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Assessment

Substances Identified as Being of Low Concern Using the Ecological Risk Classification of Inorganic Substances and Biomonitoring or Rapid Screening Science Approaches

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Health Canada

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Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted an assessment of 34 substances. The Chemical Abstracts Service Registry Numbers (CAS RN[1]), *Domestic Substances List* (DSL) names, and common names of these substances as well as the assessment approaches used are listed in the Appendix A, Table A-1.

According to information submitted in response to a CEPA section 71 survey, no consumer uses were identified for the majority of substances. Some of these substances may be used as a component in the manufacture of food packaging materials while others are present in products available to consumers including drugs, natural health products, cosmetics, sealants, lubricants and greases, paper products, paints and coatings, batteries, water treatment products, pesticides, and disinfectants. Industrial uses include use as paint additives, processing aids, lubricants, viscosity adjusters, desiccants, pH adjusters, adhesives and sealants, and intermediates.

The ecological risks of the substances in this assessment were characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I). ERC-I is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published predicted no-effect concentrations (PNEC) and water quality guidelines, and the derivation of new PNEC values when required. Exposure profiling considered two approaches: predictive modelling using a generic near-field exposure model for each substance, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs using metal concentrations as a conservative indicator of exposure for individual substances. Measured and modelled predicted environmental concentrations were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential to cause harm to the environment. Based on the outcome of the ERC-I analysis, the 34 substances in this assessment are considered unlikely to be causing ecological harm.

Considering all available lines of evidence, there is low risk of harm to the environment from the 34 substances in this assessment. It is concluded that these substances do not

[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.

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.

The human health risks of the substances in this assessment, based on current levels of exposure, were characterized using 1 of 3 science approaches: Biomonitoring-based Approach 1, Biomonitoring-based Approach 2, or the Rapid Screening of Substances with Limited General Population Exposure Approach. The Biomonitoring-based Approach 1 is a qualitative science approach used to identify substances with limited exposure based on substances or moieties measured in the Canadian population at very low frequencies. The Biomonitoring-based Approach 2 compares human biomonitoring data (as a measure of exposure) against biomonitoring guidance values that are consistent with available health-based exposure guidance values, such as biomonitoring equivalents (BEs), to identify substances with low concern for human health. Although the substances were assessed individually, the potential for cumulative effects was considered in this assessment by examining cumulative exposures for the relevant metal moieties through biomonitoring approaches. The Rapid Screening for Substances with Limited General Exposure for Human Health is used to identify low concern substances by evaluating the potential for direct exposure from products and indirect exposure from environmental media.

The human health assessment took into consideration those groups of individuals within the Canadian population who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects.

Considering all the information presented, it is concluded that the 34 substances in this assessment 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 concluded that the 34 substances in this assessment do not meet any of the criteria set out in section 64 of CEPA.

Table of Contents

List of Tables and Figures

1. Introduction

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted an assessment of 34 substances to determine whether these substances present or may present a risk to the environment or to human health. The substances were identified as priorities for assessment as they met categorization criteria as described in ECCC, HC (modified 2017).

The ecological risks of the 34 substances in this assessment were characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) (ECCC [modified 2018]). ERC-I is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of a new PNEC value when required. Exposure profiling considered two approaches: predictive modelling using a generic near-field exposure model for each substance and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs using metal concentrations as a conservative indicator of exposure for individual substances. Measured and modelled predicted environmental concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment.

The human health risks of the substances in this assessment based on current levels of exposure, were characterized using 1 of 3 science approaches: Biomonitoring-based Approach 1 (Health Canada 2016a), Biomonitoring-based Approach 2 (Health Canada 2016b), or the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC [modified 2018]). Biomonitoring-based Approach 1 is a qualitative science approach used to identify substances with limited exposure based on substances or moieties measured in the Canadian population at very low frequencies. Biomonitoring-based Approach 2 compares human biomonitoring data (systemic exposure) against biomonitoring guidance values (based on available health-based guidance values), such as biomonitoring equivalents (BEs), to identify substances with low concern for human health. The Rapid Screening of Substances with Limited General Population Exposure for Human Health is used to identify low concern substances by evaluating the potential for direct exposure from products and, as needed, indirect exposure from environmental media.

Engineered nanomaterials (1 to 100 nm) that may be present in environmental media or products are not explicitly considered in this assessment, but measured concentrations of substances in the environment or human biomonitoring could include contributions from these sources. Similarly, this assessment does not explicitly consider ecological or health effects associated with nanomaterials.

This 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 ERC-I Science Approach Document (SciAD) (ECCC [modified 2018]) was externally peer-reviewed and subject to a 60-day public comment period. External peer-review comments on the technical portions of the ERC-I SciAD were received from Dr. Peter Campbell (L'Institut national de la recherche scientifique, INRS), Mr. Geoff Granville (GCGranville Consulting Corp.), Dr. Carrie Rickwood (Natural Resources Canada), and Dr. Kevin Wilkinson (Université de Montréal). The Biomonitoring-based Approach 1 SciAD (Health Canada 2016a), the Biomonitoring-based Approach 2 SciAD (Health Canada 2016b), and the Rapid Screeningof Substances with Limited General Population Exposure (ECCC, HC [modified 2018]) were each subject to a 60-day public comment period. Additionally, the Biomonitoring-based Approach 2 SciAD was externally peer-reviewed. External peer-review comments on the Biomonitoring-based approach 2 SciAD were received from Lynne Haber and Andrew Maier from Toxicology Excellence for Risk Assessment (TERA) and Judy LaKind from LaKind Associates. Public comments were received on the ERC-I SciAD and the Biomonitoring Approach 2 SciAD. Additionally, the draft of this assessment (published on February 26, 2022) was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

Assessments focus on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by considering scientific information, including information, if available, on subpopulations who may have greater susceptibility or greater exposure, vulnerable environments and cumulative effects[2], and by incorporating a weight of evidence approach and precaution[3]. This assessment presents the critical information and considerations on which the conclusions are based.

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[2] The consideration of cumulative effects under CEPA may involve an analysis, characterization and possible quantification of the combined risks to health or the environment from exposure to multiple chemicals.

[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

2. Identity of substances

The Chemical Abstracts Service Registry Numbers (CAS RN), *Domestic Substances List* (DSL) names, and common names for the 34 substances in this assessment are presented in Appendix A, Table A-1.

3. Sources and uses

Thirty-three of the 34 substances in this assessment were included in surveys issued pursuant to section 71 of CEPA (Canada 2009, 2012). Paraffin waxes and hydrocarbon waxes, oxidized, lithium salts (CAS RN 68649-48-9) was not surveyed. Table 3-1 presents a summary of the information reported on the total manufacture and total import quantities for these substances in Canada for the reporting years 2008 or 2011.

Table 3-1. Summary of information on Canadian manufacturing and imports of 33 substances submitted in response to CEPA section 71 surveys

DSL name	CAS RN	Total manufacture[a] (kg)	Total imports[a] (kg)	Survey data reference[b]
Hexanoic acid, 2-ethyl-, cerium(3+) salt	56797-01-4	NR	100-1000	EC 2013
Germane, tetrachloro-	10038-98-9	10 000 – 100 000	NR	EC 2013
Lanthanum oxide (La_2O_3)	1312-81-8	NR	100 000-1 000 000	EC 2013
Lanthanum chloride ($LaCl_3$)	10099-58-8	NR	NR	EC 2013
Lanthanum boride (LaB_6), (OC-6-11)-	12008-21-8	NR	NR	EC 2013
Hexanoic acid, 2-ethyl-, neodymium (3+) salt	73227-23-3	NR	1000-10 000	EC 2013
Praseodymium oxide (Pr_2O_3)	12036-32-7	NR	100-1000	EC 2013
Tellurium oxide (TeO_2)	7446-07-3	100 000-1 000 000	NR[a]	EC 2013

contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

Tellurium, tetrakis (diethylcarbamodithioato-S,S')- (DD-8-''1''1''''''''''''')-	20941-65-5	NR	1 000 000-10 000 000	EC 2013
Yttrium oxide (Y_2O_3)	1314-36-9	NR	10 000-100 000	EC 2013
Bismuth oxide (Bi_2O_3)	1304-76-3	10 000 – 100 000	1000 – 10 000	EC 2013
Bismuth hydroxide nitrate oxide ($Bi_5(OH)_9(NO_3)_4O$)	1304-85-4	NR	NR	EC 2013
Nitric acid, bismuth(3+) salt	10361-44-1	NR	NR	EC 2013
Bismuth vanadium oxide ($BiVO_4$)	14059-33-7	NR	20 500-130 000	EC 2009
Bismuth, tris(dimethylcarbamodithioato-S,S')- (OC-6-11)-	21260-46-8	NR	100 – 1000	EC 2013
Neodecanoic acid, bismuth(3+) salt	34364-26-6	NR	100 – 1000	EC 2013
Hexanoic acid, 2-ethyl-, bismuth(3+) salt	67874-71-9	NR	4 910	EC 2013
Acetic acid, lithium salt	546-89-4	NR	100-1000	EC 2013
Carbonic acid dilithium salt	554-13-2	14 361	100 000-1 000 000	EC 2013
Lithium hydroxide (Li(OH))	1310-65-2	NR	9 945	EC 2013
Octadecanoic acid, lithium salt	4485-12-5	NR	1000-10 000	EC 2013
Lithium	7439-93-2	NR	1000-10 000	EC 2013
Lithium chloride (LiCl)	7447-41-8	NR	10 000-100 000	EC 2013
Octadecanoic acid, 12-hydroxy-, monolithium salt	7620-77-1	10 000-100 000	100 000 – 1 000 000	EC 2013
Lithium fluoride(LiF)	7789-24-4	NR	6 300	EC 2013
Sulfuric acid, dilithium salt	10377-48-7	NR	1000-10 000	EC 2013
Silicic acid, lithium salt	12627-14-4	NR	36 060	EC 2013
Hypochlorous acid, lithium salt	13840-33-0	NR	16 000	EC 2013
Neodecanoic acid, lithium salt	27253-30-1	NR	1 615	EC 2013
Neodecanoic acid, dilithium salt	38900-29-7	NR	10 000-100 000	EC 2013

Silicic acid, lithium magnesium sodium salt	53320-86-8	NR	72 432	EC 2013
Fatty acids, C16-18, lithium salts	68783-37-9	10 000-100 000	NR	EC 2013
Bromic acid, sodium salt	7789-38-0	NR	1 000 - 20 000	EC 2009

Abbreviations: NR = Not reported above reporting threshold of 100 kg per reporting year

[a] Values reflect quantities reported in response to CEPA section 71 surveys (Environment Canada 2009 and Environment Canada 2013). See surveys for specific inclusions and exclusions (schedules 2 and 3).

[b] Survey reference EC 2009 = Environment Canada 2009; EC 2013 = Environment Canada 2013

According to the information submitted in response to a CEPA section 71 survey, some of the substances included in this assessment are used in various consumer, industrial and commercial applications (Environment Canada 2013). Additional information was considered in order to identify food-related or consumer uses including notifications submitted under the *Cosmetic Regulations* to Health Canada, information from the Licensed Natural Health Products Database (LNHPD), the Internal Drug Product Database, publicly available databases and websites (for example, CPID [modified 2018]; CPCat 2017; US HPD 2017), email communications from the Food Directorate, the Therapeutic Products Directorate, the Pest Management Regulatory Agency and the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada and material safety and technical datasheets.

According to non-confidential use information submitted in response to a CEPA section 71 survey (Environment Canada 2009, 2013), no consumer uses were identified for these 18 substances: germane, tetrachloride-; lanthanum oxide; lanthanum chloride; lanthanum boride; praseodymium oxide; tellurium oxide; tellurium tetrakis (diethylcarbamodithioato-S,S') -, (DD-8-''1''1'''1'1'''1''')-; yttrium oxide; bismuth oxide; bismuth hydroxide nitrate oxide; nitric acid, bismuth(3+) salt; bismuth, tris(dimethylcarbamodithioato-S,S')-, (OC-6-11)-; octadecanoic acid, lithium salt; lithium; lithium fluoride; sulfuric acid, dilithium salt; silicic acid, lithium salt; and fatty acids, C16-18, lithium salts. Limited consumer uses were notified as confidential business information (CBI) for hexanoic acid, 2-ethyl-, cerium(3+) salt and hexanoic acid, 2-ethyl-, neodymium (3+) salt.

Lanthanum oxide may be used as a component in the manufacture of food packaging materials; dietary exposure is expected to be negligible (personal communication, email from Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau (ESRAB), Health Canada, dated March 09, 2018; unreferenced). Lanthanum chloride may be used to remove phosphates from swimming pools (CPID [modified 2018]). Lanthanum forms a precipitate with phosphates, and the pool water is filtered and/or vacuumed to remove the phosphates prior to swimming. Therefore, when used according to the label instructions, this use is not expected to result in significant exposure to consumers.

Consumer uses identified for bismuth-containing substances (7 CAS RNs) include medicinal or non-medicinal ingredients in licensed natural health products, medicinal ingredients in therapeutic drug products, an ingredient in cosmetics (as notified under the *Cosmetic Regulations*), sealants and solder flux. Certain bismuth-containing substances may also be used as components in the manufacture of food packaging materials (email from Food Directorate, Health Canada, to the ESRAB, Health Canada, dated March 09, 2018 unreferenced). Bismuth vanadium oxide may be used in plastics, rubber materials and in paint and coatings and hexanoic acid, 2-ethyl-, bismuth(3+) salt in adhesives and sealants.

Consumer uses identified for lithium-containing substances (16 CAS RNs) include use in water treatment, lubricants and greases, paper products, paints and coatings, sealants, batteries, water treatment (Environment Canada 2013), medicinal or non-medicinal ingredients in disinfectants, human or veterinary drug products, medicinal or non-medicinal ingredients in licensed natural health products, an ingredient in cosmetics (as notified under the *Cosmetic Regulations*), and active ingredient or formulant in registered pest control products (personal communication, email from the Pest Management Regulatory Agency, Health Canada to the ESRAB, Health Canada dated January 31, 2018; unreferenced). Certain lithium-containing substances may be used as components in the manufacture of food packaging materials and in incidental additives[4] used in food processing establishments (personal communication, email from the Food Directorate, Health Canada, to the ESRAB, Health Canada, dated March 13, 2018; unreferenced). Lithium carbonate is used as a treatment for bipolar disorder (Kunasz 2006).

Sodium bromate was included in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC [modified 2018])). Sodium bromate was previously found in a small number of cosmetic products. It was previously described as a restricted ingredient on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (F&DA), or may contravene one or more provisions of the *Cosmetic Regulations.* However, following a recent update to the Hotlist it is now described as a prohibited ingredient (Health Canada 2019). As sodium bromate is no longer permitted in cosmetics, there will no longer be potential for direct exposure to

[4] While not defined under the *Food and Drugs Act* (F&DA), 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.

sodium bromate from cosmetic products[5] (Health Canada [modified 2019]). No other consumer uses were identified for this substance. Sodium bromate may be used as a component in the manufacture of food packaging materials and in incidental additives used in food processing establishments (personal communication, email from the Food Directorate, Health Canada, to the ESRAB, Health Canada, dated September 28, 2017; unreferenced).

The substances in this group have a wide array of industrial and commercial applications. According to non-confidential use information submitted in response to a CEPA section 71 survey, these substances have various industrial uses such as paint additives, processing aids, catalysts, intermediates, viscosity adjusters, desiccants, pH adjusters, corrosion inhibitors, anti-scaling agents, adhesives and sealants, in paper products, batteries, plastics and rubber materials, industrial lubricants and greases, automotive, aircrafts and water treatments. Commercial uses in the metals sector have been reported for these 3 CAS RNs: tellurium oxide; carbonic acid, dilithium salt and lithium fluoride (Environment Canada 2013). Other uses identified in surveys issued pursuant to a CEPA section 71 notice, beyond those identified here, were notified as CBI; these uses were also considered in the risk assessment.

4. Potential to cause ecological harm

4.1 Characterization of ecological risk

The ecological risks of the 34 substances in this assessment were characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) (ECCC [modified 2018]). ERC-I is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. A summary of the approach is outlined below; the approach is described in detail in the ERC-I science approach document (ECCC [modified 2018]).

[5] The List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (FDA) or may contravene one or more provisions of the *Cosmetic Regulations*. Section 16 of the FDA states that "no person shall sell any cosmetic that has in or on it any substance that may cause injury to the health of the user." In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the FDA (Health Canada [modified 2019]).

Hazard characterization in ERC-I included a survey of published PNECs and water quality guidelines from domestic and international assessments. When no suitable existing PNEC or water quality guideline was found, hazard endpoint data were collected and, depending on data availability, either a species sensitivity distribution or an assessment factor approach was taken to derive a new PNEC value. In the case of the 34 substances in this assessment, hazard endpoint data were available from multiple sources including comprehensive literature searches for specific groups, targeted searches of the ECOTOX database and European Chemicals Agency registration dossiers (as described in ECCC [modified 2018]). In the absence of more recent information, the assumptions used in the 2006 categorization of the DSL were also considered (ECCC, HC [modified 2017]).

Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model and an analysis of measured concentrations of metals collected by federal and provincial water quality monitoring programs. The generic near-field exposure model used Canadian import and manufacture volumes and associated use information of the substances submitted in response to a CEPA section 71 survey (Environment Canada 2009; Environment Canada 2013). As an additional line of evidence, and to address substances where CEPA section 71 survey information was unavailable, trade merchandise import data were obtained for relevant harmonized system (HS) codes (CBSA 2016). Additionally, third-party market research reports were used to complement data from other sources and to fill information gaps for substances not included in a CEPA section 71 survey. Quantity data submitted in response to CEPA section 71 surveys, or obtained from the CBSA or market research were used in a conservative near-field exposure scenario similar to that used in previous rapid screening approaches (EC, HC 2013; EC, HC 2014; ECCC, HC 2016) and as further detailed in ECCC [modified 2018] to generate PECs.

In addition to using import, manufacture, and use information to model releases to the aquatic environment, reported release data were also available from the National Pollutant Release Inventory (NPRI) for certain substances or groups of substances. NPRI data for groups of substances (for example, lithium carbonate) were conservatively considered applicable to the subsets of CAS RNs that are remaining priorities. A similar near-field risk-based evaluation was performed using NPRI reported release data for the last five years available at the time of preparation (2011 to 2015).

Water quality monitoring data for surface fresh waters were collected for each substance or metal moiety, where available, from multiple federal and provincial programs and repositories covering a number of ecoregions in Canada, as described in ECCC [modified 2018]. Measured concentrations were obtained for the period 2005 to 2015. For some metal moieties, measured concentrations in waterbodies exposed to metal mining activities and corresponding reference waterbodies were available from Environmental Effects Monitoring (EEM) studies conducted under the *Metals Mining Effluent Regulations* (MMER).

Measured and modelled PECs were compared to PNECs, and statistical metrics that consider both the frequency and magnitude of exceedances were computed and compared to decision criteria to classify the potential for ecological risk. Critical data and considerations used to create substance-specific ecological profiles and classifications associated with ecological risk, as well as identification of potential need for tracking of future use patterns, are presented in ECCC [modified 2018]. According to the information considered in ERC-I, the overall risk classification for each of the 34 substances in this assessment is low (Table B-1 in Appendix B). Based on the outcome of the ERC-I analysis, the 34 substances in this assessment are considered unlikely to be causing ecological harm.

5. Potential to cause harm to human health

The human health risks of the substances in this assessment based on current levels of exposure, were characterized using 1 of 3 human health-based approaches: the Biomonitoring-based Approach 1 (Health Canada 2016a), the Biomonitoring-based Approach 2 (Health Canada 2016b), or the Rapid Screening of Substances with Limited General Population Exposure approach (ECCC, HC [modified 2018]).

For the substances assessed with biomonitoring-based approaches in this document, whole blood concentrations generated from a recent Canadian Health Measures Survey (CHMS) biobank project (Jayawardene et al. 2021) were considered. The whole blood concentrations of these elements were not measured in the core CHMS. In this project, whole blood samples from the biobank of the CHMS cycle 2 were analysed at Health Canada's Health Products Laboratory in Longueuil, Quebec, to generate nationally representative population-level data (Health Canada 2013). The CHMS is a national survey carried out by Statistics Canada in partnership with Health Canada and the Public Health Agency of Canada, which collects information from Canadians about their general health (Health Canada [modified 2020a]). This survey is designed to be nationally representative and includes a biomonitoring component; metals were measured in whole blood and urine of approximately 5 000 to 7 000 Canadians per survey cycle. The CHMS is not a targeted survey, and thus does not target individuals with high metal exposure or living near point sources of exposure. The CHMS cycle 2 samples were collected from 2009 to 2011 in approximately 5752 Canadians aged 3 to 79, including pregnant women and both fasting and non-fasting individuals at 18 sites across Canada (Health Canada 2013).

The elemental concentrations in these biobanked CHMS samples were measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). The methods used to detect these whole blood concentrations were sensitive, specific, accurate and reproducible. The limits of detection (LODs) were considered to be sufficiently low to detect exposure in the Canadian population. When generating population-level whole blood concentrations, Statistics Canada estimated the 95% confidence intervals (CIs) for all means and percentiles by applying sample weights and bootstrap weights (Rao et al.

1992; Rust and Rao 1996). Sample weights took into account the complex survey design of the CHMS. Statistics Canada imputed values less than the limit of detection with values equivalent to half of the limits of detection (Jayawardene et al. 2021).

The potential for cumulative effects was considered in this assessment by examining cumulative exposures from the total metal moiety. The biomonitoring data presented in Table 5.1 represent concentrations of elements in whole blood. These concentrations were used as surrogate exposure data for the specific substances (CAS RNs) that are evaluated in this report. There is very limited CAS RN specific exposure data, thus data on the total metal moiety was considered to be an acceptable surrogate as total metal moiety biomonitoring data include exposures from all bioavailable forms of the element. Biomonitoring data represent exposure from multiple sources. This includes indoor and outdoor air, soil, dust, water, food and/or potential exposures from products used frequently by consumers, such as some cosmetics and natural health products. Biomonitoring data also incorporate exposures from all routes (oral, dermal and inhalation). However, it should be noted that some biomonitoring data in different matrices, such as urine are starting to emerge for these elements from various community based surveys targeted for monitoring rare earth elements in Northern Canada (Cirtiu et al. 2022).

For each substance, relevant toxicokinetic data were evaluated to determine whether the concentrations of elements in whole blood from available biomonitoring data were appropriate for assessing exposure. Several criteria have been established to understand the adequacy of the biomarker (that is, chemical concentration in whole blood, plasma, serum or urine) of exposure. According to Needham and Sexton (2000), the ideal biomarker should be sensitive, specific, biologically relevant, easy to collect, inexpensive to analyze, easily identified and persists in the body for long periods.

Table 5-1. Whole blood concentrations of elements measured in biobank samples from the Canadian Health Measures Survey - Cycle 2[a]

Substance	LOD (µg/L)	Median (µg/L)	95th percentile (µg/L)	Detection frequency (%)[b]	Human health approach used
Cerium	0.05	<0.05	<0.05	0.47	BM-1
Germanium	1	<1	<1	0	BM-1
Lanthanum	0.05	<0.05	<0.05	0.28	BM-1
Neodymium	0.05	<0.05	<0.05	0.12	BM-1
Praseodymium	0.02	<0.02	<0.02	0.09	BM-1
Tellurium	0.4	<0.4	<0.4	0	BM-1
Yttrium	0.06	<0.06	<0.06	0.12	BM-1
Bismuth	0.1	<0.1	<0.1	4.57	BM-2
Lithium	0.4	0.47	1.3	66.43	BM-2

Abbreviation: LOD = limit of detection; BM-1 = Biomonitoring-based Approach 1; BM-2 Biomonitoring-based Approach 2

[a] Jayawardene et al. 2021.
[b] Percentage of population with concentrations at or above the limit of detection

In the absence of CAS RNs specific inhalation exposure information, data on the metal moiety were used as surrogate inhalation exposure data for the specific substances (CAS RNs) in the assessment. Canadian air concentration data (24-hour particulate matter less than or equal to 2.5 μm [$PM_{2.5}$] air filter samples) for total bismuth and lithium are available from a study conducted in Windsor, Ontario, for indoor residential, outdoor residential and personal environments (Rasmussen 2017). In addition, total cerium and lanthanum were measured in outdoor air $PM_{2.5}$ in 910 samples from 9 different sites across Canada as part of the National Air Pollution Surveillance (NAPS) Program (NAPS 2015). Indoor or personal air concentration data for cerium, germanium, lanthanum, neodymium, praseodymium, tellurium and yttrium have not been measured. However, a significant relationship between elemental concentrations in indoor particulate matter less than or equal to 10 μm (PM_{10}) and settled house dust has been demonstrated (Rasmussen et al. 2018). Nationally representative house dust data are available for all the elements included in this assessment (Rasmussen et al. 2022; Rasmussen et al. 2017). Therefore, by using the elemental concentrations in settled-dust (Rasmussen et al.2022), indoor air (PM_{10}) concentrations for cerium, germanium, lanthanum, neodymium, praseodymium, tellurium and yttrium were modelled (Rasmussen 2019). The measured median concentrations of elements in air $PM_{2.5}$ (ng/m^3) and house dust (μg/g) are shown in Appendix C, Table C-1. The modelled indoor air concentrations (Rasmussen 2019) for cerium, germanium, lanthanum, neodymium, praseodymium, tellurium, and yttrium result in negligible inhalation exposure of the general population. Therefore, the risk to human health from inhalation exposure to these substances was not quantified in the current assessment.

The human health assessment took into consideration those groups of individuals within the Canadian population who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects.

5.1 Biomonitoring-based Approach 1

Substances characterized using the Biomonitoring-based Approach 1 are identified in Appendix A. This science approach is a qualitative biomonitoring-based approach that identifies substances of low concern for human health at the current levels of exposure which were identified as priorities for assessment as they met categorization criteria as described in ECCC, HC (modified 2017).

This biomonitoring-based approach considers available Canadian and U.S. biomonitoring data based on the analysis of the substance or moiety in whole blood, serum, and/or urine. Total concentrations of a substance (or moiety) in blood or urine may provide a biologically-relevant, integrated measure of exposures that may occur across multiple routes (for example, oral, dermal and inhalation) and sources (including environmental media (for example, soil, sediments, dust and water), diet, and frequent

or daily use products). When biomonitoring data indicate that general population exposure is limited or unlikely, substances or moieties are considered to be of low concern with respect to human health. To determine if exposure is limited or unlikely, a number of metrics are taken into consideration. These metrics include the prevalence of exposure across the population (substances or moieties with limited biomarker[6] detection frequency in the population are considered to have limited exposure), the magnitude of the biomarker concentration (if detected at the upper tails of the exposure distribution), the limit of detection (sufficiently low), the toxicokinetic properties of the substance or moiety, and the use pattern of the substance. The use pattern takes into consideration the sources and uses identified in section 3.

Toxicokinetic data for each substance were reviewed to ensure that the biomarkers measured in the biomonitoring study were adequate. The focus of the toxicokinetic data review was on the oral route of exposure, as this would be the predominant route of potential intake for the general population. A literature search on toxicokinetic data available on each individual substance in the grouping was conducted. In the absence of kinetic data for the substance (CAS RN), the kinetic data from studies conducted on the metal moiety was used as a surrogate. The whole blood concentration of the substance can be considered as a suitable biomarker to quantify exposure from all routes and from all sources. Whole blood provides the concentration of bioavailable fraction of the substance at the target site of systemic health effects. Whole blood was preferred over plasma or serum as it contains all of the blood components (for example, proteins, erythrocytes, platelets) and therefore there is a higher chance of detection regardless of the fraction of the blood into which the element partitioned. For population-level biomonitoring studies, such as the CHMS, it is reasonable to assume that the population distribution appropriately captures the variability in biomarker concentrations, even for substances with short elimination half-lives in blood.

For the substances captured in the Biomonitoring-based Approach 1 section of this assessment, the CHMS whole blood biomonitoring data indicate reasonably low long-term exposure in the general population of Canada. Therefore, in-depth reviews of systemic health effects from long-term exposure were not conducted for substances being evaluated by Biomonitoring-based Approach 1. However, carcinogenicity, mutagenicity and reproductive/developmental health effects associated with exposure to these substances were reviewed. In addition, a review of health effects from acute and short-term exposure (for example, from substances with infrequent use) was conducted

[6] A biomarker of exposure is the chemical or its metabolite or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism (NRC 2006), for example, a metal moiety measured in blood or urine.

to identify whether substances are associated with adverse health effects following acute and short-term exposure scenarios.

Uncertainties of Biomonitoring-based Approach 1

Uncertainties associated with this approach have been outlined in the Biomonitoring-based Approach 1 SciAD (Health Canada 2016a). Additional sources of uncertainty include, but are not limited to: a lack of targeted data in CHMS, therefore the nationally representative biomonitoring data may not capture subpopulations with different exposures such as those living in the vicinity of industrial facilities or other point sources of exposure or a lack of biomonitoring data from young children under the age of 3 years; and the information on the sources of exposure to some of these substances in the general population. The CHMS cycle 2 biomonitoring data is representative of exposure during 2009 to 2011 in Canada. However, the use pattern analysis did not show any significant change in sources and uses for the substances included in this assessment from the time the CHMS survey was conducted to the present. Thus, it is likely that the biomonitoring data represent current levels of exposure, but do not capture exposures from potential future uses.

In the absence of substance specific kinetic, health effects and exposure data, data available on the metal moiety were used as a surrogate. It is important to note that there may be different bioavailability and health effects associated with specific substances versus the metal moiety, in particular with soluble and insoluble substances.

Despite the above-noted uncertainties, the confidence in the assessment of substances containing cerium, germanium, lanthanum, neodymium, praseodymium, tellurium and yttrium in this assessment conducted using Biomonitoring-based Approach 1 is considered to be high.

It was determined that the Biomonitoring-based Approach 1 was appropriate for risk characterization for 10 substances.

5.1.1 Hexanoic acid, 2-ethyl-, cerium(3+) salt

There is no toxicokinetic data or human health effects data available on hexanoic acid, 2-ethyl-, cerium(3+) salt. Therefore, available data on substances that contain the cerium metal moiety were used as a surrogate. Based on the results of the literature search, it was determined that toxicokinetic studies for cerium-containing substances are conducted primarily using cerium chloride.

Toxicokinetic data

Cerium is poorly absorbed by the gastrointestinal (GI) tract. Bouchard et al. (2017) conducted a kinetic study on rare earth metals using male Sprague-Dawley rats. The study was conducted in compliance with the OECD Test Guideline 417. Comparing

blood cerium levels following oral and intravenous (i.v.) exposures, Bouchard et al. (2017) were able to estimate oral cerium chloride absorptions corresponding to 0.4% and 0.1% of the 100 and 1000 mg/kg bw doses administered, respectively. Similarly, Moskalev (1959) reported 0.03% absorption by the GI tract 3 days after oral administration of cerium chloride to rats. Other authors have reported age-dependent variation in the absorption of radioactive cerium (Kostial et al. 1989; Inaba and Lengemann 1972, as cited in US EPA (2009a). Adult rats orally exposed to radioactive cerium salts showed less than 1% absorption (Kostial et al. 1989; Inaba and Lengemann 1972; Shiraishi and Ichikawa 1972 as cited in US EPA 2009a). US EPA (2009a) concluded that a very small fraction of ingested cerium is absorbed by the GI tract.

Once absorbed, cerium is distributed to the blood. The i.v. data showed that cerium was rapidly cleared from the blood, with an average half-life of 1.5 hours in rats in the rapid elimination phase and an average half-life of 42 hours in the slow elimination phase (Desrosiers et al. 2021). After i.v. administration of cerium chloride in rats, Jomaa et al. (2021) reported 1.6 hours and 28 hours as average elimination half-lives for slow and fast elimination phases, respectively. Absorbed radioactive cerium is primarily retained in the bone, followed by the liver, muscle, kidney and ileum (Shiraishi and Ichikawa 1972). Body burdens at forty days after oral administration were 87%, 4.1%, 2.0%, 1.1% and 0.26% of the retained dose, respectively in bone, liver, muscle, kidney and ileum (Shiraishi and Ichikawa 1972). Desrosiers et al. (2021) reported 49% of administered dose was distributed to liver followed by spleen (1.38%), kidneys (0.42% and lungs (0.22%) after i.v. administration of 1 mg/kg bw cerium chloride in rats.

The primary route of elimination for cerium is the feces (US EPA 2009a). Bouchard et al. (2017) reported that approximately 90% to 100% of orally administered cerium is eliminated in feces during 0 to 72 hours post-dosing. Urine is a minor route of elimination. The maximum percentages of orally administered dose of 100 and 1000 mg/kg bw recovered in urine from 0 to 72 hours post-dosing were 0.011 and 0.036%, respectively (Bouchard et al. 2017). Other authors have reported a similar elimination pattern; Moskalev (1959) reported fecal excretion of 99% of orally administered radio-labelled cerium within 3-days post-administration. Bjondahl (1976) reported urinary elimination of less than 1% of i.v. injected cerium chloride over 4 days in mice and Desrosiers et al. (2021) reported approximately 0.3% recovery of i.v. injected cerium (1 mg cerium chloride/kg bodyweight) in urine during the day 0 to 7 post dosing. Cerium excretion in rat urine is affected by the dose administered, as cumulative urinary excretion on day 7 post-dosing represented 0.73%, 0.39% and 0.023% of a single dose of 0.3, 1.0 and 10 mg/kg bw cerium chloride, respectively, administered via i.v. injection (Jomaa et al., 2021). A relatively short initial elimination half-life suggests there is low systemic exposure to cerium (US EPA 2009a).

Human inhalation data from occupational studies indicated that, in general, inhaled cerium (as cerium oxide) is not systemically available (Yokel et al. 2014). Based on

kinetic data from animal studies and human occupational studies, it can be expected that systemic exposure to cerium in the general population is low (US EPA 2009a).

Biomonitoring data

A summary of the biomonitoring data for total cerium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for this specific cerium-containing substance. Cerium was not detected in 99.53% of the Canadian population at the limit of detection of 0.05 µg/L (50 ng/L). The LOD was considered to be sufficiently low. The median and 95th percentile cerium concentrations were below the detection limit.

Human health effects

The toxicology of cerium-containing substances was reviewed by US EPA (2009a). While acute oral toxicity data for cerium-containing substances is limited, oral gavage studies, in which rodents were exposed up to 1000 mg/kg bw as cerium chloride-sodium citrate complex, showed GI tract irritation and hyperactive lymphoid follicles (US EPA 2009a). Limited available sub-chronic and chronic toxicity studies in animals have reported effects in the cardiovascular system, including cardiac fibrosis and changes in hemoglobin oxygen affinity. However, these studies are limited by poor study designs (US EPA 2009a). There are insufficient data to conclude on carcinogenicity, genotoxicity, reproductive and developmental effects for cerium-containing substances (US EPA 2009a). Based on kinetic data and the available toxicity data, acute and sub-chronic (or short-term) exposure to hexanoic acid, 2-ethyl-, cerium(3^+) salt is not likely to cause adverse health effects in humans.

Risk characterization

The available information on this substance, that is, low detection of total cerium in biomonitoring data (whole blood), the low absorption as indicated in the toxicokinetic data, and limited substance-specific consumer uses ([CBI], including infrequent use products), indicates that exposure is minimal for hexanoic acid, 2-ethyl- cerium (3^+) salt in the general population. Thus, hexanoic acid 2-ethyl- cerium (3^+) salt in this assessment is of low concern to the health of the general public in Canada at current levels of exposure.

5.1.2 Germane, tetrachloro-

There is no toxicokinetic data and limited human health effects data available on germane, tetrachloro-. Therefore, available data on substances that contain the germanium metal moiety were used as a surrogate. Based on the results of the literature search, it was determined that toxicokinetic studies for germanium-containing substances are conducted primarily using germanium dioxide.

Toxicokinetic data

Germanium was almost completely and rapidly absorbed after oral exposure in rats (10 mg of germanium dioxide by oral gavage), amounting to 76.3% of the administered dose within 4 hours and 96.4% in 8 hours (Rosenfeld 1954; Browning 1969; Ohri et al. 1993). Human patients that were treated with 25 to 75 mg/kg bw of radio-labelled germanium (Ge^{132}) absorbed 30% of the administered dose from the GI tract (Miyao et al. 1980).

Once absorbed, germanium is rapidly transported in blood to other tissues and organs throughout the body without binding to plasma proteins (Dudley and Wallace 1952). When rats were orally administered germanium dioxide (6 µmol/kg bw/day), the highest initial concentrations of germanium were found in kidney and liver, but these concentrations declined as early as 6 hours after absorption (Browning 1969; Kobayashi and Ogra 2009). No selective tissue localization or storage was detected in animals tested (Dudley and Wallace 1952). Twenty-four hours after mice were orally exposed to germanium dioxide, there were no detections of germanium in any of the tissues, which suggest rapid elimination of germanium from the body (Shinogi et al. 1989). The biological half-lives of germanium in the blood, brain and pancreas of mice were 1.2, 6.3 and 4.5 hours, respectively (Shinogi et al. 1989). In rats, half-lives were 1.5 days for whole body retention, 1 to 2 days in the liver and 4 days in kidneys (Rosenfeld 1954). Available data for other species (for example, rabbit) are indicative of a half-life closer to 72 hrs (Dudley and Wallace 1952).

Absorbed germanium excretes primarily via urine followed by feces without being metabolized (Dudley and Wallace 1952; Rosenfeld 1954; Browning 1969; Kobayashi and Ogra 2009). Dudley and Wallace (1952) and Dudley (1953) showed that when radio-labelled germanium dioxide was intravenously injected to dogs and rabbits, 90% and 75% of administered germanium, respectively, was excreted in urine within 72 hours. In both species, an average of 9% was excreted in the feces during that time. When human volunteers were given a single oral dose of 100 mg Ge-132, urinary excretion peaked at around 3 hours and the concentration in urine returned to pre-dosing levels after 24 hours (Tao and Bolger 1997). The inhalation elimination half-life of germanium (exposed as germanium or germanium dioxide) in occupationally exposed workers ranged from 8.2 to 18.1 hours (Roels and Buchet 2001).

Biomonitoring data

A summary of the biomonitoring data for total germanium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for this specific germanium-containing substance. Germanium was not detected in 100% of the Canadian population at the limit of detection of 1 µg/L (1 000 ng/L). The LOD was considered to be sufficiently low. The median and 95^{th} percentile germanium concentrations were below the detection limit.

Human health effects

Acute toxicity of germanium is minimal with LD_{50} values ranging from approximately 6 to 13 g radioactive germanium/kg bw in male and female mice (Tao and Bolger 1997). Animal sub-chronic and chronic dietary and drinking water studies have reported that the kidney is the primary target organ for germanium toxicity (Tao and Bolger 1997). In a sub-chronic study, when rats were fed 150 mg/kg bw/day of germanium dioxide for 13 weeks, animals showed biochemical and pathological changes associated with renal toxicity, including increased blood urea nitrogen, serum creatinine and renal cell degeneration (Tao and Bolger 1997). Based on the results of chronic studies (Toa and Bolger 1997), it is evident that germanium-containing substances are more harmful to health when administered via drinking water than in the diet.

Tao and Bolger (1997) reported human cases linking prolonged intake (2 to 22 months) of germanium products (for example, germanium-containing dietary supplements) with renal failure. Impaired renal function was observed long after germanium intake ceased (Tao and Bolger 1997). According to the available literature, germanium in the form of germanium dioxide is more harmful to humans than to rodents (Tao and Bolger 1997). However, the available toxicity data are predominantly for germanium dioxide, which is not a substance included in this grouping and lower toxicity has been observed for other germanium substances (Browning 1969). In addition, the purity or the composition of germanium compounds used in these human case studies and animal studies were not well documented. There are no indications of carcinogenicity, genotoxicity, reproductive and developmental effects for germanium-containing substances (Tao and Bolger 1997). Furthermore, due to rapid elimination from the body and lack of storage sites, germanium is not expected to be systemically available in humans.

Risk characterization

On the basis of the available information on this substance, that is, no detection of total germanium in biomonitoring data (whole blood) and no CAS RN specific consumer uses (including infrequent use products identified), exposure is minimal for germane, tetrachloro- in the general population. Thus, germane, tetrachloro- in this assessment is of low concern to the health of the general population of Canada at current levels of exposure.

5.1.3 Lanthanum oxide, lanthanum chloride and lanthanum boride

Toxicokinetic data

There is limited toxicokinetic data or human health effects data available on lanthanum oxide, lanthanum chloride or lanthanum boride. Therefore, available data on substances that contain the lanthanum metal moiety were used as a surrogate. Based on the results of the literature search, oral toxicokinetic studies for lanthanum were primarily conducted using lanthanum carbonate, which is used to prevent phosphate absorption

in patients with hyperphosphataemia due to renal failure (Pennick et al. 2006; Mohammed and Hutchison 2009; Shire Pharmaceutical 2012). Lanthanum carbonate is insoluble in water; however, it is soluble in the acidic environment of the upper gastrointestinal tract to produce free lanthanum cations (Curran and Robinson 2009).

GI tract absorption of lanthanum from orally administered lanthanum carbonate in humans is low, ranging from 0.00015% to 0.00224% (averaging about 0.001%) (Pennick et al. 2006). A similar result was reported in a dog study, in which oral absorption was reported as 0.00005% for both sexes (Shire Pharmaceutical 2002 as cited in US FDA 2004). The International Commission on Radiological Protection (ICRP) (Publication 30) recommended a reference GI absorption fraction of 3×10^{-4} for all forms of lanthanum and all lanthanoids (ICRP 1981). The primary reason for low oral absorption of lanthanum carbonate is due to the formation of chelate complexes with dietary phosphates in the gastrointestinal tract (Damment and Pennick 2008).

Plasma concentrations of lanthanum in dialysis patients receiving therapeutic doses (up to 3 g/day lanthanum carbonate for up to 4 weeks) are reported to be low (about 0.2 to 0.78 µg/L) (Pennick et al. 2006). In systemic circulation, almost all lanthanum is protein-bound (>99.7% in humans) and binding is non-specific (Shire Pharmaceutical 2012). Kinetic studies indicate that there is no significant binding of lanthanum to red blood cells (Damment and Pennick 2007). Lanthanum plasma concentrations decline either biphasically or triphasically, with a mean terminal elimination half-life of 35 hours (range 16-48 hours) (Marroum and Dorantes 2004; Pennick et al. 2006).

Lanthanum predominantly deposits in bones and liver (Pennick et al. 2006). Deposition of less than 1 µg lanthanum/g tissue has been demonstrated in long-term animal studies, in which animals were exposed to oral doses of greater than 50 g lanthanum/day (Shire Pharmaceutical 2012). Lanthanum deposited in bones eliminates slowly, with biological half-lives more than 1000 days (ICRP 1981, 1994).

Fecal elimination is the primary route of elimination for both unabsorbed and biliary excreted lanthanum, which amounts to approximately 93.4% of the administered dose (Pennick et al. 2006; Damment and Pennick 2008; Shire Pharmaceutical 2012). Approximately 1.7% of plasma clearance occurs through the renal system in humans (Pennick et al. 2006).

Biomonitoring data

A summary of the biomonitoring data for total lanthanum in whole blood is provided in Table 5-1 and are used as surrogate exposure data for these specific lanthanum-containing substances. Lanthanum was not detected in 99.72% of the Canadian population at the limit of detection of 0.05 µg/L (50 ng/L). The LOD was considered to be sufficiently low. The median and 95th percentile lanthanum concentrations were below the detection limit.

Human health effects

Lanthanum substances have been reviewed by the US EPA (2018) and a REACH dossier is available (REACH 2018a; b). On the basis of an unpublished developmental neurotoxicity study in rats conducted according to OECD Test Guideline 426, maternal rats were exposed up to 1214 mg lanthanum/kg bw/day as lanthanum carbonate from implantation (gestational day 6) throughout lactation (post-natal day 20) (REACH 2018a). It was reported that there is no convincing evidence for a possible neurotoxic or developmental neurotoxic effect of lanthanum chloride in experimental animals (REACH 2018b).

In comparison, some studies indicated developmental neurotoxicity effects of lanthanum substances at low doses of exposure in experimental animals (Feng et al. 2006a; Behets et al. 2006a; Feng et al. 2006b; He et al. 2008) to lanthanum carbonate as an analogue for lanthanum chloride. In 2018, the US EPA identified a LOAEL for chronic exposure of experimental animals to lanthanum chloride as low as 1 mg lanthanum/kg bw/day based on neurological effects reported in He et al. (2008). While observations of developmental neurotoxicity could indicate a high hazard potential, to date there are no international classifications for reproductive toxicity for the lanthanum substances in this assessment.

No carcinogenic data were identified for soluble lanthanum (US EPA 2018).

Risk characterization

There were no reports of manufacture, import or uses identified in the survey issued pursuant to section 71 of CEPA for lanthanum boride and lanthanum chloride. There were no reports of manufacture for lanthanum oxide and imports were limited to industrial uses as a catalyst. Exposure from environmental media is expected to be negligible. Consumer uses identified were very limited (that is, swimming pool use for lanthanum chloride) and were not expected to result in significant exposure.

On the basis of the available information on this substance, that is, low detection of total lanthanum in biomonitoring data (whole blood), the low absorption as indicated in the toxicokinetic data, and limited CAS RN specific consumer uses, exposure is minimal for lanthanum oxide, lanthanum chloride, and lanthanum boride in the general population. Thus, lanthanum oxide, lanthanum chloride, and lanthanum boride in this assessment are of low concern to the health of the general population of Canada at current levels of exposure. However, it should be noted that more biomonitoring data for lanthanum in different matrices, such as urine, are starting to emerge from various community based surveys targeted for monitoring rare earth elements in Northern Canada (Cirtiu et al. 2022). In addition, as noted above, the possible developmental neurotoxicity attributed to lanthanum chloride has not been fully evaluated within this assessment or internationally.

5.1.4 Hexanoic acid, 2-ethyl-, neodymium (3+) salt

There is no toxicokinetic data or human health effects data available on hexanoic acid, 2-ethyl-, neodymium (3+) salt. Therefore, available data on substances that contain the neodymium metal moiety were used as a surrogate. Based on the results of the literature search, it was determined that toxicokinetic and human health effects studies for neodymium-containing substances are conducted primarily using neodymium chloride.

Toxicokinetic data

Neodymium is poorly absorbed from the GI tract in both humans and experimental animals (US EPA 2009b). Comparing blood neodymium levels in male Sprague-Dawley rats following oral and i.v. exposures, Bouchard et al. (2017) were able to estimate oral neodymium chloride absorption at 0.6% and 0.07% of the 100 mg/kg and 1000 mg/kg bw oral doses administered, respectively. Pawel et al. (2007) reported oral absorption in the range of 0.01% to 0.1% based on human and animal data.

Once absorbed, neodymium showed rapid blood clearance, with an elimination half-life of, on average, 3 hours in rats (Bouchard et al. 2017). The ICRP kinetic model for humans applied a blood half-life of 0.25 day (6 hours) (ICRP 1981, 1994). According to Desrosiers et al. (2021), neodymium shows an initial rapid elimination from blood with an average elimination half-life of 1.3 hours, followed by a slower elimination phase with an average elimination half-life of 35 hours. Similar elimination half-lives were reported in Jomaa et al. (2021) after i.v. injection of neodymium chloride in rats.

From blood, neodymium distributes to tissues. Following i.v. administration of 1 mg neodymium chloride/kg bw to rats, the highest concentrations of neodymium were found in the liver (37% of the administered dose), followed by the spleen (0.47%), kidney (0.42%) and lungs (0.07%) (Bouchard et al. 2017; Desrosiers et al. 2021). According to the ICRP model, approximately 45% of absorbed neodymium is distributed to liver, 45% to bone, and 10% to excretion pathways, such as the kidney and lungs (ICRP 1981, 1994). The ICRP kinetic model suggests that the liver is an important organ for neodymium accumulation. The ICRP model assigned the following elimination half-lives: 5 years for liver and other excretion pathways (such as kidney and lungs); 20 years for cortical bone surfaces; and 5 years for trabecular bone surfaces (ICRP 1981, 1994).

Bouchard et al. (2017) reported that approximately 100% and 53% of neodymium from an oral. administered dose of 100 or 1000 mg neodymium chloride/kg bw, respectively, was recovered in feces of rats during the 0 to 72 hours post dosing, while a very small fraction was eliminated in urine (0.0016% and 0.0006%, respectively) (Bouchard et al. 2017). In the same study, when rats were i.v. injected with neodymium chloride at 1 mg/kg bw, approximately 0.9% of the administered neodymium was recovered in urine during the 0 to 7 days post-dosing (Bouchard et al. 2017; Desrosiers et al. 2021). Neodymium excretion in rat urine is affected by the dose administered, as cumulative

urinary excretion from day 0 to 7 post-dosing represented 0.99%, 0.62% and 0.033% of an i.v. injected dose of 0.3, 1.0 and 10 mg neodymium chloride/kg bw, respectively (Jomaa et al., 2021). Conversely, the ICRP model has assigned an equal excretion dose from the urinary or fecal route (that is, an elimination ratio of 1:1) from systemic activity (ICRP 1994).

Biomonitoring data

A summary of the biomonitoring data for total neodymium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for this specific neodymium-containing substance. Neodymium was not detected in 99.88% of the Canadian population at the limit of detection of 0.05 µg/L (50 ng/L). The LOD was considered to be sufficiently low. The median and 95th percentile neodymium concentrations were below the detection limit.

Human health effects

US EPA (2009b) has published an assessment report that derived Provisional Peer-Reviewed Toxicity Values for neodymium chloride. The oral LD_{50} values for rats and mice were 905 and 3024 mg neodymium/kg bw/day, respectively (US EPA 2009b). In a 90-day dietary study, male and female rats were administered neodymium chloride. The NOAEL was identified as the highest dose tested (that is, 840 and 950 mg neodymium chloride/kg bw/day, respectively for males and females) (Haley et al. 1964 as cited in US EPA 2009b). There are no indications of carcinogenicity, genotoxicity, reproductive and developmental effects for neodymium (US EPA 2009b).

Based on available kinetic data and limited toxicity data, acute and sub-chronic (short-term) exposure to hexanoic acid, 2-ethyl-, neodymium (3+) salt is not likely to cause adverse health effects in humans.

Risk characterization

One the basis of the available information on this substance, that is, low detection of total neodymium in biomonitoring data (whole blood), the low absorption as indicated in the toxicokinetic data, and limited CAS RN specific consumer uses (CBI), exposure is minimal for hexanoic acid, 2-ethyl-, neodymium (3+) salt. Thus, hexanoic acid, 2-ethyl-, neodymium (3+) salt in this assessment is of low concern to the health of the general population of Canada at current levels of exposure.

5.1.5 Praseodymium oxide

There is limited toxicokinetic data and human health effects data available on praseodymium oxide. Therefore, available data on substances that contain the praseodymium metal moiety were used as a surrogate. Based on the results of the literature search, it was determined that human health effects studies for

praseodymium-containing substances are conducted primarily using praseodymium chloride.

Toxicokinetic data

Praseodymium is poorly absorbed from the GI tract. Comparing blood praseodymium levels following oral and i.v. exposures to male Sprague-Dawley rats, Bouchard et al. (2017) were able to estimate 1.8% and 0.9% oral absorption of the 100 and 1000 mg/kg bw orally administered doses of praseodymium chloride, respectively. Pawel et al. (2007) reported oral absorption in the range of 0.01% to 0.1% based on animal data.

The i.v. data from the same study showed that praseodymium was rapidly cleared from blood, with an average half-life of 1.2 hours in rats during the rapid elimination phase and an average half-life of 54 hours during the slow elimination phase (Desrosiers et al. 2021). Jomaa et al. (2021) reported 1.6 hours and 32 hours as average elimination half-lives for slow and fast elimination phases, respectively, after i.v. injection of praseodymium chloride. According to the i.v. study, praseodymium is distributed throughout the body, with the highest concentration observed in the liver (39% of the administered dose), followed by the spleen (0.8%), kidney (0.5%) and lungs (0.1%) (Desrosiers et al. 2021). Approximately 0.6% of 1 mg/kg bw praseodymium chloride was recovered in urine from 0 to 7 days post-dosing (Desrosiers et al. 2021). Praseodymium excretion in rat urine is affected by the dose administered, as cumulative urinary excretion of praseodymium on day 7 post-dosing represented 0.76%, 0.48% and 0.025% of a single dose of 0.3, 1.0 or 10 mg/kg bw praseodymium chloride administered via i.v. injection, respectively (Jomaa et al., 2021).

Approximately 90% and 100% of praseodymium from the orally administered dose of 100 and 1000 mg praseodymium oxide/kg bw, respectively were recovered in feces within 72 hours post dosing, whereas a very small fraction (approximately 0.02% for both dose levels) was eliminated in urine (Bouchard et al. 2017).

Biomonitoring data

A summary of the biomonitoring data for total praseodymium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for this specific praseodymium-containing substance. Praseodymium was not detected in 99.91% of the Canadian population at the limit of detection of 0.02 µg/L (20 ng/L). The LOD was considered to be sufficiently low. The median and 95th percentile praseodymium concentrations were below the detection limit.

Human health effects

US EPA (2009c) has published an assessment report that derived Provisional Peer-Reviewed Toxicity Values for praseodymium chloride. The LD_{50} for rats and mice were 1134 and 2565 mg praseodymium/kg bw, respectively (US EPA 2009c). A REACH

dossier available on praseodymium oxide reported an LD_{50} of >2 000 mg/kg bw in rats from an unnamed study (OECD 401) (REACH 2018a). In rats exposed to praseodymium chloride through their diet for 90 days, no treatment related effects were reported. The highest doses tested in male and female rats, which were 479 and 541 mg praseodymium/kg bw/day, respectively were considered as NOAELs (Haley et al. 1964 as cited in US EPA 2009c). There are no indications of carcinogenicity, genotoxicity, reproductive and developmental effects for praseodymium (US EPA 2009c).

Based on available kinetic and toxicity data, acute and sub-chronic (short-term) exposure to praseodymium oxide is not likely to cause adverse health effects in humans.

Risk characterization

The available information on this substance, that is, low detection of total praseodymium in biomonitoring data (whole blood), the low absorption as indicated in the toxicokinetic data, and no CAS RN specific consumer uses (including infrequent use products identified)data presented above, confirms that exposure is minimal to praseodymium oxide. Thus, praseodymium oxide in this assessment is of low concern to the health of the general population of Canada at current levels of exposure.

5.1.6 Tellurium oxide and tellurium, tetrakis (diethylcarbamodithioato-S,S')

There is limited toxicokinetic data available on tellurium oxide and tellurium, tetrakis (diethylcarbamodithioato-S,S'). Therefore, available data on substances that contain the tellurium metal moiety were used as a surrogate.

Toxicokinetic data

The fraction of tellurium orally absorbed depends on its valence state. Based on volunteer studies, the estimated oral absorption of tellurate (Na_2TeO_4), tellurite (Na_2TeO_3) or metallic tellurium was 23%, 21% and 10%, respectively (Kron et al. 1991a). A study reported dermal absorption of about 5% within 15 minutes after application of an unknown quantity of radioactive tellurium to the skin of piglets (MAK 2006).

Tellurium is transferred throughout the body via systemic circulation. In blood, approximately 90% of tellurium is found in erythrocytes in both humans and rats (Agnew and Cheng 1971; Kron et al. 1991b). The highest tissue tellurium levels were found in the kidneys followed by heart, lung, spleen and liver. Bones act as a long-term storage, containing 90% of total tellurium body burden (Schroeder et al. 1967). Studies have shown that tellurium can transfer to the fetus through the placenta, and can also cross the blood brain barrier (Agnew et al. 1968; Agnew 1972). Based on tellurium retention half-lives, the tissues could be divided into three groups: lungs, blood, liver and heart

with a half-life of approximately 10 days; muscle, spleen, and kidneys with a half-life of approximately 20 days; and femur (skeleton) with a half-life greater than 200 days (Hollins 1969).

The main metabolic pathway for tellurium is through methylation. Trimethyl tellurium is a major urinary metabolite of tellurium (Ogra et al. 2007; Kobayashi and Ogra 2009).

Elimination is mainly dependent on the chemical form and route of exposure to tellurium. In rats, 79% of the orally administered radio-labelled tellurium dioxide (^{127}Te as tellurium dioxide) was found in the feces and 3% in the urine (MAK 2006). Kron et al. (1991a) showed that healthy volunteers (n=5) orally exposed to tellurite, tellurate, metallic form and bound forms in cress salad (cress was cultivated in tellurium-containing water), excreted <8%, 3% to 25%, 4% to 9% and 3% in the urine, respectively. Small amounts (0.1%) of absorbed tellurium are eliminated via exhaled air as dimethyl telluride, which causes garlic-like breath odour (Gerhardsson 2015; HSDB 2009). Orally administered radio-labelled tellurium as tellurium dioxide showed a multi-phasic elimination pattern in rats: 84% was eliminated during the first phase ($t_{1/2}$ = 3 hours), 11% in a second phase ($t_{1/2}$ = 19 hours) and 5% in a third phase ($t_{1/2}$ = 12.3 days) (MAK 2006).

After a single intra-tracheal installation of cadmium telluride in rats, the tellurium content in the lungs decreased to 75% after 3 days, 69% after 7 days, 53% after 14 days, and 33% after 28 days. One day after installation, tellurium was detected in the spleen, kidneys, femur, liver and blood, with maximum levels reached after 14 days (MAK 2006).

Biomonitoring data

A summary of the biomonitoring data for total tellurium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for these specific tellurium-containing substances. Tellurium was not detected in 100% of the Canadian population at the limit of detection of 0.4 µg/L (400 ng/L). The LOD was considered to be sufficiently low. The median and 95th percentile tellurium concentrations were below the detection limit.

Human health effects

RIVM (1998) reviewed tellurium toxicity in either laboratory animals or humans. In addition, REACH dossiers are available for tellurium dioxide and tellurium, tetrakis (diethylcarbamodithioato-S,S') (REACH 2018c). Acute toxicity of tellurium dioxide and tellurium, tetrakis (deithylcarbamodithioato-S,S') via the oral route is very low; the LD_{50} values in rats are >5000 mg/kg bw for both tellurium dioxide and tellurium, tetrakis (diethylcarbamodithioato-S,S') (REACH 2018c; REACH 2020). When volunteers were given a single oral dose up to 40 g (570 mg tellurium/kg bw/day) metallic tellurium, no toxic symptoms were observed (RIVM 1998; REACH 2017a). A short-term combined

repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) was conducted in rats administered tellurium diethyldithiocarbamate (that is tellurium, tetrakis (diethylcarbamodithioato-S,S') via oral gavage. No adverse effects were reported at the highest dose tested (NOAEL=1 mg tellurium diethyldithiocarbamate/kg bw/day) (REACH 2018c). The same study reported a NOAEL of 5 mg tellurium diethyldithiocarbamate/kg bw/day for reproductive toxicity (REACH 2018c). In addition, a 28-day repeated dose study (OECD 407) that administered tellurium dioxide to rats via oral gavage reported a LOAEL of 25 mg tellurium dioxide/kg bw/day for male rats, based on a significant decrease in body weight (21%), whereas female rats did not show any effects at the same dose (REACH 2020). A 2-year carcinogenicity studies conducted in rats and mice administered ethyl telluric [that is tellurium, tetrakis (diethylcarbamodithioato-S,S')] in diet suggested no evidence of carcinogenicity (NTP 1979). In addition, there is no evidence to indicate that tellurium, tetrakis (diethylcarbamodithioato-S,S') is genotoxic (Valencia et al. 1985; Mortelmans et al. 1986). Based on available kinetic and toxicity data, acute and sub-chronic (short-term or infrequent) exposure to tellurium oxide and tellurium, tetrakis (diethylcarbamodithioato-S,S') are not likely to cause adverse health effects in humans.

Risk characterization

On the basis of the available information on this substance, that is, no detection of total tellurium in biomonitoring data (whole blood), toxicokinetic data and no substance (CAS RN)-specific consumer uses identified (including infrequent use products), exposure to tellurium oxide and tellurium, tetrakis (diethylcarbamodithioato-S,S') is minimal. Thus, tellurium oxide and tellurium, tetrakis (diethylcarbamodithioato-S,S') in this assessment are of low concern to the health of the general population of Canada at current levels of exposure.

5.1.7 Yttrium oxide

There is no toxicokinetic data available on yttrium oxide. Therefore, available data on substances that contain the yttrium metal moiety were used as a surrogate. Based on the results of the literature search, it was determined that toxicokinetic studies for substances containing the yttrium metal moiety are conducted primarily using yttrium chloride.

Toxicokinetic data

Yttrium is more readily absorbed from the GI tract than cerium, neodymium, and praseodymium. Comparing blood yttrium levels of male Sprague-Dawley rat following oral and i.v. exposures, Bouchard et al. (2017) were able to estimate the oral absorption at 6% and 23% of the 100 and 1000 mg/kg bw orally administered doses of yttrium chloride, respectively.

Hirano et al. (1993) showed that when male rats were given 1 mg (4 mg yttrium/kg bw) of yttrium chloride via i.v. injection, blood yttrium levels decreased rapidly within 3 hours. The authors also noted approximately 75% of the dose was accumulated in the liver, with an elimination half-life of 144 days. According to the study authors, the long half-life in liver was likely due to insolubilized yttrium in lysosomal inclusions (Hirano et al. 1993). The highest concentrations of yttrium were found in the liver followed by the spleen, femur and then kidneys on day 8 following i.v. injection of yttrium at 10 mg/kg bw (Nakamura et al. 1993). The i.v. portion of the Bouchard et al. (2017) study (published as Desrosiers et al. 2021) also reported an initial rapid elimination of yttrium from blood with an average elimination half-life of 1.8 hours, followed by a slower elimination phase with an average elimination half-life of 35 hours. Similar elimination half-lives were reported in Jomaa et al. (2021) after i.v. injection of yttrium chloride in rats. The highest tissue distribution was observed in the liver (13% of the administered dose) followed by the kidney (0.44%), spleen (0.35%) and lungs (0.07%) (Desrosiers et al. 2021). Approximately 2.4% of the administered yttrium was recovered in urine from 0 to 7 days following a single i.v. injection of 1 mg/kg bw yttrium chloride (Desrosiers et al. 2021). Yttrium excretion in rat urine is affected by the dose administered, as cumulative urinary excretion on day 7 post-dosing represented 4.2%, 1.9% and 0.2% of a single i.v. dose of 0.3, 1.0 and 10 mg/kg bw yttrium chloride, respectively (Jomaa et al., 2021).

When Nakamura et al. (1991) orally administered male rats with yttrium chloride at 100 and 1000 mg/kg bw, approximately 97% and 94%, respectively, were recovered in feces. Bouchard et al. (2017) estimated fecal elimination of yttrium for the same oral dose levels of yttrium chloride as 88% and 68%, respectively. Urine is a minor route of elimination. In general, urine elimination of both orally and i.v. administered yttrium chloride was less than 1% (Hayashi et al. 2006; Kitamura et al. 2012; Bouchard et al. 2017; Desrosiers et al. 2021). Conversely, Nakamura et al. (1991) did not detect yttrium in urine or any other tissues while Jomaa et al. (2021) reported dose-dependent urinary elimination with above 1% of urinary elimination when administered dose level was relatively small.

Intra-tracheal instillation of yttrium chloride in rats indicated slow pulmonary clearance, with a half-life of 168 days (Hirano et al. 1990). Wenzel et al. (1969) documented systemic distribution of yttrium after inhalation exposure to a radio-labelled yttrium isotope. The highest levels were reported in skeleton, followed by lungs and liver (Wenzel et al. 1969).

Biomonitoring data

A summary of the biomonitoring data for total yttrium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for this specific yttrium-containing substance. Yttrium was not detected in 99.88% of the Canadian population at the limit of detection of 0.06 µg/L (60 ng/L). The LOD was considered to be sufficiently low. The median and 95th percentile yttrium concentrations were below the detection limit.

Human health effects

There are no indications of carcinogenicity, genotoxicity, reproductive and developmental effects for yttrium oxide (REACH 2017b). The results of micronucleus and comet assays in rats concluded that yttrium oxide is not genotoxic (Panyala et al. 2017; Panyala et al. 2019). The LD_{50} value in rats via oral gavage is >5000 mg yttrium oxide/kg bw (REACH 2017b). Lambert et al. (1993) reported an acute oral LD_{50} greater than 5.0 g yttrium oxide/kg in rats. A more recent acute oral toxicity study in rats (OECD 420) reported no adverse effects at 1000 mg yttrium oxide/kg bw/day (highest dose tested) (Panyala et al. 2017). A combined repeated dose toxicity study with a reproduction/developmental toxicity screen (OECD 422) in rats exposed via oral gavage for at least 28 days for males and 54 days for females did not report any effects up to the maximum dose tested (that is, 1000 mg yttrium oxide/kg bw/day, a NOAEL) (REACH 2017b). In addition, a short-term repeat dose study (OECD 407) in rats orally administered yttrium oxide reported a NOAEL of 480 mg/kg bw/day (highest dose tested) (Panyala et al. 2019). Based on the available acute and short-term toxicity data, acute and sub-chronic (short-term or infrequent) exposure to yttrium-containing substances are not likely to cause adverse health effects in humans.

Risk characterization

On the basis of the available information on this substance, that is, low detection of total yttrium in biomonitoring data (whole blood), and no substance-specific consumer uses identified (including infrequent use products), exposure to yttrium oxide is expected to be minimal in the general population. For reasonably large population samples, such as CHMS, it is reasonable to assume that the population distribution appropriately captures the variability in biomarker concentrations, even for short half-life substances. Thus, yttrium oxide in this assessment is of low concern to the health of the general population of Canada at current levels of exposure.

5.2 Biomonitoring-based Approach 2

This science approach incorporates biomonitoring data from large population level biomonitoring programs with a human biomonitoring guidance value (for example, Biomonitoring Equivalents [BEs], and/or human biomonitoring values [HBM-I] from Germany) to identify substances of low concern for human health.

Similar to Biomonitoring-based Approach 1, Biomonitoring-based Approach 2 considers available Canadian and U.S. biomonitoring data based on the analysis of the substance or moiety in whole blood, serum, and/or urine. Total concentrations of a substance in blood or urine may provide a biologically relevant, integrated measure of exposures that may occur across multiple routes (for example, oral, dermal and inhalation) and sources, including environmental media, diet, and frequent or daily use products to which they were exposed. The Biomonitoring-based Approach 2 also incorporates health effects data relevant to humans in the assessment of risk. Human biomonitoring

guidance values are typically derived from existing health-based exposure guidance values, such as a reference dose (RfD) or tolerable daily intake (TDI) and/or pharmacokinetic data. In some cases, the human biomonitoring guidance values are based on human studies or epidemiological data.

A thorough review of available toxicokinetic data is an integral part of Biomonitoring-based Approach 2. A literature search on toxicokinetic data available on each individual substance in the grouping was conducted. In the absence of kinetic data for the substance (CAS RN), the kinetic data from studies conducted on the metal moiety was used as a surrogate. Biomonitoring-based Approach 2 is only recommended for use if the biomarker is considered adequate to quantify exposure in the general population. Bismuth and lithium-containing substances were assessed under Biomonitoring-based Approach 2. Epidemiology studies conducted in the 1970s reported that oral administration of bismuth as a treatment for GI tract disorders could cause health effects in individuals. Therefore, quantification of risk under Biomonitoring-based Approach 2 was utilized as a more protective approach for the risk assessment of bismuth-containing substances than the qualitative assessment under Biomonitoring-based Approach 1. Biobank data indicated that lithium was detected [>limit of detection (LOD)] in approximately 66% of the general population of Canada. Therefore, lithium-containing substances were assessed under Biomonitoring-based Approach 2.

If exposures (on the basis of biomonitoring data from large-scale studies) are below the human biomonitoring guidance value (on the basis of an RfD, TDI or other critical health effects), then the substance or metal moiety is considered to be of low concern to human health at current levels of exposure.

Uncertainties of Biomonitoring-based Approach-2

Uncertainties associated with this approach have been outlined in the Biomonitoring-based Approach 2 SciAD (Health Canada 2016b).

Although the CHMS biobank data are representative of the general population, CHMS is not a targeted survey and therefore it does not necessarily capture subpopulations which may have different exposures such as those associated with living in the vicinity of industrial facilities. Concluded cycles of CHMS also do not cover children under 3 years of age.

The CHMS cycle 2 biomonitoring data is representative of exposure during 2009 to 2011 in Canada. However, the use pattern analysis did not show any significant change in sources and uses for the substances included in this assessment from the time the CHMS survey was conducted to the present. Thus, it is likely that the biomonitoring data represent current levels of exposure, but do not capture exposures from potential future uses.

In the absence of substance specific kinetic, health effects and exposure data, data available on the metal moiety was used as a surrogate. It is important to note that there may be different bioavailability and health effects associated specific substance versus the metal moiety, in particular with soluble and insoluble substances.
Twenty-three substances met the criteria for being assessed using Biomonitoring-based Approach 2.

5.2.1 Bismuth-containing substances (7 CAS RNs)

Exposure assessment

In the absence of substance specific exposure information, data on the bismuth moiety were used as surrogate exposure data for the specific bismuth-containing substances in the assessment. Bismuth is a naturally occurring element that is present in environmental media (for example, air, water and dust) and food in Canada. The median and 95th percentile of total bismuth concentrations measured in Canada in outdoor air $PM_{2.5}$ samples were 0.21 ng/m^3 and 0.86 ng/m^3, respectively (n=447). Seventeen percent were below the LOD of 0.04 ng/m^3 (Rasmussen 2017). The median and 95th percentile of the personal air $PM_{2.5}$ concentrations were 0.07 ng/m^3 and 0.70 ng/m^3 (n=445), respectively. Thirty-nine percent were below the LOD of 0.04 ng/m^3 (Rasmussen 2017). The median and 95th percentile of the indoor air $PM_{2.5}$ were 0.06 ng/m^3 and 0.59 ng/m^3 (n=437), respectively. Forty percent were below the LOD of 0.04 ng/m^3 (Rasmussen 2017). The median and 95th percentile of total bismuth concentrations measured in Canadian urban house dust samples were 2.42 µg/g and 21.4 µg/g (n=1025) respectively (Rasmussen et al. 2022). Canadian drinking water samples from various distribution systems were tested for bismuth and all were below the detection limit of 1.0 µg/L (Tugulea et al. 2016). Average concentrations of bismuth were estimated in various food items in the Canadian Total Diet Study (TDS), which measured bismuth concentrations in foods from both natural and anthropogenic sources by preparing and processing food samples as they would be consumed in an average household (Health Canada 2016c; [modified 2020b]). Based upon results from the 2016, 2017, and 2018 data, the highest bismuth concentration was in hard cheese (0.026 µg/g) followed by processed cheese (0.014 µg/g) and baby food dinners with meat, poultry or eggs 0.014 µg/g (Health Canada [modified 2020b]). Further, using the TDS data, dietary intakes of bismuth were estimated for different age–sex groups of the Canadian population (Health Canada [modified 2011]). According to these results, average dietary intake in Canadians (all ages, males and females) was 0.010 µg/kg bw/day, with the highest intake in the 4-6 months age group at 0.101 µg/kg bw/day (Health Canada [modified 2011]).

Biomonitoring data

A summary of the biomonitoring data for total bismuth in whole blood is provided in Table 5-1 and are used as surrogate exposure data for these specific bismuth-containing substances.

Bismuth was not detected in 95.4% of the Canadian population at the limit of detection of 0.1 µg/L (100 ng/L) (Jayawardene et aI. 2021). The median and 95th percentile were below the detection limit.

Health effects assessment

Toxicokinetic data and biomarker adequacy

The focus of the toxicokinetic data review was on the oral route of exposure as this would be the predominant route of potential intake of bismuth-containing substances for the general population. Oral absorption of tripotassium dicitrato bismuthate in humans is very low, amounting to less than 1% of the orally ingested bismuth (Gavey et al. 1989). Investigators have reported a large variation in oral absorption based on inter- and intra-individual differences and the type of bismuth administered (Slikkerveer and de Wolff 1989; Benet 1991; Lacey et al. 1994). Some of these reported variabilities seem to be attributed to the use of different study protocols (Benet 1991; Lacey et al. 1994). Bismuth absorption decreases with increased administered dose; the bioavailability of bismuth from bismuth subsalicylate in rats for 2 and 250 mg/kg bw was 0.5% and 0.025%, respectively (Slikkerveer and de Wolff 1989).

Bismuth, administered as bismuth subsalicylate, is rapidly absorbed into systemic circulation, with peak blood concentrations observed between 15 to 60 minutes post dosing (Slikkerveer and de Wolff 1989). The blood half-lives of bismuth from oral doses of ranitidine bismuth citrate are tri-phasal, averaging 20 minutes, 11.1 hours, and 20.7 days (Koch et al. 1996a). Other authors have reported plasma half-life of about 5 days for absorbed bismuth in humans (Hardman et al. 1996). According to Koch et al. (1996a), plasma bismuth takes approximately 14 to 28 days to reach a steady state. Previous multiple-dose studies in humans have also shown that bismuth (administered orally as bismuth subcitrate) takes about 7 to 29 days to reach steady state (Froomes et al. 1989). From blood, bismuth is distributed predominantly to the kidneys, followed by the spleen, brain, lungs, and liver (Prino and Klantschnigg 1960).

The main route of elimination for unabsorbed bismuth-containing substances is via the feces, whereas urine is the primary excretion pathway for absorbed bismuth in both humans and animals (Slikkerveer and de Wolff 1989; Koch et al. 1996a). Some of the absorbed bismuth is also eventually eliminated via the feces. In fact, according to Lee (1981), more than 99% of ingested bismuth in humans is excreted in the feces. Urinary elimination of the administered dose in humans has been reported in the range of 0.003% to 0.04% (Bierer et al. 1990; Koch et al. 1996a). Washout profiles in plasma and urine indicated an elimination half-life of approximately 21 days for bismuth (Froomes et al. 1989).

The concentration of bismuth in blood represents bioavailable bismuth, which is the fraction systemically available at the target sites of health effects. A frequent or daily exposure to bismuth can be expected in the general population from the presence of

bismuth in diet, products available to consumers and environmental media (Poddalgoda et al. 2020). Thus, the blood concentration of bismuth is likely at steady state. In addition, when using large population samples, such as CHMS, it is reasonable to assume the biomonitoring data would cover off potential intermittent increases in exposures due to products used by consumers on an infrequent basis. Thus, bismuth blood levels can be considered a suitable biomarker to quantify exposure from all routes to all sources of bismuth.

Health effects data and derivation of biomonitoring equivalent

Bismuth-containing substances, in particular bismuth subsalicylate and colloidal bismuth subcitrate, are widely used medicinally for the treatment of diarrhea and peptic ulcer disease in the GI tract (Bradley et al. 1989). Although the introduction of other effective drugs for reducing gastric secretion (such as histamine H2 antagonists and proton pump inhibitors) has reduced the traditional uses of bismuth salts as a generic gastric remedy, the use of bismuth in helicobacter pylori eradication and in the treatment of traveler's diarrhea remains important (Alkim et al. 2017). However, the medicinal use is limited to treatment of pathologies in the GI tract and systemic absorption is not required for efficacy (Slikkerveer and de Wolff 1989). Although adverse effects of bismuth-induced toxicity are rare, an outbreak of neurotoxicity (reversible encephalopathy) was reported in France and neighbouring countries in the mid 1970s, where people were given various forms of bismuth salts (for example, bismuth subsalicylate, bismuth subnitrate and bismuth subcarbonate) as a treatment for gastrointestinal effects (Slikkerveer and de Wolff 1989). Another small-scale outbreak of encephalopathy was reported in Australia during the same time period due to therapeutic use of bismuth salts (Slikkerveer and de Wolff 1989). These patients were exposed to approximately 370 mg Bi/day (Slikkerveer and de Wolff 1989). The encephalopathy was reported only in patients with higher serum bismuth levels (Froomes et al. 1989). In a study of 63 patients with encephalopathy after receiving bismuth therapy, the median plasma concentration of bismuth ranged from 680 to 700 µg/L (Hillemand et al. 1977). Based on these studies, the investigators of this bismuth-induced encephalopathy outbreak concluded that a blood bismuth concentration less than 50 µg/L is a safe level (Hillemand et al. 1977). In addition, reversible nephrotoxicity and osteoarthropathy were also reported for acute and chronic exposure to other forms of bismuth-containing substances. The blood levels of these patients were greater than 150 µg/L (Froomes et al. 1989; Slikkerveer and de Wolff 1989).

US FDA has derived recommended daily oral intake of bismuth subgallate of 200 to 400 mg up to 4 times a day for therapeutic use as an aid to reduce odor from a colostomy or an ileostomy (US FDA 2018). According to this recommendation, the maximum oral daily recommended intake is 848 mg Bi/day for a body weight of 70 kg or 12.1 mg/kg bw/day.

There are no indications of carcinogenicity, genotoxicity, reproductive and developmental effects for bismuth-containing substances.

The whole blood BE value associated with US FDA's recommended daily oral intake was derived using a linear regression analysis and the details of the derivation can be found in Poddalgoda et al. (2020).

The regression was conducted correlating intake with the average plasma concentration obtained from multi-day dosing studies (Figure 5-1). As bismuth takes approximately 7 to 28 days to reach steady state, short-term or single dosing studies are not suitable to conduct regression analysis. Thus, results from controlled dosing studies from Koch et al. (1996a) and Lacey et al. (1994) were selected to derive the BE (Table 5-2). In Koch et al. (1996a), 18 healthy volunteers were given 800 mg bismuth ranitidine citrate twice daily for 28 days. This dose is equivalent to 470 mg Bi/day. Plasma and urine concentrations were collected at several time points during the first 12-hour period and at day 1, 14, and 28 after the first bismuth ranitidine citrate administration. Lacey et al. (1994) administered 500 mg or 1000 mg ranitidine bismuth twice daily to 12 and 11 volunteers, respectively, for 10 days. The administered doses are equivalent to daily bismuth intake of 301 or 602 mg, respectively. Although the absorption of bismuth could have been influenced by variations of gastric pH by ranitidine, the results are consistent with previous data obtained with tripotassium dicitro bismuthate alone (Froomes et al. 1989). Considering an average body weight of 70 kg (ranged from 52.4 to 91.7 kg), the daily doses were equivalent to 4.3 and 8.6 mg Bi/kg bw/day, respectively.

Bismuth pharmacokinetic parameters were calculated for each individual after the first and last doses of each treatment. The parameters included the maximum plasma bismuth concentration (C_{max}), the time to C_{max} (t_{max}), the area under the plasma concentration-time curve (AUC) over a 12-hour dosing interval (AUCT), the total urinary recovery of bismuth over a 12-hour dosing interval, and the corresponding renal clearance (CLR). Haematology, biochemistry and urine analysis were conducted on days 3, 7 and 10 of dosing and 7 days post-dosing.

Table 5-2. Bismuth intake levels and average plasma concentrations in human volunteers based on Koch et al. (1996a) and Lacey et al. (1994)

Study	Bismuth dose (mg Bi/kg bw/day)	Geometric mean plasma concentration (µg/L)
Lacey et al. (1994)	4.3	3.0
Lacey et al. (1994)	8.6	6.2
Koch et al. (1996a)	6.9	3.9

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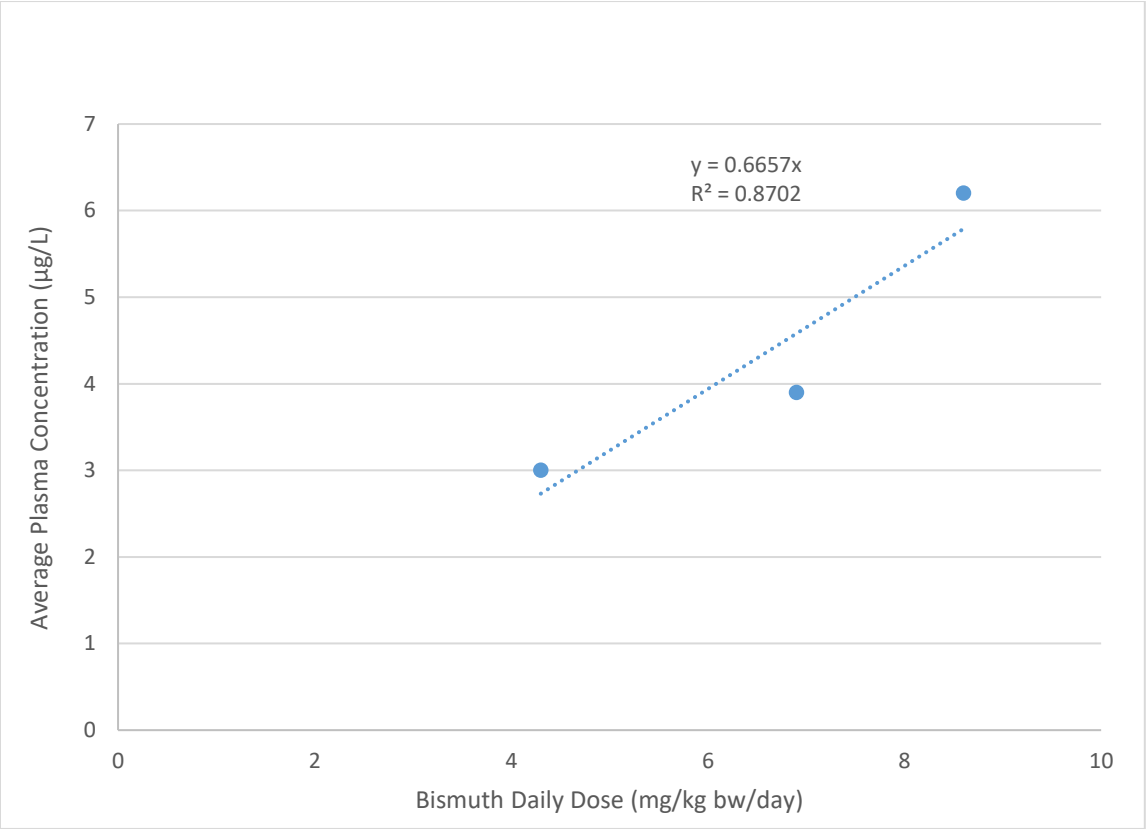


Figure 5-1. Linear correlation between bismuth daily dose (mg/kg bw/day) and average plasma concentration (µg/L) in humans (Poddalgoda et al. 2020)

[Figure 5-1 shows the regression between average bismuth plasma concentrations and bismuth daily dose. The units of the daily dose is in milligrams per kilogram body weight per day and the average plasma concentration is in microgram per liter. Three datasets from high quality volunteer studies were used for the analysis. Those data are listed in Table 5-2. The mathematic equation from the regression is average plasma bismuth concentration in micrograms per liter equals 0.6657 times mean bismuth daily dose in milligrams per kg body weight per day. The R-squared value is 0.8702.]

The linear regression resulted in the following mathematical relationship:

Average plasma concentration (µg/L) = 0.6657x

Where oral intake (x) is in mg/kg bw/day.

The plasma BE value associated with US FDA's acceptable daily intake for specific therapeutic uses (that is, 12.1 mg Bi/kg bw/day) is 8.1 µg/L.

In a single dosing study, Koch et al. (1996b) reported the bismuth concentration ratio between whole blood and plasma as 0.6.

Thus, the whole blood BE based on the FDA's acceptable daily intake for specific therapeutic uses is 4.9 µg/L, which was derived by applying the conversion factor of 0.6 to the plasma concentration (Poddalgoda et al. 2020). The use of this BE is considered conservative in light of the 10-fold higher blood bismuth concentration of 50 µg/L, which is considered as a safe level (Hillemand et al. 1977).

Risk characterization

Exposure to total bismuth in the Canadian population was characterized by whole blood concentration data (Table 5-1). Given the large sample size and steady state of bismuth in whole blood, the derived whole blood BE is considered appropriate to assess all potential exposures from bismuth in environmental media, food and through the use of products containing bismuth. The whole blood BE value of 4.9 µg/L is based on the US FDA's acceptable daily intake for specific therapeutic uses of 12.1 mg Bi/kg bw/day. The median and 95th percentile bismuth concentrations were below the detection limit of 0.1 µg/L in the whole blood of Canadians sampled as part of the CHMS (cycle 2). Using the Biomonitoring Approach 2, the limited detection of total bismuth in whole blood is well below the derived BE value. Based on the information presented, bismuth-containing substances in this assessment (that is, 7 CAS RNs) are of low concern to the health of the general population of Canada at the current levels of exposure.

Uncertainties

The regression analysis used for the BE derivation is based on a small dataset. However, the studies used for this analysis are controlled dosing studies, where volunteers were exposed to multiple doses for a period sufficient to reach a steady state. The blood samples were extracted and analyzed for bismuth at regular intervals. Therefore, this dataset is considered of high quality and represents steady state conditions. In addition, in the bismuth toxicity (encephalopathy) case studies, much higher blood bismuth concentrations were reported (>680 to 700 µg/L) than those attainable from food, environmental media and products containing bismuth.

5.2.2 Lithium-containing substances (16 CAS RNs)

Exposure assessment

In the absence of substance specific exposure information, data on the lithium moiety were used as surrogate exposure data for the specific lithium-containing substances in the assessment. Lithium is a naturally occurring element that is present in environmental media (for example, air, water and dust) and food in Canada. The median and 95th percentile of total lithium concentrations measured in Canada in outdoor air $PM_{2.5}$ (n=38) were 0.11 ng/m^3 and 0.26 ng/m^3 respectively. Twenty-six

percent of the samples were below the LOD (0.08 ng/m^3) (Rasmussen 2017). The median and 95th percentile of personal air $PM_{2.5}$ (n= 38) concentrations were <0.08 ng/m^3. Seventy-six percent of the concentrations were below the LOD (0.08 ng/m^3) (Rasmussen 2017). The median and 95th percentile of Indoor air $PM_{2.5}$ (n= 37) concentrations were <0.08 ng/m^3. Seventy-three percent of the concentrations were below the LOD (0.08 ng/m^3) (Rasmussen 2017). The median and 95th percentile of lithium concentrations in Canadian urban house dust (n=1025) were 6.50 µg/g and 12.9 µg/g respectively (Rasmussen et al. 2022). Canadian drinking water samples at various sites of the distribution systems were tested for lithium concentrations and ranged from 2.5 - 160 µg/L with a median of 2.5 µg/L (n=96) (Tugulea et al. 2016). Lithium is present in minerals in the environment; spodumene, petalite, and amblygonite and lithium can enter the aquatic environment through leaching from these minerals (CCME 2008).

Lithium was an element analysed for in the Canadian Total Diet Study starting in 2016. Based on results from the 2016, 2017 and 2018 TDS, the overall mean and median concentrations of lithium in all food composite samples are 0.025 µg/g and 0.011 µg/g, respectively. Food composites with 3-year mean concentrations greater than 0.1 µg/g were reported for: salt (0.513 µg/g), mineral water (0.280 µg/g), herbs and spices (0.265 µg/g), spinach (0.148 µg/g), melons (0.114 µg/g), tomato sauce (0.110 µg/g) and baking powder (0.101 µg/g) (Health Canada [modified 2020b]). Lithium is not monitored in the U.S. FDA's Total Diet Study program. Lithium has been monitored in the second Total Diet Study conducted in 2006 in France, where the mean dietary intake for lithium was 48.2 µg/day while the 5th and 95th percentile were 14.9 and 93.6 µg/day respectively for adults (18-79 years). For children (3 to 17 years) the mean dietary intake was 19.8 µg/day while the 5th and 95th percentiles were 9.0 and 38.6 µg/day, respectively (ANSES 2011).

Biomonitoring data

Lithium was detected in 66.43% of the Canadian population. The median concentration in the whole blood was 0.47 µg/L (95% CI 0.43 to 0.51 µg/L), and the 95th percentile concentration was 1.3 µg/L (95% CI 1.2 to 1.4 µg/L). A summary of the biomonitoring data for total lithium in whole blood is provided in Table 5-1 and are used as surrogate exposure data for these specific lithium-containing substances. In both males and females, an increase in blood lithium concentration with age was observed. The highest lithium concentration in the Canadian population was in adults aged 60 to 79 years. Overall, blood lithium concentrations were not significantly different in females and males (Jayawardene et aI. 2021).

Health effects assessment

Toxicokinetic data and biomarker adequacy

The focus of the toxicokinetic data review was on the oral route of exposure as this would be the predominant route of potential lithium intake for the general population.

Lithium is rapidly absorbed from the GI tract, with an oral bioavailability of 80% to 100% (Murphy 2008; Ward et al. 1994).

Once absorbed, lithium is rapidly distributed to blood, with peak plasma concentrations reached between 1 to 2 hours (Baldessarini and Tarazi 2006). Lithium does not bind to plasma proteins and is distributed in the body as a free ion (Baldessarini and Tarazi 2006; Grandjean and Aubry 2009). The average volume of distribution (Vd) of lithium in humans ranges from 0.7-1.0 L/kg (Baldessarini and Tarazi 2006; Grandjean and Aubry 2009). The Vd of lithium decreases with increasing age due to reduction in total body water and lean body mass (Rej et al. 2014).

The overall organ distribution of lithium in humans has not been well studied (Grandjean and Aubry 2009). As lithium readily passes across all biological barriers, it distributes throughout the body compartments (Ward et al. 1994). Lithium concentration in the plasma is twice that of erythrocytes (Ward et al. 1994). After analysing data from seven blood donors, Clarke et al. (2004) reported that the whole blood:plasma partition coefficient was 0.65. Long-term retention of lithium in bones has also been observed. From bones, lithium is slowly eliminated over several months (Grandjean and Aubry 2009).

The primary excretion pathway for lithium is urine, with approximately 90% to 95% of the absorbed dose excreted in urine (Baldessarini and Tarazi 2006). Clearance via saliva, sweat and feces accounts for less than 5% of total excretion (Baldessarini and Tarazi 2006). The urine elimination of lithium appears to reach steady state after 5 to 6 days of repeated administration (Baldessarini and Tarazi 2006). The elimination half-life of lithium is approximately 20 to 24 hours (Baldessarini and Tarazi 2006). The average whole body clearance of lithium is in the range of 0.6 to 2.4 L/hour, with significant inter-individual variation (Grandjean and Aubry 2009). Lithium clearance decreases with age (Grandjean and Aubry 2009).

The concentration of lithium in blood represents the bioavailable fraction, which is the fraction systemically available at the target sites. A steady state lithium concentration in blood can be expected in the general population because of the frequent or daily exposure to lithium from diet, drinking water, products available to consumers and environmental media (US EPA 2008; Ramoju et al. 2020). In addition, when using large population samples, such as CHMS, it is reasonable to assume the biomonitoring data would cover off potential intermittent increases in exposures due to products used by consumers on an infrequent basis. Thus, blood lithium concentration can be considered as a suitable biomarker to quantify exposure from all routes and all sources of lithium.

Health effects data and derivation of biomonitoring equivalent

Lithium is not considered an essential element; however, some reviewers have suggested that lithium may have beneficial neurological and anti-aging effects in humans (Martone 2018). Lithium salts are prescribed at the recommended daily dose of

167 mg Li/day for treatment of manic-depressive disorders (Barthelmebs et al. 1993; Nordic Expert Group Review 2002). The target serum lithium concentration for optimal therapeutic effects range from 5.6 to 6.9 mg Li/L (0.8 to 1.0 mM Li/L) (US EPA 2008). Lithium toxicity has been observed at serum concentrations ranging from 3.5 mg Li/L (0.5 mM Li/L) to 17.4 mg Li/L (2.5 mM Li/L) or higher (Nordic Expert Group Review 2002). Lithium has a narrow therapeutic index, and adverse side effects can be seen even at therapeutic dose levels (US EPA 2008; Gitlin 2016). Lithium treatment in humans is associated with reduced tubular renal function leading to kidney insufficiency (McKnight et al. 2012; Health Canada 2014; Health Canada 2016c). In addition, hypothyroidism, hyperparathyroidism, and weight gain are also reported (McKnight et al. 2012; Health Canada 2014; Gitlin 2016; Health Canada 2016c). Health Canada (2014) issued a physicians' advisory with the recommendation of monitoring blood calcium levels before and during lithium treatment because lithium treated patients have shown an increased incidence of hypercalcemia and hyperparathyroidism. Changes in calcium homeostasis has also been observed in pregnant women (n=178) exposed to elevated concentrations of lithium in drinking water (5-16600 µg/L). Median maternal blood lithium concentration was 25 µg/L (range 2.9-145). Blood lithium was inversely associated with 25-hydroxyvitamin D_3 (95% CI -9.5, -2.6) and positively associated with serum magnesium (Harari et al. 2016). In addition, lithium-treated patients show neurological effects, such as tremor, confusion, when serum concentrations are approximately 3.5 mg/L or above (Nordic Expert Group Review 2002). However, lithium induced nephrotoxicity is only reported in prolonged (several years) lithium treatment (Nordic Expert Group Review 2002; US EPA 2008). In contrast, experimental evidence suggests that short-term low doses of lithium may have a kidney-protective effect (Gong et al. 2016; Martone 2018). There are no indications of carcinogenicity, genotoxicity, reproductive and developmental effects for lithium-containing substances (Nordic Expert Group Review 2002; US EPA 2008).

Health Canada (2016c) has adopted a permitted daily exposure (PDE) value for therapeutics for oral lithium exposure derived from the International Council on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) Guideline for Elemental Impurities- Q3D (ICH 2014). The PDE indicates the maximum permitted quantity of lithium as an impurity in therapeutic products (Health Canada 2016c). ICH (2014) considered a third of the lowest recommended therapeutic daily dose of lithium carbonate (900 mg) as the point of departure (POD) to derive a PDE. Thus, the POD is equivalent to 300 mg lithium carbonate/day (56 mg Li/day). This POD value is equivalent to 0.8 mg Li/kg bw/day, assuming 70 kg body weight. As lithium toxicity may also be observed at therapeutic doses, this POD is considered a lowest observed adverse effect level (LOAEL) by ICH (2014). On the basis of this POD, a safety factor of 100 was applied to account for inter-individual variability (x10) and use of a LOAEL rather than a NOAEL (x10). The resulting PDE derived by ICH (2014) for lithium is 8 µg Li/kg bw/day.

The US EPA (2008) has developed a Provisional sub-chronic and chronic Peer-Reviewed Toxicity Value (PPRTV) (provisional Reference Dose, p-RfD) for lithium to

protect against adverse effects (mainly renal toxicity) of excess lithium exposure via the oral route. US EPA (2008) derived a LOAEL of 2.1 mg Li/kg bw/day using the lower bound values of the therapeutic serum lithium concentration range (0.6 mmol/L), lithium plasma clearance (0.5 L/kg day) and 100% absorption. An uncertainty factor of 1000 was applied to the LOAEL to account for database deficiencies (x10), inter-individual variability (x10) and the use of a LOAEL rather than a NOAEL (x10), resulting in a RfD of 2 µg Li/kg bw/day. The PDE value derived by ICH (2014) and adopted by Health Canada (2016c) is considered the most appropriate exposure guidance value for risk characterization as the guidance value (that is, PDE) is based on a more conservative POD than the US EPA's PPRTV. It is also considered that the uncertainty factor applied by US EPA (2008) to account for database deficiencies (x10) is not necessary as lithium has a rich database on human studies.

The whole blood BE value associated with the PDE was derived using a simple kinetic equation and the details of the derivation can be found in Ramoju et al. (2020).

The steady-state plasma concentration of lithium (that is, BE_{POD}) associated with the POD of 0.8 mg Li/kg bw/day was computed by applying a clearance value and the fraction of the dose absorbed as follows (US EPA 2008):

BE_{POD} (mg Li/L plasma) = [POD (mg Li/kg bw/day)] * [Fraction absorbed] / Clearance (L/kg bw/day)

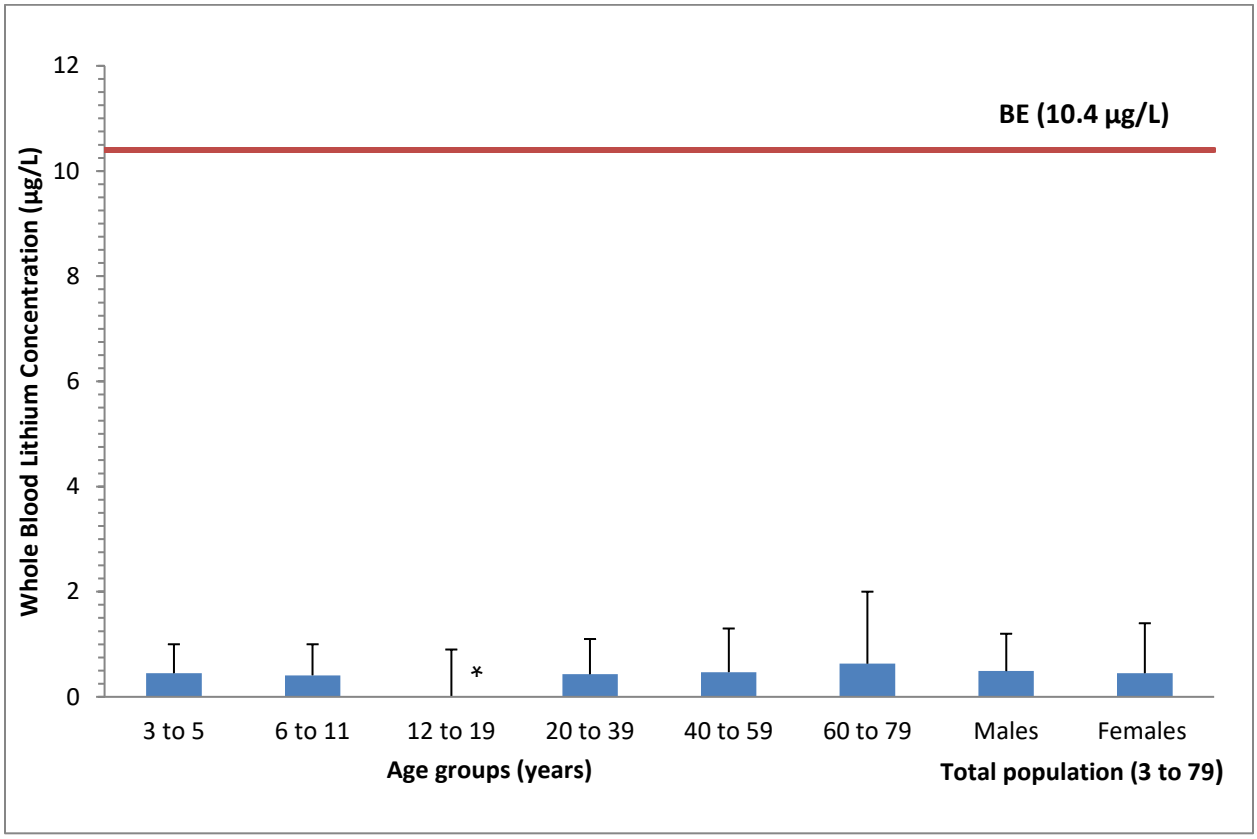
A whole body clearance value of 0.5 L/kg bw/day and 100% absorption was applied for the BE derivation based on published literature (US EPA 2008).

A steady state plasma BE for lithium was derived by applying uncertainty factors to the BE_{POD}. The plasma BE was multiplied by the whole blood:plasma partition coefficient of 0.65 to derive a steady state whole blood BE. The whole blood BE for the PDE was 10.4 µg Li/L (Ramoju et al. 2020).

Risk characterization

Exposure to total lithium in the Canadian population was characterized by whole blood concentration data (Table 5-1). Given the large sample size and steady state of lithium in whole blood, the derived whole blood BE is considered appropriate to assess all potential exposures from lithium in environmental media and through the use of products containing lithium. The BE is based on ICH's PDE value of 8 µg Li/kg bw/day, for therapeutics and which was adopted by Health Canada (2016c). The whole blood concentration data and BE for lithium are compared in Figure 5-2. The median and the 95^{th} percentile whole blood concentrations for different age groups of the Canadian general population, obtained from the CHMS cycle 2 (represented in bars and whiskers, respectively in Figure 5-2), are well below the BE value of 10.4 µg/L. Using the Biomonitoring Approach 2, the whole blood concentrations detected for lithium are well below the derived BE, which suggests that the lithium-containing substances in this

assessment (that is, 16 CAS RNs) are of low concern to the health of the general population of Canada at current levels of exposure.



* The median value for age group 12 to 19 was too unreliable to be published.

Figure 5-2. Comparison of the median (bar) and the 95th percentile (whiskers) of the concentrations of whole blood lithium (µg/L) from the CHMS- cycle 2 (2009-2011) biobank with the biomonitoring equivalent of 10.4 (µg/L) for PDE value (ICH 2014) (indicated by a solid line)

[Figure 5-2 shows a comparison of median (bar) and 95th percentile (whiskers) concentrations of whole blood lithium concentrations in micrograms per liter with a BE of 10.4 micrograms per liter based on a PDE derived by ICH (2014) for oral therapeutic use of lithium. Whole blood lithium concentration micrograms per liter from the CHMS for age groups 6 and older, 3 to 5, 6 to 11, 12 to 19, 20 to 39, 40 to 59 and 60 to 79 years and for males and females from the total population aged 3 to 79 years are presented in bars. The whole blood lithium concentrations for age groups are presented in the following Table as approximate values.

Whole blood	3-5 years	6-11 years	12-19 years	20-39 years	40-59 years	60-79 years	Male (total population	Female (total

con (µg/L)							age 3-79 years)	population age 3-79 years)
Median	0.45	0.41	*	0.43	0.47	0.63	0.49	0.45
95th percentile	1.0	1.0	0.9	1.1	1.3	2.0	1.2	1.4

* Unreliable data.]

Uncertainties

There is some uncertainty in lithium clearance in various age groups in the general population because there is less clearance per body weight expected in children and the elderly population. However, when deriving exposure guidance values, both ICH (2014) and US EPA (2008) assigned an uncertainty factor to account for intra-individual variations.

There is also some uncertainty when deriving whole blood BE using plasma BE. However, since the whole blood:plasma partitioning coefficient was derived using data from human studies, there is a high confidence in this value. There is low to moderate confidence in whole blood concentration as a biomarker to quantify exposure due to rapid elimination from blood (peak concentration is reached within 1 to 2 hours after exposure).

5.3 Rapid Screening of Substances with Limited General Population Exposure

The Rapid Screening of Substances with Limited General Population Exposure for Human Health is used to identify low concern substances by evaluating the potential for direct exposure from products and, as needed, indirect exposure from environmental media. The human health portion of this rapid screening approach consists of multiple steps which are outlined in the publication (ECCC, HC [modified 2018]). The first step is to determine if a candidate substance has the potential for direct exposure from products used by the general population of Canada. If there is no potential for direct exposure, then the substance proceeds to the second step whereby the potential for indirect exposure from environmental media is examined. If the estimated exposure is negligible (<2.5 ng/kg bw/day), then the candidate substance is considered to have a low potential for exposure.

Sodium bromate was considered in the Rapid Screening of Substances with Limited General Population Exposure Assessment (ECCC, HC 2018); however, it was identified as requiring further assessment due to the potential for direct exposure from the use of

cosmetic products. Sodium bromate was previously found in a small number of cosmetic products as a restricted ingredient on the Hotlist. However, the Hotlist was recently revised to describe sodium bromate as prohibited for use in cosmetics (Health Canada [modified 2019]). As a result, with these uses removed, there should no longer be potential for direct exposure to the general population of Canada from cosmetic products. Sodium bromate may be used as a component in the manufacture of food packaging materials and incidental additives used in food processing establishments; dietary exposure from these uses are not expected as the substance is not in direct contact with food (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 28, 2017; unreferenced).

In the absence of direct exposure to a substance for the general Canadian population, the approach considers indirect exposure from various environmental media. There is limited data on measured or predicted concentrations or releases of sodium bromate in environmental media (that is, soil, air, water). Bromate has been found in drinking water as a result of water treatment, rather than through source water contamination (Health Canada 2019). The contribution of sodium bromate to drinking water is expected to be negligible. Similar to potassium bromate, exposure to sodium bromate from environmental media is expected to be negligible (EC, HC 2010).

On the basis of the evaluation of both direct and indirect exposure conducted as part of this rapid screening approach, exposure of the general population to sodium bromate is considered to be minimal and is of low concern to the human health in Canada at current levels of exposure.

6. Conclusion

Considering all available lines of evidence presented in this assessment, there is low risk of harm to the environment from the 34 substances in this assessment. It is concluded that these 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.

Considering all of the information presented in this assessment, it is concluded that the 34 substances in this assessment 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 concluded that the 34 substances in this assessment do not meet any of the criteria set out in section 64 of CEPA.

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Appendix A. List of substances and assessment approaches

Table A-1. The 34 substances assessed, their CAS RNs, their common names, and the assessment approaches used

CAS RN	DSL name	Common name	Ecological approach	Human health approach
56797-01-4	Hexanoic acid, 2-ethyl-, cerium(3+) salt	Cerium (III) 2-ethylhexanoate	ERC-I	Biomonitoring Approach 1
10038-98-9	Germane, tetrachloro-	Germanium (IV) chloride	ERC-I	Biomonitoring Approach 1
1312-81-8	Lanthanum oxide (La_2O_3)	Lanthanum (III) oxide	ERC-I	Biomonitoring Approach 1
10099-58-8	Lanthanum chloride ($LaCl_3$)	Lanthanum (III) chloride	ERC-I	Biomonitoring Approach 1
12008-21-8	Lanthanum boride (LaB_6), (OC-6-11)-	Lanthanum hexaboride	ERC-I	Biomonitoring Approach 1
73227-23-3	Hexanoic acid, 2-ethyl-, neodymium(3+) salt	Neodymium 2-ethylhexanoate	ERC-I	Biomonitoring Approach 1
12036-32-7	Praseodymium oxide (Pr_2O_3)	Praseodymium oxide	ERC-I	Biomonitoring Approach 1
7446-07-3	Tellurium oxide (TeO_2)	Tellurium dioxide	ERC-I	Biomonitoring Approach 1
20941-65-5	Tellurium, tetrakis(diethylcarbamodithioato-S,S')-, (DD-8-111''1''1'1'1'''1''')-	Ethyl tellurac	ERC-I	Biomonitoring Approach 1
1314-36-9	Yttrium oxide (Y_2O_3)	Yttrium oxide	ERC-I	Biomonitoring Approach 1
1304-76-3	Bismuth oxide (Bi_2O_3)	Bismuth (III) oxide	ERC-I	Biomonitoring Approach 2
1304-85-4	Bismuth hydroxide nitrate oxide ($Bi_5(OH)_9(NO_3)_4O$)	Bismuth subnitrate	ERC-I	Biomonitoring Approach 2
10361-44-1	Nitric acid, bismuth(3+) salt	Bismuth (III) nitrate	ERC-I	Biomonitoring Approach 2
14059-33-7	Bismuth vanadium oxide ($BiVO_4$)	Bismuth vandate (V)	ERC-I	Biomonitoring Approach 2

CAS RN	DSL name	Common name	Ecological approach	Human health approach
21260-46-8	Bismuth, tris(dimethylcarbamodithioato-S,S')-, (OC-6-11)-	Bismuth dimethyldithiocarbamate	ERC-I	Biomonitoring Approach 2
34364-26-6	Neodecanoic acid, bismuth(3+) salt	Bismuth neodecanoate	ERC-I	Biomonitoring Approach 2
67874-71-9	Hexanoic acid, 2-ethyl-, bismuth(3+) salt	Bismuth 2-ethylhexanoate	ERC-I	Biomonitoring Approach 2
546-89-4	Acetic acid, lithium salt	Lithium acetate	ERC-I	Biomonitoring Approach 2
554-13-2	Carbonic acid, dilithium salt	Lithium carbonate	ERC-I	Biomonitoring Approach 2
1310-65-2	Lithium hydroxide (Li(OH))	Lithium hydroxide	ERC-I	Biomonitoring Approach 2
4485-12-5	Octadecanoic acid, lithium salt	Lithium stearate	ERC-I	Biomonitoring Approach 2
7439-93-2	Lithium	NA	ERC-I	Biomonitoring Approach 2
7447-41-8	Lithium chloride (LiCl)	NA	ERC-I	Biomonitoring Approach 2
7620-77-1	Octadecanoic acid, 12-hydroxy-, monolithium salt	Lithium 12-hydroxystearate	ERC-I	Biomonitoring Approach 2
7789-24-4	Lithium fluoride (LiF)	NA	ERC-I	Biomonitoring Approach 2
10377-48-7	Sulfuric acid, dilithium salt	Lithium sulfate	ERC-I	Biomonitoring Approach 2
12627-14-4	Silicic acid, lithium salt	Lithium polysilicate	ERC-I	Biomonitoring Approach 2
13840-33-0	Hypochlorous acid, lithium salt	Lithium hypochlorite	ERC-I	Biomonitoring Approach 2
27253-30-1	Neodecanoic acid, lithium salt	Lithium neodecanoate	ERC-I	Biomonitoring Approach 2
38900-29-7	Nonanedioic acid, dilithium salt	Dilithium azelate	ERC-I	Biomonitoring Approach 2
53320-86-8	Silicic acid, lithium magnesium sodium salt	Lithium magnesium sodium silicate	ERC-I	Biomonitoring Approach 2
68649-48-9	Paraffin waxes and hydrocarbon waxes,	NA	ERC-I	Biomonitoring Approach 2

CAS RN	DSL name	Common name	Ecological approach	Human health approach
	oxidized, lithium salts			
68783-37-9	Fatty acids, C16-18, lithium salts	NA	ERC-I	Biomonitoring Approach 2
7789-38-0	Bromic acid, sodium salt	Sodium bromate	ERC-I	Rapid Screening for Substances with Limited General Population Exposure Approach

Abbreviations: NA = not available, ERC-I = Ecological Risk Classification of Inorganic Substances

Appendix B. ERC-I classifications for the 34 substances addressed in this assessment

Table B-1. ERC-I classifications for the 34 substances addressed in this assessment

CAS RN	DSL name	ERC-I Predictive Modelling Ranking	ERC-I Water Quality Monitoring Ranking	Overall ERC-I Classification
56797-01-4	Hexanoic acid, 2-ethyl-, cerium(3+) salt	Low	Low	Low
10038-98-9	Germane, tetrachloro-	Low	NA	Low
1312-81-8	Lanthanum oxide (La_2O_3)	Moderate	Low	Low
10099-58-8	Lanthanum chloride ($LaCl_3$)	Moderate	Low	Low
12008-21-8	Lanthanum boride, (OC-6-11)-	Moderate	Low	Low
7446-07-03	Tellurium oxide	Low	Low	Low
20941-65-5	Tellurium, tetrakis(diethylcarbamodithioato-S,S')-, (DD-8-111''1''1'1'1'''1''')-	Low	Low	Low
73227-23-3	Hexanoic acid, 2-ethyl-, neodymium(3+) salt	Low	Low	Low
12036-32-7	Praseodymium oxide (Pr_2O_3)	Low	Low	Low
1314-36-9	Yttrium oxide (Y_2O_3)	Moderate	Low	Low
1304-76-3	Bismuth oxide	Low	Low	Low
1304-85-4	Bismuth hydroxide nitrate oxide ($Bi_5(OH)9(NO_3)4O$)	Low	Low	Low
14059-33-7	Bismuth vanadium oxide ($BiVO_4$)	Low	Low	Low
10361-44-1	Nitric acid, bismuth(3+) salt	Low	Low	Low
21260-46-8	Bismuth, tris(dimethylcarbamodithioato-S,S')-, (OC-6-11)-	Low	Low	Low
34364-26-6	Neodecanoic acid, bismuth(3+) salt	Low	Low	Low
67874-71-9	Hexanoic acid, 2-ethyl-, bismuth(3+) salt	Low	Low	Low

546-89-4	Acetic acid, lithium salt	Low	Low	Low
554-13-2	Carbonic acid, dilithium salt	Low	Low	Low
1310-65-2	Lithium hydroxide (Li(OH))	Low	Low	Low
4485-12-05	Octadecanoic acid, lithium salt	Low	Low	Low
7439-93-2	Lithium	Low	Low	Low
7447-41-8	Lithium chloride (LiCl)	Low	Low	Low
7620-77-1	Octadecanoic acid, 12-hydroxy-, monolithium salt	Low	Low	Low
7789-24-4	Lithium fluoride (LiF)	Low	Low	Low
10377-48-7	Sulfuric acid, dilithium salt	Low	Low	Low
12627-14-4	Silicic acid, lithium salt	Low	Low	Low
13840-33-0	Hypochlorous acid, lithium salt	Low	Low	Low
27253-30-1	Neodecanoic acid, lithium salt	Low	Low	Low
38900-29-7	Nonanedioic acid, dilithium salt	Low	Low	Low
53320-86-8	Silicic acid, lithium magnesium sodium salt	Low	Low	Low
68649-48-9	Paraffin waxes and Hydrocarbon waxes, oxidized, lithium salts	Low	Low	Low
68783-37-9	Fatty acids, C16-18, lithium salts	Low	Low	Low
7789-38-0	Bromic acid, sodium salt	Low	NA	Low

Abbreviations: NA =, not available

Appendix C. Median air and house dust concentrations of elements

Table C-1. Median concentrations of elements in air $PM_{2.5}$ (ng/m^3) and house dust µg/g)

Element	Indoor air	Personal air ($PM_{2.5}$)[a]	Outdoor air ($PM_{2.5}$)[a]	Outdoor air ($PM_{2.5}$)[b]	Dust data (µg/g)[a,c,e]
Bismuth	$PM_{2.5}$ = 0.06 (n=437)[a]	0.07 (n=445)	0.21 (n=447)	NA	2.42
Cerium	PM_{10} = 0.37 (modelled)[d]	NA	NA	0.030 (n=969)	24.7
Germanium	PM_{10} = 0.001 (modelled)[d]	NA	NA	NA	<0.1
Lanthanum	PM_{10} = 0.19 (modelled)[d]	NA	NA	0.028 (n=969)	12.7
Lithium	$PM_{2.5}$ <0.08 (n=37)[a]	<0.08 (n=38)	0.11 (n=38)	NA	6.5
Neodymium	PM_{10} = 0.13 (modelled)[d]	NA	NA	NA	8.6
Praseodymium	PM_{10} = 0.04 (modelled)[d]	NA	NA	NA	2.8
Tellurium	PM_{10} = 0.003 (modelled)[d]	NA	NA	NA	0.18
Yttrium	PM_{10} = 0.07 (modelled)[d]	NA	NA	NA	4.6

Abbreviations: NA = not applicable; $PM_{2.5}$ = particulate matter less than or equal to 2.5 microns; PM_{10} = particulate matter less than or equal to 10 microns.
[a] Rasmussen 2017; [b] NAPS 2015; [c] Rasmussen et al. 2017; [d] Rasmussen 2019 ;[e] Rasmussen et al. 2022