APPENDIX F TOXICITY BENCHMARKS

Appendix F: Toxicity Benchmarks

1. INTRODUCTION

This attachment describes the selection of toxicity benchmarks used in the risk characterization step in the *Human Health Risk Assessment* report. The toxicity benchmark, known as the toxicity reference value (TRV), is the level of exposure that is associated with no adverse effects to human health or acceptable risk levels.

Toxicity information is typically derived from laboratory studies, where dose-response information is extrapolated from animal test subjects to humans by applying uncertainty or safety factors. In most cases, uncertainty factors of 100 to 1,000 are applied to the laboratory-derived no observed adverse effect levels (NOAELs). The NOAELs are the highest concentration used in a toxicity test that results in no observed or measured chronic health effects. The uncertainty factors account for interspecies extrapolation and the protection of the most susceptible individuals in the population (e.g., children and the elderly). Therefore, TRVs based on animal studies generally have large margins of safety to ensure that the potential for risk from exposure to a substance for people is not underestimated. Lowest observed adverse effect levels (LOAEL) or NOAELs from human studies have smaller uncertainty factors because no extrapolation from animals to humans is required.

1.1 Selection of Regulatory Thresholds for Risk Characterization

For non-carcinogenic chemicals, the TRV is the daily dose that is tolerable or acceptable. For carcinogenic chemicals, the TRV is referred to as slope factor (SF) relating to exposure dose, or unit risk (UR) relating to exposure concentration. Examples of types of TRVs identified by different regulatory agencies include tolerable daily intake (TDI), provisional tolerable daily intake (PTDI), acceptable daily intake (ADI), reference dose (RfD), reference concentration (RfC), minimum risk revel (MRL), cancer slope factor (SF), and cancer UR, among others. Typically TDI, ADI, RfD, MRL, and SF are used for oral and dermal exposures, while RfC and UR are used for inhalation exposures.

The selection of human health-based AAQOs for the criteria air contaminants (CACs) used the following selection hierarchy:

- BC MOE human health-based ambient air quality criteria (AAQOs);
- Canadian Council of Ministers for the Environment (CCME);
- United States Environmental Protection Agency (USEPA); and
- World Health Organization (WHO).

For metal parameters of concern (POC), Health Canada (2019) states that the preferred TRV source is Health Canada (2010), which was recently updated in Health Canada (2021); however, values can be obtained from other regulatory agencies such as:

- US EPA's Integrated Risk Information System (IRIS database; US EPA 2022a);
- Joint Food and Agriculture Organization of the United Nations (FAO) and the United Nation World Health Organization (WHO) Expert Committee on Food Additives (JECFA) (WHO INCHEM and JECFA databases; WHO 2022)
- National Institute for Public Health and the Environment (Netherlands; RIVM 2001; RIVM 2009);

- US Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles (ATSDR 2022); and
- California Environmental Protection Agency (CalEPA) – Toxic Criteria Database (CalEPA 2022).

BC MOE (2017) states that the Province`s preferred TRV source is its own, US EPA Integrated Risk Information System (IRIS), Health Canada,, and the WHO followed by the following hierarchy of sources if toxicity benchmarks are not available from US EPA IRIS database, Health Canada, or the WHO:

- US ATSDR (ATSDR 2022);
- CalEPA – Toxic Criteria Database (CalEPA 2022);
- National Institute for Public Health and the Environment (Netherlands; RIVM 2001; RIVM 2009);
- US EPA Regional Screening Levels (US EPA 2022b);
- Oak Ridge National Laboratory Risk Assessment Information System (RAIS; ORNL 2022); and
- other documents or databases published by Canadian or US government agencies.

Unless rationale is provided, to be conservative the most stringent TRVs from these sources will be selected for the identified POCs. The following sections summarize the TRVs for all identified POCs for each route of exposure, key cancer and non-cancer health concerns associated with exposure to elevated levels of each POCs, and differentiates effects by exposure route.

2. TOXICITY REFERENCE VALUES FOR THRESHOLD CONTAMINANTS OF POTENTIAL CONCERN

The ambient air quality criteria for the CACs used in the HHRA are summarized in Table 1.

Table 2 lists the metal TRVs for threshold POCs selected for the HHRA. The toddler receptor was chosen for the list of TRVs as they are commonly more conservative than TRVs for adult human receptors. Rationale for each TRV is provided in Section 2.1 to 2.18.

Table 3 summarizes the SFs and URs for non-threshold POCs for cancer endpoints.

Table 1: Ambient Air Quality Objectives for Criteria Air Contaminants

Parameter	Averaging Period	AAQO (µg/m^3)
$PM_{2.5}$	24-hour Annual	25 8
PM_{10}	24-hour	50
NO_2	1-hour Annual	79 23
SO_2	1-hour Annual	170 10
CO	1-hour 8-hour	14300 5500

Notes: $PM_{2.5}$ = particulate matter equal or less than 2.5 µm in diameter; PM_{10} = particulate matter equal or less than 10 µm in diameter; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; CO = carbon monoxide

AAQO = ambient air quality objective based on the most conservative BC AAQO (BC ENV 2020) or CAAQS (CCME 2021, including standards anticipated for 2025).

Table 2: Toxicity Reference Values for Contaminants of Potential Concern

Contaminant of Potential Concern	Toxicity Reference Value (mg/kg BW-day)	Target Organ or System for Critical Effect	Source
Aluminum	0.29	Renal	JECFA (2011)
Arsenic	0.0003	Skin	US EPA (2022a)
Barium	0.2	Kidney	Health Canada (2021)
Boron	0.2	Developmental	US EPA (2022a)
Cadmium	0.0008	Kidney	Health Canada (2021)
Chromium (VI)	0.0022	Gastrointestinal	Health Canada (2021)
Cobalt	0.0014	Cardiomyopathy	RIVM (2001)
Iron	0.7	Gastrointestinal system	US EPA (2022a)
Lithium	0.002	Nervous system	ORNL (2022)
Manganese	0.025	Nervous system / developmental	Health Canada (2021)
Mercury	0.0003	Immune system, kidney	Health Canada (2021)
Molybdenum	0.005	Urinary system	US EPA (2022a)
Nickel (total nickel assumed to be nickel chloride)	0.0013	Reproductive system	Health Canada (2021)
Selenium	0.006 (toddlers) 0.0057 (adults)	Nervous system, skin (selenosis), Blood	Health Canada (2021)
Strontium	0.6	Musculoskeletal	US EPA (2022a)
Thallium	0.000088 (toddler) 0.0000025 (adult)	Not applicable (average dietary intake)	Health Canada (2011a)
Zinc	0.48 (toddler) 0.57 (adult)	Blood	Health Canada (2021)

Notes:
BW = body weight
Where only one toxicity reference value is provided for a parameter, it applies to all life stages.

Table 3: Slope Factors and Unit Risk Factors for Non-threshold Contaminants of Potential Concern

Contaminant of Potential Concern	Carcinogenic TRV	Source
Ingestion Exposure Route, Slope Factor in $(mg/kg\ BW\text{-}day)^{-1}$		
Arsenic	1.8	Health Canada (2021)
Inhalation Exposure Route, Inhalation Unit Risk in $(mg/m^3)^{-1}$		
Arsenic	6.4	Health Canada (2021)
Cadmium	4.2	Health Canada (2021)
Chromium	12	US EPA (2022a)
Nickel	1.3	Health Canada (2021)

2.1 Aluminum

Aluminum is highly reactive with water and is typically found in the environment as a constituent of inorganic and organic compounds. The primary source of human exposure to aluminum is typically from inhalation of contaminated dust in workplace and ingestion of water and food (especially foods with aluminum compounds used as food additives). The absorption of ingested aluminum in humans depends upon the solubility of the compound and is generally low (0.1 to 0.4%), with organic aluminum compounds (e.g., aluminum citrate) having slightly higher solubility (0.5 to 5%; ATSDR 2008). The extent of absorption of inhaled aluminum depends on solubility of the compound and particle size. Exposure to excess aluminum has been shown to elicit a variety of effects including neurotoxicity, bone disease, and lung disease (ATSDR 2008).

Health Canada (2011b) provided a PTDI of 0.3 mg/kg BW-day for aluminum but did not include a TRV for aluminum in Health Canada (2010, 2021).

The WHO concluded that although hazards to intrauterine and neurological development and brain function were identified through animal studies, aluminum has not been shown to pose a health risk to healthy humans.

An oral toxicity value for aluminum was developed by the US EPA (2006). The LOAEL of 100 mg Al/kg BW-day for minimal neurotoxicity in the offspring of mice (Donald et al. 1989; Golub et al. 1995) was selected as the basis for the provisional chronic RfD developed by the US EPA. The LOAEL is considered minimal because the results of the post-weaning neurobehavioral test battery indicate that performance deficits may be marginal, have unclear toxicological significance, and did not persist. Application of an UF of 100 (3 for use of a minimal LOAEL, 10 for interspecies extrapolation, and 3 for intra-human variability where the critical effects have been observed in a sensitive sub-group) results in a provisional RfD of 1.0 mg Al/kg body weight (BW)-day.

ATSDR (2008) derived an intermediate-duration and a chronic-duration oral MRL of 1.0 mg aluminum/kg BW-day but did not derive an MRL for inhalation. This MRL was also adopted by RAIS. The ATSDR study selected the NOAEL of 26 mg Al/kg BW-day identified in Golub et al. (2000) as the point of departure for the MRL. This NOAEL was based on neurological effects in offspring mice of parents exposed to aluminum in food during gestation and lactation periods (21 days of exposure each). After weaning, the pups were exposed to the same aluminum concentration as the mothers from postnatal day 21 through

35. The MRL was derived by dividing the NOAEL by an uncertainty factor (UF) of 100 (10 for animal to human extrapolation, and 10 for intra-human variability) and a modifying factor of 0.3 to account for the higher bioavailability of the aluminum lactate used in the principal study compared to the bioavailability of aluminum in the human diet and drinking water.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) provides an estimate for a provisional tolerable weekly intake (PTWI) of 2 mg/kg BW-week based on a NOAEL of 30 mg/kg BW-day and application of an UF of 100 (JECFA 2011) for effects to the kidney. This NOAEL was identified from a chronic-duration study in which aluminum citrate was administered in drinking-water to rats. JECFA noted that there continues to be a lack of consistency regarding the neurodevelopmental effects of aluminum and that the major treatment-related effect in the rat study was renal damage. The previous PTWI of 1 mg/ kg body weight was withdrawn. The PTWI of 2 mg/kg BW-week is equivalent to a PTDI of 0.29 mg/kg BW-day and similar to the Health Canada (2011) PTDI of 0.3 mg/kg-day.

The most conservative toxicity benchmark of 0.29 mg/kg BW-day (JECFA 2011) was selected for use in the HHRA.

2.2 Arsenic

Arsenic is a metalloid element with properties of both metallic and non-metallic elements. Arsenic is typically found in the environment combined with oxygen, chlorine and/or sulphur to form inorganic compounds. Arsenic can also combine with carbon and hydrogen to form organic compounds. Arsenic is considered insoluble in water (ATSDR 2007).

Health Canada does not provide a TRV for non-carcinogenic risks for arsenic.

For assessment of non-cancer risks from arsenic, IRIS (US EPA 2022a) provides a chronic oral TDI of 0.0003 mg/kg BW-day based on dermal and cardiovascular effects (hyperpigmentation, keratosis, and possible vascular complications). This is supported by the ATSDR (ATSDR 2007).

The WHO (1988) recommends a PTWI of 0.015 mg/kg BW-week (or PTDI of 0.002 mg/kg BW-day) for oral intakes of inorganic arsenic.

The more conservative TRV of 0.0003 mg/kg BW-day (US EPA, ATSDR) based on dermal and cardiovascular effects was selected for use in the HHRA for non-cancer risks.

2.3 Barium

Barium (Ba) is a highly reactive alkaline earth metal that has one stable oxidation state (+2) and only occurs in a combined state in nature (ATSDR 2019). Due to its reactivity, barium is found in the environment combined with carbon, chlorine, oxygen, and/or sulphur to form inorganic and organic compounds. The primary source of exposure for the general population is typically from drinking water and food; however, soil particles in air are an important exposure route in mining operations and in the processing industry (ATSDR 2019). Absorption ranges from approximately 1 to 60%, depending on the solubility of the barium compound, with acid-soluble barium compounds being more readily absorbed (ATSDR 2019). Exposure to barium may result in a wide-range of non-carcinogenic effects in a variety of organ systems, including cardiovascular, respiratory, developmental, gastrointestinal, hematological, hepatic, and musculoskeletal (ATSDR 2019).

Health Canada's chronic oral TDI for barium is 0.2 mg/kg BW-day based on a benchmark dose lower limit with incidence of 5% (BMDL05) of 63 mg/kg BW-day for renal (kidney) lesions in mice after 2 year exposure to barium chloride dehydrate in drinking water and an UF of 300 (100x for interspecies extrapolation and human variation, 3x for database deficiencies) (Health Canada 2021). This study and UF are also used by IRIS (US EPA 2022a) resulting in an RfD of 0.2 mg/kg BW-day. This value is also

accepted by the ATSDR as the chronic-duration oral MRL based on studies in rats and mice (using the same study as Health Canada for the point of departure) and observations in humans (ATSDR 2019).

2.4 Boron

Inorganic and organic boron compounds have a wide-range of water solubility (ATSDR 2001). The primary sources of exposure to boron are typically from ingestion of food (boron is essential in plants), inhalation of air in contaminated workplaces, and through damaged skin. Exposure to elevated concentrations of boron may have a wide-range of non-carcinogenic effects to various organ systems including gastrointestinal, nervous, hepatic, reproductive, renal, and cardiovascular. The primary target organs for boron toxicity identified in animal studies were the respiratory tract and reproductive system (ATSDR 2001).

Health Canada (2010) provided an oral ADI of 0.0175 mg/kg-day based on developmental effects in dogs exposed chronically (38 weeks to 2 years) to elevated levels of boron in the diet. An UF of 500 (10 for intra- and interspecies variability, 5 for study limitations) was applied to the NOAEL. However, this ADI was withdrawn in the 2021 update of the Health Canada TRVs (Health Canada 2021).

INCHEM (1998) reported that animal experiments demonstrated reproductive and developmental toxicity at levels that are approximately 100- to 1000-fold greater than normal exposure levels in the environment (water, soil, diet) but pointed to a lack of sufficient human toxicology data. The TDI of boron was reported as 0.4 mg/kg BW-day.

US EPA's IRIS database lists an RfD of 0.2 mg/kg BW-day (US EPA 2022a) based on developmental effects in rats (decreased fetal body weight; BMDL5 of 10.3 mg/kg BW-day and an UF of 66), which was also adopted by RAIS. The dose response data (Heindel et al. 1992; Price et al. 1996) showed a statistically significant trend of decreasing fetal weights with increasing exposure to boron throughout the range of exposures tested. The exposure associated with the 5% weight decrease fell well within the range of the experimental data. This US EPA oral TRV was selected for use in this HHRA.

2.5 Cadmium

Cadmium is typically found in the environment combined with oxygen, chlorine and/or sulphur to form inorganic compounds. Cadmium (elemental) is considered insoluble in water; however, some cadmium salts are soluble with water solubility ranging from 0.00013 to 140 g/mL (CCME 2014). Exposure to cadmium may also result in a wide-range of non-carcinogenic effects including kidney disease and fragile bones. Respiratory effects (e.g., inflammation and pulmonary edema) have been observed following inhalation of cadmium. Epidemiological studies have reported that cadmium exposure may result in adverse effects to the reproductive, skeletal, hepatic, hematological, and immune systems (ATSDR 2012a).

Health Canada (2021) provides a provisional oral TRV of 0.0008 mg/kg BW-day, which is similar to JECFA's provisional tolerable monthly intake of 0.025 mg/kg BW-month (equivalent to 0.0008 mg/kg BW-day; JECFA 2013), which accounts for the long half-life of cadmium in the body. The JECFA/Health Canada TDI of 0.0008 mg/kg BW-day will ensure cadmium concentrations in the renal cortex do not exceed 50 mg/kg; this level is thought to protect normal kidney function.

The IRIS database (US EPA 2022a) provides an RfD of 0.001 mg/kg BW-day for exposures from food and 0.0005 mg/kg BW-day from water. An UF of 10 was applied to NOAELs obtained from epidemiological studies to account for intra-human variability to the toxicity of cadmium in the absence of specific data on sensitive individuals.

The ATSDR (2012a) derived a chronic-duration oral MRL of 0.0001 mg/kg BW-day for cadmium. This MRL is based on proteinuria effects estimated from a meta-analysis of environmental exposure data. It also derived a chronic-duration inhalation MRL of 0.00001 mg/m3 for cadmium. This MRL is based on the 95% lower confidence limit of the urinary cadmium level associated with a 10% extra risk of low molecular weight proteinuria estimated from a meta-analysis of environmental exposure data.

Although the ATSDR's MRLs are lower, they are intended to be used as screening levels to identify POCs, and not as TRVs, for which the ATSDR refers to the US EPA (IRIS database). Therefore, the PTDI of 0.0008 mg/kg BW-day based on nephrotoxicity effects (kidney) provided by Health Canada (2021), which is similar to the value provided by IRIS, was adopted as the TRV for cadmium in this assessment.

2.6 Chromium

Chromium occurs in nine different oxidation states of which +3 (trivalent) and +6 (hexavalent) are the most common (CCME 1999; ATSDR 2012b). Chromium is typically found in the environment combined with oxygen and iron but can also combine with carbon and hydrogen to form organic compounds. Trivalent chromium is ubiquitous in the environment and the most dominant form, since it's the most thermodynamically stable form under ambient conditions (CCME 1999). Hexavalent chromium is a strong oxidizing agent and primarily originates from anthropogenic sources (ATSDR 2012b). It is rare in nature because it's highly reactive with organic matter and other reducing substances (CCME 1999). Chromium compounds may be highly soluble (i.e., chromic acid) or insoluble (i.e., chromium oxide) in water.

While trivalent chromium is an essential nutrient and plays a role in various body functions such as enhancing absorption and metabolism of sugars, protein and fat, hexavalent chromium has a strong correlation between exposure and the incidence of stomach, intestinal tract and lung cancer (ATSDR 2012b). The absorption of ingested hexavalent chromium compounds (2 to 10% of dose) is generally more efficient than trivalent chromium compounds (0.5 to 3%), and absorption in the lungs appears to be more efficient than in the digestive tract, with the absorption of 12% of inhaled trivalent chromium and 30% of inhaled hexavalent chromium (CCME 1999; ATSDR 2012b).

In its 2021 TRV update, Health Canada (2021) provides an oral TRV for chromium (III) of 1.5 mg/kg BW-day (based on a NOAEL and no observed dose effects) and for chromium (VI) of 0.0022 mg/kg BW-day (base on a BMDL01 of 0.67 mg/kg BW-day for gastrointestinal toxicity [diffuse epithelial hyperplasia of the small intestine] in mice and an UF of 25 [10 for intraspecies variability and 2.5 for pharmacodynamic interspecies differences]).

The IRIS database (US EPA 2022a) provides an TDI of 0.003 mg/kg BW-day, which was derived from a NOAEL of 2.5 mg/kg BW-day based on effects to the kidney after a one year chronic toxicity study with rats (MacKenzie et al. 1958). An UF of 900 was applied to the NOAEL: 10 for interspecies extrapolation, 10 for inter-human variability, 3 as modifying factor, and 3 to address concerns from other studies (Zhang and Li 1987).

The ATSDR (2012b) derived a chronic MRL for chromium (VI) of 0.0009 mg/kg BW-day based on non-neoplastic lesions of the duodenum in mice reported in a chronic drinking water study.

Although chromium speciation has not been completed for the Project, to be conservative the TRV selected was the updated Health Canada (2021) oral TRV for the more toxic species of chromium (chromium VI) of 0.0022 mg/kg BW-day for effects on the gastrointestinal system was selected for use in this HHRA.

2.7 Cobalt

Cobalt is ubiquitous in the environment at low concentrations and occurs in a variety of inorganic and organic compounds with a wide-range of water solubility (ATSDR 2004a). The primary source of exposure to cobalt for most people is in food. The absorption of ingested cobalt ranges from 18% to 97% depending on the bioavailability of the ingested cobalt compound and body burden (ATSDR 2004a). Cobalt is an essential nutrient as it is part of vitamin B12, which is required to maintain human health (ATSDR 2004a). The primary target organ for cobalt toxicity upon exposure to elevated cobalt concentrations is the cardiovascular system (ATSDR 2004a). There is inadequate evidence for the carcinogenicity of cobalt and cobalt compounds in humans (Group 2B; IARC 1991).

Health Canada, US EPA's IRIS database, WHO INCHEM, and JECFA do not provide a TRV for oral exposures to cobalt.

ATSDR (2004a) derived a sub-chronic MRL of 0.01 mg/kg BW-day based on a LOAEL of 1 mg/kg BW-day for polycythemia (increase in red blood cells).

RAIS (ORNL 2022) provides a provisional peer-reviewed toxicity value (PPRTV) of 0.0003 mg/kg BW-day for chronic oral exposures based on based on decreased radioactive iodine uptake in the thyroid (Roche and Layrisse 1956). The PPRTV was derived using the dose of 1 mg/kg BW-day as a LOAEL based on humans exposed for 2 weeks. An UF of 3000 was applied to account for the use of a LOAEL instead of NOAEL (10), extrapolation from subchronic to chronic (10), human variability (10), sensitive populations (10), and for a lack of a multi-generation toxicity study (3). The temporal relationship between prolonged oral cobalt exposure and increased severity of thyroid effects in humans (or experimental animals) is not clear, and therefore there is a low confidence in this PPRTV.

RIVM (2001) provides a TDI of 0.0014 mg/kg BW-day (based the lowest LOAEL for cardiomyopathy of 0.04 mg/kg BW-day following a subchronic oral exposure (up to 8 months) and an UF of 3 for inter-human variation and a factor of 10 to extrapolate to a NOAEL). It was noted in a sub-chronic study reviewed by ATSDR (2004a) that anemic patients have been treated with higher dosages of cobalt (e.g., 0.6 to 1.0 mg/kg BW-day) without adverse effect. However, given the relatively high and frequent consumption of beer in the study that is the basis of the RIVM TDI, it was considered likely that those individuals may have suffered from pre-existing cardiovascular disease and poor diet, increasing their sensitivity to cobalt-induced toxicity. RIVM (2001) indicates that the incidence of cardiomyopathy observed in heavy beer drinkers may have been increased as the result of the concomitant consumption of alcohol.

There are deficiencies in both studies that were the bases of the chronic TRVs in RAIS by ORNL and RIVM. In the case of RIVM's (2001) TRV, the cardiomyopathy observed in the human subject was likely affected by alcohol consumption and poor diet, which may have contributed to increased sensitivity to cobalt-induced cardiomyopathy. However, this increased sensitivity is expected to provide a more conservative estimate of toxicity and therefore a conservative (or protective) TRV. The human studies that were the basis of the PPRTV were carried out in the 1950s and while iodine uptake was reduced, it is unclear whether this finding was clinically or statistically significant and whether there was a control group from which to serve as a point of comparison.

There are considered to be more deficiencies associated with the PPRTV and, as a result, the RIVM (2001) TDI of 0.0014 mg/kg BW-day based on cardiovascular effects was selected as the chronic oral TRV for this HHRA.

2.8 Iron

Iron is the fourth most abundant element on Earth. It is highly reactive with water and generally occurs in a variety of inorganic and organic compounds with a wide-range of water solubility. It is considered by the

WHO to be an essential trace element and its uptake is primarily from food. The absorption of ingested iron is about 2% to 15% depending on the bioavailability of the ingested iron compound and body burden (National Library of Medicine 2021). Once absorbed, iron is distributed throughout the body, stored in the blood, macrophage (reticuloendothelial) system, liver and muscle, and primarily excreted in urine and feces.

Iron deficiency may result in anemia, in which the iron content in red blood cells is low resulting in reduced oxygen uptake and numerous symptoms including fatigue, weakness, shortness of breath, confusion, thirst, impaired immune system, and loss of consciousness (National Library of Medicine 2021). The primary target organs for iron toxicity when exposed to toxic concentrations of iron include the lungs, gastrointestinal tract and reproductive system (specifically with respect to fetal development; National Library of Medicine 2021).

Health Canada, US EPA's IRIS database, WHO INCHEM, JECFA, ATSDR, and RIVM do not provide a TRV for either oral or inhalation exposures to iron.

In 2006, RAIS (ORNL 2022) derived a PPRTV of 0.7 mg/kg BW-day based on a LOAEL of 1 mg/kg BW-day for adverse gastrointestinal effects in humans and an UF of 1.5 to account for use of a LOAEL rather than a NOAEL. However, study duration was 1 month only (Frykman et al. 1994).

The RAIS PPRTV of 0.7 mg/kg BW-day based on gastrointestinal effects was used as the TRV in this HHRA.

2.9 Lithium

Lithium is a simple alkali metal, the salt of which acts as a mood stabilizing agent which has been extensively used for the treatment of mania for more than 50 years. However, no physiological function has been reported for lithium (National Center for Biotechnology Information 2021). Lithium is widely distributed in nature; trace amounts are found in many minerals, in most rocks and soils, and in many natural waters. Most lithium compounds are ionic in nature and would not be expected to undergo oxidation-reduction reactions under environmental conditions, and exist in a +1 oxidation state either in compounds or as dissolved ions (National Center for Biotechnology Information 2021). It is not expected to bioconcentrate or bioaccumulate.

Only the RAIS has proposed a PPRTV for chronic and sub-chronic effects of 0.002 mg/kg BW-day, which was used as the TRV in this HHRA. The derivation was based on the lower bound of the therapeutic serum lithium concentration range in humans and includes an UF of 1000. The nervous system is the primary target organ of lithium toxicity, but adverse effects on kidney and liver function have also been observed. Lithium has not been classified by EPA as to its potential carcinogenicity.

2.10 Manganese

Manganese is ubiquitous in the environment and human exposure arises from both natural and anthropogenic activities through inhalation of air particles, ingestion of food, sediment or soil, and dermal contact with water, soil or sediment. The primary source of human exposure to manganese is typically from food and water; manganese is easily absorbed in the gastrointestinal tract (ATSDR 2012c). Once absorbed, manganese is distributed widely throughout the body. As manganese is an essential nutrient, homeostatic mechanisms are in place that control the amount of manganese in the body. The primary means of elimination is via the liver bile (ATSDR 2012c). Manganese deficiencies can result in central nervous system effects (ATSDR 2012c).

Manganese toxicity varies depending upon the route of exposure and, when ingested, is considered to be among the least toxic metal (US EPA 1995b). Manganese is an essential trace element that is required

for normal physiological function in all animal species; however, individual requirements and toxicity can be highly variable (US EPA 2022a). Excess intake of manganese can result in symptoms such as lethargy, increased muscle tonus, tremor, and mental disturbances (US EPA 2022a).

Health Canada (2021) provides a manganese TDI for all age groups of 0.025 mg/kg BW-day based on neurodevelopmental effects observed in three key studies on rats (Kern, Stanwood, and Smith 2010; Kern and Smith 2011; Beaudin, Nisam, and Smith 2013) with a LOAEL of 25 mg/kg BW-day and the application of an UF of 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for the use of a LOAEL rather than a NOAEL).

The IRIS database (US EPA 2022a) TDI is 0.14 mg/kg/day which is the same as the NOAEL for chronic human consumption of manganese in the diet from a composite of data from several studies. IRIS states that the confidence in the dietary TDI for manganese is medium (US EPA 2022a).

The Health Canada (2021) TRV of 0.025 mg/kg BW-day for neurodevelopmental effects was adopted in this HHRA.

The Institute of Medicine (IOM 2001) does not consider manganese carcinogenic to humans.

2.11 Mercury

Mercury is typically found in the environment combined with oxygen, chlorine, and/or sulphur to form inorganic compounds. It exists in one of three stable oxidation states: 0, +1 and +2. Elemental mercury is liquid at room temperature and volatile. Exposure to elemental mercury has not been shown to result in cancer (ATSDR 1999, 2013). Inorganic and organic mercury compounds are classified as Group 3 (inorganic mercury) or Group 2B (methylmercury) carcinogens by the International Agency for Research on Cancer (IARC), and Group C, a possible human carcinogen, by the USEPA. Health Canada has not classified mercury as to its potential carcinogenicity and no SF or UR factors are available.

Exposure to mercury may result in a wide-range of non-carcinogenic effects on the nervous system, kidneys, stomach, intestines, development, immune system, reproductive system, and cardiovascular system, and may cause death (ATSDR 1999, 2013).

Mercury has been shown to accumulate in plants and animals and biomagnify in food chains, particularly in the aquatic environment (CCME 2000). Mercury, particularly in tissues higher trophic level organisms in the aquatic environment (such as fish), is often found in the methylmercury form, which can cause adverse effects at lower concentrations than total mercury (Health Canada 2007).

Health Canada (2021) provides a TDI of 0.0003 mg/kg BW-day for inorganic mercury exposure for the general public based on immunotoxicity (autoimmune glomerulonephritis). The TDI was based on LOAELs from three studies in rats and application of an UF of 1000 (10 for use of subchronic studies, 10 for intraspecies and interspecies variability, and 10 for LOAEL to NOAEL conversion).

Health Canada (2021) provides a PTDI of 0.00047 mg/kg BW-day for methylmercury for non-sensitive adults of the general population and 0.0002 mg/kg BW-day for sensitive populations such as pregnant women, women of childbearing age, and children based on neurodevelopmental toxicity. The TDIs were based on epidemiological studies of accidental poisonings and chronic low-level exposure in populations with high fish consumption. The PTDI from Health Canada (2021) is similar to the PTDI provided by JECFA of 0.00023 mg/kg BW-day (JECFA 2004).

Given that most exposure pathways (i.e., inhalation, ingestion of water, incidental ingestion and contact with soil, ingestion of market foods and most subsistence foods) are exposures to mercury and not methylmercury, the PTDI for mercury from Health Canada (2021) was used in this assessment for both toddlers and adults.

2.12 Molybdenum

Molybdenum is an essential trace element that is naturally present in many foods and is available as a dietary supplement. In healthy people, consumption of a diet high in molybdenum usually does not pose a health risk because the molybdenum is rapidly excreted in urine (Office of Dietary Supplements 2021).

US EPA's IRIS database developed an oral chronic RfD of 0.005 mg/kg BW-day based on a LOEL of 0.14 mg/kg-day for an increase in uric acid levels and an UF of 30 (US EPA 2022a). The principal study by Koval'skiy, Yarovaya, and Shmavonyan (1961) correlated the dietary intake of molybdenum with serum uric acid levels, several biochemical endpoints, and with a gout- like sickness affecting the adult population in a settlement in Armenia in an area of high natural molybdenum content (and low copper content) in soils and plants. Estimated intakes corresponded to molybdenum doses of 0.14 to 0.21 mg/kg BW-day for a 70-kg adult. An UF of 3 was used for protection of sensitive human populations and a factor of 10 for the use of a LOAEL, rather than a NOAEL, from a long-term study in a human population (US EPA 1992a).

The Chemical Health Hazard Assessment Division (CHHAD) of Health Canada listed 2 mg/person-day as an upper limit (UL) TDI, obtained from the Institute of Medicine (Food and Nutrition Board), US National Academy of Sciences, but no further details were provided. Assuming and adult body weights of 70.7kg, this results in a TDI of 0.028 mg/kg-day for adults.

Health Canada (2010) used the same data source as CHHAD (Institute of Medicine) but adjusted oral TDIs for molybdenum for age and provided a TDI for toddlers of 0.023 mg/kg-day. The TRV was based on reproductive effects in a sub-chronic study on rats and included an UF of 30 (10 for interspecies variability, 3 for intraspecies variability).

However, Health Canada withdrew this TDI in its 2021 update of the TRVs (Health Canada 2021). The updated Health Canada guidance indicates that the TRVs for molybdenum were not reviewed, were removed from the update, and recommends that TRVs be identified from other regulatory agencies. Therefore, US EPA's IRIS oral chronic RfD of 0.005 mg/kg BW-day was selected as a TRV for use in this assessment. Molybdenum is not considered carcinogenic.

2.13 Nickel

Nickel compounds have a wide-range of water solubility, including insoluble compounds such as nickel cyanide, and highly soluble compounds such as nickel chloride (CCME 2015). The primary source of human exposure to nickel is typically from food (ATSDR 2005a). The absorption of ingested nickel in humans ranges from 3% to 40% depending on the form and solubility of the compound. The absorption of inhaled nickel ranges from 20% to 35%, varying with particle size and solubility. Nickel has been shown to accumulate in plants and some animals; however, it does not appear to biomagnify in food chains (ATSDR 2005a).

Health Canada (2010) provided a TDI of 0.011 mg/kg BW/day for total nickel. The TDI for total nickel (as soluble salts) was based on a dietary study in rats that found a NOAEL of 5 mg/kg BW-day for altered organ to body weight ratios (Springborn Laboratories Inc. 2000). An uncertainty factor of 200 was applied to the NOAEL: 10 for interspecies variation and 10 to protect sensitive populations. A modifying factor of 2 was also applied to account for the inadequacies of the reproductive studies.

In 2021, Health Canada updated the nickel TRV and provided chronic oral TDIs for nickel chloride (0.0013 mg/kg BW-day) and for nickel sulfate (0.012 mg/kg BW-day). The nickel chloride TDI was based on a LOAEL of 1.3 mg/ kg BW-day and application of an UF of 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for use of a LOAEL instead of a NOAEL) in a long-term study with female rats with endpoint of reproductive toxicity (perinatal death in offspring). The nickel sulfate TDI was based

on a LOAEL of 0.012 mg/kg BW-day (no UFs) from an epidemiological study with control and nickel-sensitive human subjects who experienced dermal toxicity (exacerbation of eczema) after exposure.

Nickel is measured as total nickel in environmental samples and not further speciated. To provide a conservative risk estimate, it was assumed that the majority of nickel is nickel chloride and the lower TRV for nickel chloride of 0.0013 mg/kg BW-day based on reproductive effects was selected for this assessment.

2.14 Selenium

Selenium is an essential element and is required for human nutrition. The margin between toxicity and essentiality of selenium is very narrow (BC ENV 2014). Selenium deficiencies can result in cardiovascular disease (e.g., enlarged heart, congestive heart failure), muscle pain, Kashin-Beck disease (atrophy, degeneration, and necrosis of cartilage), decreased immune function, and risk of miscarriage (ATSDR 2003; BC ENV 2014). Selenium is not considered to be a carcinogen by Health Canada (ATSDR 2003; Health Canada 2013). Exposure to excess selenium may result in non-carcinogenic effects to the respiratory and reproduction systems (ATSDR 2003). Selenium has been shown to accumulate in plants and animals and biomagnify in food chains, particularly in the aquatic environment (ATSDR 2003; BC ENV 2014).

The US EPA RfD of 0.005 mg/kg BW-day is based on a NOAEL of 0.015 mg/kg BW-day for clinical selenosis in a population living in an area with high environmental selenium levels (Yang et al. 1989b as cited in US EPA 1991). Dietary selenium intake was proportional to blood and tissue selenium levels. NOAEL and LOAEL values were calculated from a regression analysis based upon the correlation. A daily selenium intake of 1.261 mg/day (blood selenium concentration of 1.35 mg/L) resulted in signs of selenosis. The LOAEL was therefore set at 1.26 mg/day. At 0.853 mg/day (blood selenium concentration of 1.0 mg/L), no signs of selenosis were apparent and this concentration was determined to be a NOAEL. To derive the RfD, the NOAEL was adjusted for an average body weight of 55 kg. An uncertainty factor of 3 was applied for the protection of sensitive individuals.

Health Canada (2021) provides an age- and body weight-adjusted tolerable upper limit for selenium of 0.0057 to 0.0060 mg/kg BW-day (adults and toddlers, respectively). This was based on a NOAEL in adults of 0.8 mg/kg/day in a cohort study by Yang and Zhou (1994) and a NOAEL in infants of 0.006 mg/kg BW-day (Shearer and Hadjimarkos 1975). Health effects due to an exposure to elevated levels of selenium are described as selenosis (gastrointestinal disorders, hair loss, sloughing of nails, fatigue, irritability, and neurological damage). An uncertainty factor of 2 was applied to the adult tolerable upper limit for protection of sensitive individuals, resulting in an upper limit intake level of 0.4 mg/day (or 0.0057 mg/kg bw/day) for adults 19 years and over. The NOAEL for infants was adjusted for the average milk intake rate of 0.78 L/day. The resulting upper limit intake level, 47 µg/day, was rounded down to the nearest 5 µg (45 µg/day) and adjusted by body weight to an upper limit dose of 0.0055 mg/kg BW-day. The upper intake levels for toddler, child, and adolescent age groups were derived from the infant value using relative body weights.

The Health Canada TDIs of 0.0057 and 0.0060 mg/kg BW-day for adults and toddlers, respectively, were used as the oral TRVs for selenium in this assessment.

2.15 Strontium

Strontium is a natural and commonly occurring element. Strontium can exist in two oxidation states: 0 and +2. Under normal environmental conditions, only the +2 oxidation state is stable enough to be important. Food and drinking water are the largest sources of exposure to strontium (ATSDR 2004b). Because of

the nature of strontium, some of it gets into fish, vegetables, and livestock. Grain, leafy vegetables, and dairy products contribute the greatest percentage of dietary strontium to humans (ATSDR 2004b).

Health Canada has not derived a TRV for strontium (Health Canada 2021). The CHHAD of Health Canada had previously developed an internal RfD value of 0.6 mg/kg BW-day for strontium; however, no details as to how this value was derived is available (Health Canada 2011b).

US EPA's IRIS provides an RfD of 0.6 mg/kg BW-day based on musculoskeletal effects (rachitic bone) in rats, with a NOAEL of 190 mg/kg BW-day and an UF of 300 (10 for animal to human extrapolation, 10 for incomplete database, and 3 for sensitive subpopulations) (US EPA 1992b). The RfD was based on results from three medium- to long-term (20-day, 9-week, to 3-year) oral studies in young and adult rats. This value is also supported by RAIS as the oral chronic RfC. The WHO derived a lower TDI of 0.13 mg/kg BW-day (WHO 2010). A range of concentrations of strontium chloride hexahydrate was fed to weanling rats for 90 days (Kroes et al. 1977). 40 mg/kg BW-day was considered the NOAEL, with an UF of 300 applied for interspecies differences (10), inter-individual susceptibilities (3), and deficiencies in the database (10).

The ATSDR developed a MRL for stable strontium, for intermediate-duration exposures, of 2.0 mg/kg BW-day (ATSDR 2004b). This was based on a similar study in rats, fed with strontium carbonate for 20 days, with a LOAEL for bone mineralization abnormalities of 550 mg strontium/kg BW-day (Storey 1961). This study was preferred by the ATSDR as the basis for the intermediate MRL to the study by Kroes et al. (1977) and other studies, because both young and adult animals were tested, the administered doses included NOAELs and LOAELs for both age groups, and the evaluation of skeletal effects included histopathological analysis. The NOAEL of 140 mg strontium/kg BW-day was divided by an UF of 30 (10 for extrapolation from animal to human and 3 for human variability) and a modifying factor of 3 (for short study duration and limited end point examination).

The IRIS value of 0.6 mg/kg BW-day was selected as chronic oral TRV for this assessment because it is based on several principal and supporting studies that more accurately reflect the chronic exposure duration than the WHO and ATSDR principal studies.

2.16 Thallium

Thallium occurs naturally as inorganic and organic compounds with a wide-range of water solubility (ATSDR 1992). No association has been found between the occurrence of cancer in humans and occupational exposure to thallium (ATSDR 1992). Exposure to elevated concentrations of thallium may have a wide-range of non-carcinogenic effects to fetal development and various organ systems, including nervous, cardiovascular, gastrointestinal, hepatic, respiratory, ocular, and renal systems (ATSDR 1992). No specific target organ has been identified. Exposure to high doses (e.g., over one gram) of thallium may result in death, blindness, vomiting, diarrhea, hair loss, muscle fiber necrosis, bradycardia, and myocardial necrosis; whereas, chronic exposure to low doses may result in birth defects, failing eye sight, neural degeneration, and myelin sheath delamination (ATSDR 1992).

Thallium has been shown to accumulate in plants and some animals; however, it does not appear to biomagnify in food chains (ATSDR 1992).

In 2011, Health Canada (2011b) provided a PTDI of 0.00007 mg/kg BW-day for thallium. Health Canada did not provide a rationale for the derivation of this PTDI but stated that the PTDI is considered temporary as it was derived from an incomplete data set. This PTDI was withdrawn in the 2021 TRV update (Health Canada 2021).

Due to the insufficiency of data to derive a defensible TRV, the US EPA IRIS database, CalEPA, or WHO INCHEM database also do not provide a TRV for thallium. RAIS (2022) lists a PPRTV of 0.00001 mg/kg

BW-day for thallium soluble salts in the RAIS database, which was developed for the Superfund Program, and is based on an estimated NOAEL of 0.04 mg/kg BW-day for histopathological effects in the skin of rats and applied an UF of 3000 (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for lack of developmental toxicity data, and 3 for extrapolation from subchronic to chronic duration(US EPA 2012).

As thallium is considered a trace element, its average dietary intake in Canadians of all age groups (males and females) was assessed in the Total Diet Study from 1993 to 1999. The average intake for the toddler age group (1 – 4 years of age) was 0.088 µg/kg BW-day, while the average intake for the adult age groups (20 - 39, 40 - 64, and 65+ years of age) was 0.025 µg/kg BW-day (Health Canada 2011a). These values are higher than the RAIS PPRTV but did not result in observable adverse health outcomes in the Canadian population. It is therefore assumed that these average dietary intake values are safe for the general population including sensitive subgroups and were adopted as the TRVs for this assessment. Thus, the TRV for thallium is based on background EDIs for the average Canadian adult and toddler of 0.000025 mg/kg BW-day and 0.000088 mg/kg BW-day, respectively.

2.17 Zinc

Zinc is an essential element and is required for human nutrition. It is one of the most common elements in the earth's crust. Zinc exists in one of three oxidation states: +2, +1, and 0. Pure zinc is highly reactive with water and may spontaneously combust in damp areas. Consequently, zinc predominantly exists in a variety of inorganic and organic compounds. Zinc compounds have a wide-range of water solubility; however, pure zinc is considered to be insoluble in water (ATSDR 2005b). Exposure to excess zinc has been shown to elicit a variety of toxic effects including infertility, decreased birth weight, pancreatic damage, anaemia, nausea, vomiting, and skin irritation (ATSDR 2005b). Zinc deficiency can result in a wide range of adverse effects including decreased immune response, birth defects, slow wound healing, and slow growth.

Zinc has been shown to accumulate in some plants and animals; however, it does biomagnify in food chains (ATSDR 2005b). Zinc is not considered to be a carcinogen (Health Canada 2021).

Health Canada (2011b) provided a TDI of 0.7 mg/kg BW-day. This value was based on the upper safe level (USL) established by the Expert Group on Vitamins and Minerals (EGVM 2003). A LOAEL of 50 mg/day was found for both men and women exposed to zinc supplements (i.e., additional zinc exposure besides that incurred through normal food and water intake). The LOAEL was converted to a NOAEL by dividing it by an UF of 2 to give a NOAEL of 25 mg/day, which is 0.42 mg/kg BW-day in a 60 kg person. Thus, the USL for zinc supplements is 0.42 mg/kg BW-day. If the maximum zinc intake of 17 mg/day (0.28 mg/kg BW-day) from food is added to the USL, the maximum total intake for zinc is equivalent to 0.7 mg/kg BW-day.

However, Health Canada (2021) provides a more conservative TRVs for zinc for adults (using a body weight of 70.7 kg) and toddlers (using a body weight of 16.5 kg) of 0.57 and 0.48 mg/kg BW-day, respectively. The more conservative TRVs from Health Canada (2021) were used in the HHRA. A NOAEL for infants of 5.8 mg/L (in formula supplemented with zinc) adjusted for estimated average human milk intake of 0.78 L/day was used to derive upper levels for Health Canada's age groups. No target organs were identified in this 6 months exposure (no effects of zinc on serum copper or cholesterol concentrations or other adverse effects were found); however, for the purposes of target organ toxicity, it was assumed that hematological changes were the critical effect.

3. SLOPE AND UNIT RISK FACTORS FOR NON-THRESHOLD COPCS

A slope factor (SF) is the upper-bound increased cancer risk from a lifetime exposure to a chemical. It is an estimate of the probability of a response-per-unit intake of a carcinogenic COPC over an average human lifetime and is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime exposure to a particular level. It is expressed as the inverse of dose in units of $(mg/kg\ BW/day)^{-1}$. Upper-bound estimates conservatively exaggerate the risk to ensure that the risk is not underestimated if the underlying model is incorrect.

A cancer unit risk (UR) is the upper-bound incremental lifetime cancer risk that results from continuous exposure to a carcinogenic COPC at a concentration of 1 $\mu g/m^3$ in air (expressed in $(\mu g/m^3)^{-1}$).

3.1 Ingestion Slope Factor for Arsenic

Arsenic is the only metal in this report that is considered carcinogenic via the ingestion pathway. Numerous epidemiologic studies investigating occupational exposures to various forms of inorganic arsenic compounds have established a strong correlation between exposure and the incidence of cancer, including cancer in the bladder, kidneys, lungs, skin, and liver (CEPA 1993). Consequently, arsenic is classified as a Group I carcinogen by Health Canada, Group 1 carcinogen by the IARC, and Group A carcinogen by the US EPA. The carcinogenicity of arsenic can be explained at least in part by it being a mutagen that depends on reactive oxygen species for its activity (CEPA 1993). Forms of inorganic arsenic (e.g., arsenite) can induce large deletion mutations (CEPA 1993). There is some debate whether arsenic is mutagenic or just genotoxic. To be conservative, this risk assessment assumed that arsenic carcinogenicity is at least in part due to its mutagenicity.

The principal studies (Tseng et al. 1968; Tseng 1977) used to derive the oral slope factor for arsenic for the USEPA were based on the ingestion of drinking water by humans resulting in skin cancer. The extrapolation method used to derive the oral slope factor was both time- and dose-related formulation of a multistage model (US EPA 1995a).

The principal study used by Health Canada was by Morales et al. (2000), where 0.3 μg/L in drinking water was considered to pose negligible risk (95th confidence interval of the lifetime risk is 1.9×10^{-6} to 1.4×10^{-5}) and was the basis of the slope factor. Health Canada (2006) concluded that a Poisson model recommended by the US EPA and fit by Morales et al. (2000) with an external unexposed comparison population is the most appropriate for estimating the cancer risks associated with the ingestion of arsenic in drinking water resulting in bladder, liver, or lung cancer. Health Canada (2006) adopted assumptions similar to those of the US EPA regarding the choice of risk metric; however, they also applied the use of a southwestern Taiwanese to Canadian conversion factor based on skin cancer. The SF from Health Canada (2021) is 1.8 $(mg/kg\ BW\text{-}day)^{-1}$.

Of the various species of arsenic that exist, inorganic arsenic has been identified as the primary carcinogenic form, while organic arsenic compounds have relatively low carcinogenic activity but a higher bioaccumulation potential (Roy and Saha 2002). US EPA's IRIS lists an oral SF of 1.5 $(mg/kg\ BW\text{-}day)^{-1}$.

ATSDR has derived a chronic-duration oral MRL of 0.0003 mg/kg/day for inorganic arsenic based on a NOAEL of 0.0008 mg As/kg BW-day for dermal effects in a Taiwanese farming population exposed to arsenic in well water. An UF of 3 (for human variability) was applied.

The more conservative Health Canada (2021) oral SF of 1.8 $(mg/kg\ BW\text{-}day)^{-1}$ was selected for use in the HHRA.

3.2 Inhalation Unit Risk Factors

3.2.1 Arsenic

Arsenic is also carcinogenic via the inhalation route. Health Canada (2021) derived an inhalation SF of 27 $(mg/kg\text{-}day)^{-1}$ and an UR of 6.4 $(mg/m^3)^{-1}$ based on an occupational study by Higgins et al. (1986), as cited in ECCC (1993) with lung cancer as measurement endpoint. The US EPA's IRIS provides an UR factor of 4.3 $(mg/m^3)^{-1}$, based on epidemiological studies in occupationally exposed people with lung cancer as the endpoint. ATSDR (2007) has not derived inhalation RLs due to its perceived lack of suitable data.

The Health Canada (2021) inhalation UR factor of 6.4 $(mg/m^3)^{-1}$ was used to estimate the incremental lifetime cancer risk (ILCR) from inhalation exposures in the HHRA.

3.2.2 Cadmium

Cadmium is classified as a Group II carcinogen by CEPA (probably carcinogenic to humans), Group 1 carcinogen by the IARC, and Group B1 probable carcinogen by the US EPA.

Previously, Health Canada (Health Canada 2010) provided a cancer UR factor for inhalation of cadmium of 9.8 $(mg/m^3)^{-1}$, which is based on chronic exposure studies in rats with lung cancer as the endpoint. This UR was updated in Health Canada (2021) to 4.2 $(mg/m^3)^{-1}$, based on a Poisson regression model to occupational mortality data (inhalation of dusts of cadmium oxide and cadmium sulfide, and cadmium fumes with endpoint of lung cancer) and extrapolation to ambient levels in California by Cal EPA (OEHHA 2011).

The IRIS database (US EPA 2022a) provides a UR of 1.8 $(mg/m^3)^{-1}$ based on a workplace exposure study with respiratory cancer as the endpoint. While US EPA (2022a) mentions the study used by Health Canada in 2010 to derive an UR of 9.8 $(mg/m^3)^{-1}$, US EPA elected to use the less conservative UR of 1.8 $(mg/m^3)^{-1}$ since it was based on a human study; this UR was last revised in 1987 by US EPA.

The Health Canada (2021) update of the 2010 UR included a review of reports by CalEPA and the California Department of Health Services (CDHS 1986, 1990). As these data and evaluations are more recent than the US EPA IRIS assessment, the Health Canada UR of 4.2 $(mg/m^3)^{-1}$ was used in the HHRA.

3.2.3 Chromium

Total and hexavalent chromium are carcinogenic via the inhalation route and are classified as a group I carcinogens under CEPA (carcinogenic to humans), Group A (human carcinogen) by the US EPA (2022a) and Group 1 (carcinogenic to humans; hexavalent chromium only) by the IARC.

Health Canada (2010) provided cancer URs for inhalation of total and hexavalent chromium of 11 and 76 $(mg/m^3)^{-1}$, respectively, based on an epidemiological study of chromate plant workers by Mancuso (1975) with lung cancer as the endpoint. In it's 2021 update, Health Canada withdrew the UR for total chromium, but maintained the UR of 76 $(mg/m^3)^{-1}$ for hexavalent chromium.

In contrast, the US EPA's IRIS derived an inhalation UR for hexavalent chromium of 12 $(mg/m^3)^{-1}$ based on the same study by Mancuso (1975). The difference in the derived URs between the agencies originates in the assumption that cancer mortality in Mancuso (1975) was due to Cr(VI), which was further assumed to be no less than one-seventh of total chromium (US EPA 1998). The US EPA (1998b) also noted that, while the relationship between total chromium and carcinogenicity was strong, the relationship between chromium (III) or chromium (VI) concentrations and cancer was not as well defined.

Health Canada (2021) multiplied its 2010 UR for total chromium of 11 $(mg/m^3)^{-1}$ by 7 to infer an UR for hexavalent chromium of 76 $(mg/m^3)^{-1}$. However, this assumes that the ratio of total to hexavalent chromium in air is consistently 7:1 regardless of sources or environmental conditions. However, the relationship between total and hexavalent chromium concentrations is likely to be site-specific and speciation of chromium in air or environmental media has not been done for this Project (concentrations are for total chromium). Therefore, this HHRA selected the US EPA IRIS risk level for chromium of 12 $(mg/m^3)^{-1}$ for use as an inhalation UR.

3.2.4 Nickel

Nickel is carcinogenic via the inhalation route. The US EPA derived an inhalation UR based on extrapolations for lung cancer from four epidemiologic data sets for human exposure to nickel subsulfide (Enterline and March 1982; Chovil et al. 1981; Peto et al. 1984; and Magnus et al. 1982; as cited in US EPA 1987). An increased cancer risk of 1 in 100,000 was determined to be associated with a nickel concentration of 0.00002 mg/m^3, which is equivalent to 0.48 $(mg/m^3)^{-1}$.

Health Canada (2021) derived an inhalation UR based on a TC05 of 0.04 mg/m^3 for lung, nasal, kidney, prostate, and buccal cavity cancers in workers exposed to soluble nickel (primarily nickel chloride and nickel sulphate; Doll et al. 1990 as cited in Environment Canada and Health Canada 1994; Health Canada 1996). The UR is based on epidemiological studies where workers at two nickel refineries were occupationally exposed to nickel by inhalation for at least 6 months. The estimate of the concentration in air associated with a 5% tumour incidence for soluble nickel of 0.04 mg/m^3 was adjusted for a 5% extra cancer risk to derive the inhalation UR of 1.3 $(mg/m^3)^{-1}$. This UR was used for the HHRA as it was based on a more recent study.

4. REFERENCES

ATSDR. 1992. *Toxicological Profile for Thallium*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=309&tid=49 (accessed January 2022).

ATSDR. 1999. *Toxicological Profile for Mercury*. https://wwwn.cdc.gov/TSP/substances/ToxSubstance.aspx?toxid=80. http://www.atsdr.cdc.gov/toxprofiles/tp46.pdf (accessed January 2022).

ATSDR. 2001. *Toxicological Profile for Boron*. Agency for Toxic Substances and Disease Registry. https://wwwn.cdc.gov/TSP/substances/ToxSubstance.aspx?toxid=80 (accessed January 2022).

ATSDR. 2003. *Toxicological Profile for Selenium*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=153&tid=28 (accessed January 2022).

ATSDR. 2004a. *Toxicological Profile for Cobalt*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=245&tid=44 (accessed January 2022).

ATSDR. 2004b. *Toxicological Profile for Strontium*. Agency for Toxic Substances & Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp159.pdf (accessed May 2021).

ATSDR. 2005a. *Toxicological Profile for Nickel*. Agency for Toxic Substances & Disease Registry. https://www.atsdr.cdc.gov/ToxProfiles/tp15.pdf (accessed January 2022).

ATSDR. 2005b. *Toxicological Profile for Zinc*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=302&tid=54 (accessed January 2022).

ATSDR. 2007. *Toxicological Profile for Arsenic*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=22&tid=3 (accessed January 2022).

ATSDR. 2008. *Toxicological Profile for Aluminum*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=191&tid=34 (accessed January 2022).

ATSDR. 2012a. *Toxicological Profile for Cadmium*. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf (accessed January 2022).

ATSDR. 2012b. *Toxicological Profile for Chromium*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=191&tid=34 (accessed January 2022).

ATSDR. 2012c. *Toxicological Profile for Manganese*. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/ToxProfiles/tp151.pdf (accessed January 2022).

ATSDR. 2013. *Addendum to the Toxicological Profile for Mercury*. Agency for Toxic Substances and Disease Registry. https://wwwn.cdc.gov/TSP/substances/ToxSubstance.aspx?toxid=24 (accessed January 2022).

ATSDR. 2019. *Toxicological Profile for Antimony and Compounds*. Agency for Toxic Substances and Disease Registry. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=332&tid=58 (accessed January 2022).

ATSDR. 2022. *Toxicological Profiles (webpage). Agency for Toxic Substances and Disease Registry*. https://www.atsdr.cdc.gov/toxprofiledocs/index.html (accessed February 2022).

BC ENV. 2014. *Companion Document to: Ambient Water Quality Guidelines for Selenium Update. Water Protection and Sustainability Branch, Environmental Sustainability and Strategic Policy Division, British Columbia Ministry of Environment*. https://www2.gov.bc.ca/assets/gov/environment/air-land-water/water/waterquality/water-quality-guidelines/approved-wqgs/bc_moe_se_wqg_companion_document.pdf (accessed October 2020).

BC ENV. 2017. *Technical Guidance on Contaminated Sites 7: Supplemental Guidance for Risk Assessments. Version 5 November 2017*. Victoria, BC.

BC ENV. 2020. *Provincial Air Quality Objective Information Sheet: British Columbia Ambient Air Quality Objectives*. BC Ministry of Environment and Climate Change Strategy. https://www2.gov.bc.ca/assets/gov/environment/air-land-water/air/reports-pub/prov_aqo_fact_sheet.pdf (accessed January 2022).

Beaudin, S. A., S. Nisam, and D. R. Smith. 2013. Early Life versus Lifelong Oral Manganese Exposure Differently Impairs Skilled Forelimb Performance in Adult Rats. *Neurotoxicology and Teratology*, 38: 36-45.

CalEPA. 2022. *California Environmental Protection Agency*. https://data.ca.gov/dataset/toxicity-criteria-database (accessed Toxicity Criteria Database accessed February 2022).

CCME. 1999. *Canadian Water Quality Guidelines for the Protection of Aquatic Life: Chromium - Hexavalent Chromium and Trivalent Chromium*. In: Canadian Environmental Quality Guidelines, 1999. Canadian Council of Ministers of the Environment: Winnipeg, MB.

CCME. 2000. *Canadian Tissue Residue Guidelines for the Protection of Wildlife Consumers of Aquatic Biota: Methylmercury. In: Canadian Environmental Quality Guidelines, 1999*. Canadian Council of Ministers of the Environment: Winnipeg, MB.

CCME. 2014. *Canadian Water Quality Guidelines: Cadmium. Scientific Criteria Document*. PN 1515. Canadian Council of Ministers of the Environment: Winnipeg, Manitoba.

CCME. 2015. *Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Nickel*. Winnipeg, Manitoba.

CCME. 2021. *Canada's Air: CAAQOs*. Canadian Council of Ministers of the Environment. https://www.ccme.ca/en/air-quality-report#slide-7 (accessed January 2022).

CDHS. 1986. *Report to the Air Resources Board on Cadmium. Part B. Health Effects of Cadmium. California Department of Health Services. Epidemiological Studies Section*. Berkeley, CA.

CDHS. 1990. *Risk-Specific Intake Levels for the Proposition 65 Carcinogen Cadmium. Reproductive and Cancer Hazard Assessment Section, Health Hazard Assessment Division of the California Department of Health Services*. Berkeley, CA.

Donald, J., M. Golub, M. Gershwin, and C. Keen. 1989. Neurobehavioral effects in offspring of mice given excess aluminum in diet during gestation and lactation. *Neurotoxicol Teratol*, 11: 345-51.

ECCC. 1993. *Priority Substance List Assessment Report - Arsenic and its Compounds*. Environment and Climate Change Canada. http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=D4CB7B42-1 (accessed January 2022).

EGVM. 2003. *Safe Upper Limits of Vitamins and Minerals*. ISBN 10904026-11-7. Food Standard Agency, Expert Group on Vitamins and Minerals: n.p.

Environment Canada and Health Canada. 1994. *Nickel and Its Compounds. Priority Substances List Assessment Report. Canadian Environmental Protection Act. Ottawa, Ontario*. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/ewh-semt/alt_formats/hecssesc/pdf/pubs/contaminants/psl1-lsp1/compounds_nickel_composes/nickel-eng.pdf. (accessed February 2022).

Frykman, E., M. Bystrom, U. Jansson, A. Edberg, and T. Hansen. 1994. Side Effects of Iron Supplements in Blood Donors: Superior Tolerance of Heme Iron. *J Lab Clin Med*, 123 (4): 561-64.

Golub, M., S. Germann, B. Han, and C. Keen. 2000. Lifelong Feeding of a High Aluminum Diet to Mice. *Toxicology*, 150: 107-17.

Golub, M., B. Han, C. Keen, M. Gershwin, and R. Tarara. 1995. Behavioral Performance of Swiss-Webster Mice Exposed to Excess Dietary Aluminum During Development or During Development and as Adults. *Toxicol Appl Pharmacol*, 133: 64-72.

Health Canada. 1996. *Canadian Environmental Protection Act, Priority Substances List, Supporting Documentation: Health-Based Tolerable Daily Intakes/Concentrations and Tumourigenic Doses/Concentrations for Priority Substances (unedited version)*.

Health Canada. 2006. *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document - Arsenic*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada: Ottawa, ON.

Health Canada. 2007. *Human Health Risk Assessment of Mercury in Fish and Health Benefits of Fish Consumption*. November 20, 2011. Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch: Ottawa, ON.

Health Canada. 2010. *Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors*. Version 2.0. Contaminated Sites Division, Safe Environments Directorate: Ottawa, ON.

Health Canada. 2011a. *Dietary Intakes of Contaminants and Other Chemicals for Different Age-Sex Groups of Canadians - Canadian Total Diet Study*. Health Canada. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/hpfb-dgpsa/pdf/surveill/metal_intake-plomb_apport_93-99-eng.pdf (accessed February 2022).

Health Canada. 2011b. *Toxicological Reference Values, Estimated Daily Intakes or Dietary Reference Values for Trace Elements. Obtained from Chemical Health Hazard* Revised March 2011, unpublished: Ottawa, ON.

Health Canada. 2013. *Guidelines for Canadian Drinking Water Quality. Guideline Technical Document - Selenium*. Ottawa, ON.

Health Canada. 2019. *Guidance for Evaluating Human Health Impacts in Environmental Assessment: Human Health Risk Assessment*. Ottawa, ON.

Health Canada. 2021. *Federal Contaminated Site Risk Assessment in Canada: Toxicological Reference Values (TRVs)*. Version 3.0. Health Canada: Ottawa, ON.

Heindel, J. J., C. J. Price, E. A. Field, M. C. Marr, C. B. Myers, R. E. Morrissey, and B. A. Schwetz. 1992. Developmental toxicity of boric acid in mice and rats. *Fund Appl Toxicol*, 18: 266-77.

Higgins, I., M. Oh, K. Kryston, C. Burchfiel, and N. Wilkinson. 1986. Arsenic exposure and respiratory cancer in a cohort of 8 044 Anaconda smelter workers. A 43-year follow-up study. Prepared for the Chemical Manufacturers' Association and the Smelters Environmental Research Association. *unpublished*:

IARC. 1991. *Cobalt and Cobalt Compounds (Group 2B). International Agency for Research on Cancer (IARC) - Summaries & Evaluations*.

IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academy Press: Washington, DC.

JECFA. 2004. *Evaluation of Certain Food Additives and Contaminants*. Section 7.2, Methylmercury. 61st Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA):

JECFA. 2011. *Safety Evaluation of Certain Food Additives and Contaminants*. WHO Food Additives Series, No. 65. Prepared by the seventy-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA):

JECFA. 2013. *Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA): Cadmium*.

Kern, C. H. and D. R. Smith. 2011. Preweaning Mn Exposure Leads to Prolonged Astrocyte Activation and Lasting Effects on the Dopaminergic System in Adult Male Rats. *Synapse* 65 (6): 532–44.

Kern, C. H., G. D. Stanwood, and D. R. Smith. 2010. Preweaning Manganese Exposure Causes Hyperactivity, Disinhibition, and Spatial Learning and Memory Deficits Associated with Altered Dopamine Receptor and Transporter Levels. *Synapse* 64 (5): 363-78.

Koval'skiy, V., G. Yarovaya, and D. Shmavonyan. 1961. Changes of Purine Metabolism in Man and Animals Under Conditions of Molybdenum Biogeochemical Provinces (Russian trans.) *Zh Obshch Biol*, 22: 179-91.

Kroes, R., E. den Tonkelaar, A. Minderhoud, G. Speijers, D. Vonk-Visser, J. Berkvens, and G. van Esch. 1977. Short-term toxicity of strontium chloride in rats. *Toxicology*, 7 (1): 11-21.

MacKenzie, R. D., R. U. Byerrum, C. F. Decker, C. A. Hoppert, and R. F. Langham. 1958. Chronic Toxicity Studies. II. Hexavalent and Trivalent Chromium Administered in Drinking Water to Rats. *Am Med Assn Arch Indust Health*, 18: 232-34.

Mancuso, T. 1975. *Consideration of Chromium as an Industrial Carcinogen*. Paper presented at International Conference on Heavy Metals in the Environment, Toronto, Ontario, Canada.

Morales, K. H., L. Ryan, T. L. Kuo, M. M. Wu, and C. J. Chen. 2000. Risk of Internal Cancers from Arsenic in Drinking Water. *Environ Health Perspect*, 108: 655-61.

National Center for Biotechnology Information. 2021. *PubChem Compound Summary for CID 3028194, Lithium*. https://pubchem.ncbi.nlm.nih.gov/compound/Lithium (accessed May 2021).

National Library of Medicine. 2021. PubChem, Hazardous Substance Data Bank. https://pubchem.ncbi.nlm.nih.gov/compound/23925#source=Hazardous%20Substances%20Data%20Bank%20(HSDB) (Iron accessed May 2021).

OEHHA. 2011. *Technical Support Document for Cancer Potency Factors—Appendix B: Chemical-Specific Summaries of the Information used to Derive Unit Risk and Cancer Potency Values (2009, updated 2011)*. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Air Toxicology and Epidemiology Branch.:

Office of Dietary Supplements. 2021. *Molybdenum Fact Sheet for Health Professionals*. National Institutes of Health. https://ods.od.nih.gov/factsheets/Molybdenum-HealthProfessional/ (accessed May 2021).

ORNL. 2022. *Risk Assessment Information System (RAIS)*. https://rais.ornl.gov (accessed February 2022).

Price, C. J., P. L. Strong, M. C. Marr, C. B. Myers, and F. J. Murray. 1996. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. *Fund Appl Toxicol*, 32: 179-93.

RIVM. 2001. *Re-evaluation of Human-Toxicological Maximum Permissible Risk Levels*. RIVM report 711701025. Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment): Bilthove, NE.

RIVM. 2009. *Re-evaluation of Some Human Toxicological Maximum Permissible Risk Levels Earlier Evaluated in the Period 1991-2001*. Report 711701092/2009. Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment): Bilthove, NE.

Roche, M. and M. Layrisse. 1956. Effect of Cobalt on Thyroidal Uptake of I131. *J Clin Endocrin Metab*, 16 (6): 831-33.

Roy, P. and A. Saha. 2002. Metabolism and Toxicity of Arsenic: a Human Carcinogen. *Curr Sci*, 82 (1): 38-45.

Shearer, R. R. and D. M. Hadjimarkos. 1975. Geographic Distribution of Selenium in Human Milk. *Arch of Environ Health*, 30: 230-33.

Springborn Laboratories Inc. 2000. *An Oral (Gavage) Two-Generation Reproduction Toxicity Study in Sprague-Dawley Rats with Nickel Sulphate Hexahydrate*. Study No. 3472.2. Prepared by Springborn Laboratories Inc. for Nickel Producers Environmental Research Association: Durham, NC.

Storey, E. 1961. Strontium "rickets": Bone, calcium and strontium changes. *Austral Ann Med*, 10: 213-22.

Tseng, W. P. 1977. Effects and Dose-response Relationships of Skin Cancer and Blackfoot Disease with Arsenic. *Environ Health Perspect*, 19: 109-19.

Tseng, W. P., H. M. Chu, S. W. How, J. M. Fong, C. S. Lin, and S. Yeh. 1968. Prevalence of Skin Cancer in an Endemic Area of Chronic Arsenicism in Taiwan. *J Nat Cancer Inst*, 40 (3): 453-63.

US EPA. 1987. *Integrated Risk Information System (IRIS). Chemical Assessment Summary for Nickel Refinery Dust; no CASRN*. United States Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0272_summary.pdf (accessed

US EPA. 1991. Integrated Risk Information System (IRIS). Chemical Assessment Summary for Selenium and Compounds; CASRN 7782-49-2. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0472_summary.pdf#nameddest=rfd (accessed February 2022).

US EPA. 1992a. *Integrated Risk Information System (IRIS). Chemical Assessment Summary for Molybdenum; CASRN 7439-98-7*. United States Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0550_summary.pdf (accessed February 2022).

US EPA. 1992b. *Integrated Risk Information System (IRIS). Chemical Assessment Summary for Strontium; CASRN 7440-24-6*. United States Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0550_summary.pdf (accessed

US EPA. 1995a. *Integrated Risk Information System (IRIS). Chemical Assessment Summary for Arsenic; CASRN 7440-38-2*. United States Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0278_summary.pdf#nameddest=rfc (accessed February 2022).

US EPA. 1995b. *Integrated Risk Information System (IRIS). Chemical Assessment Summary for Manganese; CASRN 7439-96-5*. United States Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0373_summary.pdf (accessed February 2022).

US EPA. 1998. *Integrated Risk Information System (IRIS) Chemical Assessment Summary: Chromium (VI) ; CASRN 18540-29-9*. https://iris.epa.gov/static/pdfs/0144_summary.pdf (accessed February 2022).

US EPA. 2006. *Provisional Peer-Reviewed Toxicity Values for Aluminum (CASRN 7429-90-5)*. EPA/690/R-06/001F. Washington, DC.

US EPA. 2012. *Provisional Peer-Reviewed Toxicity Values for Thallium and Compounds*. EPA/690/R-12/026F Cincinnati, OH.

US EPA. 2022a. *Integrated Risk Information System (IRIS)*. United States Environmental Protection Agency. https://iris.epa.gov/AtoZ/?list_type=alpha (accessed February 2022).

US EPA. 2022b. https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables (Regional Screening Levels (RSLs) - Generic Tables. United States Environmental Protection Agency accessed February 2022).

WHO. 1988. *Arsenic - WHO Food Additives Series 24*.

WHO. 2010. *Concise International Chemical Assessment Document 77: Strontium and Strontium Compounds*. World Health Organization: Geneva, Switzerland.

WHO. 2022. http://www.inchem.org/#/search (INCHEM (Internationally Peer Reviewed Chemical Safety Information). World Health Organization, International Programme on Chemical Safety (IPCS) accessed February 2022).

Yang, G.-Q. and R.-H. Zhou. 1994. Further Observations on the Human Maximum Safe Dietary Selenium Intake in a Seleniferous Area of China. *J Trace Elem Electro Health Disease*, 8: 159-65.