Science approach document for substances with low human health hazard potential

Health Canada

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Synopsis

Pursuant to section 68 of the Canadian Environmental Protection Act, 1999 (CEPA), Health Canada has evaluated a subset of 14 substances of the approximately 1550 remaining priority substances under the Chemicals Management Plan.

These 1550 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA and/or were considered a priority based on human health concerns. This Science Approach Document (SciAD) presents a qualitative hazard-based approach to identify substances of low concern for human health from the remaining priorities.

This hazard-based approach considers available toxicity data (animal and human). When sufficient toxicity data indicate that health effects are unlikely up to the Limit Doses (of 1000 mg/kg-bw/day as defined by the Organisation for Economic Co-operation and Development) in animal studies, or are limited to recoverable or localized effects above 100 mg/kg-bw/day, in repeated dose studies of high quality, the substances or moieties are considered to be of low concern with respect to human health. To determine if health effects of the substance are limited or unlikely, a number of metrics are taken into consideration, including the effects noted in animal and human studies, and the relevant route of exposure of the substance.

Application of the hazard-based approach is illustrated by 14 substances, which are of low concern with respect to human health. An assessment of these substances conducted under section 74 of CEPA will be published at a later date.

A consultation period on this SciAD is being provided to the public who will have an opportunity to provide comments and additional information in advance of this approach being applied in Screening Assessment Reports. The publication of this scientific approach will assist the government in addressing substances that are of low concern.

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1. Introduction

Following the categorization of substances on the Domestic Substances List (DSL), which was completed in 2006, approximately 4300 of the 23 000 substances on the DSL were identified for assessment. Among these substances, 1550 remain to be addressed under the Chemicals Management Plan (CMP) (ECCC, HC [modified 2016a]). From this group, 14 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (Canada 1999, ECCC, HC [modified 2007]), and they are being evaluated through a hazard-based approach, as detailed in this Science Approach Document (SciAD).

The purpose of this SciAD is to provide stakeholders and the public with the opportunity to review and comment on this approach and the results of its application to 14 priority substances prior to publication of screening assessments under section 74 of CEPA. The publication of the scientific approach document in the SciAD will assist the government in addressing substances that are of low concern to human health.

This SciAD does not represent an exhaustive or critical review of all available data; rather, it presents the studies deemed most critical after a review of all available data and the lines of evidence pertinent to this science approach. Relevant data up to March 2017 are incorporated into this approach. Results are intended to form the basis for the human health portion of screening assessments that will be published subsequently, in conjunction with the assessment of potential ecological risks.

This SciAD was prepared by staff in the CEPA Risk Assessment Program at Health Canada. This SciAD has undergone external written peer review and consultation. Comments on the technical portion of this approach were received from Gary Drendel and Katherine Super from Tetra Tech. While external comments were taken into consideration, the final content and outcome of the hazard-based approach remain the responsibility of Health Canada.

Table A-1 provides a list of the CAS RN[1] that are considered to be of low concern for human health according to this hazard-based approach. These substances are included to illustrate application of the approach. The critical information and considerations upon which the SciAD are based are given below.

[1] 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.

2. Application of the Hazard-based Approach

2.1 Background

Under the CMP, substances undergo an assessment to determine if there is potential for harm to human health or the environment. Rather than focusing on the potential for exposure, as the Rapid Screening (ECCC, HC [modified 2013; 2014; 2016b]), TTC (HC 2016a), and Biomonitoring-based Approach 1 (HC 2016b) are built upon, this approach focuses on the inherent toxicity of a substance. The aim of this approach was to identify those substances with low concern for human health on the basis of hazard, without the need to characterize general population exposures. Nano-scale substances were not considered for this approach

A step-wise approach was developed where available toxicity data (animal and human) are reviewed to examine the potential for serious health effects (consistent with the Globally Harmonized System (GHS) definition of relevant toxic effects for specific target organ toxicity, UNECE 2015). For the purposes of this approach, permanent tissue/organ damage or impairment noted in repeat dose studies may be considered serious health effects, while localized site of contact, recoverable or acute health effects might not be considered. The determination of whether an effect is serious has been adopted from the Globally Harmonized System of Classification and Labelling of Chemicals (UNECE 2015, section 3.9.2.7.3). Further details of the approach are noted below. If there are no serious health effects identified, it is proposed that quantitative risk characterization is not warranted and the substance is considered to be low concern for human health. There are several important considerations for this approach including effects associated with high hazard (i.e., carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity), the Limit Dose in repeated-dose toxicity studies, and what constitutes an adverse effect. Acute morbidity (typically noted in acute lethality studies) or site of contact effects are not a focus of this approach as chemical products used by consumers are already regulated vis a vis these types of effects (Canada 2001). Additionally, exposures in workplace settings where individuals may be exposed to highly concentrated substances are addressed 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 and are beyond the scope of assessment activity under CEPA (Canada 2015, HC 2016d). Therefore, the approach is also limited to repeated dose health effects. This SciAD will outline the rationale for the approach, the steps and important considerations, as well as some of the uncertainties associated with this approach.

2.2 Rationale of the Approach

In evaluating the potential health effects of a substance, it is the purpose of the assessment to determine a level at which adverse health effects occur. Effects are

considered to be adverse if they result in functional impairment or pathological lesions that may affect the lifespan of the organism, its ability to reproduce, or reduce the ability of the organism to respond to an additional challenge (Lewis et al. 2002; US EPA 2011; IPCS 2004). For most substances, some level of exposure can be tolerated due to the presence of systems for metabolic detoxification, physiological homeostasis, and cellular repair and adaptation. These compensatory mechanisms can mitigate the effects of a substance, even when exposure occurs on a continuing basis. In a traditional risk assessment, quantifying the dose at which a critical health effect will occur (e.g., the lowest observed adverse effect level (LOAEL)) and the magnitude of exposure are important to determine if there is potential for harm to human health.

However, for substances that have inherently low toxicity, a qualitative approach to risk characterization on the basis of hazard may be considered. This approach focuses on substances where no health effects are observed below the OECD Limit Dose of 1000 mg/kg-bw/day (i.e., no or lowest observed adverse effect level ≥ 1000 mg/kg-bw/day) or where there are no serious health effects (permanent or irreversible effects) noted between 100 and 1000 mg/kg-bw/day in studies of sufficient quality and duration of exposure. The Limit Dose is defined as the highest dose which should be used in the absence of a maximum tolerated dose (MTD) and is typically set at 1000 mg/kg-bw/day (OECD 2013). The OECD recommends a Limit Dose of 1000 mg/kg-bw/day for all repeated-dose animal testing (OECD 1997, 2001a, b, 2007a, 2009a, b; 2016). The OECD Limit Dose is applicable for substances that are exposed through oral and dermal route (OECD 2016). While the idea of a Limit Dose is appropriate for oral and dermal routes of exposure, there is no Limit-Dose equivalent for inhalation route. The Limit Dose was implemented by the OECD with the purpose of protecting test animals from exposure to excessively high doses of test substances. If administration at the Limit Dose fails to demonstrate toxicity, the test substance is considered to have low inherent toxicity and further testing is not recommended, in the interest of reducing the number of animals tested.

If the substance is a carcinogen, a mutagen/genotoxicant, a reproductive/developmental toxicant, or if there are serious health effects occurring between 100 and 1000 mg/kg-bw/day in repeated dose studies, then this approach would not be considered appropriate and a quantitative approach to risk characterization may be warranted. For the purpose of this approach, the range of health effects considered to be serious are noted in Table 2-1, and are consistent with the GHS classification system. This list includes neurotoxicity, organ impairment and other effects demonstrative of permanent tissue damage.

This concept of low inherent toxicity is already utilized in other regulatory jurisdictions. For example, the Generally Recognized As Safe (GRAS) designation by the United States Food and Drug Administration (US FDA) signals that a chemical or substances added to food is generally recognized, among qualified experts, to be safe under the conditions of intended use and as such is not subject to pre-market approval

requirements (US FDA 2016). The Commission of the European Communities' report on Dietary Food Additive Intake in the European Union has identified many substances as having an Acceptable Daily Intake (ADI) "not-specified". These substances are considered non-toxic at dose levels noted in total diet surveys, which represent the majority of the sources of exposure for these substances (JECFA 1975; EU 2001; HC 2016c). The Environmental Protection Agency (US EPA) has also developed a system to identify safer alternatives for product formulation (US EPA 2017). Through its Safer Choice program, US EPA lists chemicals that meet low-hazard thresholds (based on EPA New Chemicals Program and UN Globally Harmonized System criteria) on the Safer Chemical Ingredients List (SCIL). Chemicals on SCIL must meet the Safer Choice master criteria or functional-use-specific criteria. These criteria define low hazard for an array of toxicological human health and environment endpoints, including cancer, mutagenicity, reproductive and developmental toxicity, systemic toxicity, and aquatic toxicity (more at https://www.epa.gov/saferchoice/standard). SCIL lists chemicals by functional-use class (surfactants, solvents, etc.) and listed chemicals are among those with the lowest hazard potential in their class. Because of SCIL's stringent low-hazard requirements—and in the interests of furthering continuous improvement toward inherently safer chemistry—assessments for listing do not include exposure.

While these regulatory systems rely on hazard characterizations as the basis of their risk assessments, the current hazard-based approach has incorporated other considers as outlined below.

2.3 Summary of the Approach

At the onset of the approach, the potential for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental (CMR) toxicity must be determined. This evaluation should be based upon the weight of evidence of animal and human data, and take into consideration the (MTD) in the studies (i.e., dose producing signs of toxicity such that higher dose levels would be expected to produce lethality (OECD 2013)). Read-across is appropriate to address data gaps, as necessary. If the substance is considered to have CMR effects, then the substance is not considered further for a hazard-based approach and a quantitative approach to risk characterization may be warranted.

If there are no indications of CMR effects, the first consideration (i.e., Decision point 1 in Figure 2-1) is used to determine if a substance is potentially low concern to human health. The assessment of all health effects of a substance should be based on a weight of evidence approach and take into account the totality of the findings including structure-activity relationship, knowledge of mode of action, pharmacokinetics and the acknowledgement of limitations of the available data. Adequate repeat-dose studies relevant to the primary route of exposure are strongly recommended for this approach. The determination of the primary route of exposure is based on collected survey data, and data provided from Health Canada databases which may encompass cosmetics, natural health products, and consumer products. The details of these determinations are not included in this approach document. Once a decision has been made as to the

CMR classification of the substance, the assessment of repeated-dose health effects is initiated.

Decision Point 1: Does the substance only cause health effects at or above the Limit Dose of 1000 mg/kg-bw/day in repeated-dose testing?

If exposures below the Limit Dose demonstrate an absence of health effects in repeated-dose studies, then the substance is considered as having low concern for human health and no further risk characterization is warranted. This Limit Dose of 1000 mg/kg-bw/day is applicable to both animal and human data. In addition to toxicity data, it is also important to understand the pharmacokinetic data, to ensure there are no species differences in the kinetic properties of the substance. Read across data from structurally similar substances can be used for the determination of the Limit Dose (OECD 2016).

If health effects are noted at dose levels below Limit Dose testing, then the substance is subjected to the next decision point to determine if it is to be considered low concern for human health (i.e., Decision Point 2 in Figure 2-1). This step determines if health effects noted in the database are considered serious or recoverable/compensatory.

Decision Point 2: Does the substance cause any permanent/irreversible or otherwise serious health effects at dose between 100 to 1000 mg/kg-bw/day?

Some substances may cause health effects at concentrations below the Limit Dose and still be considered to be low concern to human health according to this approach. If health effects are limited to site-of-contact effects or reversible, compensatory effects and do not cause any serious effects, (death, morbidity or organ impairment) with doses starting at 100 mg/kg-bw/day and up to a dose of 1000 mg/kg-bw/day, then the substance may be considered as low concern for human health. Neurotoxic effects are considered as serious for the purposes of this approach. This dose range between 100 and 1000 mg/kg-bw/day is applicable to both animal and human data. Further details on these health effects are presented in Table 2-1. If there are health effects at doses below 100 mg/kg-bw/day or inadequate assays exist to determine the hazard potential of the substance, a hazard-based approach is not considered appropriate and a different approach for risk assessment may be warranted.

Table 2-1 Examples of health effects that should or should not be considered to support hazard classification, based upon Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Health effects that should be considered	Health effects that should <u>not</u> be considered
Significant functional changes in the (central	Changes in bodyweight, food

Health effects that should be considered	Health effects that should <u>not</u> be considered
or peripheral) nervous systems or other organ systems, including depression or sensory (visual, auditory, or olfactory) deficits.[1]	consumption or water intake that may have some toxicological importance but do not, by themselves, indicate significant toxicity.[2]
Any significant and consistent adverse change in clinical biochemistry, haematology or urinalysis parameters.[3]	Small changes or transient effects in clinical biochemistry, haematology or urinalysis parameters that represent minimal toxicological importance.
Significant organ damage that may be noted in necropsy or microscopic examination.	Changes in organ weights with no evidence of organ dysfunction.
Necrosis, fibrosis, or granuloma formation in vital organs with regenerative capacity.	Adaptive responses that are not considered toxicologically relevant.
Morphological changes in organs that are potentially reversible but provide clear evidence of marked dysfunction.[4]	Species-specific mechanisms of toxicity that are considered not relevant to human health.
Significant cell death, cell degeneration, or reduced cell numbers in vital organs incapable of regeneration. Morbidity or death.	

For the purposes of this hazard-based approach, the determination of adversity will be considered case-by-case.

[2] In some incidences, significant changes in bodyweight, food consumption, or water intake should be considered as adverse effects, which will be determined case-by-case

[3] To meet the criteria of adverse, haematological changes indicative of anaemia or other similarly adverse changes must be noted. These changes will be considered case-by-case.

[4] Changes in endocrine function should be considered adverse in the absence of evidence of adaptation.

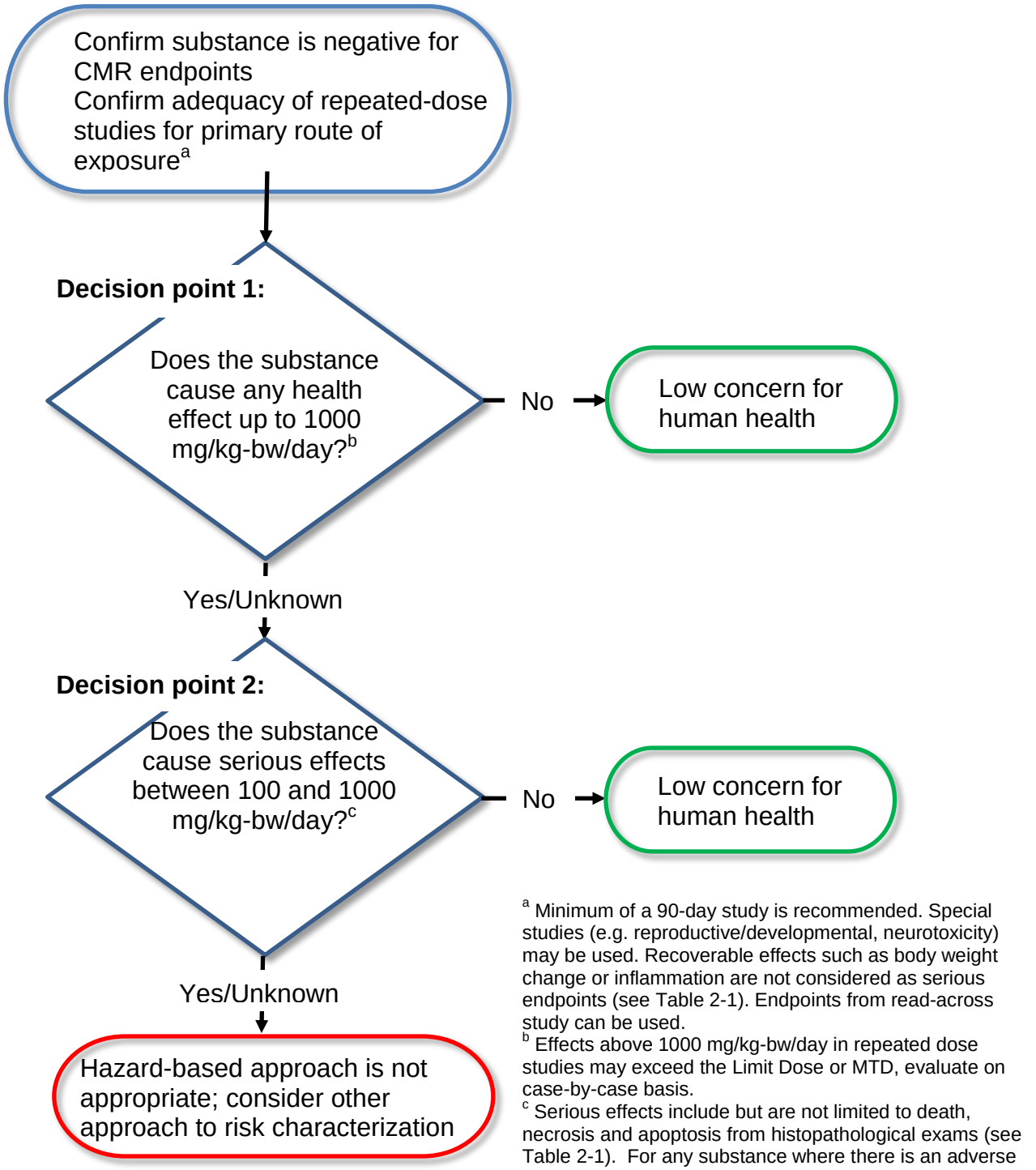
This approach is similar in nature to the system employed by the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals (UNECE 2015). The GHS was developed to aid in product labelling, based on hazard classification. The GHS is mainly used for label requirements for substances demonstrating health effects (in humans or experimental animals) at exposures less than 100 mg/kg-bw/day. The range of health endpoints considered by the GHS (presented in Table A-2) are considered appropriate for a determination of health effects for this hazard-based approach. Similarly, the EPA Safer Choice program lists chemicals based on GHS hazard classifications, to allow product formulators, and consumers access to chemicals with low inherent hazard potentials (US EPA 2017).

While the GHS approach is only applied to substances noting serious health effects at 100 mg/kg-bw/day and lower, the proposed hazard-based approach recommends the use of the same definitions of serious health effects as the GHS up to Limit Dose testing (1000 mg/kg-bw/day). In this regard, the hazard-based approach described in this SCIAD is an order of magnitude more protective than the GHS system. In addition, while the GHS system is only applicable for serious health effects, the hazard based approach also considers “soft” endpoints, which would not trigger GHS regulation. The proposed approach considers hazard data from animals and humans.

Additional considerations

Although this approach builds upon the OECD Limit Dose concept, the spectrum of tests or assays considered acceptable for this approach are not limited to those experiments conducted according to OECD guidelines. Well-conducted repeated-dose studies of appropriate duration are also considered in this approach.

This approach may be used for assessing substances through all routes of exposure. While the idea of a Limit Dose is appropriate for oral and dermal routes of exposure, there is no Limit-Dose equivalent for inhalation route. For substances where inhalation is expected to be a major route of exposure, the appropriateness of use of this approach will be determined on a case-by-case basis, taking into consideration the available data, physical-chemical properties, maximum achievable concentrations and exposure potential. Route-specific effects such as respiratory sensitization will also be considered.



[a] Minimum of a 90-day study is recommended. Special studies (e.g. reproductive/developmental, neurotoxicity) may be used. Recoverable effects such as body weight change or inflammation are not considered as serious endpoints (see Table 2-1). Endpoints from read-across study can be used.

[b] Effects above 1000 mg/kg-bw/day in repeated dose studies may exceed the Limit Dose or MTD, evaluate on case-by-case basis.

[c] Serious effects include but are not limited to death, necrosis and apoptosis from histopathological exams (see Table 2-1). For any substance where there is an adverse effect below 100 mg/kg-bw/day, a different approach to risk characterization may be considered.

Figure 2-1 Considerations for determination of substance with low concern for human health.

3. Results of Hazard-based Approach

A total of 14 substances were chosen to illustrate the application of the Hazard-based Approach and are summarized in Table A-1. Rationales for justification of each substance classified as low concern for human health are listed below. While details of individual studies are not provided, decisions for each substance were based on a weight of evidence, which considered the adequacy of available data. Hazard summary tables are included in the Appendix (Tables A-3 – A-13).

CAS RN 409-21-2: Silicon carbide (Non-fibrous)

Oral intake for the general Canadian population is the primary route of exposure to non-fibrous silicon carbide. While workers may be exposed to this substance via inhalation, this route of exposure is not considered relevant for the general population, based on environmental media and product information. Silicon dioxide (CAS RN 7631-86-9) was used as read-across due to lack of data on silicon carbide. This is a suitable supporting substance as it shares a similar chemical composition and similar health effects are expected due to its biological inertness (Brunch et al. 1993). The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day. In repeated oral dosing studies, there were no health effects of concern below the Limit Dose of 1000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1) (Takizawa et al. 1988; Litton Bionetics Inc. 1974; Johnston et al. 2000; Mortelmans and Griffin. 1981; Cabot 1989a,b, 1990a,b; Degussa 1963, 1981; FDRL 1972, 1973a, 1973b; OECD 2004a). Therefore, non-fibrous silicon carbide is considered to be of low concern for human health according to the hazard-based approach.

CAS RN 1310-58-3: Potassium hydroxide and CAS RN 12136-45-7: Potassium oxide

Oral intake for the general Canadian population is expected to be the primary route of exposure to potassium hydroxide and potassium oxide, based on environmental media and product information. These substances were negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (Fujita et al. 1992; FDRL 1975; Imai et al. 1986; Morita et al. 1989; OECD 2002a, 2007b; PSL 2002; Sleight and Atallah 1968). In repeated dosing studies, there were no health effects of concern below the Limit Dose of 1000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1). Therefore, potassium hydroxide and potassium oxide are considered to be of low concern for human health according to the hazard-based approach.

CAS RN 1310-73-2: Sodium hydroxide

Oral intake and dermal contact for the general Canadian population are expected to be the primary routes of exposure to sodium hydroxide, based on environmental media and

product information. Acute and/or site-of-contact irritation/corrosion were not considered relevant to the general population and are not health effects considered for this approach. The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1) (Aaron et al. 1989; De Flora et al.1984; Morita et al.1989; OECD 2002b). Furthermore, sodium hydroxide is not expected to be systemically available in the body under normal handling and use conditions and hence will not be able to cause any health effects (OECD 2002b). Therefore, sodium hydroxide is considered to be of low concern for human health according to the hazard-based approach.

CAS RN 1312-76-1: Silicic acid, potassium salt and 1344-09-8: Silicic acid, sodium salt

Oral intake and dermal contact for the general Canadian population are expected to be the primary routes of exposure to silicic acid, sodium salt and potassium salt, based on environmental media and product information. These substances were negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (OECD 2004b; Latvian Environment, Geology and Meteorology Centre 2016). The results from repeated dose studies with soluble silicates demonstrate no treatment related systemic health effects of concern in animals up to Limit Dose (i.e., Decision Point 2 in Figure 2-1) (OECD 2004b). Therefore, silicic acid, sodium salt and potassium salt are considered to be of low concern for human health according to the hazard-based approach.

CAS RN 1314-56-3: Phosphorus oxide and CAS RN 7664-38-2: Phosphoric acid

Oral intake and dermal contact for the general Canadian population are expected to be the primary routes of exposure to phosphoric acid and phosphorous oxide, based on environmental media and product information. Phosphoric acid, phosphorous oxide or their chemical analogs were negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (NIER 2005, 2008a, b; OECD 2009c). In repeated oral dosing studies, there were no health effects of concern below the limit dose Limit Dose of 1000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1). Health effects are not considered of concern in the hazard-based approach when the extensive mechanisms of biological phosphate regulation and GRAS classification are considered (Gattineni and Friedman 2015). Therefore, phosphoric acid and phosphorous oxide are considered to be of low concern for human health according to the hazard-based approach.

CAS RN 7631-90-5: Sulfurous acid, monosodium salt

Oral intake for the general Canadian population is expected to be the primary route of exposure to sulfurous acid, monosodium, based on environmental media and product information. Repeated dose studies with sulfurous acid, monosodium salt are not

available. Potassium metabisulfite (CAS RN 16731-55-8) and sodium metabisulfite (CAS RN 7681-57-4) are used as read across due to lack of data on sulfurous acid, monosodium salt. These are suitable supporting substances as there is a pH dependent equilibrium with the different forms of S (IV) being bisulfite, sulfite, metabisulfite and sulfur dioxide in the aqueous milieu of biological systems and hence are expected to have similar health effects (OECD 2008). The substances were negative in tests for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day. In repeated dosing studies, there were no health effects of concern below the Limit Dose of 1000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1) (Tanaka et al. 1979; Til et al. 1972). Based on read-across with studies on supporting substances, sulfurous acid, monosodium salt is considered to be of low concern for human health according to the hazard-based approach.

CAS RN 7647-01-0: Hydrochloric acid (Hydrogen chloride)

Inhalation for the general Canadian population is expected to be the primary route of exposure for hydrogen chloride, based on environmental media and product information. While the test material has acute irritation/corrosion potential, site-of-contact and/or acute effects were not considered relevant to the general population and are not addressed in the hazard-based approach. The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity in repeat dose studies that were conducted up to vapor saturation concentrations (i.e., Decision Point 1 in Figure 2-1) (CIIT 1984; OECD 2002c; NRC 2009). Protons and chloride ions are normal constituents in the body fluid of animal species; hydrogen chloride gas/mist or solution do not cause systemic health effects to animals. Repeat dose studies were conducted up to atmospheric concentrations which would not cause excessive localized tissue effects (OECD 2002c). Therefore, hydrogen chloride is considered to be of low concern for human health according to the hazard-based approach.

CAS RN 7664-93-9: Sulfuric acid

Oral intake for the general Canadian population is expected to be the primary route of exposure to sulfuric acid, based on environmental media and product information. While the test material has acute irritation/corrosion potential, site-of-contact and/or acute effects were not considered relevant to the general population and are not addressed in the hazard-based approach. Mists of strong inorganic acids have been classified as carcinogens in humans (IARC 2012; NTP 2014) however; the general population is not exposed to sulfuric acid mists. The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the oral Limit Dose of 1,000 mg/kg-bw/day (Cipollaro et al. 1986; IARC 1992, 2012; Morita et al. 1989; Murray 1979; NICNAS IMAP 2015; OCED 2001c; Scott et al. 1991). In repeated dosing studies no human health effects of concern were seen at doses well beyond the Limit Dose (i.e., Decision Point 1 in Figure 2-1) (Capdevielle and Scanes 1995a,b).

Therefore, sulfuric acid is considered to be of low concern for human health according to the hazard-based approach.

CAS RN 7681-57-4: Disulfurous acid, disodium salt

Oral intake for the general Canadian population is expected to be the primary route of exposure to disulfurious acid, disodium salt, based on environmental media and product information. The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (Ishidate et al. 1984; Maxwell and Newell 1974; NTIS 1972a, b, 1974, 1978; OECD 2001d; Prival et al. 1991; Til et al. 1972). In repeated dosing studies no human health effects of concern were seen at doses well beyond the Limit Dose (i.e., Decision Point 1 in Figure 2-1) (OECD 2001d; Til et al. 1972). Therefore, disulfurous acid, disodium salt is considered to be of low concern for human health based on the hazard-based approach.

CAS RN 7722-84-1: Hydrogen peroxide

Oral intake for the general Canadian population is expected to be the primary route of exposure to hydrogen peroxide, based on environmental media and product information. The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (Ito et al. 1984; Hirota and Yokoyama 1981; Takahashi et al. 1986; Takayama 1980; Abril and Pueyo 1990; Abu-Shakra and Zeiger 1990; Sawada et al. 1988; FMC Corporation 1997; Ito et al. 1981a, b). In repeated oral dosing studies, health effects were limited to recoverable, indications of irritation at dose levels between 76-785 mg/kg bw/day (i.e., Decision Point 2 in Figure 2-1) (FMC Corporation 1997). Therefore, hydrogen peroxide is considered to be of low concern for human health according to the hazard-based approach.

CAS RN 7789-20-0: Deuterium oxide

Oral intake for the general Canadian population is expected to be the primary route of exposure to deuterium oxide, based on environmental media and product information. The substance was negative for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the Limit Dose of 1,000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1) (Haggquist and von Hevesy 1956; Naruse and Kajiwara 1991; Hughes and Laurel 1965; Hughes and Calvin 1958; Oakberg and Hughes 1968; Thomson 1960; Tanaka et al. 1993; Tatewaki et al. 1992; Coward 1979; Kushner et al. 1999). However, other health effects were noted to take place at doses well in excess of Limit Doses. Therefore, deuterium oxide is considered to be of low concern for human health according to the hazard-based approach.

3.1 Uncertainties in the Approach

For the consideration of effects between 100 and 1000 mg/kg-bw/day, there is some uncertainty about the use of 100 mg/kg-bw/day as a cut-off for decision making. However, based on an analysis of estimates of exposure to the Canadian public from substances in consumer products, environmental media and food under the Chemicals Management Plan, exposure estimates greater than 10 mg/kg-bw/day are rare. Therefore, the selection of 100 mg/kg-bw/day as a cut-off in this approach is considered to be a conservative value. Health effects considered for the hazard-based approach within the range of 100 and 1000 mg/kg-bw/day are limited to compensatory or recoverable changes which are typically addressed in risk assessments by standard uncertainty factors, without the need for application of additional uncertainty factors.

There is no generally accepted Limit Dose for toxicity studies via the inhalation route. If inhalation is a relevant route of exposure for a given substance, this hazard-based approach should be evaluated on a case-by-case basis. Thus, substances should be tested up to the highest concentrations achievable based on their physical-chemical properties (OECD 2009a).

For substances lacking CMR data, there is uncertainty associated with the use of this approach for determining if a substance is of low concern for human health. Similarly, the use of analogues to address data gaps in substance databases imparts a degree of uncertainty. Under these circumstances, this approach would be considered on a case-by-case basis.

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Appendix

Table A-1 Substances classified as having low concern for human health

CAS RN	Domestic Substances List Name
409-21-2	Silicon carbide
1310-58-3	Potassium hydroxide
1310-73-2	Sodium hydroxide
1312-76-1	Silicic acid, potassium salt
1314-56-3	Phosphorus oxide
1344-09-8	Silicic acid, sodium salt
7631-90-5	Sulfurous acid, monosodium salt
7647-01-0	Hydrochloric acid
7664-38-2	Phosphoric acid
7664-93-9	Sulfuric acid
7681-57-4	Disulfurous acid, disodium salt
7722-84-1	Hydrogen peroxide
7789-20-0	Deuterium oxide
12136-45-7	Potassium oxide

Table A-2 Hazard summary for silicon carbide

Hazard Summary Table	
Silicon carbide (CAS 409-21-2)	
Primary route of exposure	Oral
Read-across Rationale	Silicon dioxide (CAS 7631-86-9) is used for read across for silicon carbide. The basis for the read-across is that silicon carbide and silicon dioxide share a similar chemical composition and therefore, similar health effects are expected due to their biological inertness.
Carcinogenicity	Negative Study: 2-year oral administration of synthetic amorphous silica (SAS) (up to 5% diet) in rats. Tumour responses in all organs were not statistically significant from controls. (Takizawa et al. 1988) Group 3: inadequate evidence in humans and experimental animals for the carcinogenicity of amorphous silica. (IARC 1997)
Mutagenicity (in vivo)	Negative Assays: ex-vivo HPRT gene-mutation assay, long term inhalation exposure of 50mg/m^3 for 13 weeks. (Litton Bionetics 1974; Johnston et al. 2000; OECD 2004a)
Mutagenicity (in vitro)	Negative Assays: bacterial gene mutation test, non-bacterial in-vitro GMT, non-bacterial in-vitro chromosomal aberration test (Mortelmans et al. 1981; Cabot 1989a,b, 1990a,b; Litton Bionetics 1974; OECD 2004a)

Reproductive Toxicity	NOAEL = 500 mg/kg-bw/day Study: SAS oral exposure (500 mg/kg-bw/day in diet) did not cause any adverse effects in males or females in a one-generation study (Degussa 1963; OECD 2004a)
Developmental Toxicity	NOAEL = 1600 mg/kg-bw/day Study: no signs of maternal or embryonic/developmental toxicity at highest dose tested (oral gavage) in rat, mouse, hamster, rabbit. (FDRL 1972, 1973a, 1973b; OECD 2004a)
Repeated Dose Toxicity	NOAEL = 4000-4500 mg/kg-bw/day Study: 13-week oral feed study in rats (n=10/sex/group) dosed at 0.5, 2, 6.7% diet; estimated mean doses: 300-330, 1200-1400, 4000-4500 mg/kg BW/d. No adverse clinical, haematological, blood chemistry, urinary or histopathological effects. (Degussa 1981; OECD 2004a) NOAEL ≈ 2500 mg/kg-bw/day Study: 2-year oral feed study in rats (n=160/sex) dosed at 0, 1.25, 2.5 and 5% showed no changes in BW, hematology, organ weights (significantly lower liver weights from 12-23 months @ 2.5-5% dose in females), no pathology or cancer that was dose-related (Takizawa et al. 1988) No evidence of significant lung effects (no signs of pneumoconiosis, silicosis or fibrosis) attributable to occupational long term exposure based on medical surveillance reports (OECD 2004a)

Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to silicon carbide. Silicon dioxide (CAS RN 7631-86-9) was used as read-across due to lack of data on silicon carbide. This is a suitable supporting substance as it shares a similar chemical composition and similar health effects are expected due to its biological inertness. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (i.e., Decision point 1 in Figure 2-1) (Takizawa 1988; Litton Bionetics Inc. 1974; Johnston et al. 2000; Mortelmans et al. 1981; Cabot 1989a,b, 1990a,b; Degussa 1963, 1981; FDRL 1972, 1973a,b; OECD 2004a). Therefore, silicon carbide is considered to be of low concern for human health according to the hazard-based approach.

Table A-3. Hazard summary for potassium hydroxide and potassium oxide

Hazard Summary Table	
Potassium hydroxide (CAS 1310-58-3) and Potassium oxide (CAS 12136-45-7)	
Primary route of exposure	Oral
Grouping Rationale	Potassium hydroxide and potassium oxide are evaluated together due to structural similarity as well as limited data. The substances share the same moiety of interest, the potassium cation. Potassium oxide is reduced by water to potassium hydroxide, which dissociates completely in water to its component ions. (NIOSH 2006)
Read-across Rationale	Potassium chloride (CAS RN 7447-40-7) and other potassium containing compounds are used as read across due to lack of data on potassium hydroxide and potassium oxide.
Carcinogenicity	There is no clear link between potassium oxide and cancer. (OECD 2002a)
Mutagenicity/Genotoxicity	Negative Chinese hamster ovary chromosomal aberration test and Ames assay suggest no evidence of genotoxicity or mutagenicity. (Fujita et al. 1992; Morita et al. 1989; OECD 2002a)
Reproductive/Developmental Toxicity	LOAEL = 2250 mg/kg-bw/day Hindered reproductive performance at 2250 mg/kg-bw/day. No other reproductive/developmental effects on mice or rats. (FDRL 1975; PSL 2002; Sleight and Atallah 1968; OECD 2007b)
Repeated-Dose Toxicity	NOAEL >1820 mg KCl/kg-bw/day Local gastric irritation and slight increase in blood urea nitrogen, no health effects of concern related to general toxicity endpoints. (Imai et al. 1986; PSL 2002; OECD 2002a, 2007b)

Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to potassium hydroxide and potassium oxide. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day in potassium hydroxide, potassium oxide or its chemical analogs (Fujita et al. 1992; FDRL 1975; Imai et al. 1986; Morita et al. 1989; OECD 2002a, 2007b; PSL 2002; Sleight and Atallah 1968). In repeated dosing studies, there were no health effects of concern below the limit dose of 1000 mg/kg-bw/day (i.e., Decision point 1 in Figure 2-1 of SciAD). Therefore, potassium hydroxide and potassium oxide are considered to be of low concern for human health according to the hazard-based approach.

Table A-4. Hazard summary for sodium hydroxide

Hazard Summary Table	
Sodium hydroxide (CAS 1310-73-2)	
Primary route of exposure	Oral and dermal
Mutagenicity (in vivo)	Negative Assay: micronucleus test (Aaron et al. 1989)
Mutagenicity (in vitro)	Negative Assay type: Ames test, chromosome aberration test (De Flora et al.1984; Morita et al.1989)
Reproductive/Developmental Toxicity	No valid studies were identified regarding effects on fertility or developmental toxicity in animals after oral, dermal or inhalation exposure to NaOH. NaOH is not expected to be systemically available in the body under normal handling and use conditions and for this reason it can be stated that the substance will not reach the foetus nor reach male and female reproductive organs. (OECD 2002b)
Repeated dose Toxicity	NaOH is not expected to be systemically available in the body under normal handling and use conditions (OECD 2002b)
Recommendation and rationale for the recommendation	Oral intake and dermal contact for the general Canadian population are the primary routes of exposure to sodium hydroxide. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (i.e., Decision point 1 in Figure 2-1 of SciAD) (Aaron et al. 1989; De Flora et al. 1984; Morita et al.1989; OECD 2002b). Furthermore, sodium hydroxide is not expected to be systemically available in the body under normal handling and use conditions and hence will not be able to cause any health effects (OECD 2002b). Therefore, sodium hydroxide is considered to be of low concern for human health

	according to the hazard-based approach.

Table A-5. Hazard summary for silicic acid, potassium salt and silicic acid, sodium salt

Hazard Summary Table	
Silicic acid, potassium salt (CAS 1312-76-1) and Silicic acid, sodium salt (CAS 1344-09-8)	
Primary route of exposure	Oral and dermal
Grouping Rationale	The soluble silicates are structurally very similar and based on the available data the members of the soluble silicates category exhibit a similar toxicological profile. (OECD 2004b)
Mutagenicity	Negative (OECD 2004b)
Carcinogenicity	No valid studies are available. (OECD 2004b)
Reproductive/Developmental Toxicity	NOAEL = 200 – 2400 mg/kg-bw/day No treatment-related effects on reproductive organs by their macroscopic and microscopic examination in rats and dogs. No treatment related effects on number of pregnancies and living or dead fetuses, body weight and malformations of inner organs and the skeleton. (OECD 2004b; Latvian Environment; Geology and Meteorology Centre 2016)
Repeated dose Toxicity	NOAEL = 227 – 892 mg/kg-bw/day No clear systemic health effects in rats and mice dosed with soluble silicates (OECD 2004b)
Recommendation and rationale for the recommendation	Oral intake and dermal contact for the general Canadian population are the primary routes of exposure to silicic acid, sodium salt and potassium salt. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (OECD 2004b; Latvian

	Environment, Geology and Meteorology Centre 2016). The results from repeated dose studies with soluble silicates demonstrate no treatment related systemic health effects of concern in animals up to limit dose (i.e., Decision point 2 in Figure 2-1 of SciAD) (OECD 2004b). Therefore, silicic acid, sodium salt and potassium salt are considered to be of low concern for human health according to the hazard-based approach.

Table A-6. Hazard summary for phosphorus oxide and phosphoric acid

Hazard Summary Table	
Phosphorous Oxide (CAS 1314-56-3) and Phosphoric Acid (CAS 7664-38-2)	
Primary route of exposure	Oral and dermal
Grouping Rationale	Phosphorous oxide and phosphoric acid are evaluated as a group as phosphorous readily reacts with water to phosphoric acid. The substances therefore share the same moiety of interest and can be considered together when assessing risk.
Carcinogenicity	No carcinogenicity studies available yet no evidence of increased tumour occurrence in repeated dose studies.
Mutagenicity	Negative in bacterial reverse mutation assay and mammalian cell gene mutation assay. (OECD 2009c; NIER 2005, 2008a)
Repeated dose Toxicity	Read across from supporting substance Sodium Aluminum Phosphate (structural analogue) used to support findings. NOAEL: 322 mg/kg-bw/day No toxicological changes of the test substance were observed in dogs In humans, the level of phosphate is closely regulated by many hormones, acting in concert in a variety of biochemical pathways. Phosphate homeostasis is preserved, regardless of dietary intake, due to the vast number of compensatory mechanisms to deal with excess phosphate in the body. (ECHA c2007-2017; OECD 2009c; NIER 2008b; Gattineni and Friedman 2015)
Reproductive/Developmental Toxicity	NOAEL = 500 mg/kg-bw/day No health effects of concern related to reproduction or development at highest dose tested, 500 mg/kg-bw/day. (OECD 2009c; NIER 2008b)

Recommendation and rationale for the recommendation	Oral intake and dermal contact for the general Canadian population are the applicable routes of exposure to phosphoric acid and phosphorous oxide. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day in phosphoric acid, phosphorous oxide or their chemical analogs (NIER 2005, 2008a, b; OECD 2009c). In repeated dosing studies, there were no health effects of concern below the limit dose Limit Dose of 1000 mg/kg-bw/day (i.e., Decision Point 1 in Figure 2-1) Therefore, phosphoric acid and phosphorous oxide are considered to be of low concern for human health according to the hazard-based approach.

Table A-7. Hazard summary for sulfurous acid, monosodium salt

Hazard Summary Table	
Sulfurous acid, monosodium salt (CAS 7631-90-5)	
Primary route of exposure	Oral
Read-across Rationale	Potassium metabisulfite (CAS RN 16731-55-8) and sodium metabisulfite (CAS RN 7681-57-4) are used as read across due to lack of data on sulfurous acid, monosodium salt. These are suitable supporting substances as there is a pH dependent equilibrium with the different forms of S (IV) being bisulfite, sulfite, metabisulfite and sulfur dioxide in the aqueous milieu of biological systems and hence are expected to have similar health effects. (OECD 2008)
Carcinogenicity	NOAEL > 2500 mg/kg-bw/day $K_2S_2O_5$ (or about 1450 mg/kg-bw/day as SO2 equivalents) (Tanaka et al.1979)
Mutagenicity (in vivo and in vitro)	Negative Assay type: mammalian cell gene mutation assay (ECHA c2007-2017)
Reproductive/Developmental Toxicity	NOAEL: 2% metabisulphite corresponding to 955 mg/kg-bw/day of Na2S2O5 (or 640 mg/kg-bw/day as SO2 equivalents) Effect: no evidence of a treatment-related effect on reproduction and fertility was seen; there was a slight growth retardation during lactation in offspring of the 2% group (Til et al. 1972)
Repeated dose Toxicity	NOAEL: 2% metabisulphite corresponding to 955 mg/kg-bw/day of Na_2S_2O5 (or 640 mg/kg-bw/day as SO2 equivalents) Effect: no evidence of systemic toxicity following chronic treatment (Til et al. 1972)

Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to sulfurous acid, monosodium. Repeated dose studies with sulfurous acid, monosodium salt are not available. Potassium metabisulfite (CAS RN 16731-55-8) and sodium metabisulfite (CAS RN 7681-57-4) are used as read across due to lack of data on sulfurous acid, monosodium salt. These are suitable supporting substances as there is a pH dependent equilibrium with the different forms of S (IV) being bisulfite, sulfite, metabisulfite and sulfur dioxide in the aqueous milieu of biological systems and hence are expected to have similar health effects (OECD 2008). There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (i.e., Decision point 1 in Figure 2-1 of SciAD) (Tanaka et al. 1979; Til et al. 1972). Based on read-across with studies on supporting substances, sulfurous acid, monosodium salt is considered to be of low concern for human health according to the hazard-based approach.

Table A-8. Hazard summary for hydrochloric acid

Hazard Summary Table	
Hydrochloric acid (CAS 7647-01-0)	
Primary route of exposure	Inhalation
Carcinogenicity	NOAEL = 10 ppm (15 mg/m^3) No pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study with SD male rats at 10 ppm (the maximum tolerable dose for human exposure) hydrogen chloride gas. No evidence of treatment related carcinogenicity was observed either in other animal studies performed by inhalation, oral or dermal administration. (OECD 2002c)
Weight of Evidence for mutagenicity (in vivo and in vitro)	Negative (OECD 2002c)
Reproductive/Developmental Toxicity	"No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because protons and chloride ions are normal constituents in the body fluid of animal species, low concentrations of hydrogen chloride gas/mist or solution do not seem to cause adverse effects to animals." "These facts indicate that hydrogen chloride/hydrochloric acid is not expected to have developmental toxicity. In addition, no effects on the gonads were observed in a good quality 90-day inhalation study up to 50 ppm." (OECD 2002c)
Repeated dose Toxicity	LOEL= 50 ppm (75 mg/m^3) Localized tissue effects in the absence of systemic effects. (CIIT 1984, NRC 2009, OECD 2002c)
Recommendation and rationale for the recommendation	Inhalation for the general Canadian population is the primary route of exposure for hydrogen chloride. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity in repeat dose

	studies that were conducted up to atmospheric concentrations (i.e., Decision point 1 in Figure 2-1 of SciAD) (OECD 2002c, CIIT 1984, NRC 2009). Protons and chloride ions are normal constituents in the body fluid of animal species; hydrogen chloride gas/mist or solution do not cause systemic health effects to animals. Repeat dose studies were conducted up to atmospheric concentrations which would not cause excessive localized tissue effects (OECD 2002c). The US EPA assessment was included in the dataset for hydrogen chloride, however the EPA itself has low confidence in the database it used due to lack of information on chronic or reproductive studies (US EPA 1995). This is re-iterated by OECD when they state that “no reliable studies have been reported regarding toxicity” with respect to hydrochloric acid (OECD 2002c). Therefore, hydrogen chloride is considered to be of low concern for human health according to the hazard-based approach.

Table A-9. Hazard summary for sulfuric acid

Hazard Summary Table	
Sulfuric Acid (CAS 7664-93-9)	
Primary route of exposure	Oral
Carcinogenicity	Increase in incidence of lesions in the respiratory tract in occupational setting when exposed to strong inorganic acid mists, attributed to irritant nature of the mist. The general public is not expected to be chronically exposed, via inhalation, due to the difficulty in achieving high airborne concentrations, as well as the irritating and corrosive nature of the mists of sulfuric acid. (OECD 2001c; NICNAS IMAP 2015; IARC 1992, 2012)
Mutagenicity	Negative (Scott et al. 1991; Cipollaro et al. 1986; Morita et al. 1989; OCED 2001c)
Reproductive/Developmental Toxicity	NOAEL= 8.26 mg/kg-bw/day (20 mg/m^3) No signs of reproductive/ developmental toxicity in mice and rabbits exposed by inhalation to sulfuric acid at the highest achievable concentrations. Sulfuric acid is not expected to be absorbed or distributed throughout the body due to direct acting toxicant effects. Therefore, it is not likely that it will reach male and female reproductive organs following exposures by any route. (Murray 1979; OECD 2001c)
Repeated Dose Toxicity	Following inhalation, effects are limited to histopathology and cell proliferation of the larynx in rats, consistent with a local irritant effect of the substance. No indication of toxicity in 14 day oral studies at levels of 2338 mg/kg/day. Longer term dosing was not possible due to the corrosive nature of the material. (OECD 2001c; Capdevielle and Scanes 1995a, b)

Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to sulfuric acid. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (Cipollaro et al. 1986; IARC 1992, 2012; Morita et al. 1989; Murray 1979; NICNAS IMAP 2015; OCED 2001c; Scott et al. 1991). In repeated dosing studies no human health effects of concern were seen at doses well beyond the limit dose (i.e., Decision point 1 in Figure 2-1 of SciAD) (Capdevielle and Scanes 1995a, b). Therefore, sulfuric acid is considered to be of low concern for human health according to the hazard-based approach.

Table A-10. Hazard summary for disulfurous acid, disodium salt

Hazard Summary Table	
Disulfurous acid, disodium salt (CAS 7681-57-4)	
Primary route of exposure	Oral
Carcinogenicity	NOAEL = 942 mg/kg-bw/day Under the conditions of this study, the compound is not considered to be a carcinogen. (Til et al.1972; OECD 2001d)
Mutagenicity	NOAEL = 1200 mg/kg-bw/day Disulfurous acid, disodium salt is not mutagenic under the conditions of these studies. (Maxwell and Newell 1974, NTIS 1972a,1978; Prival et al. 1991; Ishidate et al. 1984; OECD 2001d)
Reproductive/Developmental Toxicity	NOAEL = 942 mg/kg-bw/day In doses approaching the limit dose, the test material did not cause any reproductive or developmental effects in rabbits or rats. (Til et al.1972; NTIS 1972b, 1974; OECD 2001d)
Repeated-Dose Toxicity	NOAEL = 942 mg/kg-bw/day Effect: stomach lesions due to local irritation. No signs of systemic toxicity. (Til et al.1972; OECD 2001d)
Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to disulfurious acid, disodium salt. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (Ishidate et al. 1984; Maxwell and Newell 1974; NTIS 1972a, b, 1974, 1978; OECD 2001d; Prival et al.1991; Til et al.1972). In repeated dosing studies no human health effects of concern were seen at doses well beyond the limit dose (i.e., Decision point 1 in Figure 2-1 of SciAD) (OECD 2001d; Til et al.1972). Therefore, disulfurous acid, disodium salt is considered to be of low concern for

	human health based on the hazard-based approach.

Table A-11. Hazard summary for hydrogen peroxide

Hazard Summary Table	
Hydrogen peroxide (CAS 7722-84-1)	
Primary route of exposure	Oral
Carcinogenicity	NOEL= 433 mg/kg-bw/day male Hydrogen peroxide is not a frank carcinogen, at doses below MTD. (Ito et al. 1984; Hirota and Yokoyama 1981; Takahashi et al. 1986; Takayama 1980; EU RAR 2003).
Mutagenicity (in vivo)	NOAEL = 1000 mg/kg-bw/day Negative up to limit dose testing. (CEFIC 1995; EU RAR 2003)
Mutagenicity (in vitro)	Negative up to limit dose testing. (Abril and Pueyo 1990; Abu-Shakra and Zeiger 1990; Sawada et al.1988; EU RAR 2003).
Repeated-dose Toxicity	LOAEL = 76 – 785 mg/kg-bw/day In the 90-day drinking water study, Charles River catalase-deficient mice were noted to have significant reductions in water consumption and duodenal mucosal hyperplasia after treatment; no hyperplasia after recovery in any dose group. The nature of the effects was not considered to be adverse, and similar severity was observed in a wide range of doses. (FMC Corporation 1997; EU RAR 2003)
Reproductive/Developmental Toxicity	An appropriate 90-day drinking water study with catalase-deficient mice and carcinogenicity studies with catalase-deficient mice and F344 rat did not identify testes or ovaries as target organs for toxicity. (FMC Corporation 1997; Ito et al. 1981a, b; Takayama 1980; EU RAR 2003)
Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to hydrogen peroxide. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose

	of 1,000 mg/kg-bw/day (Ito et al. 1984; Hirota and Yokoyama 1981; Takahashi et al. 1986; Takayama 1980; Abril and Pueyo 1990; Abu-Shakra and Zeiger 1990; Sawada et al.1988; FMC Corporation1997; Ito et al. 1981a, b). In repeated dosing studies, health effects were limited to recoverable, indications of irritation at dose levels between 76-785 mg/kg bw/day (i.e., Decision point 2 in Figure 2-1 of SciAD) (FMC Corporation 1997). Therefore, hydrogen peroxide is considered to be of low concern for human health according to the hazard-based approach.

Table A-12. Hazard summary for deuterium oxide

Hazard Summary Table	
Deuterium oxide (CAS 7789-20-0)	
Primary route of exposure	Oral
Mutagenicity (in vivo)	Negative up to limit dose testing. (Haggquist and von Hevesy 1956)
Mutagenicity (in vitro)	Negative up to limit dose testing in early mouse embryos. (Naruse and Kajiwara 1991)
Reproductive Toxicity	Negative up to limit dose testing. (Hughes and Laurel 1965; Hughes and Calvin 1958; Oakberg and Hughes 1968; Thomson 1960)
Developmental Toxicity	LOAEL = 66420 mg/kg-bw/day Negative up to limit dose testing. (Tanaka et al. 1993; Tatewaki et al. 1992)
Recommendation and rationale for the recommendation	Oral intake for the general Canadian population is the primary route of exposure to deuterium oxide. There was no health effect of concern for carcinogenicity, mutagenicity/genotoxicity, and reproductive/developmental toxicity up to the limit dose of 1,000 mg/kg-bw/day (i.e., Decision point 1 in Figure 2-1 of SciAD) (Haggquist and von Hevesy 1956; Naruse and Kajiwara 1991; Hughes and Laurel 1965; Hughes and Calvin 1958; Oakberg and Hughes 1968; Thomson 1960; Tanaka et al. 1993; Tatewaki et al. 1992). Therefore, deuterium oxide is considered to be of low concern for human health according to the hazard-based approach.