amines in foods under very specific conditions. Nitrosamine formation can be increased by the application of heat to meat products containing nitrates and nitrites. An increase in nitrosamines has been observed in meat products containing nitrite heated above 130°C, such as in bacon cooked by frying (Honikel 2008). Possible endogenous formation of *N*-nitroso compounds has also been proposed to occur in humans after consuming nitrate (Vermeer et al. 1998). The nitrite to *N*-nitroso conversion is very complex and depends on many factors such as the nitrite concentration, the amount and chemical nature of secondary amines present, the acidity of environment, cooking temperature and time. Due to the specific conditions required for the nitrite to *N*-nitroso conversion many of these factors are mitigating

factors that combine to limit the formation of *N*-nitroso compounds. Further, the range of available amines in foods results in potential formation of a variety of *N*-nitroso compounds, which exhibit widely varying carcinogenic potentials and not all of them share the same toxicological properties (EFSA 2017a). Certain food additive preservatives, such as ascorbic acid and erythorbic acid,[15] are permitted in Canada to be used in conjunction with nitrate and nitrite salts, to help prevent the reactions of nitrites that lead to the generation of nitrosamines. Ascorbate has been shown to compete with foodborne amines to react with available nitrite (Mirvish 1972) and both ascorbate and erythorbate effectively reduce the formation of *N*-nitroso compounds (Rywotycki 2002; Herrmann 2015; EFSA 2017a). The EFSA has also concluded that when nitrate is consumed as part of a normal diet containing vegetables, other bioactive substances that are also consumed, such as vitamin C (ascorbic acid), can reduce the amount of nitrosamine formation by up to half (EFSA 2008).

Products available to consumers

Exposure to nitrate and nitrite from the use of products available to consumers can occur through the oral, inhalation or dermal routes; uptake into systemic circulation via the dermal route is heavily dependent on the pH of the product formulation.

A study using pH-neutral and acidified nitrite-releasing liniments on human skin biopsies demonstrated that dermal absorption of nitrite is dependent on the pH of the product or formulation being applied on the skin (Opländer et al. 2012). Dermal application of acidified nitrite-containing liniments (pH 5.5) resulted in transepidermal penetration of nitrite through skin grafts, whereas pH-neutral nitrite-containing liniments did not (Opländer et al. 2012). A possible explanation for these results is that acidified products containing nitrite result in the protonation of nitrite to nitrous acid (pKa 3.37). Nitrous acid can readily penetrate the dermal barrier and enter systemic circulation because it is uncharged, unlike nitrite. Within neutral or basic products nitrite is unprotonated and negatively charged, which does not lend to dermal absorption. This concept is likely applicable to nitrate, which is also negatively charged at neutral or basic pH. However, the pH of the nitrate-containing product would need to be significantly more acidic to allow for dermal absorption (pKa -1.4). Many products that may result in incidental dermal exposure, such as paints, cleaning products, auto care products, are neutral or slightly basic; therefore, no systemic exposure is expected via dermal exposure to these products containing nitrate or nitrite. For products where the pH of the formulation is unknown or the skin membrane may be disrupted, a dermal exposure estimate has been derived. This assumes that dermal penetration may be possible in a slightly acidic formulation (pH ~3 or less) or where the skin membrane is disrupted.

[15] In Canada, ascorbic acid, calcium ascorbate, sodium ascorbate, erythorbic acid (iso-ascorbic acid), and sodium erythorbate (sodium iso-ascorbate) are permitted to be used as preservatives at a level consistent with Good Manufacturing practices in the same preserved meats and preserved meat by-products as nitrate and nitrite. See the *List of Permitted Preservatives*.

Nitrate and nitrite are found in products available to consumers such as cosmetics, cleaning products and NHPs. For the purpose of this screening assessment, products that resulted in the highest levels of exposure were selected as sentinel scenarios and are considered to be representative of typical products that could result in direct exposure to nitrate and nitrite.

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, sodium nitrate and potassium nitrate are found in a number of cosmetics including bath products, shampoo/conditioners, hair products, makeup, non-fluorinated toothpaste, teeth whitener, mouth wash, moisturizers and massage products (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 17, 2018; unreferenced). Products with the potential for oral exposure to nitrate (i.e., toothpaste, teeth whitener, and mouthwash) range in concentration from 0.2 up to 4.4% nitrate. Oral exposure to nitrate from toothpaste was selected as the sentinel scenario and results in a daily intake ranging from 0.1 mg/kg bw/day in adults to 1.5 mg/kg bw/day in toddlers (2 to 3 years old). The estimates are presented in Table 8-4 and are expected to cover exposure from other cosmetics that may result in oral exposure (e.g., teeth whitener, mouthwash).

Nitrate is present as a non-medicinal ingredient in a number of topical, ophthalmic, dental and oral NHPs as potassium nitrate, sodium nitrate or nitric acid (LNHPD [modified 2021]). Exposure to nitrate-containing NHPs taken orally was estimated; nitrate present in NHPs as a non-medicinal ingredient may be as a colour additive or as an antimicrobial preservative. A scenario was derived using an oral NHP for cardiovascular health, which is limited to 12 weeks use. Based on the product label, it is assumed that an adult may take this product twice daily for up to 12 weeks (contains 130 mg of nitrate per capsule). A second scenario was derived for products containing nitrate with no duration restrictions. An oral NHP intended to help maintain a healthy blood pressure was selected for the chronic scenario. According to label instructions, it is assumed an adult may take this product up to 6 times daily with no duration restrictions (contains 30 mg nitrate per capsule). Intake estimates from use of oral NHPs are presented below (Table 8-4). An acute dermal scenario was also derived for exposure to nitrate from use of a caustic wand for wart removal. In this scenario, dermal penetration may be possible due to the function of the product (cauterisation of the skin or removal of granulation tissue or warts), which disrupts the skin membrane and may result in systemic exposure. In order to activate the product, the wand is moistened with water and then applied to the skin. It is estimated that the volume of water used on the tip of the applicator is similar to the volume of water produced from an eye drop bottle (0.0634 mL per drop) (German et al. 1999). The estimated exposure amount is 9.7 mg of nitrate per application. Intake estimates normalized via body weight for infants and adults are presented in a range below (Table 8-4).

Nitrite is present as a non-medicinal ingredient in oral NHPs as sodium nitrite (LNHPD [modified 2021]); however, no concentrations were available.

Nitrite is also found in disinfectant products as a non-medicinal ingredient at a maximum concentration of 0.379% (personal communication, email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated January 15, 2019; unreferenced). Inhalation exposure to nitrite was estimated using ConsExpo modeling program (ConsExpo Web [modified 2019]). The '*exposure to spray: spraying'* model was used to estimate exposure to spray droplets during application of the product. It is assumed that the user sprays a kitchen counter and remains in the area for one hour. The resulting exposure estimates are shown in Table 8-4.

Table 8-4. Estimated exposures to nitrate and nitrite from the use of products available to consumers

Substance	Product scenario (duration)	Age group	Route of exposure	Systemic exposure (mg/kg bw[a])
Nitrate	Toothpaste (chronic)	Child (2 to 3 year old)	Oral	1.5
Nitrate	Short-term oral NHP (per event)	Adult (19+)	Oral	3.5
Nitrate	Long-term oral NHP (chronic)	Adult (19+)	Oral	2.5
Nitrate	Caustic applicator (per event)[b]	Adult (19+); infant (0 to 5 months)	Dermal (broken skin)	0.13 to 1.54
Nitrite	Cleaning kitchen counters (chronic)	Adult (19+)	Inhalation	0.000096

[a] Exposure for "daily" scenarios is estimated on a mg/kg bw/day basis; exposure for "per event" scenarios is estimated on a mg/kg bw/event basis.
[b] As this product might damage the protective layer of the skin, absorption by the dermal route was assumed to be 100%.

Other products available to consumers that contain nitrite include degreasers, vinyl cleaners, paint/primers, leak sealant, engine coolant and tire cleaning products. Systemic exposure is not expected from the use of these products due to the lack of dermal penetration and because nitrite is non-volatile.

8.4.3 Characterization of risk to human health

Nitrate and nitrite have been assessed by EFSA (2017a, 2017b). The EFSA based their ADIs on the results from a 14-week repeated-dose drinking water study in rats (NTP 2001). The ADIs derived from this study, based on an increase in methaemoglobin, were 0.07 mg/kg bw/day for nitrite and 3.7 mg/kg bw/day for nitrate. The ADIs are more conservative than the drinking water MACs for nitrate and nitrite derived by Health Canada (2013) based on a lack of adverse health effects in human studies at levels of 5.9 mg/kg bw/day. Since the Health Canada MAC (Health Canada 2013) is specifically protective of the most sensitive population of bottle-fed infants, the ADIs derived by EFSA are also considered by Health Canada to be protective of this population.

Therefore, while conservative in nature, the ADIs of 0.07 mg/kg bw/day for nitrite and 3.7 mg/kg bw/day for nitrate were selected for risk characterization of nitrate and nitrite.

Exposure to nitrate and nitrite from environmental media is comprised almost entirely from its natural presence in food and drinking water, more than 99% of total intake. Drinking water concentrations in treated water were found to be below the MAC for both nitrate and nitrite, though concentrations may be higher in homes on well water. Health Canada recommends that homeowners with a well to test their water for concentrations of nitrate and nitrite (Health Canada 2013). In all age groups above 6 months of age, food comprised more than 92% of total intake. Though nitrate and nitrite are both added to foods as a permitted food additive, this use contributes less than 2% to total intake from dietary sources. The natural presence of nitrate and nitrite in food is a much more significant contributor to total intake.

Comparison with the ADIs was not considered appropriate for natural occurrence in food due to a number of factors. The nitrate and nitrite content in vegetables varies significantly and when combined with the recommendation of a varied diet consisting of many different foods[16] these factors together help to mitigate the probability of excess exposure to nitrate and nitrite. Additionally, the concentration of nitrate naturally present or added to foods will decrease over time due to the activity of nitrate-reducing bacteria or as a result of chemical instability and reactivity. Cooking vegetables, for example, has been shown to significantly reduce the levels of both nitrate and nitrite (EFSA 2008; EFSA 2017b). While the level of nitrite in foods is increased by conversion from nitrate, the levels present in foods also decrease over time as nitrite is consumed through reactions with various components of food such as myoglobin, ascorbate and amino acids (Sen and Baddoo 1997). Estimated intake from the permitted food additive use is less than intake from natural occurrence and is also less than the ADIs derived by EFSA (2017a, 2017b) and the MAC derived by Health Canada (2013).

Exposure to nitrate from environmental media (air, dust, soil, and drinking water) and use as a permitted food additive is much lower than background levels in food, ranging from less than 0.001 mg/kg bw/day to 0.35 mg/kg bw/day. When excluding exposure from natural occurrence in food, exposure to nitrite is expected to be primarily from its permitted food additive uses and drinking water. Intake from air, soil and dust is considered to be minimal. The points of departure selected for risk characterization are ADIs, which take into account safety factors. Risk is determined by whether or not the exposure values exceed the ADIs. Exposure to nitrate or nitrite from its permitted food additive uses and environmental media do not exceed the ADIs (Table 8-6). Exposure can also occur from products available to consumers. The sentinel scenarios presented

[16] Canada's Food Guide recommends consuming a variety of vegetables each day as part of a varied diet.

in section 8.2 include exposure from toothpaste, oral and dermal NHPs and spray disinfectants.

Table 8-5. Relevant exposure and hazard values for nitrate and nitrite for determination of risk

Substance	Exposure scenario (duration)	Systemic exposure (mg/kg bw/day)	Critical health effect endpoint	Acceptable daily intake (mg/kg bw/day)	Exceedance (Y/N)
Nitrate	Exposure from food additive use, air, soil, dust and drinking water (chronic)	0.35	Increase in methaemoglobin levels from nitrite	3.7	No
Nitrate	Oral exposure via toothpaste (chronic)	1.5	Increase in methaemoglobin levels from nitrite	3.7	No
Nitrate	Oral exposure via NHPs (per event to chronic)	2.5 to 3.5	Increase in methaemoglobin levels from nitrite	3.7	No
Nitrate	Dermal exposure to caustic applicator (per event)	0.13 to 1.54	Increase in methaemoglobin levels from nitrite	3.7	No
Nitrite	Exposure from food additive use and drinking water (chronic)	0.052	Increase in methaemoglobin levels	0.07	No
Nitrite	Inhalation exposure via cleaning kitchen counter (chronic)	0.0000096	Increase in methaemoglobin levels	0.07	No

The exposure estimates for the sentinel scenarios do not exceed the ADIs for nitrate or nitrite and therefore are considered to be of low concern to human health at current levels of exposure.

Formation of N-nitroso compounds

Based on the results of the EFSA (2017a, 2017b) and Health Canada (2013) assessments, the various mitigating factors that limit *N*-nitroso formation and the consideration that a range of *N*-nitroso compounds could potentially be generated, with only some having known carcinogenicity, it is concluded that the formation of *N*-nitroso compounds from the conversion of nitrate and nitrite in foods from their use as permitted food additives represents a low concern for human health. This is supported by data from the Canadian Total Diet Study (Health Canada 2017) which show that

concentrations of nitrosamines in foods prepared as consumed, and hence dietary exposure, are low.

9. Uncertainties

9.1 Uncertainties in evaluation of ecological risk

There are various limitations regarding the information from CEPA section 71 surveys and NPRI data used in this screening assessment. Survey data for 15 out of the 22 substances in the Acids and Bases Group were available. In the absence of measured environmental concentrations, assumptions are made in order to examine potential environmental release, including obtaining data from other sources such as CBSA, CIMT and Hazardous Substances Data Bank. Similarly, there are 2012-2016 NPRI data for only six of 16 substances in the group, and thus the magnitude, frequency and sources of releases for the other substances are more uncertain. . Although spills and accidental releases may cause adverse ecological effects in the immediate and surrounding environment, these types of releases were not considered in the assessment given their likely low frequency. In addition, some of the substances (i.e., nitric acid, chlorine, chlorine dioxide, and sodium chlorate) are subject to the *Environmental Emergency Regulations* (Canada 2019), which aim to reduce the frequency and severity of accidental releases of hazardous substances into the environment.

Environmental fate and behaviour and ecotoxicity data were limited for hydroxylammonium chloride, sodium bisulfite, diphosphorus pentoxide, and phosphoric acid. When available and necessary, a read-across process was implemented using analogue substances to identify missing information.

The ecological effects assessment of the substances in the Acids and Bases Group was limited to their direct toxicological effects. While some substances in the group are nutrients that can stimulate biomass growth in aquatic ecosystems (e.g., phosphates and nitrates), eutrophication and its associated secondary ecological effects (e.g., oxygen depletion) are not in the scope of this assessment. Releases of these substances to the environment may be relevant to evaluations of eutrophication in the Canadian environment, as documented previously by Chambers et al. (2001).

9.2 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 9-1. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
The intake of nitrate from soil and dust was determined assuming 100% measured nitrogen was in the form of nitrate and assuming 100% bioavailability	+

Key source of uncertainty	Impact
Lack of monitoring data or release data of sodium chlorate to air	+/-
There are no acute, subchronic or chronic toxicity studies for inhalation or dermal exposure to sodium chlorate	+/-
There are no cancer studies available to characterize the carcinogenic potential of chlorine dioxide	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure/risk; +/- = unknown potential to cause over or under estimation of risk.

Conclusion

Six of 22 substances in the Acids and Bases Group (hydroxylammonium chloride, sodium hypochlorite, sodium chlorate, calcium hypochlorite, chlorine, and chlorine dioxide) were previously addressed by Environment Canada under the Priority Substances Assessment Program; however, a conclusion for potential harm to human health was not determined. As these substances were not re-assessed from an ecological perspective, the conclusion for these six substances is limited to a conclusion under paragraph 64(c) of CEPA.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from 16 substances in the Acids and Bases Group. It is proposed to conclude that 16 of the substances in the Acids and Bases Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Considering all the information presented in this draft screening assessment, it is proposed to conclude that the 22 substances in the Acids and Bases Group do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that 16 substances in the Acids and Bases Group (sodium bisulfite, sodium metabisulfite, potassium hydroxide, sodium hydroxide, potassium silicate, sodium silicate, hydrochloric acid, sulphuric acid, potassium oxide, diphosphorus pentoxide, phosphoric acid, sodium nitrate, sodium nitrite, nitric acid, potassium nitrate, and calcium nitrate) do not meet any of the criteria set out in section 64 of CEPA. In addition, it is proposed to conclude that the other six substances in the Acids and Bases Group (hydroxylammonium chloride, sodium hypochlorite, sodium chlorate, calcium hypochlorite, chlorine, and chlorine dioxide) do not meet the criteria under paragraph 64(*c*) of CEPA.

References

Abdel-Rahman MS, Couri D, Bull RJ. 1982. Metabolism and pharmacokinetics of alternate drinking water disinfectants. Environ Health Perspect. 46:19-23.

Abdel-Rahman MS, Couri D, Bull RJ. 1984. The kinetics and chlorite and chlorate in the rat. J Am Coll Toxicol. 3(4):261-267.

Ali SN, Ahmad MK, Mahmood R. 2017a. Sodium chlorate, a herbicide and major water disinfectant byproduct, generates reactive oxygen species and induces oxidative damage in human erythrocytes. Environ Sci Pollut Rest Int. 24(2):1898-1909.

Ali SN, Ansari FA, Khan AA, Mahmood R. 2017b. Sodium chlorate, a major water disinfection byproduct, alters brush border enzymes, carbohydrate metabolism and impairs antioxidant system of Wistar rat intestine. Environ Toxicol. 32(5)1607-1616.

[AMGMedical] A.M.G. Medical Inc. 1997-2021. MedPro Flexible Caustic Applicators, 6 inch (118-395). [PDF] [accessed May 2021].

Atkins PW. 1978. Physical Chemistry. 4th edition. New York (NY): W. H. Freeman and Company.

Ator SW, Brakebill JW, Blomquist JD. 2011. Sources, fate, and transport of nitrogen and phosphorus in the Chesapeake Bay watershed: An empirical model [PDF]. Reston (VA): U.S. Geological Survey. [accessed 2019 Mar 05].

[ATSDR] Agency for Toxic Substances and Disease Registry. 1998. Toxicological profile for sulfur trioxide and sulfuric acid [PDF]. Atlanta (GA): U.S. Department of Health and Human Services. [accessed 2019 Apr 03].

[ATSDR] Agency for Toxic Substances and Disease Registry. 2004. Toxicological profile for chlorine dioxide and chlorite [PDF]. Atlanta (GA): U.S. Department of Health and Human Services. [accessed 2019 Feb 25].

[ATSDR] Agency for Toxic Substances and Disease Registry. 2010. Toxicological profile for chlorine [PDF]. Atlanta (GA): U.S. Department of Health and Human Services. [accessed 2019 Feb 25].

[ATSDR] Agency for Toxic Substances and Disease Registry. 2017. Toxicological profile for nitrate and nitrite [PDF]. Atlanta (GA): U.S. Department of Health and Human Services. [accessed 2019 Apr 05].

Basu OD, Dorner SM. 2010. Potential aquatic health impacts of selected dechlorination chemicals. Water Qual Res J Can. 45(3):353-363.

[BC MOE] British Columbia Ministry of Environment. 2002. Ambient Water Quality Guidelines for Chlorate – Technical Background Report [PDF]. Victoria (BC): BC MOE. [accessed 2021 Jun 30].

Blevins DW. 2004. Hydrology and cycling of nitrogen and phosphorus in Little Bean Marsh: A remnant riparian wetland along the Missouri River in Platte County, Missouri [PDF]. Reston (VA): U.S. Geological Survey. [accessed 2019 Mar 05].

Bommaraju TV, O'Brien TF. 2015. Brine Electrolysis. Grand Island (NY): The Electrochemical Society. [accessed 2019 Feb 15].

Brinch-Pedersen, H., Sørensen, L.D. and Holm, P.B., 2002. Engineering crop plants: getting a handle on phosphate. Trends in plant science, 7(3), pp.118-125.

Broughton PL. 1971. Origin and distribution of mineral species in limestone caves. Can J Earth Sci. 5(1):36-43.

Canada. 1985. *Fertilizers Act, 1985. R.S.C. 1985, c. F-10.*

Canada. 1999. *Canadian Environmental Protection Act, 1999. S.C. 1999, c 33.*

Canada. 2002a. *Fisheries Act, 1985: Metal and Diamond Mining Effluent Regulations*. P.C. 2002-987, 6 June, 2002, SOR/2002-222.

Canada. 2002b. *Pest Control Products Act*, 2002. S.C. 2002, c 28.

Canada. 2012. *Fisheries Act, 1985: Wastewater Systems Effluent Regulations*. P.C. 2012-942, 29 June, 2012, SOR/2012-139.

Canada. 2019. *Canadian Environmental Protection Act, 1999: Environmental Emergency Regulations*. P.C. 2019-96, 23 February, 2019, SOR/2019-51.

Canada, Dept. of the Environment. 2004. *Canadian Environmental Protection Act, 1999: Guideline for the release of ammonia dissolved in water found in wastewater effluents* [PDF]. Canada Gazette, Part I, vol. 138, no. 49, p. 3489-3497.

[CASTNET] Clean Air Status and Trends Network. (modified 2016 December). U.S. EPA database (accessed April 24 2019).

[CBSA] Canada Border Services Agency. 2015. Information gathered on the import of commodities corresponding to the codes HS 2834100010, 2834210000. Confidential information.

[CBSA] Canada Border Services Agency. 2016. Information gathered on the import of commodities corresponding to the HS codes 2829110000, 2815120000, 2815110000, 2815200020, 2806100000, 2807000000, and 2815200010. Confidential information.

[CCME] Canadian Council of Ministers of the Environment. 1987. Nitrite summary table. [accessed 2019 Oct 10]

[CCME] Canadian Council of Ministers of the Environment. 1999. Canadian water quality guidelines for the protection of aquatic life – Reactive chlorine [PDF]. Winnipeg (MB): CCME. [accessed 2019 Feb 26].

[CCME] Canadian Council of Ministers of the Environment. 2004. Canadian water quality guidelines for the protection of aquatic life – Phosphorus: Canadian guidance framework for the management of freshwater systems [PDF]. Winnipeg (MB): CCME. [accessed 2019 Feb 26].

[CCME] Canadian Council of Ministers of the Environment. 2010. Canadian water quality guidelines for the protection of aquatic life – Ammonia [PDF]. Winnipeg (MB): CCME. [accessed 2019 Feb 26].

[CCME] Canadian Council of Ministers of the Environment. 2012. Scientific criteria document for the development of the Canadian water quality guidelines for the protection of aquatic life: Nitrate ion [PDF]. Winnipeg (MB): CCME. [accessed 2019 Feb 26].

[CCME] Canadian Council of Ministers of the Environment. 2021. Canadian water quality guidelines for the protection of aquatic life . Ottawa (ON): CCME. [accessed 2019 Mar 06].

[CEH] Chemical Economics Handbook. 2018. Sodium Chlorate. Schlag S, Funada C, Gao A, Davis S. IHS Markit. [accessed 2020 Jan 28]. [restricted access].

[CFIA] Canadian Food Inspection Agency. [modified 2018 Jun 13]. Preventive control recommendations on the use of nitrites in the curing of meat products. Ottawa (ON): Government of Canada. [accessed 2019 Feb 21].

Chambers P.A., M. Guy, E.S. Roberts, M.N. Charlton, R. Kent, C. Gagnon, G. Grove, and N. Foster. 2001. Nutrients and their impact on the Canadian environment. Hull (QC): Agriculture and Agri-Food Canada, Environment Canada, Fisheries and Oceans Canada, Health Canada and Natural Resources Canada. 241 p.

[CIMT] Canadian International Merchandise Trade Database. 1997- . Ottawa (ON): Statistics Canada. [accessed 2019 Mar 01].

[ConsExpo Web] Consumer Exposure Web Model. [modified 2019 Feb 13]. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu. [National Institute for Public Health and the Environment].

[CWWA] Canadian Water and Wastewater Association. June 14, 2001. National Survey of Wastewater Treatment Plants. Final Report. Ottawa (ON): Environment Canada.

Drury CF, Yang JY, De Jong R. 2011. Trends in residual soil nitrogen for agricultural land in Canada, 1981-2006. Canadian Biodiversity: Ecosystem Status and Trends 2010, Technical Thematic Report No. 15. Canadian Councils of Resource Ministers. Ottawa, ON.

Duncan SM. 1997. Examining early nineteenth century saltpeter caves: an archaeological perspective. J Caves Karst Stud. 59(2):91-94.

[ECCC] Environment and Climate Change Canada. [modified 2013 Jul 24]. Effluents from pulp mills using bleaching. Gatineau (QC): ECCC. [accessed 2019 Apr 11].

[ECCC] Environment and Climate Change Canada. 2016a. Science approach document: ecological risk classification of organic substances. Ottawa (ON): Government of Canada.

[ECCC] Environment and Climate Change Canada. 2016b. Guide for reporting to the National Pollutant Release Inventory (NPRI). Gatineau (QC): Government of Canada. [accessed 2019 Mar 14].

[ECCC] Environment and Climate Change Canada and the Ontario Ministry of the Environment and Climate Change. 2017a. Canada-Ontario Lake Erie Action Plan. Ontario. [accessed 27 Jul 2021]

[ECCC] Environment and Climate Change Canada. 2017b. Lake of the woods water sustainability foundation. [accessed 27 Jul 2021]

[EC, HC] Environment Canada, Health Canada. 1991. Priority Substances List Assessment Report for Effluents from Pulp Mills using Bleaching [PDF]. Ottawa (ON): Government of Canada. [accessed 2019 Feb 25].

[EC, HC] Environment Canada, Health Canada. 1993. Priority Substances List Assessment Report for Chlorinated Wastewater Effluents. Ottawa (ON): Government of Canada. [accessed 2019 Feb 25].

[EC, HC] Environment Canada, Health Canada. 2001a. Priority Substances List Assessment Report for Ammonia in the Aquatic Environment. Ottawa (ON): Government of Canada. [accessed 2019 Mar 27].

[EC, HC] Environment Canada, Health Canada. 2001b. Priority Substances List Assessment Report for Inorganic Chloramines [PDF]. Ottawa (ON): Government of Canada. [accessed 2019 Mar 27].

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2017 Mar 12]. Categorization of chemical substances. Ottawa (ON): Government of Canada. [accessed 2017 Oct 02].

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2018a. Rapid Screening of Substances with Limited General Population Exposure Final Screening Assessment. [PDF] Ottawa (ON): Government of Canada.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2018b. Screening assessment substances identified as being of low concern using the ecological risk classification of organic substances and the threshold of toxicological concern (TTC)-based approach for certain substances. Ottawa (ON): Government of Canada.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2019. Draft screening assessment phosphonic acid, [[(phosphonomethyl)Imino]bis[2,1-

ethanediylnitrilobis(methylene)]]tetrakis-. Ottawa (ON): Government of Canada. [accessed 2020 Aug 18]

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2021. Supporting documentation: Sources and uses data relevant to the screening assessment of Acids and Bases. Gatineau (QC): ECCC. Information in support of the draft screening assessment for the Acids and Bases. Available from: eccc.substances.eccc@canada.ca.

ECHA. 2007- . Helsinki (Finland): [ECHA] European Chemicals Agency. [accessed 2018 May 04].

[ECHA] European Chemicals Agency. 2007a. Registered Dossier – Potassium chlorate. [accessed February 2019].

[EFSA] European Food Safety Authority. 2008. Nitrate in vegetables - Scientific Opinion of the Panel on Contaminants in the Food chain. The EFSA Journal. 689: 1-79.

[EFSA] European Food Safety Authority. 2017a. Re-evaluation of potassium nitrite (E 249) and sodium nitrite (E 250) as food additives. EFSA Journal. 15(6):4786, 157 pp.

[EFSA] European Food Safety Authority. 2017b. Re-evaluation of sodium nitrate (E 251) and potassium nitrate (E 252) as food additives. EFSA Journal. 15(6):4787, 123 pp.

Environment Canada. 2002. Pollution Prevention Planning for Ammonia, Inorganic Chloramines and Chlorinated Wastewater Effluents in Municipal Wastewater Effluents: Working Document [PDF]. Gatineau (QC): Environment Canada.

Environment Canada. 2007. Pulp and paper technical guidance: criteria and guidance for pronounced eutrophication. National Environmental Effects Monitoring Office, National Water Research Institute, Gatineau, QC., Canada.

Environment Canada. 2009. DSL Inventory Update data collected under the *Canadian Environmental Protection Act, 1999*, section 71: *Notice with respect to certain inanimate substances (chemicals) on the Domestic Substances List.* Data prepared by: Environment Canada, Health Canada; Existing Substances Program

Environment Canada. 2012. Performance Report – Pollution Prevention Planning for Chlorine in Wastewater Effluents [PDF]. Ottawa (ON): Government of Canada.

Environment Canada. 2013a. DSL Inventory Update data collected under the *Canadian Environmental Protection Act, 1999*, section 71: *Notice with respect to certain substances on the Domestic Substances List.* Data prepared by: Environment Canada, Health Canada; Existing Substances Program.

Environment Canada. 2013b. Overview- Lake Winnipeg Basin Initiative [PDF]. Ottawa (ON). [accessed 27 Jul 2021]

[EU] European Commission. 2007a. European Union Risk Assessment Report: Chlorine. Rome (ITL): European Commission. [accessed 2019 Mar 29].

[EU] European Commission. 2007b. European Union Risk Assessment Report: Sodium Hypochlorite. Rome (ITL): European Commission. [accessed 2019 Mar 29].

[EU] European Union. 2009. Sodium hypochlorite : Summary Risk Assessment Report. Rome (ITL): European Union.[accessed 2019 Mar 29].

[EU] European Union. 2017. Active chlorine released from sodium hypochlorite [PDF]. Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products.

Farkouh A, Frigo P, and Czejka M. 2016. Systemic side effects of eye drops: a pharmacokinetic perspective. Clin Ophthalmol 10:2433-1441.

Faxon C, Bean J, Hildebrandt Ruiz L. 2015. Inland Concentrations of Cl2 and ClNO2 in Southeast Texas Suggest Chlorine Chemistry Significantly Contributes to Atmospheric Reactivity. Atmosphere 6:1487-1506.

Ficheux AS, Wesolek N, Chevillotte G, Roudot AC, 2015. Consumption of cosmetic products by the French population. First part: Frequency data. Food and Chemical Toxicology 78: 159-169.

Ficheux AS, Chevillotte G, Wesolek N, Morisset T, Dornic N, Bernard A, Bertho A, Romanet A, Leroy L, Mercat AC, Creusot T, Simon E, Roudot AC. 2016. Consumption of cosmetic products by the French population second part: Amount data. Food and Chemical Toxicology 90: 130-141.

Gangolli SD, van den Brandt PA, Feron VJ, Janzowsky C, Koeman JH, Speijers GJA, Spiegelhalder B, Walker R, Wishnok JS. 1994. Nitrate, nitrite and *N*-nitroso compounds. Eur J Pharmacol. 292:1-38.

German EJ, Hurst MA, Wood D. 1999. Reliability of drop size from multi-dose eye drop bottles: is it cause for concern? Eye. 13:93-100.

Gill MT, Swanson MS, Murphy SR, Bailey GP. 2000. Two-generation reproduction and developmental neurotoxicity study with sodium chlorite in the rat. J Appl Toxicol. 20(4): 291-303.

Globus M, Samuel D. 1978. Effect of maternally administered sodium nitrite on hepatic erythropoiesis in fetal CD-1 mice. Teratology. 18(3):367-378.

Gorham E. 1961. Factors influencing supply of major ions to inland waters, with special reference to the atmosphere. Geol Soc Am Bull. 72(6):795-840.

Government of Canada. [modified 2017 Feb 13]. Great lakes water quality agreement; nutrients. [accessed 27 Jul 2021]

Government of Canada. [modified 2021 Mar 26]. Canada Water Act annual report for 2019 to 2020: chapter 7. [accessed date 28 Jul 2021]

Halevy I, Zuber MT, Schrag DP. 2007. A sulfur dioxide climate feedback on early Mars. Sci. 318(5858):1903-1907.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Government of Canada

Health Canada. 2008a. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorite and Chlorate [PDF]. Ottawa (ON): Government of Canada. [accessed 2019 Feb 15].

Health Canada. 2008b. Proposed Re-evaluation Decision – Sodium Chlorate and Sodium Chlorite [PDF]. Ottawa (ON): Government of Canada. [accessed 2019 Feb 15].

Health Canada. 2009. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Chlorine [PDF]. Ottawa (ON): Government of Canada. [accessed 2019 Jan 11].

Health Canada. 2013. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Nitrate and Nitrite [PDF]. Ottawa (ON): Government of Canada. [accessed 2019 Jan 11].

Health Canada. 2015. Food consumption table derived from Statistics Canada, Canadian Community Health Survey, Cycle 2.2, Nutrition (2004), Share file. Ottawa.

Health Canada. 2016. Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances. Ottawa (ON): Government of Canada. [accessed 2019 Jan 11].

Health Canada. 2017. Investigation of N-nitrosamines on the Canadian market -2017 year [Dataset]. The Canadian Laboratory Information Network (CANLINE). [accessed May 2021].

Health Canada. [modified 2017 December 27]. Science approach document for substances with low human health hazard potential. Ottawa (ON): Government of Canada. [accessed 2019 Feb].

Health Canada. 2018a. Draft backgrounder document of default values for breast milk and formula intake. Unpublished report. Ottawa (ON): Government of Canada.

Health Canada. [modified 2018 June 14]. Cosmetic Ingredient Hotlist – List of Ingredients that are Prohibited for Use in Cosmetic Products. Ottawa (ON): Government of Canada. [accessed 2019 Feb 5].

Health Canada. 2019. Canadian exposure factors used in human health risk assessment. Unpublished report. Ottawa (ON): Government of Canada.

[HERA] Human and Environmental Risk Assessment. 2005. Soluble silicates (draft) [PDF]. [accessed 2019 Feb 22].

[HSDB] Hazardous Substances Data Bank. 1983a- . Bethesda (MD): National Library of Medicine (US). [revised 2015 Oct 19; accessed 2019 Jan 10]. Hydrogen chloride; CAS RN 7647-01-0.

[HSDB] Hazardous Substances Data Bank. 1983b- . Bethesda (MD): National Library of Medicine (US). [revised 2016 Oct 25; accessed 2019 Jan 10]. Chlorine; CAS RN 7782-50-5.

[HSDB] Hazardous Substances Data Bank. 1983c- . Bethesda (MD): National Library of Medicine (US). [revised 2018 Nov 28; accessed 2019 Jan 10]. Chlorine dioxide; CAS RN 10049-04-4.

[HSDB] Hazardous Substances Data Bank. 1983d- . Bethesda (MD): National Library of Medicine (US). [revised 2014 Jun 30; accessed 2019 Jan 10]. Calcium hypochlorite; CAS RN 7778-54-3.

[HSDB] Hazardous Substances Data Bank. 1983e- . Bethesda (MD): National Library of Medicine (US). [revised 2003 Mar 05; accessed 2019 Jan 10]. Sodium hypochlorite; CAS RN 7681-52-9.

[HSDB] Hazardous Substances Data Bank. 1983f- . Bethesda (MD): National Library of Medicine (US). [revised 2016 Oct 25; accessed 2019 Jan 10]. Sulfuric acid; CAS RN 7664-93-9.

[HSDB] Hazardous Substances Data Bank. 1983g- . Bethesda (MD): National Library of Medicine (US). [revised 2002 Feb 13; accessed 2019 Jan 10]. Potassium polysilicate; CAS RN 1312-76-1.

[HSDB] Hazardous Substances Data Bank. 1983h- . Bethesda (MD): National Library of Medicine (US). [revised 2007 Oct 11; accessed 2019 Jan 10]. Sodium silicate; CAS RN 1344-09-8.

[HSDB] Hazardous Substances Data Bank. 1983i- . Bethesda (MD): National Library of Medicine (US). [revised 2002 Nov 08; accessed 2019 Jan 10]. Phosphorus pentoxide; CAS RN 1314-56-3.

[HSDB] Hazardous Substances Data Bank. 1983j- . Bethesda (MD): National Library of Medicine (US). [revised 2007 Jun 04; accessed 2019 Jan 10]. Sodium nitrite; CAS RN 7632-00-0.

[HSDB] Hazardous Substances Data Bank. 1983k- . Bethesda (MD): National Library of Medicine (US). [revised 2007 Jun 04; accessed 2019 Jan 10]. Potassium nitrate; CAS RN 7757-79-1.

[HSDB] Hazardous Substances Data Bank. 1983l- . Bethesda (MD): National Library of Medicine (US). [revised 2007 Jun 04; accessed 2019 Jan 10]. Sodium nitrate; CAS RN 7631-99-4.

[HSDB] Hazardous Substances Data Bank. 1983m- . Bethesda (MD): National Library of Medicine (US). [revised 2012 Apr 26; accessed 2019 Feb 21]. Sodium hydroxide; CAS RN 1310-73-2.

[HSDB] Hazardous Substances Data Bank. 1983n- . Bethesda (MD): National Library of Medicine (US). [revised 2015 Oct 19; accessed 2019 Jan 10]. Potassium hydroxide; CAS RN 1310-58-3.

Herrmann SS, Granby K, Duedahl-Olesen L. 2015. Formation and mitigation of *N*-nitrosamines in nitrite preserved cooked sausages. Food Chem. 174:516-526.

Honikel KO. 2008. The use and control of nitrate and nitrite for the processing of meat products. Meat Science. 78:68-76.

[IARC] International Agency for Research on Cancer. 1991. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans - Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds. IARC Monogr Carcinog Risks Hum. No. 52.

[IARC] International Agency for Research on Cancer. 2010. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans - Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Carcinog Risks Hum. No. 94.

Jarvis B. 2014. Cider (Cyder; Hard Cider). Encyclopedia of Food Microbiology. Vol. 1. Elsevier Ltd, Academic Press. p. 437-443.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 1996. Toxicological evaluation of certain food additives and contaminants in food prepared by the forty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives. Geneva (CH).

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2003. Intake assessment Nitrate and Nitrite. WHO Food Additive Series 50, Geneva (CH).

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2008. Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 59, Geneva (CH).

Klonne DR, Ulrich CE, Riley MG, Hamm TE, Morgan KT, Barrow CS. 1987. One-year inhalation toxicity study of chlorine in rhesus monkeys (*Macaca mulatta*). Fundam Appl Toxicol. 9(3):557-72.

Krassován K, Kertész Z, Imre K, Gelencsér A. 2015. Indirect evidence for the presence of secondary phosphorus in continental fine aerosol. Aerosol Air Qual. Res 15: 38-45

Lazrus AL, Gandrud BW. 1974. Distribution of stratospheric nitric acid vapor. J Atmos Sci. 31(4):1102-1108.

Library of Parliament. 1998. Acid rain. Ottawa (ON): Library of Parliament, Parliament Canada. [accessed 2019 03 Apr 2019].

[LNHPD] Licensed Natural Health Products Database [database]. [modified 2021 Apr 8]. Ottawa (ON): Government of Canada. [accessed 2021 April 30].

Margiocco C, Arillo A, Mensi P, Schenone G. 1983. Nitrite bioaccumulation in *Salmo gairdneri* Rich. and hematological consequences. Aquat Toxicol. 3(3):261-270.

McCauley PT, Robinson M, Daniel FB, Olsen GR. 1995. The effects of subchronic chlorate exposure in Sprague-Dawley rats. Drug and Chemical Toxicology. 18(2-3):185-199.

Mendiratta SK, Duncan BL. 2003. Chloric Acid and Chlorates. Kirk-Othmer Encyclopedia of Chemical Technology. Vol. 6. New York: Wiley. p. 103-120.

Mirvish S, Wallcave L, Egan M, Shubik P. 1972. Ascorbate-nitrite reaction: possible means of blocking the formation of carcinogenic N-nitroso compounds. Science. 177:65-67.

[NICS] National Institute of Chemical Safety. 2014. Disodium disulphite. Substance evaluation report [PDF]. Budapest (Hungary): National Institute of Chemical Safety. [accessed 2019 Mar 01].

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2021 Jan 15]. Ottawa (ON): Government of Canada. [accessed 2021 April 30].

[NPRI] National Pollutant Release Inventory. 2012-2016 . Gatineau (QC): Government of Canada. [modified 2019 Feb 12; accessed 2018 Nov 15]. Bulk data.

[NTP] National Toxicology Program (US). 1990. Final report on the reproductive toxicity of sodium nitrite (CAS No. 7632-00-0). Research Triangle Park (NC): U.S. Department of Health and Human Services, National Toxicology Program.

[NTP] National Toxicology Program (US). 1992. Toxicology and Carcinogenesis Studies of Chlorinated Water (CAS Nos. 7782-50-5 and 7681-52-9) and Chloraminated Water (CAS No. 10599-90-3) (Deionized and Charcoal-Filtered) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies) [PDF]. Research Triangle Park (NC): U.S. Department of Health and Human Services, National Toxicology Program.

[NTP] National Toxicology Program (US). 2001. Toxicology and Carcinogenesis Studies of Sodium Nitrite in F344/N Rats and B6C3F1 Mice [PDF]. Research Triangle Park (NC): U.S. Department of Health and Human Services, National Toxicology Program.

[NTP] National Toxicology Program (U.S.). 2005. Toxicology and carcinogenesis studies of sodium chlorate (CAS No. 7775-09-9) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park (NC): U.S. Department of Health and Human Services, National Toxicology Program.

[NRC] Natural Resources Canada. [modified 2019 Feb 01]. Explosives regulations – restricted components. Ottawa (ON): Government of Canada. [accessed 2019 Feb 21].

[OECD] Organisation for Economic Co-operation and Development. 2001a. Disodium disulphite. SIDS initial assessment report for SIAM 13 [PDF]. UNEP Publications. [accessed 2019 Apr 02].

[OECD] Organisation for Economic Co-operation and Development. 2001b. Potassium hydroxide. SIDS initial assessment report for SIAM 13 [PDF]. Bern (Switzerland): UNEP Publications. [accessed 2019 Apr 02].

[OECD] Organisation for Economic Co-operation and Development. 2001c. Sulfuric acid. SIDS initial assessment report for SIAM 11 [PDF]. Orlando (FL): UNEP Publications. [accessed 2019 Apr 02].

[OECD] Organisation for Economic Co-operation and Development. 2002a. Hydrogen chloride. SIDS initial assessment report for SIAM 15 [PDF]. Boston (USA): UNEP Publications. [accessed 2019 Apr 02].

[OECD] Organisation for Economic Co-operation and Development. 2002b. Sodium hydroxide. SIDS initial assessment report for SIAM 15 [PDF]. Paris (FR): UNEP Publications. [accessed 2019 Apr 02].

[OECD] Organisation for Economic Co-operation and Development. 2004a. Calcium hypochlorite. SIDS initial assessment report for SIAM 18 [PDF]. Paris (FR): UNEP Publications. [accessed 2019 Feb 22].

[OECD] Organisation for Economic Co-operation and Development. 2004b. Soluble silicates. SIDS initial assessment report for SIAM 18 [PDF]. Paris (FR): UNEP Publications. [accessed 2019 Feb 22].

[OECD] Organisation for Economic Co-operation and Development. 2005. Sodium nitrite. SIDS initial assessment profile for SIAM 20 [PDF]. Paris (FR): OECD. [accessed 2019 Apr 05].

[OECD] Organisation for Economic Co-operation and Development. 2006a. SIDS Initial Assessment Report for SIAM 22: sodium chlorate: CAS No. 7775-09-9. Paris (FR).

[OECD] Organisation for Economic Co-operation and Development. 2006b. SIDS Initial Assessment Report: Category Sodium Chlorite and Chlorine Dioxide: CAS No. 7758-19-2 and 7758-19-2. Jeju (SK).

[OECD] Organisation for Economic Co-operation and Development. 2007. Sodium nitrate, potassium nitrate, potassium sodium nitrate, ammonium nitrate, calcium nitrate fertilizer, calcium ammonium nitrate (CAN), nitrogen solutions (UAN). SIDS initial assessment profile for SIAM 25 [PDF]. Paris (FR): OECD. [accessed 2019 Apr 05].

[OECD] Organisation for Economic Co-operation and Development. 2008a. Bis(hydroxylammonium)sulphate. SIDS initial assessment profile for SIAM 27 [PDF]. Paris (FR): OECD. [accessed 2019 Mar 01].

[OECD] Organisation for Economic Co-operation and Development. 2008b. Nitric acid. SIDS initial assessment profile for SIAM 26 [PDF]. Paris (FR): OECD. [accessed 2019 Feb 22].

[OECD] Organisation for Economic Co-operation and Development. 2008c. Sodium sulfite. SIDS initial assessment profile for SIAM 26 [PDF]. Paris (FR): OECD. [accessed 2019 Feb 22].

[OECD] Organisation for Economic Co-operation and Development. 2009. Phosphoric acid. SIDS initial assessment report [PDF]. [accessed 2019 Apr 04].

Olivieri VP, Snead MC, Krusé CW, Kawata K. 1986. Stability and effectiveness of chlorine disinfectants in water distribution systems. Environ Health Perspect. 69:15-29.

[ON MOE] Ontario Ministry of the Environment. 2007a. Ontario air standards for chlorine dioxide [PDF]. Toronto (ON): ON MOE. [accessed 2019 Feb 25].

[ON MOE] Ontario Ministry of the Environment. 2007b. Ontario air standards for phosphoric acid [PDF]. Toronto (ON): ON MOE. [accessed 2019 Apr 03].

[ON MOE] Ontario Ministry of the Environment. 2007c. Ontario air standards for sulphuric acid [PDF]. Toronto (ON): ON MOE. [accessed 2019 Apr 03].

Opländer C, Römer A, Paunel-Görgülü A, Fritsch T, can Faassen EE, Mürtz M, Bozkurt A, Grieb C, Fuchs P, Pallua N, Suschek CV. 2012. Dermal application of nitric oxide in vivo: Kientics, biological responses, and therapeutic potential in humans. Nature. 91(6):1074-1082.

Orme J, Taylor DH, Laurie RD, Bull RJ. 1985. Effects of chlorine dioxide on thyroid function in neonatal rats. J Toxicol Environ Health. 15(2):312-22.

Pannala AS, Mani AR, Spencer JPE, Skinner V, Richard Bruckdorfer K, Moore KP, Rice-Evans CA. 2003. The effect of dietary nitrate on salivary, plasma, and urinary nitrate metabolism in humans. Free Radic Biol Med. 34(5):576-584.

Paulet G, Desbrousses S. 1972. On the toxicology of chlorine dioxide. Archives des Maladies Professionnelles et de Médecine du Travail. 33:59-61.

Paulet G, Desbrousses S. 1974. Action of a discontinuous exposure to chlorine dioxide (ClO_2) on the rat. Archives des Maladies Professionnelles et de Médecine du Travail. 35 :797-804.

Puckett LJ, Tesoriero AJ, Dubrovsky NM. 2011. Nitrogen contamination of surficial aquifers—a growing legacy. Environ Sci Technol. 45(3):839-844.

Reuss JO, Johnson DW. 1986. Acid deposition and the acidification of soils and waters. Vol 59 of Ecological Studies. New York (NY): Springer-Verlag. 119 p.

Rivett MO, Buss SR, Morgan P, Smith JWN, Bemment CD. 2008. Nitrate attenuation in groundwater: A review of biogeochemical controlling processes. Water Res. 42(16):4215-4232.

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. 2006. Pest Control Products Fact Sheet: to assess the risks for the consumer: updated version for ConsExpo 4 [PDF]. Bilthoven (NL): RIVM. Report No.: 320005002/2006. [accessed 2020 Apr 6].

Ryon MG, Stewart AJ, Kszos LA, Phipps TL. 2002. Impacts on streams from the use of sulfur-based compounds for dechlorinating industrial effluents. Water Air Soil Pollut. 136(1-4):255-268.

Rywotycki R. 2002. The effect of selected functional additives and heat treatment on nitrosamine content in pasteurized pork ham. Meat Science. 60:335-339.

Scatina J, Abdel-Rahman MS, Gerges SE, Alliger H. 1983. Pharmacokinetics of Alcide®, a Germicidal Compound in Rat. J Appl Toxicol. 3(3):150-153.

Scatina J, Abdel-Rahman MS, Gerges SE, Khan YM, Gona O. 1984. Pharmacodynamics of Alcide, a New Antimicrobial Compound, in Rat and Rabbit. Fundamental and Applied Toxicology. 4:479-484.

[SCF] Scientific Committee for Food. 1997. Food – science and techniques. Reports of the Scientific Committee for Food (Thirty-eight series). Nitrates and nitrites (opinion expressed on 22 September 1990). Brussels (BE).

Schins RPF, Emmen H, Hoogendijk L, Borm PJA. 2000. Nasal inflammatory and respiratory parameters in human volunteers during and after repeated exposure to chlorine. Eur Respir J. 16:626-632.

Schumann U, Huntrieser H. 2007. The global lightning-induced nitrogen oxides source. Atmos Chem Phys. 7(14):3823-3907.

[SDS] Safety Data Sheet. 2013. N-O-DOR ® Liquid Odor Oxidizer Part A Concentrate and Activator Solution Part B. Orangeburg (SC): Atsko Inc.

Sen NP, Baddoo PA. 1997. Trends in the Levels of Residual Nitrite in Canadian Cured Meat Products over the Past 25 Years. J. Agri. Food Chem. 45:4714-4718.
Shimada T. 1989. Lack of teratogenic and mutagenic effects of nitrite on mouse foetuses. Arch Environ Health. 44(1):59-63.

Sosiak M. 1994. An overview of water quality in Frank Lake 1990-1993. Edmonton (AB). Alberta Environmental Protection

Statistics Canada. 2004. Canadian Community Health Survey (CCHS)—Cycle 2.2: Nutrition. Share File. Ottawa (ON). Canada. Estimates generated using SAS 9.3 [GRID] through SAS EG 5.1.

Statistics Canada. 2015. Canadian Community Health Survey (CCHS) 2015 Share File. Ottawa, ON. Canada. Estimates generated using SAS 9.3 [GRID] through SAS EG 5.1.

Stewart DJ, Taylor CM, Reeves CE, McQuaid JB. 2008. Biogenic nitrogen oxide emissions from soils: impact on NOx and ozone over west Africa during AMMA (African Monsoon Multidisciplinary Analysis): observational study. Atmos Chem Phys. 8(9):2285-2297.

Strittholt CA, McMillan DA, He T, Baker RA, Barker ML 2016. A randomized clinical study to assess ingestion of dentrifrice by children. Regulatory Toxicology and Pharmacology 75: 66-71.

[TDS] Canadian Total Diet Study. 2000–2001. Ottawa and St. John's. Concentrations of Nitrite and Nitrate in Food Composites. Food Research Division, Bureau of Chemical Safety, Food Directorate. Ottawa (ON). [accessed 2019].

Tsunogai S. 1971. Oxidation rate of sulfite in water and its bearing on the origin of sulfate in meteoric precipitation. Geochem J. 5(4):175-185.

Urbansky ET, Brown SK, Magnuson ML, Kelty CA. 2000. Perchlorate levels in samples of sodium nitrate fertilizer derived from Chilean caliche. Environ Pollut. 112(2001):299-302.

[U.S. EPA] United States Environmental Protection Agency. 1991. Reregistration Eligibility Document: Inorganic nitrate/nitrite (sodium and potassium nitrates) (Case 4052) [PDF]. Washington (DC): U.S. EPA, Office of Pesticide Programs. [accessed 2019 Apr 05].

[U.S. EPA] United States Environmental Protection Agency. Revised 1991. Integrated Risk Information System (IRIS) Chemical Assessment Summary Nitrate; CASRN 14797-55-8. U.S. EPA, National Center for Environmental Assessment.

[U.S. EPA] United Sates Environmental Protection Agency. 1999. Reregistration Eligibility Decision (RED) for Chlorine Gas [PDF]. U.S. EPA, Office of Prevention, Pesticides and Toxic Substances.

[U.S. EPA] United States Environmental Protection Agency. 2006a. Reregistration Eligibility Decision (RED) for Chlorine Dioxide and Sodium Chlorite, Case No. 4023 [PDF]. U.S. EPA, Office of Prevention, Pesticides and Toxic Substances.

[U.S. EPA] United States Environmental Protection Agency. 2006b. Reregistration Eligibility Decision Document (RED) for Inorganic chlorates [PDF]. U.S. EPA, Office of Prevention, Pesticides and Toxic Substances.

[U.S. EPA] United States Environmental Protection Agency. 2006c. Revised Inorganic Chlorates. HED Chapter of the Reregistration Eligibility Decision Document (RED). U.S. EPA, Office of Prevention, Pesticides and Toxic Substances.

[U.S. EPA] United States Environmental Protection Agency. 2006d. Chlorine Dioxide Final Risk Assessment. U.S. EPA, Office of Pesticide Programs.

[U.S. EPA] United States Environmental Protection Agency. 2007. Potassium silicate [PDF]. U.S. EPA Office of Pesticide Programs. [accessed 2019 Feb 22].

[U.S. EPA] United States Environmental Protection Agency. 2011. Chapter 6: Inhalation rates. Exposure Factors Handbook 2011 Edition (Final). U.S. Environmental Protection Agency: Washington, DC. EPA/600/R-09/052F.

[U.S. EPA] United States Environmental Protection Agency. 2012. Standard operating procedure for residential exposure and risk assessment of pesticides. [accessed 2019 May 9].

[U.S. EPA] United States Environmental Protection Agency. 2016. Six-Year Review 3 Technical Support Document for Chlorate [PDF]. U.S. EPA Office of Water. [accessed 2019 Feb 15].

[U.S. EPA] United States Environmental Protection Agency. 2018. 2018 Edition of the Drinking Water Standards and Health Advisories Tables. [PDF] U.S. EPA, Office of Water. [amended March 2018].

Vermeer ITM, Pachen DMFA, Dallinga JW, Kleinjans JCS, van Maanen JMS. 1998. Volatile N-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. Environ. Health Perspect. 106(8):459-463.

Vymazel, J., 2007. Removal of nutrients in various types of constructed wetlands. Sci. Total Environ. 380, 48-65

White CW, Martin JG. 2010. Chlorine gas inhalation: human clinical evidence of toxicity and experience in animal models. Proc Am Thorac Soc. 7(4):257-263.

[WHO] World Health Organization. 2002. Concise International Chemical Assessment Document 37 [PDF]. Chlorine Dioxide (Gas). Geneva (CH). ISBN 9241530375.

[WHO] World Health Organization. 2003. Chlorine in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality [PDF]. Geneva (CH): WHO. [accessed 2019 May 13].

[WHO] World Health Organization. 2011. Nitrate and nitrite in drinking water [PDF]. Geneva (Switzerland): WHO. [accessed 2019 Apr 05].

[WHO] World Health Organization. 2016. Chlorine dioxide, chlorite and chlorate in drinking-water [PDF]. Geneva (Switzerland): WHO. [accessed 2019 Apr 17].

[WHO] World Health Organization. 2019. GEMS/Food Contaminants database, Global Environment Monitoring System - Food Contamination Monitoring and Assessment Programme.

[Wilson and Meridian] Wilson Scientific Consulting Inc. and Meridian Environmental Inc. 2015 modified. Critical review of soil ingestion rates for use in contaminated site human health risk assessments in Canada. Contractor report prepared for the Contaminated Sites Division, Safe Environments Programme, Health Canada: Ottawa (ON).

Wolf DC, Morgan KT, Gross EA< Barrow C, Moss OR, James RA, Popp JA. 1995. Two-year inhalation exposure of female and male B6C3F1 mice and F344 rats to chlorine gas induces lesions confined to the nose. Fundamental and Applied Toxicology. 24: 111-131.

Zhu D, Ryan MC, Gao H. 2019. The role of water and mass balances in treatment assessment of a flooded natural wetland receiving wastewater effluent (Frank Lake, Alberta, Canada). Ecol. Eng. 137, pp. 34-45.

Zwart A, Woutersen RA. 1988. Acute inhalation toxicity of chlorine in rats and mice: Time-concentration-mortality relationships and effects on respiration. J Hazard Mater. 19:195-208.

Appendix A. Substances and approaches used in this screening assessment

Table A-1. List of substances and approaches used in this screening assessment

Substance subgroup	CAS RN	Common name	Ecological approach	Human health approach
Ammonia	5470-11-1[a]	Hydroxylammonium chloride	NA[b]	Rapid screening of substances with limited general population exposure
Free available chlorine, chlorate and chlorite	7775-09-9	Sodium chlorate	NA[b]	Quantitative
Free available chlorine, chlorate and chlorite	10049-04-4	Chlorine dioxide	NA[b]	Quantitative
Free available chlorine, chlorate and chlorite	7681-52-9	Sodium hypochlorite	NA[b]	Low human health hazard potential
Free available chlorine, chlorate and chlorite	7778-54-3	Calcium hypochlorite	NA[b]	Low human health hazard potential
Free available chlorine, chlorate and chlorite	7782-50-5	Chlorine	NA[b]	Quantitative
Sulphite	7631-90-5	Sodium bisulfite	Qualitative	Low human health hazard potential
Sulphite	7681-57-4	Sodium metabisulfite	Qualitative	Low human health hazard potential

Substance subgroup	CAS RN	Common name	Ecological approach	Human health approach
Hydrogen and hydroxide	1310-58-3	Potassium hydroxide	Qualitative	Low human health hazard potential
Hydrogen and hydroxide	1310-73-2	Sodium hydroxide	Qualitative	Low human health hazard potential
Hydrogen and hydroxide	1312-76-1	Potassium silicate	Qualitative	Low human health hazard potential
Hydrogen and hydroxide	1344-09-8	Sodium silicate	Qualitative	Low human health hazard potential
Hydrogen and hydroxide	7647-01-0	Hydrochloric acid	Qualitative	Low human health hazard potential
Hydrogen and hydroxide	7664-93-9	Sulphuric acid	Qualitative	Low human health hazard potential
Hydrogen and hydroxide	12136-45-7	Potassium oxide	Qualitative	Low human health hazard potential
Phosphate	1314-56-3	Diphosphorus pentoxide	Qualitative	Low human health hazard potential
Phosphate	7664-38-2	Phosphoric acid	Qualitative	Low human health hazard potential
Nitrate and nitrite	7631-99-4	Sodium nitrate	Quantitative	Quantitative
Nitrate and nitrite	7632-00-0	Sodium nitrite	Quantitative	Quantitative
Nitrate and nitrite	7697-37-2	Nitric acid	Qualitative	Quantitative

Substance subgroup	CAS RN	Common name	Ecological approach	Human health approach
Nitrate and nitrite	7757-79-1	Potassium nitrate	Quantitative	Quantitative
Nitrate and nitrite	10124-37-5	Calcium nitrate	Quantitative	Quantitative

Abbreviation: NA, Not Applicable
[a] Did not meet criteria under subsection 73 (1); was considered a priority of the basis of other human health concerns.
[b] These substances are considered to have been addressed previously for ecological concerns through Priority Substances List assessment reports.

The following substances were assessed using the Low Human Health Hazard Potential Approach (Table A-2). For eleven substances, details and studies used to support these decisions are available in the Science Approach Document for Substances with Low Human Health Hazard Potential (Health Canada [modified 2017]). For sodium and calcium hypochlorite, these details can be found in Appendix C.

Table A-2. Summary of hazard findings for the 13 substances addressed using the Low Human Health Hazard Potential Approach

CAS RN	Common name	CMR[a]	Decision point 1: Does the substance cause any health effects up to Limit Dose (1000 mg/kg bw/day)?	Decision point 2: Does the substance cause serious effects between 100 and 1000 mg/kg bw/day?
7681-52-9	Sodium hypochlorite	No	No	No
7778-54-3	Calcium hypochlorite	No	No	No
7631-90-5	Sodium bisulfite	No	No	No
7681-57-4	Sodium metabisulfite	No	No	No
1310-58-3	Potassium hydroxide	No	No	No
1310-73-2	Sodium hydroxide	No	No	No
1312-76-1	Potassium silicate	No	No	No
1344-09-8	Sodium silicate	No	No	No
7647-01-0	Hydrochloric acid	No	No	No
7664-93-9	Sulphuric acid	No	No	No
12136-45-7	Potassium oxide	No	No	No
1314-56-3	Diphosphorus pentoxide	No	No	No
7664-38-2	Phosphoric acid	No	No	No

Abbreviations: CMR: carcinogenic, mutagenic, or toxic to reproduction
[a] Identified on the basis of classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity for the oral route of exposure which is considered to be most relevant for general population exposure

Appendix B. Physico-chemical properties

Table B-1. Physico-chemical properties of the 22 substances in the Acids and Bases Group

Subgroup	CAS RN	Common name (Molecular formula)	pK_a	Water solubility (g/L)	Vapour pressure (mmHg)
Ammonia	5470-11-1	Hydroxylammonium chloride (ClH_4NO)	N/A	340[b]	2×10^{-5} (at 20˚C)[b]
Free available chlorine, chlorate and chlorite	7775-09-9	Sodium chlorate ($NaClO_3$)	N/A	696-736 (at 20˚C)[b]	N/A
Free available chlorine, chlorate and chlorite	10049-04-4	Chlorine dioxide)	N/A	3.01 (at 25˚C)[c]	758 (at 20˚C)[c]
Free available chlorine, chlorate and chlorite	7778-54-3	Calcium hypochlorite ($CaCl_2O_2$)	N/A	210 (at 25˚C)[d]	N/A
Free available chlorine, chlorate and chlorite	7681-52-9	Sodium hypochlorite ($NaClO$)	N/A	293 (at 0˚C)[e]	13-15 (at 20˚C)[m]
Free available chlorine, chlorate and chlorite	7782-50-5	Chlorine (Cl_2)	N/A	9.78 (at 10˚C)[b]	5 085 (at 20˚C)[b]
Sulphite	7681-57-4	Sodium metabisulfite ($Na_2O_5S_2$)	N/A	667 (at 25˚C)[b]	N/A
Sulphite	7631-90-5	Sodium bisulfite ($HNaO_3S$)	N/A	724 (at 20˚C)[b]	N/A

Subgroup	CAS RN	Common name (Molecular formula)	pK_a	Water solubility (g/L)	Vapour pressure (mmHg)
Hydrogen and hydroxide	7664-93-9	Sulphuric acid (H_2SO_4)	-2[a] (pK_{a1}); 1.92[a] (pK_{a2})	Miscible[f]	5 x 10^{-5} (at 25˚C)[f]
Hydrogen and hydroxide	7647-01-0	Hydrochloric acid (HCl)	-7[a]	724.7 (at 20˚C)[b]	34 652 (at 25˚C)[b]
Hydrogen and hydroxide	1310-58-3	Potassium hydroxide (KOH)	Strong base (~14)	1 000 (at 25˚C)[b]	N/A
Hydrogen and hydroxide	1310-73-2	Sodium hydroxide (NaOH)	Strong base (~14)	1 000 (at 25˚C)[b]	N/A
Hydrogen and hydroxide	12136-45-7	Potassium oxide (K_2O)	Strong base (~14)	1 000 (at 25˚C)[b]	N/A
Hydrogen and hydroxide	1312-76-1	Potassium silicate (HKO_3Si)	9.9-12 (at 30˚C)[b]	Slightly soluble[g]; dissolves slowly (anhydrous solid)[b]; dissolves readily (spray-dried solutions)[b]; miscible (solutions)[b]; 336 (at 25˚C)[n]	N/A
Hydrogen and hydroxide	1344-09-8	Sodium silicate ($HNaO_3Si$)	9.9-12 (at 30˚C)[b]	Slightly soluble[g]; dissolves slowly (anhydrous solid)[b]; dissolves readily (spray-dried solutions)[b]; miscible (solutions)[b]	N/A

Subgroup	CAS RN	Common name (Molecular formula)	pK_a	Water solubility (g/L)	Vapour pressure (mmHg)
Phosphate	7664-38-2	Phosphoric acid (H_3PO_4)	2.12[a] (pK_{a1}); 7.21[a] (pK_{a2}); 12.67[a] (pK_{a3});	1 000 (at 20˚C)[b]	0.03 (at 20˚C)[b]
Phosphate	1314-56-3	diphosphorus oxide (P_2O_5)	N/A	Reacts with water to form phosphoric acid[i]	N/A
Nitrate and nitrite	7632-00-0	Sodium nitrite ($NaNO_2$)	N/A	848 (at 25˚C)[j]	N/A
Nitrate and nitrite	7757-79-1	Potassium nitrate (KNO_3)	N/A	383 (at 25˚C)[k]	N/A
Nitrate and nitrite	7697-37-2	Nitric acid (HNO_3)	-1.38-0[b]	>500 (at 20˚C)[b]	47 (at 20˚C)[b]
Nitrate and nitrite	7631-99-4	Sodium nitrate ($NaNO_3$)	N/A	912 (at 25˚C)[l]	N/A
Nitrate and nitrite	10124-37-5	Calcium nitrate ($Ca(NO_3)_2$)	N/A	>100[b]	N/A

Abbreviations: N/A, Not Available.
[a] Atkins (1978). [b] ECHA (2007-). [c] HSDB (1983c-). [d] HSDB (1983d-). [e] HSDB (1983e-). [f] HSDB (1983f-). [g] HSDB (1983g-). [h] HSDB (1983h-). [i] HSDB (1983i-). [j] HSDB (1983j-). [k] HSDB (1983k-). [l] HSDB (1983l-). [m] EU (2007b). [n] U.S. EPA (2007).

Appendix C. Results of the Low Human Health Hazard Potential Approach for sodium hypochlorite and calcium hypochlorite

Oral intake for the general Canadian population is expected to be the primary route of exposure to hypochlorous acid, sodium salt (CAS RN 7681-52-9) and hypochlorous acid, calcium salt (CAS RN 7778-54-3). Sodium and calcium salts of hypochlorous acid are evaluated as a group because both substances dissociate into hypochlorous acid in water. Hypochlorous acid cannot be tested up to a limit dose of 1000 mg/kg bw/day due to taste aversion at high concentrations in drinking water. Health Canada's drinking water quality program did not consider it necessary to establish a guideline for chlorine in drinking water, based on its low toxicity at concentrations found in drinking water as a result of treatment (Health Canada 2009). Based on available information and conclusions from international organizations, hypochlorous acid is negative for carcinogenicity, mutagenicity and reproductive/developmental toxicity. In repeated-dosing studies, there were no serious effects up to 14.4 mg/kg bw/day (NTP 1992). Therefore, hypochlorous acid is considered to be of low concern for human health according to the hazard-based approach (Health Canada 2009; NTP 1992).

Table C-1. Hazard summary for sodium hypochlorite (CAS RN 7681-52-9) and calcium hypochlorite (CAS RN 7778-54-3)

Primary route of exposure	**Oral**
Grouping rationale	Sodium hypochlorite and calcium hypochlorite are evaluated as a group because both substances generate hypochlorous acid in water (Health Canada 2009).
Carcinogenicity	Negative. Health Canada (2009) classified chlorine, in the form of hypochlorite ion or hypochlorous acid, as unlikely to be carcinogenic to humans.
Mutagenicity	Both positive and negative results have been reported in mutagenicity assays (EU 2007b; Health Canada 2009). Health Canada (2009) concluded that the results of the mutagenicity tests indicate that sodium hypochlorite is not considered to be genotoxic.
Reproductive and developmental toxicity	Negative. There is no evidence to suggest that sodium hypochlorite would present adverse effects on development or fertility (Health Canada 2009).
Repeated-dose toxicity	No systemic effects observed up to 14.4 mg/kg bw/day via the oral route of administration in a two-year repeated-dose study in rats (NTP 1992). Decreases in body weight following treatment with the highest doses tested were attributed to secondary effect linked with low water consumption, most likely due to aversion to the taste of high levels of hypochlorous acid in drinking water (Health Canada 2009).

Appendix D. Intake estimates from environmental media and food for nitrate and nitrite subgroup

For each food and beverage category for which data were reported in the TDS (2000-2001), the highest concentration was conservatively applied to represent the entire category. In the absence of available Canadian data, the nitrate and nitrite concentrations in food reported in assessments by EFSA (EFSA 2008, EFSA 2017a, EFSA 2017b), the GEMS/Food Database (WHO 2019), or submitted by the U.S. to the Codex Committee on Food Additives of the Codex Alimentarius Commission were

considered. In these instances, for each food and beverage category, the highest concentration reported by the U.S. was employed when available, or when not, the 95th percentile concentration reported by EFSA, or in the GEMS/Food database was conservatively applied to represent the entire food category.

Food consumption was based on individual one-day "all-persons" food intakes reported by respondents to the 2004 Canadian Community Health Survey (CCHS) for 6 to 11 month-olds[17] and the 2015 CCHS for all other age groups (Statistics Canada 2004 and 2015). No infant respondents in the CCHS were reported to consume foods permitted to contain nitrate or nitrite salts as food additives.

Table D-1. Mean and 90th percentile dietary exposure estimates to nitrate

Age group (males and females)	Mean dietary exposure from all sources (mg/kg bw/day)	90th Percentile dietary exposure from all sources (mg/kg bw/day)	Mean dietary exposure from food additive use (mg/kg bw/day)	90th Percentile dietary exposure from food additive use (mg/kg bw/day)	Food additive contribution to mean exposure from all sources (%)
0 to <6 months, breast milk fed	0.79	0.94	0.00	0.00	0
0 to <6 months, formula fed	0.79	1.24	0.00	0.00	0
6 months to 1 year	4.08	11.23	0.03	0.04	0.65
1 to 3 years	7.63	15.15	0.06	0.12	0.81
4 to 8 years	6.49	16.76	0.06	0.15	0.90
9 to 13 years	3.90	9.60	0.04	0.11	0.96
14 to 18 years	2.97	7.33	0.02	0.07	0.82
19 + years	3.46	8.88	0.02	0.04	0.48

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Table D-2. Mean and 90th percentile dietary exposure estimates to nitrite

[17] The 2015 CCHS did not include children under 1 year of age.

Age group (males and females)	Mean dietary exposure from all sources (mg/kg bw/day)	90th Percentile dietary exposure from all sources (mg/kg bw/day)	Mean dietary exposure from food additive use (mg/kg bw/day)	90th Percentile dietary exposure from food additive use (mg/kg bw/day)	Food additive contribution to mean exposure from all sources (%)
0 to <6 months, breast fed	0.02	0.24	0.00	0.00	0.0
0 to <6 months, formula fed	0.34	0.53	0.00	0.00	0.00
6 months to 1 year	1.27	3.90	0.02	0.05	1.73
1 to 3 years	4.69	12.64	0.05	0.12	1.11
4 to 8 years	4.34	11.83	0.04	0.11	0.95
9 to 13 years	2.47	6.47	0.03	0.07	1.07
14 to 18 years	1.83	4.70	0.02	0.05	1.01
19 + years	2.32	5.96	0.01	0.03	0.52

Table D-3. Derivation of estimated NO_3 soil concentrations from residual nitrogen levels in agricultural soil

Residual nitrogen levels (kg N/ha)[a]	Density (g/cm^3)	Furrow slice (cm)	Residual nitrogen concentration (mg N/kg)	Molecular weight conversion	Estimated NO_3 concentration in soil (mg/kg)[b]
17.8	1.5	15	7.9	$\frac{62.0049 \frac{g}{mol} NO_3}{14 \frac{g}{mol} N}$	35.037

[a] Residual nitrogen levels from Drury et al. (2011).
[b] Concentration was estimated using the following equation: residual nitrogen levels (kg N/ha) * ha/10 000 m^2 * m^2/10 000 cm^2 * density (g/cm^3) * furrow slice (cm) * 1 000 000 mg/kg *1 000 g/kg * molecular weight conversion.

Table D-4. Estimates of daily intake of nitrate from environmental media and food (µg/kg bw/day)

Age groups	Food additive use[a]	Air[b]	Drinking water[c]	Soil and dust[d,e]	Combined intake[f]
0 to 5 months[g] (breast milk-fed[h])	0	0.52	NA	0.12	**0.64**
0 to 5 months (formula fed[i])	0	0.52	NA	0.12	**0.64**
6 to 11 months[j]	30	0.52	319	0.13	**350**
1 year[k]	60	0.64	124	0.14	**185**
2 to 3 years[l]	60	0.54	109	0.06	**170**
4 to 8 years[m]	60	0.43	88	0.05	**148**
9 to 13 years[n]	40	0.29	67	0.03	**107**
14 to 18 years[o]	20	0.23	67	0.002	**87**
19+ years[p]	20	0.18	79	0.002	**99**

Abbreviations: NA, not applicable

[a] Intake is equal to the mean dietary exposure from food additive use for all age groups from Table D-1.

[b] Intake was estimated using a concentration of 0.88 µg/m^3 in ambient air (Health Canada 2013). Ambient air was assumed to be representative of exposure to indoor air since there is no indication of additional source of nitrate in indoor environments (Health Canada 1998).

[c] Intake was estimated using a concentration of 3.8 mg/L in treated drinking water (Health Canada 2013).

[d] Intake for soil was estimated using a concentration of 35 mg/kg derived from residual nitrogen levels in Canada (see Table D-3, Appendix D).

[e] Intake for dust was estimated using soil concentration as a surrogate, as dust concentrations were not identified in the literature.

[f] Combined intake (µg/kg bw/d) represents intake from food additive use, air, drinking water, soil and dust.

[g] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (U.S. EPA 2011 [modified]), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[h] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018a), and breast milk is assumed to be the only dietary source.

[i] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018a), where water is used to reconstitute formula. See footnote on drinking water for details.

[j] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 0.764 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[l] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[m] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[n] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[o] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[p] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (U.S. EPA 2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

Table D-5. Estimates of daily intake of nitrite from food and drinking water (µg/kg bw/day)

Age groups	Food additive use[a]	Drinking water[b]	Combined intake
0 to 5 months[c] (breast milk-fed[d])	0	NA	0
0 to 5 months[c] (formula fed[e])	0	NA	0
6 to 11 months[f]	20	4	24
1 year[g]	50	2	52
2 to 3 years[h]	50	1	51
4 to 8 years[i]	40	1	41
9 to 13 years[j]	30	1	31
14 to 18 years[k]	20	1	21
19+ years[l]	10	1	11

Abbreviations: N/A, not applicable

[a] Intake is equal to the mean dietary exposure from food additive use for all age groups from Table D-2.

[b] Intake was estimated using a concentration of 0.05 mg/L in treated drinking water (Health Canada 2013).

[c] Assumed to weigh 6.3 kg (Health Canada 2015).

[d] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018a), and breast milk is assumed to be the only dietary source.

[e] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018a), where water is used to reconstitute formula.

[f] Assumed to weigh 9.1 kg (Health Canada 2015) and to drink 0.764 L of water per day (Health Canada 2017).

[g] Assumed to weigh 11.0 kg (Health Canada 2015) and to drink 0.36 L of water per day (Health Canada 2017).

[h] Assumed to weigh 15 kg (Health Canada 2015) and to drink 0.43 L of water per day (Health Canada 2017).

[i] Assumed to weigh 23 kg (Health Canada 2015) and to drink 0.53 L of water per day (Health Canada 2017).

[j] Assumed to weigh 42 kg (Health Canada 2015) and to drink 0.74 L of water per day (Health Canada 2017).

[k] Assumed to weigh 62 kg (Health Canada 2015) and to drink 1.09 L of water per day (Health Canada 2017).

[l] Assumed to weigh 74 kg (Health Canada 2015) and to drink 1.53 L of water per day (Health Canada 2017).

Appendix E. Intake estimates from the use of products

Sentinel exposure scenarios were used to estimate exposure to substances in the Acids and Bases Group from use of products. Assumptions for each scenario are summarized in Table E-1. Exposures were estimated using ConsExpo Web and default model parameters unless otherwise noted (ConsExpo Web [modified 2019 Feb 13]). Estimates are based on the weight (74 kg) of an adult (Health Canada 2019). Table E-2 summarizes the calculation of the relative bioavailable fraction for chlorine dioxide.

Table E-1. Sentinel exposure scenario parameter assumptions

Exposure scenario	**Assumptions**
Substance: sodium chlorate Dermal and inhalation exposure via cleaning kitchen counter (chronic) Reference: Cleaning Products Fact Sheet: All-purpose cleaning spray (ConsExpo Web [modified 2019])	Frequency: 365 / year <u>Dermal during pouring</u> Model: direct product contact Loading: instant application Undiluted concentration: 0.43% Product amount (g): 0.53 Absorption fraction: 0.1 <u>Inhalation during spraying</u> Model: Exposure to spray Mode of release: spraying (non-volatiles) Spray duration (min): 0.23 Exposure duration (min): 60 Diluted concentration: 0.014% (0.43% sodium chlorate in 120mL product diluted in 3.8L water) Room volume (m^3): 15 Room height (m): 2.5 Ventilation rate (/hr): 2.5 Inhalation rate (m^3/day): 15.1 (Health Canada 2019) Mass generation rate (g/sec): 1.6 Airborne fraction: 0.006 Density non-volatile (g/cm^3): 1 Inhalation cut-off (µm): 10 Aerosol diameter distribution type: log-normal Median diameter (µm): 2.4 Coefficient of variation: 0.37 Maximum diameter (µm): 50 Absorption fraction: 1 <u>Dermal during spraying</u> Model: direct product contact Exposed area (cm^2): 225 Loading: constant rate Diluted concentration: 0.014% (0.43% sodium chlorate in 120mL product diluted in 3.8L water) Contact rate (mg/min): 46 Release duration (min): 0.46 Absorption fraction: 0.1 <u>Dermal during wiping</u> Model: Direct product contact Loading: instant application Exposed area (cm^2): 225 Diluted concentration: 0.014% (0.43% sodium chlorate in 120mL product diluted in 3.8L water) Product amount (g): 0.31 Absorption fraction: 0.1

Exposure scenario	Assumptions
	Total combined exposure (mg/kg bw/day) = inhalation during spraying (mg/kg bw/day) + dermal during pouring (mg/kg bw/d) + dermal during spraying (mg/kg bw/day) + dermal during wiping (mg/kg bw/day) Note: Even though this is a concentrated product, it is assumed that a consumer could create a diluted solution in a ready-to-use trigger bottle; therefore, exposure during pouring of the concentrated product into a trigger bottle is also estimated.
Substance: sodium chlorate Dermal exposure from hand-washing laundry (per event) Reference: Cleaning and Washing Factsheet: hand-washing laundry detergents (ConsExpo Web [modified 2019])	Frequency: 1 / week <u>Inhalation</u>: Vapour pressure negligible at room temperature; therefore, considered non-volatile. <u>Dermal</u> Undiluted concentration: 0.43% Product amount during pouring (g): 0.53 (pouring with caps) Product amount during washing (g): 0.154 (based off diluted product concentration of 7 g/L (label information) * 22mL in contact with skin (ConsExpo Web [modified 2019])) Product amount during hanging (g): 0.063 (based off diluted product concentration of 7g/L (label information) * 9mL in contact with skin (ConsExpo Web [modified 2019])) Absorption fraction: 0.1 Total exposure (mg/kg bw/day) = exposure-pouring (mg/kg bw/day) + exposure-washing (mg/kg bw/day) + exposure-hanging (mg/kg bw/d)
Substance: sodium chlorate Dermal exposure from cleaning floor (chronic) Reference: Cleaning Products Factsheet: floor, carpet and furniture products (ConsExpo Web [modified 2019])	<u>Inhalation</u>: Vapour pressure negligible at room temperature; therefore, considered non-volatile. <u>Dermal</u> Frequency: 161 / year Undiluted concentration: 0.43% Product amount during pouring (g): 0.01 (direct pouring) Product amount during cleaning (g): 0.69 (based off diluted product concentration of 31.5 g/L (label information) * 22mL in contact with skin (ConsExpo Web [modified 2019])) Absorption fraction: 0.1 Total exposure (mg/kg bw/day) = exposure during pouring (mg/kg bw/day) + exposure during cleaning (mg/kg bw/day)
Substance: sodium chlorate	<u>Dermal</u> *Exposure (mg/kg bw/d) = [deposited residue (mg/cm^2) * fraction available for transfer (%) * transfer coefficient*

Exposure scenario	**Assumptions**
Dermal and oral exposure via post-application exposure to floor cleaning (chronic) Reference: U.S. EPA 2012	*(cm^2/hr) * exposure time (hr) * dermal absorption fraction]/body weight (kg)* Deposited residue (mg/cm^2): 0.00054 (assuming [0.04L solution/m^3 of floor * 31.5 g/L of product * weight fraction (0.0043) * 1000 mg/g * 1 m^2/10 000cm^2) Fraction available for transfer: 0.08 Transfer coefficient (cm^2/hr): 1927 (derived on the basis of the adult transfer coefficient (6800 cm^2/hr) adjusted for body surface of a 1 year old (5300 cm^2/18700cm^2 = 0.28) (U.S. EPA 2011 (1 year old surface area); Health Canada 2019) Exposure time (hr): 2 Absorption fraction: 0.1 Body weight (kg): 11 (based on default HC body weight for a 1 year old) (Health Canada 2015) <u>Hand-to-mouth oral exposure</u> *Dose = hand residue (mg/cm^2) * (Fraction mouthed * SAh (cm^2)) * (ET (hr/d) * N Replen (N/hr)) * (1 – [1-SE]^(Freq [/hr]/N Replen [N/hr]) / BW (kg)* Hand residue (mg/cm^2): 0.000084 (based on: fraction of active ingredient on hands compared to total surface residue [0.15] * dermal exposure [0.16 mg] (from above) / surface area of one hand [150 cm^2] * 2) Fraction mouthed: 0.13 (fraction of hand mouthed per event) Surface Area of hand (cm^2): 150 Exposure Time (hr/d): 2 Number of Replenishments (/hr): 4 Saliva Extraction factor: 0.48 Frequency of hand to mouth events (/hr): 20 Body weight (kg): 11 (based on a 1 year old child) (Health Canada 2015) Total combined exposure = dermal exposure (mg/kg bw/d) + hand-to-mouth oral exposure (mg/kg bw/d)
Substance: sodium chlorate Dermal exposure via bubble bath (chronic)	Concentration fraction: 0.01 Product amount (g): 27 (Ficheux et al. 2016) Frequency (/day): 0.38 (Ficheux et al. 2015) Retention factor: 0.001 Dermal absorption fraction: 0.1 Body weight (kg): 62 (age 14 to 18 year olds) (Health Canada 2015)
Substance: chlorine dioxide Ophthalmic exposure via moisturizing lubricant eye drop (chronic)	*Exposure (mg/kg bw/d) = volume drop (mL/drop) * concentration (mg/mL) * frequency (drops/day) * retention factor / body weight (kg)* Frequency (drops/day): Up to 8 (2 per eye, twice per day) (based on professional judgement; ECCC, HC 2019)

Exposure scenario	**Assumptions**
References: ECCC,HC 2019; Farkouh et al. 2016	Concentration (mg/mL): 0.05 Volume (mL/drop): 0.01 (based on maximum capacity of the conjunctival sac of 10 µL (Farkouh et al. 2016)) Retention factor: 1 Body weight (kg): 74 (Health Canada 2015)
Substance: chlorine dioxide Inhalation exposure via hunting spray (per event) Reference: ConsExpo Web [modified 2019 Feb]	Dermal: due to the substance's high volatility and low relative oral to dermal bioavailability; inhalation was determined to be the predominant route of exposure Inhalation Model: exposure to spray Mode of release: instantaneous release Exposure duration (min): 5 (based on professional judgement) Released mass (g): 1.102 [Dermal loading (mg/cm^2) * Surface area (cm^2)] Dermal loading (mg/cm^2): 0.53 (estimated from RIVM 2006; U.S. EPA 2012) Surface area (cm^2): 2080 (head and hands) (Health Canada 2019) Weight fraction substance: 0.01 (1% chlorine dioxide) Room volume (m^3): 10 (assumed based on immediate proximity) Ventilation rate (/hr): 5 (higher ventilation rate is assumed based on spraying outdoors) Inhalation rate (m^3/day): 15.1 (Health Canada 2019) Time-weighted average*: Mean event concentration (mg/m^3): 0.9 Exposure time (hr): 0.083 Exposure duration (hr): 5 Adjusted concentration (mg/m^3): 0.015 *A time weighted average (TWA) was calculated on the basis of: adjusted concentration (mg/m^3) = [mean event concentration (mg/m^3) * exposure time (hr)] / exposure duration (hr)
Substance: nitrate Oral exposure to non-fluorinated toothpaste (chronic)	Concentration fraction: 0.036 nitrate ion (based off 6% of potassium nitrate) Product amount (mg/application): 210 (for a child age 2 to 3 years old; Strittholt et al. 2016) Frequency (/day): 2.9 (for a child age 2 to 3 years old; Ficheux et al. 2015) Oral absorption fraction: 1 Body weight (kg): 15 (child aged 2 to 3 years old) (Health Canada 2015)
Substance: nitrate	Amount of nitrate (mg/capsule): 30 to 130 Frequency (/day): 2 to 6 Absorption fraction: 1

Exposure scenario	Assumptions
Oral exposure via natural health product (chronic)	Body weight (kg): 74 (Health Canada 2015)
Substance: nitrate Dermal exposure to caustic applicator (per event)	*Exposure (mg/kg bw/d) = volume (mL) * density (g/mL) * weight fraction nitrate ion * conversion factor (1000 mg/1 g) * frequency (/day) * dermal absorption fraction / body weight (kg)* Weight fraction: 0.153 (nitrate ion) (molecular weight nitrate ion (62 g/mol) / molecular weight potassium nitrate (101.1 g/mol) x concentration potassium nitrate in product (0.25)) Concentration potassium nitrate in product: 25% (AMGMedical 1997-2021) Volume (mL): 0.0634 (water used to moisten tip assumed similar volume as eye drop; German et al. 1999) Density (g/mL): 1 (density of water) Frequency: 1 (AMGMedical 1997-2021) Absorption fraction: 1 Body weight (kg): 74 (Health Canada 2015)
Substance: nitrite Inhalation exposure via cleaning spray (chronic) Reference: Cleaning Products Fact Sheet: All-purpose cleaning spray (ConsExpo Web [modified 2019])	<u>Inhalation during spraying</u> Model: Exposure to spray Mode of release: spraying (non-volatiles) Spray duration (min): 0.23 Exposure duration (min): 60 Substance concentration: 0.379% (sodium nitrite) Room volume (m^3): 15 Room height (m): 2.5 Ventilation rate (/hr): 2.5 Inhalation rate (m^3/day): 15.1 (Health Canada 2019) Mass generation rate (g/sec): 1.6 Airborne fraction: 0.006 Density non-volatile (g/cm^3): 1 Inhalation cut-off (µm): 10 Aerosol diameter distribution type: log-normal Median diameter (µm): 2.4 Coefficient of variation: 0.37 Maximum diameter (µm): 50 Absorption fraction: 1

Table E-2. Relative bioavailable fraction for dermal exposure for chlorine dioxide

Equation	Parameters
From the OECD (2010) and (2011) guidance documents: $F = \frac{AUC_D}{AUC_O} * \frac{Dose_O}{Dose_D}$	Where; F = relative bioavailable fraction AUC_D = area under the curve for the dermal study (66 µg/ml*hr) AUC_O = area under the curve for the oral-gavage study (27,981 µg/ml*hr) $Dose_O$ = dose administered in the oral study (0.05 µCi) $Dose_D$ = dose administered in the dermal study (0.1 µCi)

	Parameters for the AUC calculation and doses were extracted from the Scatina et al. 1983 oral-gavage study and the Scatina et al. 1984 dermal study