FEDERAL CONTAMINATED SITE RISK ASSESSMENT IN CANADA:

Toxicological Reference Values (TRVs)

VERSION 3.0

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PREFACE

The Federal Contaminated Sites Action Plan (FCSAP) was established in 2005 as a 15-year horizontal program with funding of $4.54 billion from the Government of Canada. In 2019, the program was renewed for another 15 years, from 2020 until 2035.

The primary objective of FCSAP is to reduce environmental and human health risks from known federal contaminated sites in Canada and their associated federal financial liabilities. To achieve this objective, FCSAP funds federal departments, agencies and Consolidated Crown corporations (collectively referred to as "custodians") to assess, remediate and risk manage the federal contaminated sites for which they are responsible. FCSAP also provides guidance, tools and resources to custodians to ensure that federal contaminated sites are managed in a scientifically sound and a nationally consistent manner. The *Federal Approach to Contaminated Sites* and the *FCSAP Decision-Making Framework (DMF)* provide a 10-step roadmap that outlines the specific activities, requirements and key decisions to effectively address federal contaminated sites in Canada. The *DMF* along with other FCSAP-related resources can be found on the **FCSAP website**.

This guidance document supplements Health Canada's (HC's) preliminary and detailed quantitative risk assessment guidance and assists federal custodial departments with the consistent assessment of human health risks posed by federal contaminated sites across Canada.

Guidance documents on human health risk assessment (HHRA) prepared by HC in support of FCSAP may be obtained by contacting HC at **hc.cs-sc.sc@canada.ca** or from our website at: **www.canada.ca/en/health-canada/services/environmental-workplace-health/contaminated-sites.html**.

As is common with any national guidance, this document will not satisfy all requirements presented by federal contaminated sites, custodial departments or risk assessors. As the practice of HHRA advances and as FCSAP proceeds, new and updated information on various aspects of HHRA will be published. As a result, it is anticipated that revisions and/or addendums to this document will be necessary from time to time to reflect this new information. Please consult the HC website above to confirm that the version of the document in your possession is the most recent.

HC requests that any questions, comments, suggested additions or revisions to this document be directed to HC at the email address identified above.

SUMMARY OF REVISIONS

Federal Contaminated Site Risk Assessment in Canada: Toxicological Reference Values (TRVs), Version 3.0 reflects numerous revisions to text and tables, relative to the previous version, *Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors, Version 2.0* (HC, 2010). Significant technical revisions to this document include:

- TRVs in **Table 1** (TRVs Recommended for use in Human Health Risk Assessments of Federal Contaminated Sites) and **Appendix A** were updated for the following substances:
  - benzene: updated inhalation unit risk [UR]
  - benzo[a]pyrene: new tolerable daily intake [TDI] and tolerable concentration [TC], updated oral slope factor [SF] and inhalation UR
  - cadmium: updated TDI [provisional] and inhalation UR
  - carbon tetrachloride: new inhalation UR
  - chromium, hexavalent: new TDI and TC
  - copper: new TDI (single TDI for all age groups)
  - dichlorobenzene, 1,4-: updated TC
  - dichloroethane, 1,2-: updated oral SF
  - dichloromethane: updated TDI, new TC, updated oral SF and inhalation UR
  - ethylbenzene: updated TDI and TC
  - manganese: new TDI (single TDI for all age groups)
  - naphthalene: new TC
  - nickel chloride: updated TDI
  - nickel (oxidic, sulphidic, soluble): inhalation TCs are presented for individual compounds
  - nickel (soluble): an inhalation UR is presented for a mixture of oxidic, sulfidic and soluble inorganic nickel compounds
  - nickel sulfate: updated TDI and TC
  - polychlorinated biphenyls (non dioxin-like, i.e., non-coplanar): updated provisional TDI
  - selenium: updated TDIs
  - tetrachloroethylene (PCE): updated TDI and TC
  - toluene: updated TDI and TC
  - trichloroethylene (TCE): new TC and updated inhalation UR
  - uranium: TDI reaffirmed (based on a recent review of the Canadian drinking water quality guideline)
  - vinyl chloride: updated oral SF (separate SFs for continuous lifetime exposure during adulthood vs continuous lifetime exposure from birth), and new inhalation URs for continuous lifetime exposure during adulthood vs continuous lifetime exposure from birth
  - xylenes (mixed isomers): updated TDI and TC
  - zinc: updated TDIs

- The following substances were added to **Table 1** and **Appendix A**:
  - beryllium: TDI, TC and inhalation UR
  - chromium, trivalent: TDI and TC
  - lead: provisional TRV (risk-specific dose) from the European Food Safety Authority [EFSA]
  - perfluorooctanoic acid (PFOA): TDI
  - perfluorooctane sulfonate (PFOS): TDI
- Inhalation slope factors (expressed in $[mg/kg_{BW}\text{-}day]^{-1}$) were removed from Table 1 and Appendix A. Inhalation unit risks (expressed in $[mg/m^3]^{-1}$) are recommended to be used to characterize incremental lifetime cancer risks (ILCRs) from inhalation exposure. Inhalation unit risks are provided in **Table 1** and **Appendix A**.
- Substances and/or TRVs removed from version 2.0 of this guidance (HC, 2010) are listed below. The update to this guidance did not involve a review of the toxicological data for these substances and/or TRVs; however, if these substances are considered to be potential contaminants of concern at a federal contaminated site, then it is recommended that the risk assessor include them in the risk assessment and identify TRVs published by other regulatory agencies, with scientific rationale provided in the report.
  - aniline
  - benzo[a]pyrene (dermal slope factor was removed)
  - bis(2-ethyl hexyl)phthalate
  - bis(chloro methyl)ether
  - boron
  - cyanide (free)
  - chromium (total); TRVs are presented for trivalent and hexavalent chromium
  - dibromoethane, 1,2-
  - dibutyl phthalate
  - dichlorobenzidine, 3,3'-
  - dichlorophenol, 2,4-
  - fluoride (inorganic)
  - isopropylbenzene
  - methyl *tert*-butyl ether (MTBE)
  - molybdenum
  - nitrilotriacetic acid (NTA)
  - pentachlorobenzene
  - phenol
  - styrene
  - tetrachlorobenzene, 1,2,3,4-
  - tetrachlorobenzene, 1,2,3,5-
  - tetrachlorobenzene, 1,2,4,5-
  - tetrachlorophenol, 2,3,4,6-

- tributyltin oxide (TBTO)
- trichlorobenzene, 1,2,3-
- trichlorobenzene, 1,2,4-
- trichlorobenzene, 1,3,5-
- trichlorophenol, 2,4,6-
- trichloropropane, 1,2,3-

- The table of polycyclic aromatic hydrocarbon (PAH) relative potency factors (RPFs) that was published in PQRA Part I (HC, 2012) is now presented in **Table 2** (Recommended RPFs) and **Table 3** (Provisional RPFs) of this document. Because of limited data and a lack of CAS numbers, six PAHs were excluded from the list of provisional RPFs (5,8- and 5,9-dimethylchrysene, and 7-, 8-, 9-, and 10-methylchrysene).
- The table of dioxin toxic equivalency factors (TEFs) that was published in PQRA Part I (HC, 2012) is now presented in **Table 4** of this document.
- The table containing pesticide TRVs (formerly Table 2) was removed. For federal contaminated sites where pesticides are contaminants of potential concern, please contact HC.

ACRONYMS AND ABBREVIATIONS

ADAF	age-dependent adjustment factor
AROI	acceptable range of oral intake
ATSDR	Agency for Toxic Substances and Disease Registry (United States)
B[a]P	benzo[a]pyrene
CalEPA	California Environmental Protection Agency
CCME	Canadian Council of Ministers of the Environment
DRI	dietary reference intake
DQRA	detailed quantitative risk assessment
EFSA	European Food Safety Authority
ETE	essential trace element
FCSAP	Federal Contaminated Sites Action Plan
HC	Health Canada
HHRA	human health risk assessment
HQ	hazard quotient
ILCR	incremental lifetime cancer risk
IOM	Institute of Medicine of the National Academies (renamed the *National Academy of Medicine* in 2015)
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System (US EPA)
LOAEL	lowest observable adverse effect level
MECP	Ontario Ministry of Environment, Conservation and Parks (formerly the *Ontario Ministry of the Environment*)
MRL	minimal risk level
NOAEL	no observable adverse effect level
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCE	perchloroethylene (tetrachloroethylene)
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PQRA	preliminary quantitative risk assessment
RAF	relative absorption factor
RAF_{Derm}	dermal relative absorption factor
RAIS	Risk Assessment Information System
RDA	recommended dietary allowance

RPF	relative potency factor
RfC	reference concentration
RfD	reference dose
SF	slope factor
TC	tolerable concentration
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCE	trichloroethylene
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalent
TRV	toxicological reference value
UF	uncertainty factor
UL	tolerable upper intake level
UR	unit risk
US EPA	United States Environmental Protection Agency
VOC	volatile organic compound
WHO	World Health Organization

1.0 INTRODUCTION

This document is part of a series of guidance documents published by HC for use in assessment of human health risks at federal contaminated sites in Canada. TRVs are parameters used to quantitatively assess potential human health risks associated with exposure to environmental contaminants and are published by a variety of national and international agencies for the purpose of characterizing toxicity of substances. TRVs have been established for two categories of chemical substances: those with a threshold mode of action, and those with a non-threshold mode of action.

- For substances with a threshold mode of action, the TRV is provided as a **tolerable daily intake** (**TDI**) for oral exposures, or **tolerable concentration** (**TC**) for inhalation exposures, typically derived from a dose or exposure level at or below which no toxic effects are assumed to occur. To characterize potential risks for substances with a threshold mode of action, the estimated exposure is divided by the corresponding oral TDI or inhalation TC to obtain a hazard quotient (HQ). For Canadian federal contaminated sites, human health risks are considered to be negligible or acceptable when the HQ ≤ 0.2, or ≤ 1.0 where background exposures are included (HC, 2021).
- For substances without a threshold (such as certain carcinogens and germ cell mutagens), for which it is possible that any level of exposure may result in an adverse effect, the TRV is derived from the fit of a model (dose-response relationship linking exposure levels and effects in the observable range) which is then extrapolated to low doses. This extrapolation allows for the estimation of oral **slope factors** (**SFs**) and inhalation **unit risks** (**URs**). To characterize risks for substances with a non-threshold mode of action, the estimated exposure is multiplied by the corresponding oral SF or inhalation UR to obtain an incremental lifetime cancer risk (ILCR). For Canadian federal contaminated sites, human health risks are considered to be negligible when the ILCR is ≤ 1 in 100 000 ($\leq 1 \times 10^{-5}$) (HC, 2021).

Sources of TRVs for use in assessment of potential human health risks at Canadian federal contaminated sites include, but are not limited to the following:

- Health Canada (HC)—various sources including:
  - Contaminated Sites Reports and Publications—Federal Contaminated Site Risk Assessment in Canada: **www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites.html**
  - Environmental Contaminants: **www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants.html**
  - Chemicals Management Plan: **www.canada.ca/en/health-canada/services/chemical-substances/chemicals-management-plan.html**
  - Water Quality—Reports and Publications: **www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality.html**
  - Air Quality and Health: **www.canada.ca/en/health-canada/services/air-quality.html**
- United States Environmental Protection Agency (US EPA)
  - Integrated Risk Information System (IRIS): **www.epa.gov/iris**. TRVs are generally identified by the US EPA as oral reference doses (RfDs), inhalation reference concentrations (RfCs), oral slope factors (SFs), and inhalation unit risks (URs).

- California Environmental Protection Agency (CalEPA)
  - Chemicals Database: **https://oehha.ca.gov/chemicals**
  - The CalEPA employs the same general terminology as the US EPA.
- World Health Organization (WHO) and the International Programme on Chemical Safety (IPCS)—various sources including:
  - Chemical Safety Information from Intergovernmental Organizations: **www.inchem.org**
  - International Programme on Chemical Safety: **www.inchem.org; www.who.int/ipcs/en**
  - Air Quality: **www.euro.who.int/en/what-we-do/health-topics/environmental-health/air-quality**
  - TRVs are generally identified by the WHO and the IPCS as tolerable daily intakes (TDIs).
- United States Agency for Toxic Substances and Disease Registry (ATSDR)
  - Toxicological Profiles: **www.atsdr.cdc.gov/toxprofiles/index.asp**
  - The ATSDR generally identifies TRVs as minimal risk levels (MRLs).

2.0 TRVs RECOMMENDED BY HEALTH CANADA

2.1 TRVs FOR ENVIRONMENTAL CONTAMINANTS

For the assessment of potential human health risks posed by substances found at federal contaminated sites in Canada, HC TRVs are recommended when available, unless justification is provided for the use of TRVs published by other regulatory agencies and based on more recent science. TRVs recommended for environmental contaminants are presented in **Table 1**; however, not all of the TRVs were derived by HC. In order to enable standardization of HHRAs for federal contaminated sites, where HC did not have a published TRV, TRVs were identified from other regulatory agencies. The TRV basis, method of derivation, level of protection, uncertainty or confidence level, and any modifications made were considered in the identification of TRVs for use in HHRAs of federal contaminated sites.

For substances that lack a TRV from regulatory or advisory agencies, please contact HC. If risk assessors prefer to apply published TRVs other than those presented in **Table 1** (e.g., more recent data have been used by a different agency), these TRVs may be applied with scientific rationale to support such use.

The TRVs presented in **Table 1** are recommended for chronic exposures. At this time, HC does not prescribe TRVs for exposures of lesser duration (i.e., acute, subchronic). Short-duration TRVs from other regulatory agencies may be used in risk assessments of federal contaminated sites, with scientific rationale.

2.2 TRVs FOR ESSENTIAL TRACE ELEMENTS

Recommended TRVs for essential trace elements (ETEs) are presented in **Table 1**.

The approach for establishing TRVs for ETEs considers the benefits and risks associated with these substances; this approach reflects their characterization as essential elements. For potential risks posed at federal contaminated sites in Canada from exposure to contaminants considered to be ETEs, it is recommended that the **tolerable upper intake level** (UL) be used as the reference exposure level for human health risk assessment—specifically, the ULs published by the Institute of Medicine of the National Academies (IOM, 2000, 2001). In other words, the UL is interpreted and applied as a TDI for oral exposure. The use of ULs to assess the non-carcinogenic risks of an ETE does not preclude the need to quantify cancer risks for ETEs that may also be carcinogenic.

Some elemental contaminants found at federal contaminated sites can also be ETEs. For example, the WHO considers the following trace elements to be essential in human nutrition: iron (FAO/WHO, 2001), chromium, cobalt, copper, iodine, molybdenum, selenium and zinc (WHO, 1996, 2002). For this reason, the underlying assumption for RfDs and TDIs that a zero intake is without risk, is inappropriate for ETEs (WHO, 2002). Manganese is now fully recognized as essential to human health (IOM, 2001), and there is a growing body of evidence that suggests that silicon, boron, nickel, and vanadium play essential metabolic roles in some species. These latter substances have been considered to be **probable ETEs** by the WHO since 1996. However, given that human data on ULs for probable ETEs are limited, HHRAs of federal contaminated sites should address exposure to such ETEs based on the TRVs presented in **Table 1**.

ETE deficiency in the diet can result in functional or structural abnormalities associated with biochemical changes. These effects may be reversed by adequate supplementation of the ETE (e.g., Mertz, 1980; WHO, 1996). Conversely, excess intake of an ETE may result in toxicity, which is considered when establishing TDIs or RfDs. However, some TDIs or RfDs for ETEs can be overly conservative when compared to dietary reference intakes (DRIs) established by the IOM's Food and Nutrition Board (IOM, 2000, 2001).

The Expert Advisory Committee on Dietary Reference Intakes (DRI Committee) developed a framework for development of dietary allowances and recommendations (IOM, 2000, 2001). The DRIs apply to healthy Canadian populations and consider bioavailability as well as nutrient and dietary interactions (Mertz, 1995; IOM, 2000, 2001; WHO, 2002). DRIs are normally developed for the general population, according to age and gender (IOM, 2000, 2001). These DRIs consider physiological state to protect sensitive subpopulations (Mertz, 1998; Munro, 1999).

For each ETE, a safe range of intakes has been established to avoid deficiency and toxicity ('acceptable range of oral intake' or AROI [WHO, 2005]). Each ETE has a homeostatic mechanism which involves regulation of absorption, excretion, and tissue retention. This mechanism allows adaptation to varying nutrient intakes for optimal systemic supply in order for essential functions to be carried out (WHO, 2002). AROIs, including intake from food and water, are maintained under homeostasis in healthy populations (IOM, 2000, 2001). As nutrient needs vary considerably among individuals, deficiency and toxicity are not necessarily encountered at the lower and upper bounds of the AROIs, respectively (Becking, 1998). For DRIs within AROI limits, IOM (2000, 2001) defined the following:

- **Recommended Dietary Allowance (RDA):** average daily nutrient intake level sufficient to meet the nutrient requirement of nearly all (97% to 98%) healthy individuals in a particular life stage and gender group;
- **Adequate Intake:** recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate—used when an RDA cannot be determined;
- **Estimated Average Requirement:** average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group; and,
- **Tolerable Upper Intake Level (UL):** highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population—as intake increases above the UL, potential risk of adverse effects may increase.

The ULs are not specific data points from any particular dose-response relationship, but are derived using well-established principles of risk assessment (WHO, 2002). Various data sources, such as epidemiological studies, clinical trials, and experimental studies, can be used to estimate ULs (WHO, 1996, 2002; IOM, 2000, 2001). ULs are derived from **no observable adverse effect levels** (NOAELs) and/or **lowest observable adverse effect levels** (LOAELs) (IOM, 2000, 2001). Uncertainty factors (UFs) are applied to NOAELs or LOAELs in the calculation of ULs (WHO, 2002). However, these UFs tend to be lower than those traditionally used to establish TDIs or RfDs, while fully protecting human health (Mertz, 1995). The UFs used to establish ULs are generally less than 10, owing to the quality of available human data (Becking, 1998; Munro, 1999; Dourson et al., 2001). The ULs consider risks from nutrient deficiencies and toxicity, as well as inter-individual variability (WHO, 2002).

2.3 RELATIVE POTENCY FACTORS/TOXIC EQUIVALENCY FACTORS

Some substances, such as polycyclic aromatic hydrocarbons (PAHs) and polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), are typically present as complex mixtures in the environment; however, for many individual PAHs and PCDDs/PCDFs, toxicological data are insufficient to establish TRVs.

Mixtures of carcinogenic PAHs are assessed using relative potency factors (RPFs), also referred to as potency equivalence factors. An RPF is the ratio of carcinogenic potential of an individual PAH relative to benzo[a]pyrene (B[a]P). For a given mixture, the concentration of each carcinogenic PAH is multiplied by its RPF, and the resulting concentrations are summed to estimate a B[a]P equivalent concentration. Recommended RPFs for carcinogenic PAHs provided in **Table 2** are those recommended by the Canadian Council of Ministers of the Environment (CCME, 2010). For PAHs that are not routinely analyzed or for which no regulatory RPFs currently exist, provisional RPFs are presented in **Table 3**. These RPFs are subject to uncertainty and are therefore considered provisional. The RPFs are based on an analysis of available RPFs and scientific literature (Equilibrium Environmental Inc. [EEI], 2006). The PAHs considered by EEI (2006) were those that may be present at Canadian federal contaminated sites. EEI (2006) compiled RPFs for each individual PAH from several regulatory agencies, in order to analyze their variation. Where RPFs varied by < 1 order of magnitude, this was considered to suggest a general consensus; for those that varied by > 1 order of magnitude, EEI (2006) conducted a more detailed analysis to support the selection of a potentially appropriate RPF. Risk assessors are encouraged to consult other sources for more recent data; RPFs based on more recent literature can be used in an HHRA with supporting rationale.

Exposures to mixtures of PCDDs/PCDFs and dioxin-like polychlorinated biphenyls (PCBs) are assessed using the WHO's toxic equivalency factors (TEFs) (van den Berg et al., 2006). For a given mixture, the concentration of each PCDD, PCDF and PCB is multiplied by its respective TEF, and the resulting concentrations are summed to estimate a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxic equivalent (TEQ) concentration. TEFs for PCDDs, PCDFs and certain carcinogenic PCBs are provided in **Table 4**.

3.0 RELATIVE ABSORPTION FACTORS FOR DERMAL EXPOSURE

The degree of absorption of a substance into the systemic circulation depends on the route of exposure (oral, inhalation or dermal), the medium of exposure (e.g., soil, drinking water, food), as well as other factors, such as the physico-chemical properties of the substance, duration and frequency of exposure.

Ideally, health risks from an environmental exposure would be evaluated using a TRV derived from a study using the same route of exposure and the same medium of exposure. When this is not possible, relative absorption factors (RAFs) may be used to account for differences in absorption under environmental exposure conditions vs. conditions in the TRV study. As dermal TRVs are rarely available, dermal exposure associated with a contaminant is typically assessed in relation to an oral TRV, by incorporating a dermal absorption factor.

An RAF_{Derm} is calculated as follows:

$$RAF_{Derm} = \frac{\text{fraction of chemical absorbed through the skin from environmental medium}}{\text{fraction of chemical absorbed in principal oral TRV study}}$$

The denominator represents the chemical absorption efficiency in the principal study used to derive the oral TRV. For example, if dermal absorption is 10% and oral absorption in the principal TRV study is 100%, the RAF_{Derm} would be 10% ÷ 100% = 10%. Similarly, if oral absorption in the principal TRV study is only 50%, then the RAF_{Derm} would be 10% ÷ 50% = 20%. As such, an RAF_{Derm} of 1 (i.e., 100%) does not indicate that absorption is complete; rather, absorption from environmental exposure is considered equivalent to the absorption observed in the principal study upon which the TRV is based.

Recommended RAF_{Derm} values are provided in **Table 5**. Unless otherwise indicated, these values were obtained from the Ontario Ministry of the Environment, Conservation and Parks (MECP, 2011; formerly the Ontario Ministry of the Environment). For substances not listed in Table 5, RAF_{Derm} may be obtained from the sources listed at the beginning of this section, as well as from the Risk Assessment Information System (RAIS; **http://rais.ornl.gov**) or other recognized sources. Where alternate data sources are used, rationale with references should be provided in the report.

Dermal absorption of contaminants from contact with water during activities such as swimming, bathing, and showering can be estimated by employing dermal permeability constants (P_{Derm}, available from US EPA, 2004) and using methods described by the US EPA (1992, 2007a). HC uses a 'multiroute assessment approach' to determine the relative contribution of inhalation and dermal exposure associated with bathing and showering in relation to the total dose from exposure to a contaminant in drinking water (Krishnan and Carrier, 2008).

4.0 SUMMARY TABLES

The following tables provide a summary of recommended TRVs (**Table 1**), recommended RPFs for PAHs (**Table 2**), provisional RPFs for PAHs (**Table 3**), TEFs for PCDDs, PCDFs and PCBs (**Table 4**), and dermal RAFs (**Table 5**). A summary of the basis of each TRV recommended by HC for use in HHRA of federal contaminated sites is presented in **Appendix A**. It is recommended that selected TRVs and associated key health effects be described and summarized in the risk assessment report, with a discussion of both carcinogenic and non-carcinogenic effects by exposure route (i.e., oral, dermal, inhalation), as appropriate.

Table 1: TRVs Recommended for Use in Human Health Risk Assessments of Federal Contaminated Sites

Substance	Non-Carcinogenic TRVs*		Carcinogenic TRVs*	
	Oral Tolerable Daily Intake TDI mg/kg_{BW}-day	Inhalation Tolerable Concentration TC mg/m^3	Oral Slope Factor SF $(mg/kg_{BW}\text{-day})^{-1}$	Inhalation Unit Risk UR $(mg/m^3)^{-1}$
Arsenic			1.8	6.4
Barium	0.2			
Benzene			0.083	0.016
Benzo[a]pyrene (B[a]P)	0.0000667	0.000002	1.289	0.6
Beryllium	0.002	0.00002		2.4
Cadmium	0.0008[P]			4.2
Carbon tetrachloride[1]	0.00071			0.006
Chlorobenzene	0.43	0.01[P]		
Chromium, trivalent	1.5	0.0001		
Chromium, hexavalent	0.0022	0.0001		76
Copper	0.426			
Dichlorobenzene, 1,2-	0.43			
Dichlorobenzene, 1,4-	0.11	0.06		
Dichloroethane, 1,2-			0.0033	
Dichloroethylene, 1,1-	0.003			
Dichloromethane (methylene chloride)[2]	0.014	0.6	0.002	0.00001

Substance		Non-Carcinogenic TRVs*		Carcinogenic TRVs*	
		Oral Tolerable Daily Intake TDI mg/kg_{BW}-day	Inhalation Tolerable Concentration TC mg/m^3	Oral Slope Factor SF $(mg/kg_{BW}\text{-day})^{-1}$	Inhalation Unit Risk UR $(mg/m^3)^{-1}$
Ethylbenzene		0.022	2		
n-Hexane		0.1[P]	0.7[P]		
Lead[3]		0.0005[P]			
Manganese		0.025			
Mercury, inorganic[4]		0.0003			
Methylmercury women of child-bearing age, infants and children < 12 years non-sensitive adults of the general population		 0.0002[P] 0.00047[P]			
Methylnaphthalene, 2-		0.004			
Naphthalene		0.02	0.01		
Nickel chloride		0.0013			
Nickel oxide			0.000025		
Nickel subsulfide			0.000018		
Nickel, metallic			0.000018[P]		
Nickel sulfate		0.012	0.00002		
Nickel, mixture of oxidic[5], sulfidic[6], and soluble[7] inorganic nickel compounds					1.3
Perfluorooctanoic acid (PFOA)		0.000021			
Perfluorooctane sulfonate (PFOS)		0.00006			
Polychlorinated biphenyls (PCBs), non dioxin-like (i.e., non-coplanar)		0.00001[P]			
Polychlorinated biphenyls (PCBs), dioxin-like (i.e., coplanar)[8]		2.3E-09 TEQ[P]			
Polychlorinated dibenzo-*p*-dioxins/ Polychlorinated dibenzofurans (PCDDs/PCDFs)[8]		2.3E-09 TEQ[P]			
Pyrene		0.03			
Selenium	0 to < 6 months	0.0055[UL]			
	6 months to < 5 years	0.0060[UL]			
	5 to < 12 years	0.0063[UL]			
	12 to < 20 years	0.0062[UL]			
	≥ 20 years	0.0057[UL]			
Tetrachloroethylene (PCE)		0.0047	0.04		
Toluene		0.0097	2.3		
Trichloroethylene (TCE)		0.00146	0.002	0.000811	0.0041
Uranium, non-radioactive		0.0006			
Vinyl chloride[9]	for continuous lifetime exposure during adulthood			0.24	0.0044
	for continuous lifetime exposure from birth			0.48	0.0088
Xylenes, mixed isomers		0.013	0.1		

Substance		Non-Carcinogenic TRVs*		Carcinogenic TRVs*	
		Oral Tolerable Daily Intake TDI mg/kg_{BW}-day	Inhalation Tolerable Concentration TC mg/m^3	Oral Slope Factor SF $(mg/kg_{BW}\text{-day})^{-1}$	Inhalation Unit Risk UR $(mg/m^3)^{-1}$
Zinc	0 to < 6 months	0.49[UL]			
	6 months to < 5 years	0.48[UL]			
	5 to < 12 years	0.51[UL]			
	12 to < 20 years	0.54[UL]			
	≥ 20 years	0.57[UL]			

mg/kg_{BW}-day = milligrams per kilogram of body weight per day, $(mg/kg_{BW}\text{-day})^{-1}$ = per milligram per kilogram of body weight per day, mg/m^3 = milligrams per cubic metre, $(mg/m^3)^{-1}$ = per milligram per cubic metre

* Extracted from a variety of sources. A summary of key information used in the derivation of the TRVs is provided in Appendix A.

[UL] Tolerable upper intake level

[P] Provisional value

[1] The carbon tetrachloride inhalation UR should not be used if the concentration of carbon tetrachloride in air exceeds 18 mg/m^3 (US EPA, 2010).

[2] The dichloromethane oral SF and inhalation UR should not be used with exposures exceeding 60 mg/kg_{BW}-day (oral) and 7700 mg/m^3 (inhalation), respectively (US EPA, 2011). Application of ADAFs is recommended when assessing incremental cancer risk from exposure during early life stages (US EPA, 2011).

[3] HC has not derived a TRV for lead. Based on the available scientific literature, no threshold could be established for the identified critical effect for lead (neurodevelopmental toxicity). HC (2013a,b) therefore recommended that lead be considered a non-threshold substance. The risk-specific dose from EFSA (2013) is recommended as a provisional TRV.

[4] Exposure to mercury through consumption of fish, seafood, and marine mammals should be compared with the TRV for methylmercury, the predominant form of mercury in these foods.

[5] Oxidic nickel includes nickel oxide, nickel-copper oxide, nickel silicate oxides, and other complex nickel oxides.

[6] Sulfidic nickel includes nickel subsulfide

[7] Soluble nickel includes water-soluble forms of nickel (primarily nickel sulfate and nickel chloride), as well as other more stable forms (e.g., nickel-bearing sulfide minerals and nickel oxide) that can dissolve under certain environmental pH conditions (e.g., acidic mine tailings) or redox potential conditions (e.g., buried reducing sediment).

[8] PCDDs, PCDFs, and dioxin-like PCBs are assessed by converting their concentrations to units of 2,3,7,8-TCDD TEQs using TEFs. These TEFs are published in van den Berg et al. (2006) and provided in Table 4 below. The sum of the TEQs is then compared to the TDI for 2,3,7,8-TCDD.

[9] The vinyl chloride inhalation UR should not be used if the concentration of vinyl chloride in air exceeds 10 mg/m^3 (US EPA, 2000).

Table 2: Recommended RPFs for Carcinogenic PAHs

PAH	CAS No.	Benzo[a]Pyrene RPF[1]
Benzo[a]pyrene	50-32-8	1
Benzo[a]anthracene	56-55-3	0.1
Benzo[b]fluoranthene	205-99-2	0.1
Benzo[g,h,i]perylene	191-24-2	0.01
Benzo[j]fluoranthene	205-82-3	0.1
Benzo[k]fluoranthene	207-08-9	0.1
Chrysene	218-01-9	0.01
Dibenzo[a,h]anthracene	53-70-3	1
Indeno[1,2,3-cd]pyrene	193-39-5	0.1

[1] The PAH RPFs in this table are those published in CCME (2010), and are recommended to evaluate the carcinogenic potential of PAH mixtures at federal contaminated sites.

Table 3: Provisional RPFs for Carcinogenic PAHs

PAH	CAS No.	Provisional Benzo[a]pyrene RPF[1]
Anthanthrene	191-26-4	0.1
Benzo[c]chrysene	194-69-4	0.01
Benzo[g]chrysene	196-78-1	0.1
Benzo[c]phenanthrene	195-19-7	0.01
Cyclopenta[c,d]pyrene	27208-37-3	0.1
Dibenzo[a,e]fluoranthene	5385-75-1	1
Dibenzo[a,e]pyrene	192-65-4	1
Dibenzo[a,h]pyrene	189-64-0	1
Dibenzo[a,i]pyrene	189-55-9	1
Dibenzo[a,l]pyrene	191-30-0	100
9,10- Dimethylanthracene	781-43-1	0.01
7,12- Dimethylbenzo[a]anthracene	57-97-6	10
1,2- Dimethylbenzo[a]pyrene	16757-85-0	1
1,6- Dimethylbenzo[a]pyrene	16757-90-7	0.1
3,6- Dimethylbenzo[a]pyrene	16757-91-8	1
4,5- Dimethylbenzo[a]pyrene	16757-89-4	1
5,6- Dimethylchrysene	3697-27-6	0.1
5,7- Dimethylchrysene	52171-92-3	0.1
5,11- Dimethylchrysene	14207-78-4	1
1,4- Dimethylphenanthrene	22349-59-3	0.01
4,10- Dimethylphenanthrene	23189-63-1	0.001
5- Ethylchrysene	54986-62-8	0.1
Fluoranthene	206-44-0	0.001
7- Methylbenzo[a]anthracene	2541-69-7	1
8- Methylbenzo[a]anthracene	2381-31-9	1
9- Methylbenzo[a]anthracene	2381-16-0	0.1
12- Methylbenzo[a]anthracene	2422-79-9	0.1
11- Methylbenzo[b]fluorene	77969-74-5	0.01
1- Methylbenzo[a]pyrene	40568-90-9	1
2- Methylbenzo[a]pyrene	16757-82-7	1
3- Methylbenzo[a]pyrene	16757-81-6	1
4- Methylbenzo[a]pyrene	16757-83-8	1
5- Methylbenzo[a]pyrene	31647-36-6	0.1
6- Methylbenzo[a]pyrene	2381-39-7	0.1
11- Methylbenzo[a]pyrene	16757-80-5	1
12- Methylbenzo[a]pyrene	4514-19-6	1
5- Methylchrysene	3697-24-3	1
6- Methylchrysene	1705-85-7	0.1
2- Methylfluoranthene	33543-31-6	0.001
Phenanthrene	85-01-8	0.001
2,9,10- Trimethylanthracene	63018-94-0	0.01
2,3,9,10- Tetramethylanthracene	66552-77-0	0.01

[1] The RPFs in this table are based on an analysis of available RPFs and scientific literature by EEI (2006), and may be used if these PAHs are measured at federal contaminated sites.The RPFs are relative to benzo[a]pyrene, provisional and based on limited data. RPFs based on more recent literature can be used with rationale.

Table 4: TEFs for PCDDs, PCDFs, and Dioxin-Like PCBs

Substance	CAS No.	TEF[1]
Polychlorinated Dibenzo-*p*-dioxins		
2,3,7,8- Tetrachlorodibenzo-*p*-dioxin (TCDD)	1746-01-6	1
1,2,3,7,8- Pentachlorodibenzo-*p*-dioxin (PeCDD)	40321-76-4	1
1,2,3,4,7,8- Hexachlorodibenzo-*p*-dioxin (HxCDD)	39227-28-6	0.1
1,2,3,6,7,8- Hexachlorodibenzo-*p*-dioxin (HxCDD)	57653-85-7	0.1
1,2,3,7,8,9- Hexachlorodibenzo-*p*-dioxin (HxCDD)	19408-74-3	0.1
1,2,3,4,6,7,8- Heptachlorodibenzo-*p*-dioxin (HpCDD)	35822-46-9	0.01
Octachlorodibenzo-*p*-dioxin (OCDD)	3268-87-9	0.0003
Polychlorinated Dibenzofurans		
2,3,7,8- Tetrachlorodibenzofuran (TCDF)	51207-31-9	0.1
1,2,3,7,8- Pentachlorodibenzofuran (PeCDF)	57117-41-6	0.03
2,3,4,7,8- Pentachlorodibenzofuran (PeCDF)	57117-31-4	0.3
1,2,3,4,7,8- Hexachlorodibenzofuran (HxCDF)	70648-26-9	0.1
1,2,3,6,7,8- Hexachlorodibenzofuran (HxCDF)	57117-44-9	0.1
1,2,3,7,8,9- Hexachlorodibenzofuran (HxCDF)	72918-21-9	0.1
2,3,4,6,7,8- Hexachlorodibenzofuran (HxCDF)	60851-34-5	0.1
1,2,3,4,6,7,8- Heptachlorodibenzofuran (HpCDF)	67562-39-4	0.01
1,2,3,4,7,8,9- Heptachlorodibenzofuran (HpCDF)	55673-89-7	0.01
Octachlorodibenzofuran (OCDF)	39001-02-0	0.0003
Non-*ortho* Substituted PCB Congeners		
PCB 77	32598-13-3	0.0001
PCB 81	70362-50-4	0.0003
PCB 126	57465-28-8	0.1
PCB 169	32774-16-6	0.03
Mono-*ortho* Substituted PCB Congeners		
PCB 105	32598-14-4	0.00003
PCB 114	74472-37-0	0.00003
PCB 118	31508-00-6	0.00003
PCB 123	65510-44-3	0.00003
PCB 156	38380-08-4	0.00003
PCB 157	69782-90-7	0.00003
PCB 167	52663-72-6	0.00003
PCB 189	39635-31-9	0.00003

[1] Source: van den Berg et al. (2006)

Table 5: Recommended Dermal Relative Absorption Factors (RAF_{Derm})

Substance	RAF_{Derm} [1]	Substance	RAF_{Derm} [1]
Arsenic	0.03	n-Hexane[4]	1
Barium	0.1	Lead[5]	0.006
Benzene[2]	0.03	Mercury[6]	1
Benzo[a]pyrene (B[a]P)[3]	0.148	Methylmercury	0.06
Beryllium	0.1	Nickel[7]	0.09
Cadmium	0.01	PAHs[3]	0.148
Carbon tetrachloride	0.03	PCBs	0.14
Chlorobenzene	0.03	PCDDs/PCDFs	0.03
Chromium, total	0.1	Selenium	0.01
Chromium, hexavalent	0.1	Tetrachloroethylene	0.03
Copper	0.06	Toluene	0.03
Dichlorobenzene, 1,2- (o-DCB)	0.03	Trichloroethylene	0.03
Dichlorobenzene, 1,4- (p-DCB)	0.03	Uranium	0.1
Dichloroethane, 1,2-	0.03	Vinyl chloride	0.03
Dichloroethylene, 1,1-	0.03	Xylenes, mixed isomers	0.03
Dichloromethane (methylene chloride)	0.03	Zinc	0.1
Ethylbenzene	0.03		

[1] RAF_{Derm} are those recommended by the Ontario MECP (2011), unless otherwise noted.

[2] Unless otherwise indicated, the default value for volatile organic compounds (VOCs), including benzene, is 0.03 (MECP, 2011).

[3] HC research on *in vitro* dermal absorption of B[a]P from commercial gardening soil spiked with 14C-B[a]P (Moody et al., 2007) identified a mean dermal absorption (total of receiver + skin depot) of 0.148 (14.8%) and is recommended as the dermal absorption of B[a]P from soil. Consistent with the MECP (2011) approach for other PAHs, the default RAF_{Derm} for all PAHs is the same as that for B[a]P (i.e., 0.148 or 14.8%).

[4] No data regarding the relative dermal absorption of n-hexane were identified; therefore, an RAF_{Derm} of 1 is recommended, as per CCME (2011).

[5] The dermal RAF for lead was determined by dividing 0.3% (absolute dermal absorption value [Moore et al., 1980]) by 50% (oral absorption of lead from food and water [US EPA 2007b]), i.e., 0.3% / 50% = 0.006 or 0.6%.

[6] The RAF_{Derm} for mercury is based on the absolute dermal absorption (46.6%) in human skin (Moody et al. [2009]), and is comparable to the range of oral absorption of mercuric chloride (HgCl2) in water (30–40%) observed in male rats (Morcillo and Santamaria [1995]). Given the observed similarity in dermal and oral absorption of mercury, an RAF_{Derm} of 1 is recommended.

[7] The RAF_{Derm} for nickel was determined by dividing 1.0% (absolute dermal absorption value [Moody et al., 2009]) by 11% (approximate oral bioavailability [Ishimatsu et al., 1995]), i.e., 1.0% / 11% = 0.09 or 9%.

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APPENDIX A: SUMMARY OF THE KEY STUDIES USED TO DERIVE THE RECOMMENDED TRVs

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Arsenic	Oral SF	1.8E+00 $(mg/kg_{BW}\text{-}day)^{-1}$	**Study Type:** epidemiological **Species:** humans **Mode of Exposure:** oral (drinking water) **Exposure Concentrations:** concentration of arsenic in drinking water varied from less than 10 to greater than 600 µg/L (groundwater arsenic concentrations) **Duration:** chronic **Uncertainty Factors:** N/A	Range of unit risks associated with ingesting 1 µg/L of arsenic in drinking water: 3.06E-06 to 3.85E-05 $(µg/L)^{-1}$ (based on a 1% increase in risk)	TRV based on upper end of range of unit risks (URs) in drinking water: 3.85E-05 $(µg/L)^{-1}$ Conversion to oral SF in $(mg/kg_{BW}\text{-}day)^{-1}$: Oral SF = $UR \times BW_{adult} \times CF / IR_W$ [where BW_{adult} = 70.7 kg, IR_W = 1.5 L/day, and CF (conversion factor) = 1000 µg/mg]	Cancer (bladder, lung, liver)	CEPA: Group I carcinogenic to humans (EC and HC, 1993a) IARC: Group 1 carcinogenic to humans (IARC, 2012a) US EPA IRIS: Group A carcinogenic to humans (US EPA, 1995a)	HC, 2006 (based on Morales et al., 2000; Chen et al., 1985; Wu et al., 1989)
	Inhalation UR	6.4E+00 $(mg/m^3)^{-1}$	**Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation **Exposure Concentrations:** N/A **Duration:** chronic **Uncertainty Factors:** N/A	TC_{05} (5% tumourigenic concentration) = 7.83 $µg/m^3$	Relative risk model Inhalation UR = $0.05/TC_{05}$ where 0.05 = 5% extra cancer risk	Cancer (lung)		EC and HC, 1993a (based on Higgins et al., 1986)
Barium	Oral TDI	2.0E-01 mg/kg_{BW}-day	**Study Type:** chronic **Species:** male and female B6C3F1 mice **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 500, 1250, and 2500 ppm barium chloride dihydrate in drinking water (daily doses estimated to be 0, 30, 75, and 160 mg barium/kg_{BW}-day for males, and 0, 40, 90, and 200 mg barium/kg_{BW}-day for females) **Duration:** 2 years **Uncertainty Factors:** 300 (10 for intraspecies variability, 10 for interspecies variability, and 3 for database deficiencies)	$BMDL_{05}$ = 63 mg/kg_{BW}-day	TDI = $BMDL_{05}$ / UF	Nephrotoxicity (renal lesions)	CEPA: Group VA inadequate data for evaluation (HC, 1990) IARC: not classified US EPA IRIS: inhalation route - carcinogenic potential cannot be determined; oral route - not likely to be carcinogenic to humans (US EPA, 1998a)	US EPA, 2005a (based on NTP, 1994)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Benzene	Oral SF	8.3E-02 $(mg/kg_{BW}\text{-}day)^{-1}$	**Study Type:** chronic **Species:** rats and mice **Mode of Administration:** gavage, corn oil **Exposure Regime:** 0, 50, 100, and 200 mg/kg_{BW}-day (male rats); 0, 25, 50, and 100 mg/kg_{BW}-day (female rats, male and female mice), 5 days/week **Duration:** 103 weeks **Uncertainty Factors:** N/A	Range of unit risks associated with ingesting 1 µg/L of benzene in water: 2.03E-06 to 4.17E-06 $(µg/L)^{-1}$	Linearized multistage model and allometric scaling TRV based on upper bound estimate of unit risks (URs) in drinking water: 4.17E-06 $(µg/L)^{-1}$ Conversion to oral SF in $(mg/kg_{BW}\text{-}day)^{-1}$: Oral SF = $UR \times BW_{adult} \times CF / IR_W$ [where BW_{adult} = 70.7 kg, IR_W = 1.5 L/day, and CF = 1000 µg/mg]	Cancer (malignant lymphomas) and Bone marrow hematopoietic hyperplasia	CEPA: Group I carcinogenic to humans (EC and HC, 1993b) IARC: Group 1 carcinogenic to humans (IARC, 2012b) US EPA IRIS: Group A carcinogenic to humans (US EPA, 2000a)	HC, 2009 (based on NTP, 1986a)
	Inhalation UR	1.6E-02 $(mg/m^3)^{-1}$	**Study Type:** epidemiological (occupational) **Species:** human **Mode of Exposure:** inhalation **Exposure Concentrations:** N/A **Duration:** chronic **Uncertainty Factors:** N/A	Unit lifetime leukemia risk to the general population, derived from these studies: Ohio Pliofilm cohort: 0.044 $(ppm)^{-1}$ [0.014 $(mg/m^3)^{-1}$] Chinese cohorts: 0.056 $(ppm)^{-1}$ [0.018 $(mg/m^3)^{-1}$]	Poisson regression and linear relative risk models + Inhalation UR for lifetime inhalation exposures of the general population (based on the geometric mean of upper bound estimates of leukemia risk from these studies) Inhalation UR = $[0.044\ (ppm)^{-1} \times 0.056\ (ppm)^{-1}]^{1/2}$ = 0.050 $(ppm)^{-1}$ [0.016 $(mg/m^3)^{-1}$]	Cancer (leukemia)		HC, 2013a and OEHHA, 2001 (based on Rinsky et al., 1987; Paxton et al., 1994; Hayes et al., 1997)
Benzo[a]pyrene (BaP)	Oral TDI	6.67E-05 mg/kg_{BW}-day	**Study Type:** developmental **Species:** neonate Sprague-Dawley rat pups (10 males and 10 females) **Mode of Administration:** gavage **Exposure Regime:** 0 (peanut oil only), 0.02, 0.2, or 2 mg/kg_{BW} administered daily from postnatal day (PND) 5 until PND 11 **Duration:** until PND 71 **Uncertainty Factors:** 300 (10 for intraspecies variability, 10 for interspecies variability, and 3 for database deficiencies)	NOAEL = 0.020 mg/kg_{BW}-day	TDI = NOAEL/UF	Neuro-developmental toxicity	CEPA: Group II probably carcinogenic to humans (EC and HC, 1994a) IARC: Group 1 carcinogenic to humans (IARC, 2012b) US EPA carcinogenic to humans (US EPA, 2017)	HC, 2016a (based on Chen et al., 2012)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Benzo[a]pyrene (BaP)	Inhalation TC	2.0E-06 mg/m^3	**Study Type:** developmental **Species:** F344 rats (pregnant females) **Mode of Administration:** inhalation (nose only) **Exposure Regime:** 0 ("sham" carbon black or unexposed), 25, 75, and 100 $\mu g/m^3$, 4 hours per day for 10 days (gestation days 11 to 20) **Duration:** 10 days (gestation days 11-20) **Uncertainty Factors:** 3000 (3 for toxicodynamic differences, 10 for intraspecies variability, 10 for LOAEL to NOAEL extrapolation, and 10 for database deficiencies)	LOAEL = 0.025 mg/m^3	LOAEL adjusted for continuous daily exposure and converted to a human equivalent concentration based on a regional deposited dose ratio for extrarespiratory effects $LOAEL_{HEC}$ = 0.0046 mg/m^3 RfC = $LOAEL_{HEC}$/UF	Developmental toxicity (decreased embryo/foetal survival)	CEPA: Group II probably carcinogenic to humans (EC and HC, 1994a) IARC: Group 1 carcinogenic to humans (IARC, 2012b) US EPA carcinogenic to humans (US EPA, 2017)	US EPA, 2017 (based on Archibong et al., 2002)
	Oral SF	1.289E+00 $(mg/kg_{BW}\text{-day})^{-1}$	**Study Type:** chronic **Species:** B6C3F1 female mice **Mode of Administration:** diet **Exposure Regime:** 0, 5, 25, and 100 ppm (corresponding to approximately 0, 0.7, 3.3, and 13.0 mg/kg_{BW}-day, as per HC, 2016a) **Duration:** 2 years **Uncertainty Factors:** N/A	$BMDL_{10}$ = 0.5389 mg/kg_{BW}-day	Allometric scaling of the $BMDL_{10}$ (to account for interspecies variability and derive a human equivalent value) $BMDL_{10, HEC}$ = 0.07758 mg/kg_{BW}-day Oral SF = $0.1/BMDL_{10, HEC}$ where 0.1 = 10% extra cancer risk	Digestive tract toxicity (tumours of the forestomach)		HC, 2016a (based on Culp et al., 1998 and Moffat et al., 2015)
	Inhalation UR	6.0E-01 $(mg/m^3)^{-1}$	**Study Type:** chronic **Species:** Syrian golden male hamsters **Mode of Administration:** inhalation (nose only) of benzo[a]pyrene condensed onto sodium chloride aerosols **Exposure Regime:** 2.2, 9.5, and 46.5 mg BaP/m^3 (time-weighted average concentrations of 0, 0.25, 1.01, and 4.29 mg/m^3, corresponding to 0, 2, 10, and 50 mg/m^3 nominal study concentrations), 4.5 hours/day for the first 10 weeks, then 3 hours/day for the remainder of the study **Duration:** minimum of 10 weeks up to 130 weeks **Uncertainty Factors:** N/A	$BMCL_{10}$ = 0.16 mg/m^3	Multistage Weibull time-to-tumour dose-response model + Linear extrapolation from the POD associated with 10% extra cancer risk Inhalation UR = $0.1/BMCL_{10}$ where 0.1 is 10% extra cancer risk	Cancer (tumours of the upper gastrointestinal tract and upper respiratory tract [squamous cell neoplasia in the larynx, pharynx, trachea, nasal cavity, esophagus, and forestomach])		US EPA, 2017 (based on Thyssen et al., 1981)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Beryllium	Oral TDI	2.0E-03 mg/kg_{BW}-day	**Study Type:** chronic **Species:** dogs (5 male and 5 female beagles) **Mode of Administration:** diet **Exposure Regime:** 0, 1, 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate (diets fed for 1 hour per day), corresponding to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg_{BW}-day for male dogs and 0.029, 0.15, 1.3, and 17.4 mg/kg_{BW}-day for female dogs (using estimated time-weighted average body weights and a reported average food intake of 300 g/day) **Duration:** 0, 5, and 50 ppm group exposed for 172 weeks; 500 ppm dose group terminated at 33 weeks because of overt signs of toxicity; 1 ppm group exposed for 143 weeks. **Uncertainty Factors:** 300 (10 for intraspecies variability, 10 for interspecies variability, and 3 for database deficiencies)	$BMDL_{10}$ = 4.6E-01 mg/kg_{BW}-day	$BMDL_{10}$ derived from exponential polynomial model corresponding to an extra risk of 10% TDI = $BMDL_{10}$/UF (TDI rounded to 2.0E-03 mg/kg_{BW}-day)	Gastrointestinal toxicity (lesions of the small intestine)	CEPA: see 2019 (draft) Chemicals Management Plan (CMP) assessment (ECCC and HC, 2019a) IARC: Group 1 carcinogenic to humans (IARC, 2012a) US EPA IRIS: oral route – carcinogenic potential cannot be determined; inhalation route – known/likely human carcinogen (US EPA, 1998b)	US EPA, 1998b (based on Morgareidge et al., 1976)
	Inhalation TC	2.0E-05 mg/m^3	**Study Type** epidemiological (occupational study) **Species:** human **Mode of Exposure:** inhalation **Exposure Concentrations:** individual average exposures for six chronic beryllium disease cases and two sensitized cases ranged from 0.2 to 1.1 $\mu g/m^3$, and the median of estimated average beryllium exposure for the sensitized cases was approximately 0.55 $\mu g/m^3$. Cumulative exposure ranged from 92.6 to 1945 $\mu g/m^3$-day. **Duration:** chronic **Uncertainty Factors:** 10 (3 to account for the sensitive nature of the subclinical endpoint [beryllium sensitization], and 3 for poor quality of exposure monitoring) [total uncertainty factor rounded to 10]	LOAEL = 0.55 $\mu g/m^3$	LOAEL adjusted for occupational inhalation rate and for an intermittent working week schedule $LOAEL_{HEC}$ = 0.20 $\mu g/m^3$ TC = $LOAEL_{HEC}$/UF	Immunotoxicity and Respiratory toxicity (beryllium sensitization and progression to chronic beryllium disease [chronic inflammatory lung lesions])		US EPA, 1998b (based on Kreiss et al., 1996)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Beryllium	Inhalation UR	2.4E+00 $(mg/m^3)^{-1}$	**Study Type:** epidemiological (occupational) **Species:** humans (male) **Mode of Exposure:** inhalation **Exposure Concentrations:** range of median exposure levels inside plants (100-1000 $\mu g/m^3$) estimated in NIOSH's industrial hygiene reviews **Duration:** The cohort employed between 1942 and 1967 was followed through 1975. The subcohort upon which the inhalation UR is based was followed for at least 25 years. **Uncertainty Factors:** N/A	Range of upper bound unit risks: 1.6E-04 $(\mu g/m^3)^{-1}$ to 7.2E-03 $(\mu g/m^3)^{-1}$	Linear relative risk model Geometric mean of upper bound unit risks = 2.4E-03 $(\mu g/m^3)^{-1}$	Cancer (lung)	CEPA: see 2019 (draft) Chemicals Management Plan (CMP) assessment (ECCC and HC, 2019a) IARC: Group 1 carcinogenic to humans (IARC, 2012a) US EPA IRIS: oral route – carcinogenic potential cannot be determined; inhalation route – known/likely human carcinogen (US EPA, 1998b)	US EPA, 1998b (based on Wagoner et al., 1980; NIOSH, 1972)
Cadmium	Oral TDI (provisional)	8.0E-04 mg/kg_{BW}-day	**Study Type:** epidemiological (meta-analysis) **Species:** humans **Mode of Exposure**: environmental (primarily through food) **Exposure Concentrations:** N/A **Duration:** chronic **Uncertainty Factors:** toxicodynamic and toxicokinetic variability incorporated (using Monte Carlo simulation) into the toxicokinetic model relating cadmium concentration in urine to dietary intake	NOAEL = 5.24 µg Cd/g creatinine in urine (corresponds to a dietary cadmium exposure of 1.2 µg Cd/kg_{BW}-day [5^{th}-95^{th} percentiles: 0.8-1.8 µg Cd/kg_{BW}-day])	Lower bound of 0.8 $\mu g/kg_{BW}$-day retained as oral TDI to account for particularly susceptible individuals This oral TDI is reported by WHO (2011) as a provisional monthly tolerable intake of 25 $\mu g/kg_{BW}$	Nephrotoxicity (renal tubular dysfunction)	CEPA: probably carcinogenic to humans (inhalation pathway) (EC and HC, 1994b) IARC: Group 1 carcinogenic to humans (IARC, 2012a) US EPA IRIS: Group B1 probably carcinogenic to humans (US EPA, 1987a)	WHO, 2011
	Inhalation UR	4.2E+00 $(mg/m^3)^{-1}$	**Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation of dusts of cadmium oxide and cadmium sulfide, and cadmium fumes **Exposure Concentrations:** Equivalent lifetime exposure in $\mu g/m^3$ = 2, 11.8, and 41 µg Cd/m^3 (based on 24 hour/day exposure and an estimated average lifetime of 61.5 years) **Duration:** at least two years **Uncertainty Factors:** N/A	Range of excess cancer risk for the exposed population: 2.0E-03 $(\mu g/m^3)^{-1}$ to 1.2E-02 $(\mu g/m^3)^{-1}$	Poisson regression model fitted to occupational mortality data + Extrapolation to ambient levels in California	Cancer (lung)		OEHHA, 2011 (based on Thun et al., 1985, 1986; CDHS, 1986; CDHS, 1990)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Carbon tetrachloride	Oral TDI	7.1E-04 mg/kg_{BW}-day	**Study Type:** subchronic **Species:** male Sprague-Dawley rats **Mode of Administration:** gavage (corn oil) **Exposure Regime:** 0, 1, 10, or 33 mg/kg_{BW}-day, administered as a single oral bolus, 5 days/week **Duration:** 12 weeks **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for major database deficiencies including lack of adequate chronic studies and evidence regarding carcinogenic mode of action in animals)	NOAEL = 1 mg/kg_{BW}-day	NOAEL adjusted for weekly continuous exposure $NOAEL_{adj}$ = 0.71 mg/kg_{BW}-day TDI = $NOAEL_{adj}$/UF	Hepatotoxicity (increased serum sorbitol dehydrogenase levels and mild centrilobular vacuolization in the liver)	CEPA: not assessed IARC: Group 2B possibly carcinogenic to humans (IARC, 1999a) US EPA IRIS: likely to be carcinogenic to humans (US EPA, 2010)	HC, 2010 (based on Bruckner et al., 1986)
	Inhalation UR	6.0E-03 $(mg/m^3)^{-1}$ [US EPA (2010): do not use with exposures >18 mg/m^3]	**Study Type:** chronic **Species:** male BDF1 mice **Mode of Administration:** inhalation **Dosing Regime:** 0, 5, 25, or 125 ppm carbon tetrachloride vapour (0, 31, 157, or 786 mg/m^3), 6 hours/day, 5 days/week **Duration:** 104 weeks **Uncertainty Factors:** N/A	LEC_{10} = 18 mg/m^3 (lowest effective concentration)	Internal mouse doses determined using PBPK model + BMD modelling using a log-probit model and an extra 10% cancer risk + Linear extrapolation from the POD (LEC_{10}) converted to a human equivalent concentration using a human PBPK model Inhalation UR = 0.1 / LEC_{10} [UR rounded to 6.0E-03 $(mg/m^3)^{-1}$]	Cancer (adrenal gland [pheochromocytomas])		HC, 2018a (based on US EPA, 2010 [derived from Nagano et al., 2007 and JBRC, 1998])

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Chlorobenzene	Oral TDI	4.3E-01 mg/kg_{BW}-day	**Study Type:** chronic **Species:** F344/N rats and B6C3F1 mice **Mode of Administration:** gavage, corn oil **Exposure Regime:** 0, 60, or 120 mg/kg_{BW}-day (male and female rats, and female mice); 0, 30, or 60 mg/kg_{BW}-day (male mice), 5 days per week, as monochlorobenzene **Duration:** 103 weeks **Uncertainty Factors:** 100 (10 for intraspecies variability and 10 for interspecies variability)	NOAEL = 60 mg/kg_{BW}-day	NOAEL adjusted for continuous exposure $NOAEL_{adj}$ = 43 mg/kg_{BW}-day TDI = $NOAEL_{adj}$/UF	Hepatotoxicity (neoplastic nodules in the liver)	CEPA: Group III possibly carcinogenic to humans (EC and HC, 1992a) IARC: not classified US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 1990a)	HC, 1996 (based on NTP, 1985a; Kluwe et al., 1985)
	Inhalation TC (provisional)	1.0E-02 mg/m^3	**Study Type:** subchronic **Species:** Sprague-Dawley male rats, and male rabbits **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 75, or 250 ppm (0, 341, or 1138 mg/m^3) chlorobenzene vapours, 7 hours/day, 5 days per week, for up to 120 exposure days **Duration:** 24 weeks **Uncertainty Factors:** 5000 (10 for intraspecies variability, 10 for interspecies variability, 10 for a less than chronic study, and 5 for use of a LOAEL rather than NOAEL)	LOAEL = 341 mg/m^3	LOAEL adjusted for continuous exposure and differences in volume inhaled and body weight between rats and the human child $LOAEL_{HEC}$ = 50.2 mg/m^3 TC = $LOAEL_{HEC}$/UF	Nephrotoxicity (increased kidney weight, kidney lesions) and Endocrine system toxicity (lesions in the adrenal cortex) and Changes in red cell parameters		HC, 1996 and EC and HC, 1992a (based on Dilley, 1977)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Chromium, trivalent	Oral TDI	1.5E+00 mg/kg_{BW}-day	**Study Type:** chronic **Species:** male and female BD rats **Mode of Administration:** diet **Exposure Regime:** chromic oxide (Cr_2O_3) in diet: 0% (control), 1%, 2%, or 5%, 5 days/week, for a total of 600 feedings; average total amounts of ingested Cr_2O_3 were 360, 720, and 1800 g/kg_{BW} for each treatment group, respectively **Duration:** 840 days **Uncertainty Factors:** 1000 (10 for intraspecies variability and 10 for interspecies variability, and 10 for database deficiencies)	NOAEL = 5% Cr_2O_3 in diet, corresponding to an average total dose of 1,800 g/kg_{BW} (over 600 meals)	NOAEL was converted to a NOAEL for Cr(III) using a factor of 0.6849 g Cr(III) / g Cr_2O_3 and adjusted for continuous exposure $NOAEL_{adj}$ Cr (III) = 1468 mg Cr(III)/kg_{BW}-day TDI = $NOAEL_{adj}$ Cr(III) / (UF)	No effects observed at any dose level	CEPA: Group VI unclassifiable with respect to carcinogenicity to humans (EC and HC, 1994c) IARC: Group 3 not classifiable with respect to carcinogenicity to humans (IARC, 1990) US EPA IRIS: Group D not classifiable with respect to human carcinogenicity (US EPA, 1998c)	US EPA, 1998c (based on Ivankovic and Preussmann, 1975)
	Inhalation TC	1.0E-04 mg/m^3 intermediate duration minimal risk level for soluble Cr(III) particulates	**Study Type:** subchronic **Species:** male and female CDF rats **Mode of Administration:** inhalation (nose only) **Exposure Regime:** nose-only inhalation exposure to chromic oxide (Cr_2O_3) or basic chromium sulfate ($CrHO_5S$) dusts, at measured concentrations of 0, 3, 10, or 30 mg chromium(III)/m^3 for 6 hours/day, 5 days/week **Duration:** 13 weeks **Uncertainty Factors:** 300 (10 for use of a LOAEL, 10 for intraspecies variability, and 3 for interspecies variability)	LOAEL = 3 mg Cr (III)/m^3	LOAEL adjusted for intermittent exposure (0.54 mg Cr (III)/m^3) and converted to a $LOAEL_{HEC}$ using a regional deposited dose ratio for the respiratory tract $LOAEL_{HEC}$ = 0.04 mg/m^3 Inhalation TC = $LOAEL_{HEC}$ Cr(III) / UF	Respiratory tract toxicity		ATSDR, 2012 (based on Derelanko et al., 1999)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Chromium, hexavalent	Oral TDI	2.2E-03 mg/kg_{BW}-day	**Study Type:** chronic **Species:** male and female B6C3F1 mice **Mode of Administration:** oral (drinking water) **Exposure Regime:** Male mice received 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dehydrate (SSD)/L (equivalent to 0, 5, 10, 30, and 90 mg Cr (VI)/L or 0, 0.4, 0.9, 2.4 and 5.9 mg Cr (VI)/kg_{BW}-day respectively). Female mice received 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L (equivalent to 0, 5, 20, 60, and 180 mg Cr (VI)/L or 0, 0.4, 1.4, 3.1, and 8.7 mg Cr (VI)/kg_{BW}-day). **Duration:** 2 years **Uncertainty Factors:** 25 (10 for intraspecies variability and 2.5 for pharmacodynamic interspecies differences)	$BMDL_{01}$ = 0.67 mg Cr(VI)/ kg_{BW}-day	PBPK model used to convert mouse $BMDL_{01}$ into a human equivalent dose of 0.054 mg Cr (VI)/ kg_{BW}-day TDI = human equivalent dose/UF	Gastrointestinal toxicity (diffuse epithelial hyperplasia of the small intestine)	CEPA: Group I carcinogenic to humans (EC and HC, 1994c) IARC: Group 1 carcinogenic to humans (IARC, 2012a) US EPA IRIS: Group A inhalation route: carcinogenic to humans (US EPA, 1998d); Group D oral route: not classifiable as to human carcinogenicity (US EPA, 1998d)	HC, 2016b (based on NTP, 2008 Stout et al., 2009; Thompson et al., 2014; Summit Toxicology, 2014)
	Inhalation TC	1.0E-04 mg/m^3	**Study Type:** subchronic **Species:** male Wistar rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** sodium dichromate (chromium particulates), 0.05-0.4 mg Cr (VI)/m^3 for 22 hours/day, 7 days/week **Duration:** 30 to 90 days **Uncertainty Factors:** 300 (10 for use of a subchronic study, 10 for intraspecies variability, and 3 for pharmacodynamic interspecies differences)	BMC_{10} = 0.034 mg Cr (VI)/m^3	BMC_{10} selected as POD and adjusted for continuous exposure + Animal to human conversion based on regional deposited dose ratio for particulates TC for Cr (VI) = BMC_{10} /UF	Respiratory tract toxicity (increased albumin and lactate dehydrogenase in bronchioalveolar lavage fluid, reflecting initial injury and chronic inflammation)		US EPA, 1998d (based on Glaser et al., 1990 and Malsch et al., 1994)
	Inhalation UR	7.6E+01 $(mg/m^3)^{-1}$	**Study Type:** epidemiological (occupational) **Species:** humans (adult men) **Mode of Exposure:** inhalation **Exposure Concentrations:** N/A **Duration:** at least 1 year, up to 8 years **Uncertainty Factors:** N/A	TC_{05} (5% tumourigenic concentration) = 0.66 µg/m^3	Inhalation UR = $0.05/TC_{05}$ where 0.05 = 5% extra cancer risk	Cancer (lung)		HC, 1996 (based on Mancuso, 1975)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Copper	Oral TDI	4.26E-01 mg/kg_{BW}-day	**Study Type:** epidemiological (prospective) **Species:** humans **Mode of Exposure:** oral (drinking water) **Exposure Concentrations:** healthy infants 3 to 12 months of age (n = 128) were given drinking water with < 0.1 mg copper/L (n = 48) or 2 mg copper/L (n = 80) (added to drinking water as copper sulfate) **Duration:** nine months **Uncertainty Factors:** none (attributed to the homeostatic regulation of copper absorption and excretion)	NOAEL = 2 mg/L (corresponding to a mean daily intake of 0.318 mg/kg_{BW}-day)	TDI = upper bound of the 95% confidence interval of the NOAEL	Gastrointestinal toxicity and Hepatotoxicity (liver function)	CEPA: see 2019 (draft) CMP assessment (ECCC and HC, 2019b) IARC: not classified US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 1988a)	HC, 2019a (based on Olivares et al., 1998)
Dichlorobenzene, 1,2-	Oral TDI	4.3E-01 mg/kg_{BW}-day	**Study Type:** chronic **Species:** rats and mice **Mode of Administration:** gavage, corn oil **Exposure Regime:** 0, 60, or 120 mg/kg_{BW}-day (male and female rats, female mice), 30 and 60 mg/kg_{BW}-day (male mice), 5 days per week **Duration:** 103 weeks **Uncertainty Factors:** 100 (10 for intraspecies variability and 10 for interspecies variability)	NOAEL = 60 mg/kg_{BW}-day	NOAEL adjusted for continuous exposure $NOAEL_{adj}$ = 43 mg/kg_{BW}-day TDI = $NOAEL_{adj}$/UF	Nephrotoxicity (increase in tubular regeneration in the kidney)	CEPA: Group V probably not carcinogenic to humans (EC and HC, 1993c) IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 1999b) US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 1990b)	HC, 1996 (based on NTP, 1985b)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Dichlorobenzene, 1,4-	Oral TDI	1.1E-01 mg/kg_{BW}-day	**Study Type:** chronic **Species:** rats and mice **Mode of Administration:** gavage, corn oil **Exposure Regime:** male rats: 0, 150, or 300 mg/kg_{BW}-day, 5 days/week; female rats and male and female mice: 0, 300, or 600 mg/kg_{BW}-day, 5 days/week **Duration:** 103 weeks **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for use of LOAEL vs NOAEL)	LOAEL = 150 mg/kg_{BW}-day	LOAEL adjusted for continuous exposure $LOAEL_{adj}$ = 107 mg/kg_{BW}-day TDI = $LOAEL_{adj}$/UF	Nephrotoxicity (renal tubular degeneration and atrophy)	CEPA: Group III possibly carcinogenic to humans (EC and HC, 1993d) IARC: Group 2B possibly carcinogenic to humans (IARC, 1999b) US EPA IRIS: not assessed	HC, 1996 (based on NTP, 1987)
	Inhalation TC	6.0E-02 mg/m^3	**Study Type:** chronic **Species:** male and female F344 rats and BDF_1 mice **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 1,4-dichlorobenzene vapour at concentrations of 0, 20, 75, or 300 ppm (equivalent to 0, 120, 451, and 1804 mg/m^3) for 6 hours/day, 5 days/week **Duration:** 104 weeks **Uncertainty Factors:** 30 (3 for intraspecies variability and 10 for interspecies variability)	$BMCL_{10}$ = 9.51 ppm (57.2 mg/m^3)	$BMCL_{10}$ adjusted for duration (1.70 ppm [10.2 mg/m^3]) + Conversion to a $BMCL_{10\_HEC}$ using a regional gas deposition ratio $BMCL_{10\_HEC}$ = 0.27 ppm (1.6 mg/m^3) TC = $BMCL_{10\_HEC}$/UF	Respiratory tract toxicity (nasal lesions [eosinophilic changes in the nasal olfactory epithelium])		HC, 2018a (based on ATSDR, 2006 [derived from Aiso et al., 2005 and JBRC, 1995])
Dichloroethane, 1,2- (DCA, 1,2-)	Oral SF	3.3E-03 $(mg/kg_{BW}\text{-day})^{-1}$	**Study Type:** chronic **Species:** male and female F344 rats and BDF1 mice **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** rats: 0, 10, 40, or 160 ppm 1,2-dichloroethane vapour (0, 202, 809 and 2024 mg/m^3 or 0, 12, 50, 200 mg/kg_{BW}), 6 hours/day, 5 days/week; mice: 0, 10, 30, or 90 ppm 1,2-dichloroethane vapour (0, 40, 121, 364 mg/m^3 or 0, 54, 162, 486 mg/kg_{BW}), 6 hours/day, 5 days/week **Duration:** 104 weeks **Uncertainty Factors:** N/A	BMD of the 1,2-DCA concentration rat blood based on an excess lifetime risk of 10^{-5} = 0.00027 mg/L	Rat PBPK model used to extrapolate between exposure routes (inhalation to oral) and to estimate the lifetime average daily concentration in rat blood + Multistage modeling to determine rat BMD corresponding to an excess lifetime risk of 10^{-5} + PBPK model to extrapolate from internal animal dose to external dose in humans (0.003 mg/kg_{BW}-day) Oral SF = 10^{-5} / 0.003 mg/kg_{BW}-day	Cancer (combined mammary gland tumours [adenoma, fibroadenoma, and adenocarcinoma of the mammary gland])	CEPA: Group II probably carcinogenic to humans (EC and HC, 1994d) IARC: Group 2B possibly carcinogenic to humans (IARC, 1999a) US EPA IRIS: Group B2 probably carcinogenic to humans (US EPA, 1987b)	HC, 2014a (based on Nagano et al., 2006)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Dichloroethylene, 1,1	Oral TDI (referred to as an 'acceptable daily intake' in HC, 1994)	3.0E-03 mg/kg_{BW}-day	**Study Type:** chronic **Species:** Sprague-Dawley rats **Mode of Administration:** oral (drinking water) **Exposure Regime:** time weighted average daily doses: 0, 7, 10, and 20 mg/kg_{BW}-day (males); 0, 9, 14, and 30 mg/kg_{BW}-day (females) **Duration:** 2 years **Uncertainty Factors:** 3000 (10 for intraspecies variability, 10 for interspecies variability, 10 for use of a LOAEL, and 3 for limited evidence of carcinogenicity)	LOAEL = 9 mg/kg_{BW}-day	TDI = LOAEL/UF	Hepatoxicity (hepatocellular swelling with mid-zonal fatty changes)	CEPA: not assessed IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 1999a) US EPA IRIS: inhalation route: suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential; oral route: inadequate data for assessment of human carcinogenic potential (US EPA, 2002)	HC, 1994 (based on Quast et al., 1983)
Dichloromethane (methylene chloride)	Oral TDI	1.4E-02 mg/kg_{BW}-day	**Study Type:** chronic **Species:** male and female F344 rats **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 5, 50, 125, and 250 mg/kg_{BW}-day; additional group at 250 mg/kg_{BW}-day **Duration:** 104 weeks; additional group was exposed for 78 weeks + 26 week recovery period **Uncertainty Factors:** 300 (10 for intraspecies variability, 10 for interspecies variability, and 3 for database deficiencies)	$BMDL_{10}$ = 4.2 mg/kg_{BW}-day	TDI = $BMDL_{10}$/UF	Hepatotoxicity (increased incidences of foci and areas of cellular alterations in liver)	CEPA: Group II probably carcinogenic to humans (EC and HC, 1993e) IARC: Group 2A probably carcinogenic to humans (IARC, 2017) US EPA IRIS: carcinogenic by a mutagenic mode of action (US EPA, 2011a)	HC, 2011a (based on Serota et al., 1986a)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Dichloromethane (methylene chloride)	Inhalation TC	6.0E-01 mg/m^3	**Study Type:** chronic **Species:** Sprague-Dawley rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 50, 200, or 500 ppm (equivalent to 0, 174, 695, or 1737 mg/m^3) dichloromethane (> 99.5% pure) for 6 hours/day, 5 days/week **Duration:** 2 years **Uncertainty Factors:** 30 (3.16 for intraspecies variability, 3.16 for interspecies variability, and 3 for database deficiencies)	1st percentile HEC = 17.2 mg/m^3	Rat PBPK model to estimate rat internal dose ($BMDL_{10}$) + Adjustment to a human equivalent internal $BMDL_{10}$ + Conversion to an HEC using a human PBPK model TC = 1st percentile HEC/UF	Hepatoxicity (hepatic vacuolation)	CEPA: Group II probably carcinogenic to humans (EC and HC, 1993e) IARC: Group 2A probably carcinogenic to humans (IARC, 2017) US EPA IRIS: carcinogenic by a mutagenic mode of action (US EPA, 2011a)	HC, 2018a (based on US EPA, 2011a [derived from Nitschke et al., 1988])
	Oral SF [US EPA (2011a): do not use with exposures >60 mg/ kg_{BW}-day; apply ADAFs to the oral SF for early life exposures]	2.0E-03 (mg/ kg_{BW}-day)$^{-1}$	**Study Type:** chronic **Species:** male and female B6C3F1 mice **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 60, 125, 185, or 250 mg/kg_{BW}-day (in deionized drinking water) **Duration:** 104 weeks **Uncertainty Factors:** N/A	$BMDL_{10}$ = 60 mg/kg_{BW}-day	$BMDL_{10}$ estimated using a linearized multistage model Oral SF calculated from adult exposure data and does not reflect presumed early-life susceptibility	Cancer (liver [hepatocellular carcinomas or adenomas])		US EPA, 2011a (based on Serota et al., 1986b, and Hazleton Laboratories, 1983)
	Inhalation UR [US EPA (2011a): do not use with exposures exceeding >7700 mg/m^3; apply ADAFs for early life exposures]	1.0E-05 (mg/m^3)$^{-1}$	**Study Type:** chronic **Species:** male $B6C3F_1$ mice **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 2000 or 4000 ppm (approximately 0, 7000, 14 000 mg/m^3); 6 hours/day, 5 days/week **Duration:** 2 years **Uncertainty Factors:** N/A	$BMDL_{10}$ (mouse liver tumours) = 544.4 mg/m^3 $BMDL_{10}$ (mouse lung tumours) = 48.6 mg/m^3	PBPK model to estimate internal mouse dose + Multistage dose-response model to determine mouse $BMDL_{10}$ values for liver tumours and lung tumours + Allometric scaling to convert mouse $BMDL_{10}$ values to human equivalent $BMDL_{10}$ values + Probabilistic human PBPK model to determine distribution of internal human doses + corresponding inhalation URs expressed as external concentrations Inhalation UR based on combined risk for liver and lung tumours	Cancer (liver and lung) [hepatocellular and bronchoalveolar carcinomas or adenomas])		US EPA, 2011a (based on NTP, 1986b, Mennear et al., 1988)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Ethylbenzene	Oral TDI	2.2E-02 mg/kg_{BW}-day	**Study Type:** chronic **Species:** B6C3F1 mice **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 75, 250, or 750 ppm (0, 330, 1100, or 3300 mg/m^3) for 6 hours/day, 5 days/week **Duration:** 103 weeks **Uncertainty Factors:** 25 (10 for intraspecies variability and 2.5 for interspecies variability)	NOAEL = 330 mg/m^3 (75 ppm)	Estimated mouse internal liver concentration corresponding to NOAEL = 0.08 mg/L + PBPK model to obtain external oral dose that is relevant in humans = 0.54 mg/kg_{BW}-day TDI = human external oral dose/UF	Pituitary gland toxicity (hyperplasia) and Hepatotoxicity (cellular alterations of the liver)	CEPA: see 2016 CMP assessment (ECCC and HC, 2016) IARC: Group 2B possibly carcinogenic to humans (IARC, 2000) US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 1998e)	HC, 2014b (based on NTP 1999)
	Inhalation TC	2.0E+00 mg/m^3	**Study Type:** chronic **Species:** male and female F344/N rats and B6C3F1 mice **Mode of Administration:** inhalation **Exposure Regime:** 0, 75, 250, or 750 ppm (0, 330, 1100, or 3300 mg/m^3), 6 hours/day, 5 days/week **Duration:** 104 weeks (rats); 103 weeks (mice) **Uncertainty Factors:** 30 (10 for intraspecies variability and 3 for interspecies variability)	NOAEL = 75 ppm (330 mg/m^3)	NOAEL adjusted for continuous exposure $NOAEL_{adj}$ = 57 mg/m^3 TC = $NOAEL_{adj}$/UF	Pituitary gland toxicity (hyperplasia) and Hepatotoxicity (liver cellular alterations and necrosis)		HC, 2018a (based on OEHHA, 2000 [derived from NTP, 1999 and Chan et al., 1998])

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
***n*-Hexane**	Oral TDI (provisional)	1.0E-01 mg/kg_{BW}-day	**Study Type:** subchronic **Species:** rats **Mode of Administration:** gavage **Exposure Regime:** 0, 66, 132, or 264 mg/day, 7 days/week **Duration:** 4 weeks **Uncertainty Factors:** 90 (10 for intraspecies variability, 3 for interspecies variability, and 3 for deficiencies in the database)	POD = 8 mg/kg_{BW}-day	TDI = POD/UF	Neurotoxicity (motor nerve conduction velocity, mixed nerve conduction velocity)	CEPA: not assessed IARC: not classified US EPA IRIS: inadequate information to assess carcinogenic potential (US EPA, 2005b)	CCME, 2011 (based on EEI, 2008 [derived from Ono et al., 1979, 1981])
	Inhalation TC (provisional)	7.0E-01 mg/m^3	**Study Type:** subchronic **Species:** Wistar male rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 500, 1200, or 3000 ppm nhexane vapour (0, 1762, 4230, or 10 574 mg/m^3), 12 hours/day, 7 days/week **Duration:** 16 weeks **Uncertainty Factors:** 300 (10 for intraspecies variability, 3 for interspecies variability, 3 for use of a subchronic study, and 3 for database deficiencies)	BMCL = 122 ppm (430 mg/m^3)	BMCL adjusted for continuous exposure $BMCL_{HEC}$ = 215 mg/m^3 TC = $BMCL_{HEC}$/UF	Neurotoxicity (peripheral neuropathy – decreased motor nerve conduction velocity)		US EPA, 2005b (based on Huang et al., 1989)
Lead[1]	Risk-specific dose (provisional)	5.0E-04 mg/kg_{BW}-day	**Study Type:** epidemiological (meta-analysis) **Species:** humans **Mode of Exposure:** N/A **Exposure Concentrations:** N/A **Duration:** from birth or infancy until 5 to 10 years of age **Uncertainty Factors:** none	$BMDL_{01}$ = 0.5 $\mu g/kg_{BW}$-day	95th lower confidence limit of the BMD-associated with a 1 IQ point decrement (intake rate associated with a drop of 1 IQ point in a population of children) Risk-specific dose = $BMDL_{01}$ (no adjustment)	Neuro-developmental toxicity (cognitive function)	CEPA: not classified IARC: Group 2A probably carcinogenic to humans (IARC, 2006) US EPA IRIS: Group B2 probable human carcinogen (US EPA, 1988b)	EFSA, 2013 (based on Lanphear et al., 2005)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Manganese	Oral TDI	2.5E-02 mg/kg_{BW}-day	**Kern et al., 2010** **Study Type:** neonatal exposure **Species:** Sprague-Dawley rats **Mode of Administration:** oral **Exposure Regime:** 0, 25, or 50 mg manganese/kg_{BW}-day in a sucrose solution for 21 days following birth (postnatal days [PND] 1-21) **Duration:** follow-up through PND 46 **Kern and Smith, 2011** **Study Type:** neonatal exposure **Species:** Sprague-Dawley rats **Mode of Administration:** oral **Exposure Regime:** 0, 25, or 50 mg manganese/kg_{BW}-day in a sucrose solution for 21 days following birth (PND 1-21) **Duration:** sacrificed on PND 24 or observed to PND 107 **Beaudin et al., 2013** **Study Type:** adult and neonatal exposure **Species:** Long-Evans rats **Mode of Administration:** oral **Exposure Regime:** 0, 25, or 50 mg manganese/kg_{BW}-day in a stevia for 21 days following birth (PND 1-21) or through adulthood; oral manganese exposure post-weaning (PND 22 to end of study) via drinking water **Duration:** exposure during PND 1-21 or through adulthood **Uncertainty Factors (for the three studies):** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for the use of a LOAEL rather than a NOAEL)	LOAEL = 25 mg/kg_{BW}-day	TDI = LOAEL/UF	Neuro-developmental toxicity	CEPA: not assessed IARC: not assessed US EPA: Group D not classifiable as to human carcinogenicity (US EPA, 1988c)	HC, 2019b (based on Kern et al., 2010, Kern and Smith, 2011, and Beaudin et al., 2013)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Mercury (inorganic)	Oral TDI [For exposure to mercury through consumption of fish, seafood, and marine mammals, use the TRV for methylmercury, the predominant form of mercury in these foods.]	3.0E-04 mg/kg_{BW}-day	**Druet et al., 1978** **Study Type:** subchronic **Species:** Brown Norway rats **Mode of Administration:** subcutaneous injection **Exposure Regime:** 0, 0.1, 0.25, 0.5, 1, and 2 mg/kg_{BW}, 3 times a week for 8 weeks; additional group at 0.05 mg/kg_{BW} for 12 weeks **Duration:** 8 or 12 weeks	LOAEL = 0.226 mg/kg_{BW}-day (after conversion from subcutaneous to oral route)	US EPA selected a drinking water equivalent level (DWEL) of 0.010 mg/L based on the three studies. US EPA used the DWEL to derive an RfD: Oral RfD = DWEL × IR_W / BW_{adult} [where IR_W = 2 L/day and BW_{adult} = 70 kg]	Immunotoxicity (autoimmune glomerulonephritis)	CEPA: not classified IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 1993) US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 1995b)	CCME, 1999a,b and US EPA, 1995b (based on Druet et al., 1978; Bernaudin et al., 1981; Andres, 1984)
			Bernaudin et al., 1981 **Study Type:** subchronic **Species:** Brown Norway rats **Mode of Administration:** gavage (food) **Exposure Regime:** 0 or 3 mg $HgCl_2$ (equivalent to 2.22 mg Hg)/kg_{BW} per week **Duration:** 60 days	LOAEL = 0.317 mg/kg_{BW}-day				
			Andres, 1984 **Study Type:** subchronic **Species:** Brown Norway rats and Lewis rats **Mode of Administration:** gavage (water) **Exposure Regime:** 3 mg $HgCl_2$ (equivalent to 2.22 mg Hg)/kg_{BW}, 2 times per week **Duration:** 60 days **Uncertainty Factors:** 1000 (10 for use of subchronic studies, 10 for intraspecies and interspecies variability, and 10 for LOAEL to NOAEL conversion)	LOAEL = 0.633 mg/kg_{BW}-day				

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Methylmercury	Oral TDI (provisional)	2.0E-04 mg/kg_{BW}-day (women of child-bearing age, infants, and children < 12 years)	**Study Type:** epidemiological **Species**: humans (children) **Mode of Exposure:** diet **Estimated Exposure:** daily intake estimated at 0.001 mg/kg_{BW}-day **Duration:** chronic (maternal exposure) **Uncertainty Factors**: 5 (see HC [2007] for details)	Approximate threshold of 10 µg/g mercury in maternal hair, corresponding to a dietary methylmercury intake level of 0.001 mg/kg_{BW}-day	TDI = dietary methylmercury intake level of 0.001 mg/kg_{BW}-day /UF	Neuro-developmental toxicity	CEPA: not assessed IARC: Group 2B possibly carcinogenic to humans (IARC, 1993) US EPA IRIS: Group C possibly carcinogenic to humans (US EPA, 1995c)	HC, 2007 (based on Grandjean et al., 1997)
		4.7E-04 mg/kg_{BW}-day (non-sensitive adults of the general population)	**Study Type:** epidemiological **Species:** humans (children) **Mode of Exposure:** diet **Exposure Concentrations:** daily intake estimated at 0.0015 mg/kg_{BW}-day **Duration:** chronic (maternal exposure) **Uncertainty Factors:** 6.4 (2 for interindividual variability in the hair:blood mercury ratio, and 3.16 [$10^{0.5}$] for inter-individual variability in the rate of elimination)	Average mercury concentration of 14 µg/g in maternal hair, corresponding to an estimated dietary methylmercury daily intake of 0.0015 mg/kg_{BW}-day	FAO/WHO (2007) pTWI = provisional tolerable dietary methylmercury weekly intake (daily intake × 7 days/week)/UF= 0.0016 mg/kg_{BW}-week Provisional TDI = pTWI x 2 for non-sensitive adults of the general population / 7 days in a week	Neuro-developmental toxicity		FAO/WHO, 2007
Methylnaphthalene, 2-	Oral TDI	4.0E-03 mg/kg_{BW}-day	**Study Type:** chronic **Species:** male and female B6C3F1 mice **Mode of Administration:** diet **Exposure Regime:** 0, 54.3, or 113.8 mg/kg_{BW}-day (males); 0, 50.3, or 107.6 mg/kg_{BW}-day (females) **Duration:** 81 weeks **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for database deficiencies)	$BMDL_{05}$ = 3.5 mg/kg_{BW}-day	TDI = $BMDL_{05}$/UF (rounded to 4.0E-03 mg/kg_{BW}-day)	Respiratory tract toxicity (pulmonary alveolar proteinosis)	CEPA: not assessed IARC: not assessed US EPA IRIS: inadequate information to assess human carcinogenic potential (US EPA, 2003a)	US EPA, 2003a (based on Murata et al., 1997)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Naphthalene	Oral TDI	2.0E-02 mg/kg_{BW}-day	**Study Type:** subchronic **Species:** male and female F344 rats **Mode of Administration:** gavage (corn oil) **Exposure Regime:** 0, 25, 50, 100, 200, or 400 mg/kg_{BW}, 5 days/week **Duration:** 13 weeks **Uncertainty Factors:** 3000 (10 for intraspecies variability, 10 for interspecies variability, 10 for use of a subchronic study, and 3 for database deficiencies)	NOAEL = 100 mg/kg_{BW}-day	NOAEL adjusted for continuous exposure $NOAEL_{adj}$ = 71 mg/kg_{BW}-day TDI = $NOAEL_{adj}$/UF (rounded to 2.0E-02 mg/kg_{BW}-day)	Decreased body weight	CEPA: not assessed IARC: Group 2B possibly carcinogenic to humans (IARC, 2002) US EPA IRIS: Group C possibly carcinogenic to humans (US EPA, 1998f)	US EPA, 1998f (based on BCL, 1980)
	Inhalation TC	1.0E-02 mg/m^3	**Study Type:** chronic **Species:** F344 rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 10, 30, or 60 ppm (0, 52, 157, or 315 mg/m^3) for 6 hours per day plus T_{90} (12 minutes for the time to achieve 90% of the target concentration after vapour generation), 5 days per week **Duration:** 105 weeks **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for database deficiencies)	LOAEL = 52 mg/m^3 (10 ppm)	LOAEL adjusted for continuous exposure $LOAEL_{adj}$ = 9.3 mg/m^3 (1.8 ppm) TC = $LOAEL_{adj}$/UF	Respiratory tract toxicity (nasal lesions [neuroblastoma of the olfactory epithelium, and adenoma of the respiratory epithelium of the nose])		HC, 2013b (based on NTP, 2000)
Nickel chloride	Oral TDI	1.3E-03 mg/kg_{BW}-day	**Study Type:** reproductive **Species:** female Long-Evans rats **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 10, 50, and 250 ppm Ni^{2+} (equivalent to 0, 1.3, 6.7, and 31.6 mg Ni^{2+}/kg_{BW}-day, respectively) **Duration:** 11 weeks prior to mating (with unexposed males). Nickel administration continued through two successive gestation and lactation periods. **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for use of a LOAEL instead of a NOAEL)	LOAEL = 1.3 mg Ni^{2+}/kg_{BW}-day	TDI = LOAEL/UF	Reproductive toxicity (perinatal death)	See nickel, mixture of oxidic, sulfidic and soluble inorganic nickel compounds	HC, 1996 (based on Smith et al., 1993)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Nickel oxide	Inhalation TC	2.5E-05 mg/m^3	**Study Type:** subchronic **Species:** Wistar rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 0.025 and 0.150 mg nickel/m^3 as NiO aerosols, 24 hours/day, 7 days/week **Duration:** 4 months **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for less than chronic study)	LOAEL = 0.025 mg/m^3	TC = LOAEL/UF	Respiratory tract toxicity (increase in the number of alveolar macrophages, increase in the size and number of macrophages with more than one nucleus, and an increase in phagocytic activity)	CEPA: Group I carcinogenic to humans (EC and HC, 1994e) IARC: see nickel, mixture of oxidic, sulfidic and soluble inorganic nickel compounds US EPA IRIS: not classified	HC, 1996 (based on Spiegelberg et al., 1984)
Nickel subsulfide (sulfidic nickel)	Inhalation TC	1.8E-05 mg/m^3	**Study Type:** subchronic **Species:** F344/N rats and B6C3F1 mice **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 0.11, 0.22, 0.44, 0.88, and 1.8 mg nickel/m^3, 6 hours/day, 5 days/week **Duration:** 13 weeks **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for less than chronic study)	LOAEL = 0.1 mg/m^3	LOAEL adjusted for continuous exposure $LOAEL_{adj}$ = 0.018 mg/m^3 TC = $LOAEL_{adj}$/UF	Respiratory tract toxicity (increase in number of alveolar macrophages, hyperplasia of alveolar macrophages)	CEPA: Group I carcinogenic to humans (EC and HC, 1994e) IARC: see nickel, mixture of oxidic, sulfidic and soluble inorganic nickel compounds US EPA IRIS: Group A carcinogenic to humans (US EPA, 1987c)	EC and HC, 1994e and HC, 1996 (based on Benson et al., 1990; Dunnick et al., 1989)
Nickel sulfate	Oral TDI	1.2E-02 mg/kg_{BW}-day	**Study Type:** epidemiological (human controlled studies) **Species:** humans (1st study [men] = 8 non-allergic volunteers; 2nd study [women] = 20 nickel-sensitive subjects and 20 non-allergic age-matched controls, both groups having existing vesicular hand eczema of the pompholyx type) **Mode of Exposure:** oral (drinking water) **Exposure Concentrations:** 12 µg nickel/kg_{BW} in drinking water (exposed subjects in both studies), followed by a 72-hour observation period **Duration:** N/A (single administration) **Uncertainty Factors:** none (LOAEL was based on a highly sensitive human population [WHO, 2007])	LOAEL = 12 µg Ni/kg_{BW}-day	TDI = LOAEL	Dermal toxicity (exacerbation of eczema in nickel-sensitive subjects)	CEPA and IARC: see nickel, mixture of oxidic, sulfidic and soluble inorganic nickel compounds US EPA IRIS: not assessed	CCME, 2015 (based on WHO, 2007 [derived from Nielsen et al., 1999])

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Nickel sulfate	Inhalation TC	2.0E-05 mg/m^3	**Study Type:** chronic **Species:** male and female F344/N rats and B6C3F1 mice **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** rats: 0, 0.12, 0.25, or 0.5 mg nickel sulfate hexahydrate/m^3 (equivalent to 0, 0.03, 0.06, or 0.11 mg nickel/m^3); mice: 0, 0.25, 0.5, or 1 mg nickel sulfate hexahydrate/m^3 (equivalent to 0, 0.06, 0.11, or 0.22 mg nickel/m^3); about 6 hours/day, 5 days/week **Duration:** 104 weeks **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for use of a LOAEL)	LOAEL = 0.06 mg/m^3	LOAEL adjusted for continuous exposure $LOAEL_{adj}$ = 0.011 mg/m^3 Intermediate TC = $LOAEL_{adj}$/UF = 1.1E-05 mg/m^3 Value of 0.02 µg/m^3 was recommended as the European air quality standard based on soluble nickel compounds constituting <50% of total nickel compounds in ambient air	Respiratory tract toxicity (lung inflammation [chronic active inflammation, macrophage and lymphoid hyperplasia, alveolar proteinosis, fibrosis, lung lesions, and atrophy of the olfactory epithelium])	CEPA and IARC: see nickel, mixture of oxidic, sulfidic and soluble inorganic nickel compounds US EPA IRIS: not assessed	CCME, 2015 (based on ECB, 2008 and CSTEE, 2001, derived from NTP 1996)
Nickel, mixture of oxidic, sulfidic and soluble inorganic nickel compounds	Inhalation UR	1.3E+00 (mg/m^3)$^{-1}$	**Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation **Exposure Concentrations:** N/A **Duration:** > 6 months **Uncertainty Factors:** N/A	TC_{05} (5% tumourigenic concentration) = 0.04 mg/m^3	Inhalation UR = 0.05/TC_{05} where 0.05 = 5% extra cancer risk	Cancer (lung, nasal, kidney, prostrate, buccal cavity)	CEPA: classified as Group I carcinogenic to humans (EC and HC, 1994e) IARC: Group 1 classified as carcinogenic to humans (IARC, 2012a) US EPA: see individual nickel substances	EC and HC, 1994e, and HC 1996 (based on Doll et al., 1990)
Nickel, metallic	Inhalation TC (provisional)	1.8E-05 mg/m^3	**Study Type:** subchronic **Species:** rabbits **Mode of Administration:** inhalation **Exposure Regime:** 0, 0.13 mg/m^3 metallic nickel dust, 6 hours/day, 5 days/week **Duration:** 4 and 8 months **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for database deficiencies and a less than chronic study)	LOAEL = 0.13 mg/m^3	LOAEL (rounded to 0.1 mg/m^3) adjusted for continuous exposure $LOAEL_{adj}$ = 0.018 mg/m^3 TC = $LOAEL_{adj}$/UF	Respiratory tract toxicity (morphological and biological effects on alveolar cells)	CEPA: Group VI unclassifiable with respect to carcinogenicity to humans (EC and HC, 1994e) IARC: Group 2B possibly carcinogenic to humans (IARC, 1990) US EPA IRIS: not classified	EC and HC, 1994e and HC, 1996 (based on Johansson et al., 1983)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Perfluorooctanoic acid (PFOA)	Oral TDI	2.1E-05 mg/kg_{BW}-day	**Study Type:** subchronic **Species:** rats **Mode of Administration:** diet **Exposure Regime:** 0, 0.06, 0.64, 1.94, and 6.5 mg/kg_{BW}-day, for 4, 7, or 13 weeks; each dose had a recovery group that was observed for 8 additional weeks after cessation of exposure at week 13 **Duration:** up to 13 weeks **Uncertainty Factors:** 25 (10 for intraspecies variability and 2.5 for the toxicodynamic component of the default interspecies uncertainty factor). No uncertainty factor was used for subchronic-to-chronic extrapolation, as liver effects were investigated in a chronic study (Butenhoff et al., 2012) and increasing duration of exposure did not appear to worsen the effects in the key study (Perkins et al., 2004).	$BMDL_{10}$ = 0.05 mg/kg_{BW}-day	POD_{HEQ} = 0.000521 mg/kg_{BW}-day ($BMDL_{10}$/96, where 96 is the uncertainty factor to account for interspecies toxicokinetic differences, for rats exposed in the 0.01 mg/kg_{BW}-day range) TDI = POD_{HEQ}/UF	Hepatotoxicity (hepatocellular hypertrophy)	CEPA: not classified IARC: Group 2B possibly carcinogenic to humans (IARC, 2017) US EPA IRIS: suggestive evidence of carcinogenic potential in animals and humans (US EPA, 2016a)	HC, 2018b (based on Perkins et al., 2004, and Summit Toxicology, 2015)
Perfluorooctane sulfonate (PFOS)	Oral TDI	6.0E-05 mg/kg_{BW}-day	**Study Type:** chronic **Species:** male and female Sprague-Dawley rats **Mode of Administration:** diet **Exposure Regime:** 0, 0.5, 2, 5, and 20 ppm (mean daily doses: 0, 0.024, 0.098, 0.242, and 0.984 mg/kg_{BW}-day for males; 0, 0.029, 0.120, 0.299, and 1.251 mg/kg_{BW}-day for females) **Duration:** 2 years **Uncertainty Factors:** 25 (10 for intraspecies variability, and 2.5 for the toxicodynamic component of the default interspecies uncertainty factor)	NOAEL = 0.024 mg/kg_{BW}-day	NOAEL adjusted to account for decreased purity of the test material $NOAEL_{adj}$ = 0.021 mg/kg_{BW}-day POD_{HEQ} = $NOAEL_{adj}$/14 = 0.0015 mg/kg_{BW}-day [where 14 = dose- and species-specific adjustment factor] TDI = POD_{HEQ}/UF	Hepatotoxicity (hepatocellular hypertrophy)	CEPA: not classified IARC: not classified US EPA IRIS: suggestive evidence of carcinogenic potential in animals (US EPA, 2016b)	HC, 2018c (based on Butenhoff et al., 2012)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Polychlorinated biphenyls (PCBs) (non dioxin-like i.e., non-coplanar)	Oral TDI (provisional)	1.0E-05 mg/kg_{BW}-day (based on an $Aroclor_{1254}$ mixture)	**Study Type:** chronic **Species:** female rhesus monkeys **Mode of Administration:** oral (ingestion of capsules containing $Aroclor_{1254}$ in a 1:1 glycerol/corn oil mixture) **Exposure Regime:** 0, 0.005, 0.02, 0.04, or 0.08 mg/kg_{BW}-day **Duration:** 23 months and 55 months (same group) **Uncertainty Factors:** 300 (10 for intraspecies variability, 3 for interspecies variability, and 10 to extrapolate from a LOAEL to a NOAEL)	LOAEL for $Aroclor_{1254}$ = 0.005 mg/kg_{BW}-day	As per Baars et al., 2001, TDI for mixture of non dioxin-like (i.e., non-coplanar PCBs) = 50% of the TDI of $Aroclor_{1254}$ (based on chemical analysis of seven "indicator PCBs" [PCB # 28, 52, 101, 118, 138, 153, and 180]) LOAEL $Aroclor_{1254}$/UF = 1.7E-05 mg/kg_{BW}-day (rounded to 2.0E-05 mg/kg_{BW}-day) TDI $Aroclor_{1254}$ = 2.0E-05 mg/kg_{BW}-day × 50% = 1.0E-05 mg/kg_{BW}-day	Immunotoxicity (decreased antibody response)	CEPA: not classified IARC: not classified US EPA IRIS: not classified	WHO, 2003 (based on Tryphonas et al., 1989, 1991), and Baars et al., 2001
Polychlorinated biphenyls (PCBs)[2] (dioxin-like, i.e. coplanar)	Oral TDI	2.3E-09 TEQ mg/kg_{BW}-day	See PCDDs/PCDFs for study details. Dioxin-like (i.e., coplanar) PCBs should be evaluated with PCDDs/PCDFs, using appropriate TEFs (see Table 4).				CEPA: not classified IARC: Group 1; dioxin-like (i.e., coplanar) PCBs classified as carcinogenic to humans (IARC, 2016) US EPA IRIS: Group B2 probably carcinogenic to humans (US EPA, 1996)	See PCDDs/ PCDFs for source information.

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Polychlorinated dibenzo-*p*-dioxins/ polychlorinated dibenzofurans[2] **(PCDDs/PCDFs)**	Oral TDI (provisional)	2.3E-09 TEQ mg/kg$_{BW}$-day	**Faqi et al., 1998** **Study Type:** subchronic (developmental) **Species:** Wistar rats **Mode of Administration:** subcutaneous **Exposure Regime and Duration:** initial doses of 0, 25, 60, or 300 ng tetrachlorodibenzo-*p*-dioxin (TCDD)/kg$_{BW}$ followed by weekly maintenance doses at 0, 5, 12, or 60 ng TCDD/kg$_{BW}$ beginning 2 weeks prior to mating and continuing through mating, gestation, and lactation **Uncertainty Factors:** 9.6 (3 for use of a LOAEL rather than a NOAEL, and 3.2 for intraspecies variability)	LOAEL (maternal body burden) = 25 ng/kg$_{BW}$-day	BMD modeling to extrapolate NOAEL and LOAEL based on maternal body burden, to estimate equivalent monthly human intakes (EHMIs) pTMI = EHMI/UF Range of pTMIs = 40-100 pg/kg$_{BW}$-month mid-point of pTMI range = 70 pg/kg$_{BW}$-month pTDI = pTMI/30 days per month	Developmental toxicity (decreased sperm production and altered sexual behaviour in male offspring)	CEPA: not assessed IARC: Group 3 not classifiable as to carcinogenicity to humans for PCDDs (other than 2,3,7,8-TCDD and 2,3,4,7,8-PCDF) (IARC, 1997) IARC: Group 1, carcinogenic to humans for 2,3,7,8-TCDD and 2,3,4,7,8-PCDF (IARC, 2012b) US EPA: Group B2 probable human carcinogen for HxCDD; other PCDDs/ PCDFs not assessed (US EPA, 1987d)	WHO, 2002 (based on Faqi and Chahoud, 1998; Ohsako et al., 2001)
			Ohsako et al., 2001 **Study Type:** subchronic (developmental) **Species:** pregnant Holtzman rats **Mode of Administration:** single oral bolus dose by gavage on day 15 of gestation **Exposure Regime and Duration:** single bolus dose (0, 12.5, 50, 200, or 800 ng 2,3,7,8-TCDD/kg$_{BW}$) on day 15 of gestation **Uncertainty Factors:** 3.2 for intraspecies variability	NOAEL (maternal body burden) = 13 ng/kg$_{BW}$-day		Developmental toxicity (decrease of ventral prostate weight and anogenital distance in male offspring)		
Pyrene	Oral TDI	3.0E-02 mg/kg$_{BW}$-day	**Study Type:** subchronic **Species:** male and female CD-1 mice **Mode of Administration:** gavage (corn oil) **Exposure Regime:** 0, 75, 125, or 250 mg/kg$_{BW}$-day **Duration:** 13 weeks **Uncertainty Factors:** 3000 (10 for intraspecies variability, 10 for interspecies variability, 10 for a less than chronic study, and 3 for database deficiencies)	NOAEL = 75 mg/kg$_{BW}$-day	TDI = NOAEL/UF (TDI rounded to 3.0E-02 mg/kg$_{BW}$-day)	Nephrotoxicity (renal tubular pathology [lesions], decreased kidney weights)	CEPA: not assessed IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 2010) US EPA: Group D not classifiable as to human carcinogenicity (US EPA, 1990c)	US EPA, 1990c (based on US EPA, 1989)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Selenium	UL (HC) 0 to <6 mo 6 mo to <5 yrs 5 to <12 yrs 12 to <20 yrs ≥20 yrs	mg/kg$_{BW}$-day 5.5E-03 6.0E-03 6.3E-03 6.2E-03 5.7E-03	**Yang and Zhou, 1994 (adults)** **Study Type:** epidemiological **Species:** humans (adults) **Mode of Exposure:** dietary intake **Exposure Concentrations:** initial estimated range of intake: 913 to 1907 µg/day; range of intake during re-examination (8 years later): 654 to 952 µg/day **Duration:** chronic **Uncertainty Factors:** 2 (to protect sensitive individuals)	NOAEL = 800 µg/day (mean selenium intake upon re-examination) (adults)	UL (IOM) = NOAEL/UF IOM adult ULs were adjusted to account for differences in HC's adult age group (HC, 2010)	Hair and nail brittleness and loss (signs and symptoms of chronic selenosis)	CEPA: see 2017 CMP assessment (ECCC and HC, 2017) IARC: Group 3 not classifiable as to human carcinogenicity (IARC, 1987) US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 1991)	IOM, 2000 (based on Yang and Zhou, 1994; Shearer and Hadjimarkos, 1975)
			Shearer and Hadjimarkos, 1975 (infants, children, and adolescents) **Study Type:** epidemiological **Species:** humans (infants, 0-6 months of age) **Mode of Exposure:** diet (human milk) **Exposure Concentrations:** selenium concentration of human milk of unsupplemented women ranged from 7 to 60 µg/L (average of 18 µg/L) **Duration:** N/A (stage of lactation ranged from 17 to 869 days) **Uncertainty Factors:** 1 (because of a lack of evidence that maternal intake associated with a human milk level of 60 µg selenium/L results in infant or maternal toxicity)	NOAEL = 60 µg/L (infants)	NOAEL adjusted for estimated average human milk intake of 0.78 L/day NOAEL$_{adj}$ = 47 µg/day (rounded to 45 µg/day) Infant UL (IOM) = NOAEL$_{adj}$/UF IOM derived ULs for older infants, children, and adolescents based on the infant UL and relative body weight TRVs were calculated in mg/kg$_{BW}$-day for age groups in HC (2010) guidance	No evidence of selenium toxicity		

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Tetrachloroethylene (PCE)	Oral TDI	4.7E-03 mg/kg_{BW}-day	**Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation **Exposure Concentrations:** Two exposure groups. High exposure group (dry cleaners): exposure range = 0.38-31.19 ppm (2.6 to 211 mg/m^3); mean 8-hour time-weighted average exposure = 7.27 ppm (49 mg/m^3). Moderate exposure group (ironers): exposure range = 0.52-11.28 ppm (3.5 to 77 mg/m^3); mean of 8-hour time-weighted average exposure = 4.8 ppm (33 mg/m^3) **Duration:** 8.8 years (average) **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 to extrapolate from a less than lifetime exposure, and 10 for database deficiencies)	NOAEL = 4.8 ppm (33 mg/m^3) BMD_{10} = 7.2 ppm (49 mg/m^3)	BMD power model $BMDL_{10}$ = 6.6 ppm (45 mg/m^3) PBPK model used to extrapolate from inhalation exposures to equivalent oral doses Peak kidney PCE concentrations used to estimate brain concentrations External dose associated with $BMDL_{10}$ = 4.7 mg/kg_{BW}-day TDI = external dose associated with the $BMDL_{10}$/UF	Neurotoxicity (colour confusion)	CEPA: Group III possibly carcinogenic to humans (EC and HC, 1993f) IARC: Group 2A probably carcinogenic to humans (IARC, 2014) US EPA IRIS: likely to be carcinogenic to humans (US EPA, 2012)	HC, 2015 (based on Cavalleri et al., 1994)
	Inhalation TC	4.0E-02 mg/m^3	**Cavalleri et al., 1994** **Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation **Exposure Concentrations:** Two exposure groups. High exposure group (dry cleaners): exposure range = 0.38-31.19 ppm (2.6 to 211 mg/m^3); mean 8-hour time-weighted average exposure = 7.27 ppm (49 mg/m^3). Moderate exposure group (ironers): range = 0.52-11.28 ppm (3.5 to 77 mg/m^3); mean of 8-hour time-weighted average exposure level = 4.8 ppm (33 mg/m^3). **Duration:** 8.8 years (average) **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for uncertainties in extrapolating from a LOAEL to a NOAEL, and 10 for database uncertainties)	LOAEL (Cavalleri et al., 1994) = 42 mg/m^3 (time-weighted average mean concentration of both exposure groups) LOAEL (Echeverria et al., 1995) = 156 mg/m^3	LOAELs adjusted for continuous exposure and breathing rate $LOAEL_{adj}$ (Cavalleri et al., 1994) = 15 mg/m^3 $LOAEL_{adj}$ (Echeverria et al., 1995) = 56 mg/m^3 TC = midpoint of the range of LOAELs/UF = 0.04 mg/m^3	Neurotoxicity (alterations in reaction times, cognitive function, and colour vision)		HC, 2018a (based on US EPA, 2012 [derived from Cavalleri et al., 1994, and Echeverria et al., 1995])

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Tetrachloroethylene (PCE)	Inhalation TC	4.0E-02 mg/m^3	**Echeverria et al., 1995** **Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation **Exposure Concentrations:** Three exposure zones identified for counter clerks, pressers, and operators, corresponding to air levels of 11.2, 23.2, and 40.8 ppm respectively (76, 156, and 277 mg/m^3) **Duration:** chronic **Uncertainty Factors:** 1000 (10 for intraspecies variability, 10 for uncertainties in extrapolating from a LOAEL to a NOAEL, and 10 for database uncertainties)	LOAEL (Cavalleri et al., 1994) = 42 mg/m^3 (time-weighted average mean concentration of both exposure groups) LOAEL (Echeverria et al., 1995) = 156 mg/m^3	LOAELs adjusted for continuous exposure and breathing rate $LOAEL_{adj}$ (Cavalleri et al., 1994) = 15 mg/m^3 $LOAEL_{adj}$ (Echeverria et al., 1995) = 56 mg/m^3 TC = midpoint of the range of LOAELs/UF = 0.04 mg/m^3	Neurotoxicity (alterations in reaction times, cognitive function, and colour vision)	CEPA: Group III possibly carcinogenic to humans (EC and HC, 1993f) IARC: Group 2A probably carcinogenic to humans (IARC, 2014) US EPA IRIS: likely to be carcinogenic to humans (US EPA, 2012)	HC, 2018a (based on US EPA, 2012 [derived from Cavalleri et al., 1994, and Echeverria et al., 1995])
Toluene	Oral TDI	9.7E-03 mg/kg_{BW}-day	**Study Type:** epidemiological (occupational) **Species:** humans (printing shop workers) **Mode of Exposure:** inhalation **Exposure Concentrations:** high exposure group (106 subjects) = 26 ppm (98 mg/m^3); low exposure group (86 subjects) = 3 ppm (11 mg/m^3) **Duration:** long duration (21 years) and shorter duration (6 years) **Uncertainty Factors:** 10 for intraspecies variability	NOAEL = 26 ppm (98 mg/m^3)	PBPK modeling to estimate an internal toluene blood concentration following inhalation exposure = 0.0075 mg/L + Conversion to external oral human dose assuming ingestion of 1.5 L drinking water/day: $NOAEL_{HEC}$ = 0.097 mg/kg_{BW}-day TDI = $NOAEL_{HEC}$/UF	Neurotoxicity (cognitive function: attention, memory, and psychomotor function)	CEPA: Group IV unlikely to be carcinogenic to humans (EC and HC, 1992b) IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 1999a) US EPA IRIS: inadequate information to assess carcinogenic potential (US EPA, 2005c)	HC, 2014b (based on Seeber et al., 2004, 2005)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Toluene	Inhalation TC	2.3E+00 mg/m^3	**Study Type:** epidemiological (occupational) **Species:** humans (printing shop workers) **Mode of Exposure:** inhalation **Exposure Concentrations:** high exposure group (106 subjects) = 26 ppm (98 mg/m^3); low exposure group (86 subjects) = 3 ppm (11 mg/m^3) **Duration:** long duration (21 years) and shorter duration (6 years) **Uncertainty Factors:** 10 (3.16 for pharmacokinetic variability and 3.16 for pharmacodynamics variability)	NOAEL = 26 ppm (98 mg/m^3)	NOAEL adjusted for continuous exposure (assuming 8 hours/day, 5 days/week to 24 hours/ day, 7 days/week) $NOAEL_{adj}$ = 23 mg/m^3 TC = $NOAEL_{adj}$/UF	Neurotoxicity (cognitive function: attention, memory and psychomotor function)	CEPA: Group IV unlikely to be carcinogenic to humans (EC and HC, 1992b) IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 1999a) US EPA IRIS: inadequate information to assess carcinogenic potential (US EPA, 2005c)	HC, 2011b (based on Seeber et al., 2004, 2005)
Trichloroethylene (TCE)	Oral TDI	1.46E-03 mg/kg_{BW}-day	**Study Type:** subchronic (developmental) **Species:** Sprague-Dawley rats **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 1.5, and 1100 ppm (equivalent to 0, 0.18, and 132 mg/kg_{BW}-day); 3 dosing regimes: 1) 3 months before pregnancy, 2) 2 months before and 21 days during pregnancy, or 3) 21 days during pregnancy only **Duration:** variable (see Exposure Regime above) **Uncertainty Factors:** 100 (10 for intraspecies variability and 10 for interspecies variability)	$BMDL_{10}$ = 0.146 mg/kg_{BW}-day	BMD model TDI = $BMDL_{10}$/UF	Developmental toxicity (fetal heart defects)	CEPA: Group II probably carcinogenic to humans (EC and HC, 1993g) IARC: Group 1 carcinogenic to humans (IARC, 2014) US EPA IRIS: carcinogenic to humans (US EPA, 2011b)	HC, 2005 (based on Dawson et al., 1993)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Trichloroethylene (TCE)	Inhalation TC	2.0E-03 mg/m^3	**Keil et al., 2009** **Study Type:** chronic **Species:** female B6C3F1 mice **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 1.4, and 14 ppm (0, 0.35, 3.5 mg/kg_{BW}-day) **Duration:** 30 weeks **Uncertainty Factors:** 100 (10 for extrapolating from a LOAEL rather than a NOAEL, 3 for intraspecies variability, and 3 for interspecies variability) [total uncertainty factor rounded to 100]	LOAEL = 0.35 mg/kg_{BW}-day $POD_{internal\ dose}$ (LOAEL) = 0.139 mg TCE metabolized / $kg_{BW}^{3/4}$/day $HEC_{99,\ LOAEL}$ = 0.033 ppm (0.19 mg/m^3)	Candidate RfCs derived using a PBPK model integrating combined intraspecies, interspecies, and route-to-route extrapolation, and dividing by a UF. Candidate RfC (Keil et al., 2009) = 0.0019 mg/m^3 Candidate RfC (Johnson et al., 2003) = 0.0021 mg/m^3 Selected RfC = midpoint between the candidate RfCs = 0.002 mg/m^3	Developmental toxicity (fetal heart malformations) and Immunotoxicity (decreased thymus weight)	CEPA: Group II probably carcinogenic to humans (EC and HC, 1993g) IARC: Group 1 carcinogenic to humans (IARC, 2014) US EPA IRIS: carcinogenic to humans (US EPA, 2011b)	US EPA, 2011b (based on Keil et al., 2009 and Johnson et al., 2003)
			Johnson et al., 2003 **Study Type:** developmental **Species:** pregnant Sprague-Dawley rats **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 0.0025, 0.25, 1.5, and 1100 ppm (0, 0.00045, 0.048, 0.218 or 129 mg/kg_{BW}-day) on gestational days 1 to 22 **Duration:** 3 weeks during pregnancy **Uncertainty Factors:** 10 (3 for intraspecies variability, and 3 for interspecies variability) [total uncertainty factor rounded to 10]	$POD_{internal\ dose}$ = $BMDL_{01}$ = 0.0142 mg TCE metabolized by oxidation/$kg_{BW}^{3/4}$/day $HEC_{99,\ BMDL01}$ = 0.0037 ppm (0.021 mg/m^3)				
	Oral SF	8.11E-04 $(mg/kg_{BW}\text{-day})^{-1}$	**Study Type:** chronic **Species**: male and female rats **Mode of Administration:** gavage **Exposure Regime:** 0, 500, and 1000 mg/kg_{BW}-day, 5 days/week **Duration:** 103 weeks **Uncertainty Factors:** N/A	Range of oral SFs: 5.82E-04 to 8.11E-04 $(mg/kg_{BW}\text{-day})^{-1}$	Linearized multistage model and allometric scaling Most conservative oral SF: 8.11E-04 $(mg/kg_{BW}\text{-day})^{-1}$	Cancer (kidney [combined tubular cell adenomas and adenocarcinomas])		HC, 2005 (based on NTP, 1988 and NTP, 1990)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Trichloroethylene (TCE)	Inhalation UR	4.1E-03 $(mg/m^3)^{-1}$	**Study Type:** epidemiological (occupational) **Species:** humans **Mode of Exposure:** inhalation **Exposure Concentrations:** N/A **Duration:** chronic **Uncertainty Factors:** N/A	LEC_{01} = 2.4 mg/m^3 (lowest effective concentration)	Linear low-dose extrapolation from the LEC_{01} (95% lower bound on the exposure associated with a 1% extra cancer risk) + Application of a factor of 4 to include non-Hodgkin's lymphoma and liver cancer risks Inhalation UR = 0.01 / LEC_{01} where 0.01 = 1% extra cancer risk	Cancer (liver, kidney [renal cell carcinoma], non-Hodgkin's lymphoma)	CEPA: Group II probably carcinogenic to humans (EC and HC, 1993g) IARC: Group 1 carcinogenic to humans (IARC, 2014) US EPA IRIS: carcinogenic to humans (US EPA, 2011b)	US EPA, 2011b (based on Charbotel et al., 2006 and Raaschou-Nielsen et al., 2003)
Uranium (non-radioactive)	Oral TDI	6.0E-04 mg/kg_{BW}-day	**Study Type:** subchronic **Species:** male and female Sprague-Dawley rats **Mode of Administration:** oral (drinking water) **Exposure Regime:** 0, 0.96, 4.8, 24, 120, or 600 mg/L uranyl nitrate hexahydrate (equivalent to uranium doses of 0, 0.06, 0.31, 1.52, 7.54, and 36.73 mg/kg_{BW}-day in male rats, and 0, 0.09, 0.42, 2.01, 9.98, and 53.56 mg/kg_{BW}-day in female rats) **Duration:** 91 days **Uncertainty Factors:** 100 (10 for intraspecies variability and 10 for interspecies variability). Other points of departure (including a NOAEL) were higher than the LOAEL identified by Gilman et al. (1998) and therefore HC (2019c) did not consider an uncertainty factor for use of a LOAEL instead of a NOAEL necessary. HC (2019c) did not apply an uncertainty factor for use of a subchronic study because the study was considered adequately sensitive since the observed kidney effects were similar to the minimal effects seen in a number of longer-term studies and since human absorption values were found to be independent of exposure duration (HC, 2019c).	LOAEL = 0.06 mg/kg_{BW}-day (males)	TDI = LOAEL/UF	Nephrotoxicity (renal lesions)	CEPA: not assessed IARC: not assessed US EPA IRIS: not assessed	HC, 2019c (based on Gilman et al., 1998)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Vinyl chloride	Oral SF	2.4E-01 $(mg/kg_{BW}\text{-}day)^{-1}$ for continuous lifetime exposure during adulthood 4.8E-01 $(mg/kg_{BW}\text{-}day)^{-1}$ for continuous lifetime exposure from birth	**Study Type:** chronic **Species:** male and female rats **Mode of Administration:** diet (mixture of vinyl chloride monomer [VCM] and polyvinyl chloride [PVC] powder) **Exposure Regime:** 0, 1.7, 5.0, or 14.1 mg/kg_{BW}-day, 4 hour feeding period/day; a positive control group was administered 300 mg/kg_{BW} VCM in soybean oil by stomach tube, 5 days/week **Duration:** lifetime (the experiment was terminated once 75% mortality was observed in the positive control group, i.e. 135 weeks for males and 144 weeks for females) **Uncertainty Factors:** N/A	External human dose associated with an excess lifetime risk of 10^{-5} for combined liver cancers = 4.19E-05 mg/kg_{BW}-day	Rat PBPK model to determine daily internal doses of vinyl chloride liver metabolites + Multistage model to determine a POD + Human PBPK model to estimate external doses Oral SF = 10^{-5} / external human dose Given animal evidence of early-life sensitivity to vinyl chloride, a factor of 2 was applied to the oral SF of 2.4E-01 $(mg/kg_{BW}\text{-}day)^{-1}$ for exposure during adulthood, to account for continuous lifetime exposure from birth (HC, 2013c).	Cancer (liver [hepatocellular angiosarcomas and carcinomas])	CEPA: known human carcinogen (EC and HC, 2016) IARC: Group 1 carcinogenic to humans (IARC, 2012b) US EPA IRIS: Group A carcinogenic to humans (US EPA, 2000b)	HC, 2013c (based on Feron et al., 1981)
	Inhalation UR [US EPA (2000b): should not be used for exposures >10 mg/m^3]	4.4E-03 $(mg/m^3)^{-1}$ for continuous lifetime exposure during adulthood 8.8E-03 $(mg/m^3)^{-1}$ for continuous lifetime exposure from birth	**Study Type:** chronic **Species:** Sprague-Dawley female rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** 0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, 6000, or 10 000 ppm (0, 2.6, 12.8, 25.6, 63.9, 128, 256, 383, 511, 639, 1278, 6390, 15 340, 25 560 mg/m^3) vinyl chloride, 4 hours/day, 5 days/week **Duration:** 52 weeks **Uncertainty Factors:** N/A A two-fold safety factor was applied to the adult value to account for continuous lifetime exposure from birth.	Based on the 95% upper confidence limit on excess cancer risk in female rats	PBPK model and linearized multistage model	Cancer (liver [angiosarcomas, angiomas, hepatomas, and neoplastic nodules])		US EPA, 2000b (based on Maltoni et al., 1981 and 1984)

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Xylenes, mixed isomers	Oral TDI	1.3E-02 mg/kg_{BW}-day	**Study Type:** subchronic **Species:** male Wistar rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** a control group and 3 exposure groups: 1) m-xylene concentrations of 50 ppm (217 mg/m^3) and 100 ppm (435 mg/m^3), or 2) n-butyl alcohol 50 ppm (154 mg/m^3) and 100 ppm (308 mg/m^3), or 3) a 1:1 mixture of m-xylene and n-butyl alcohol (100 ppm [217 mg/m^3 m-xylene + 154 mg/m^3 of n-butyl alcohol] and 200 ppm [435 mg/m^3 m-xylene + 308 mg/m^3 of n-butyl alcohol]), 6 hours/day, 5 days/week **Duration:** 3 months **Uncertainty Factors:** 75 (10 for intraspecies variability, 2.5 for interspecies variability, and 3 for use of a subchronic study)	NOAEL = 50 ppm (217 mg/m^3) m-xylene	PBPK modeling to estimate internal rat blood concentration corresponding to NOAEL of 50 ppm = 0.138 mg/L + Conversion to external oral human dose using human PBPK model and assuming ingestion of 1.5 L drinking water/day $NOAEL_{HEC}$ = 1.0 mg/kg_{BW}-day $TDI = NOAEL_{HEC}/UF$	Neurotoxicity (impaired motor coordination)	CEPA: Group IV unlikely to be carcinogenic to humans (EC and HC, 1993h) IARC: Group 3 not classifiable as to its carcinogenicity to humans (IARC, 1999a) US EPA IRIS: inadequate information to assess carcinogenic potential (US EPA, 2003b)	HC, 2014b (based on Korsak et al., 1994)
	Inhalation TC	1.0E-01 mg/m^3	**Study Type:** subchronic **Species:** male Wistar rats **Mode of Administration:** inhalation (whole body exposure chambers) **Exposure Regime:** a control group and 3 exposure groups: 1) m-xylene concentrations of 50 ppm (217 mg/m^3) and 100 ppm (435 mg/m^3), or 2) n-butyl alcohol 50 ppm (154 mg/m^3) and 100 ppm (308 mg/m^3), or 3) a 1:1 mixture of m-xylene and n-butyl alcohol (100 ppm [217 mg/m^3 m-xylene + 154 mg/m^3 of n-butyl alcohol] and 200 ppm [435 mg/m^3 m-xylene + 308 mg/m^3 of n-butyl alcohol]), 6 hours/day, 5 days/week **Duration:** 3 months **Uncertainty Factors:** 300 (10 for intraspecies human variability, 3 for interspecies variability, 3 for extrapolation from subchronic to chronic duration, and 3 for database uncertainties)	NOAEL = 50 ppm (217 mg/m^3)	NOAEL adjusted for continuous exposure and difference in blood/gas partitioning in rats vs humans $NOAEL_{HEC}$ = 39 mg/m^3 $TC = NOAEL_{HEC}/UF$	Neurotoxicity (impaired motor coordination)		HC, 2018a (based on US EPA, 2003b [derived from Korsak et al., 1994])

Substance	Type of TRV	TRV Value	Study Details	Threshold/ Non-threshold Endpoint	TRV Derivation Method	Critical Effect(s)	Carcinogenicity Classification	Source
Zinc	UL (HC) 0 to <6 mo 6 mo to <5 yrs 5 to <12 yrs 12 to <20 yrs ≥20 years	mg/kg_{BW}-day 4.9E-01 4.8E-01 5.1E-01 5.4E-01 5.7E-01	**Yadrick et al., 1989 (adults)** **Study Type:** epidemiological (prospective) **Species:** humans (adult women) **Mode of Exposure:** dietary supplements **Exposure Concentrations:** 10 mg/day (estimated dietary intake) + supplemental intake of 50 mg/day as zinc gluconate **Duration:** 10 weeks **Uncertainty Factors:** 1.5 (for intraspecies variability and extrapolation from a LOAEL to a NOAEL)	LOAEL = 60 mg/day (adults)	UL (IOM) = LOAEL/UF for intake of zinc from food, water, and supplements IOM adult ULs were adjusted to account for differences in HC's adult age group (HC, 2010)	Decrease in erythrocyte superoxide dismutase (ESOD) activity (sensitive indicator of copper status, reflecting copper utilization and the risk of copper deficiency)	CEPA: see 2019 (draft) CMP assessment (ECCC and HC, 2019c) IARC: not assessed US EPA IRIS: Group D not classifiable as to human carcinogenicity (US EPA, 2005d)	IOM, 2001 (based on Yadrick et al., 1989, and Walravens and Hambidge, 1976)
			Walravens and Hambidge, 1976 (infants, children, and adolescents) **Study Type:** epidemiological (prospective) **Species:** humans (infants, 0-6 months) **Mode of Exposure:** dietary supplements **Exposure Concentrations:** control group: formula with 1.8 mg zinc/L; exposure group: formula with 1.8 mg zinc/L + supplement with 4 mg zinc/L (total of 5.8 mg zinc/L) **Duration:** 6 months **Uncertainty Factors:** 1 (because of a lack of evidence that formula intakes of 5.8 mg zinc/L result in infant toxicity)	NOAEL = 5.8 mg/L (infants)	NOAEL adjusted for estimated average human milk intake of 0.78 L/day $NOAEL_{adj}$ = 4.5 mg/day Infant UL (IOM) = $NOAEL_{adj}$/UF = 4.5 mg/day (4 mg/day rounded down) IOM derived ULs for older infants, children, and adolescents based on the infant UL and relative body weight IOM ULs were adjusted to account for differences in HC's age groups (HC, 2010)	No effects of zinc on serum copper or cholesterol concentrations or other adverse effects were found		

NOTES:

mg/kg_{BW}-day = milligrams per kilogram of body weight per day, $(mg/kg_{BW}\text{-day})^{-1}$ = per milligram per kilogram of body weight per day, mg/m^3 = milligrams per cubic metre, $(mg/m^3)^{-1}$ = per milligram per cubic metre

N/A: not applicable

[1] HC has not derived a TRV for lead. Based on the available scientific literature, no threshold of effect could be established for the identified critical effect for lead (neurodevelopmental toxicity). HC (2013d,e) therefore recommended that lead be considered a non-threshold substance. The risk-specific dose from EFSA (2013) is recommended as a provisional TRV.

[2] PCDDs, PCDFs, and dioxin-like PCBs are assessed by converting their concentrations to units of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) TEQs using TEFs. These TEFs are published in van den Berg et al., 2006. The sum of the TEQs is then compared to the TDI for 2,3,7,8-TCDD.

ACRONYMS FOR **APPENDIX A**

ADAF	age-dependent adjustment factor
BMC	benchmark concentration
BMCL	benchmark concentration lower limit of a one-sided 95% confidence interval on the BMC
BMD	benchmark dose
BMDL	benchmark dose lower limit of a one-sided 95% confidence interval on the BMD
$BMDL_{01/05/10}$	lower 95% confidence limit on a benchmark dose associated with a 1%, 5%, or 10% response
BW	body weight
CF	conversion factor
CMP	Chemicals Management Plan
DWEL	drinking water equivalent level
EHMI	equivalent human monthly intake
ESOD	erythrocyte superoxide dismutase
HEC	human equivalent concentration
HEQ	human equivalent
IR_w	water ingestion rate
LEC	lowest effect concentration
LOAEL	lowest observable adverse effect level
MF	modifying factor
NOAEL	no observable adverse effect level
PBPK	physiologically based pharmacokinetic (model)
PND	postnatal day
POD	point of departure
pTDI	provisional tolerable daily intake
pTMI	provisional tolerable monthly intake
pTWI	provisional tolerable weekly intake
RfC	reference concentration
RfD	reference dose
SF	slope factor
TC	tolerable concentration
TC_{05}	tumorigenic concentration found to induce a 5% increase in the incidence of, or deaths due to, tumours considered to be associated with exposure
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalent

TRV	toxicological reference value
UF	uncertainty factor
UL	tolerable upper intake level (for essential elements)
UR	unit risk

ACRONYMS FOR TRV SOURCES

ATSDR	Agency for Toxic Substances and Disease Registry
BCL	Battelle's Columbus Laboratories
CCME	Canadian Council of Ministers of the Environment
CDHS	California Health and Human Services Agency's Department of Health Services
CEPA	*Canadian Environmental Protection Act*
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
HC	Health Canada
EC	Environment Canada
ECB	European Chemicals Bureau
ECCC	Environment and Climate Change Canada
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization (United Nations)
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine of the National Academies
IRIS	Integrated Risk Information System (US EPA)
JBRC	Japan Bioassay Research Centre
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OEHHA	California Environmental Protection Agency's Office of Environmental Health Hazard Assessment
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

UNITS

g/kg$_{BW}$	grams per kilogram of body weight
kg	kilograms
L/day	litres per day
mg/day	milligrams per day
mg/L	milligrams per litre
mg/kg$_{BW}$	milligrams per kilogram of body weight
mg/kg$_{BW}$-day	milligrams per kilogram of body weight per day
(mg/kg$_{BW}$-day)$^{-1}$	per milligram per kilogram of body weight per day
mg/m^3	milligrams per cubic metre
(mg/m^3)$^{-1}$	per milligram per cubic metre
µg/day	micrograms per day
µg/g	micrograms per gram
µg/kg$_{BW}$	micrograms per kilogram of body weight
µg/kg$_{BW}$-day	micrograms per kilogram of body weight per day
µg/L	micrograms per litre
(µg/L)$^{-1}$	per microgram per litre
µg/m^3	micrograms per cubic metre
ng/kg$_{BW}$	nanograms per kilogram of body weight
ng/kg$_{BW}$-day	nanograms per kilogram of body weight per day
pg/kg$_{BW}$	picograms per kilogram of body weight
pg/kg$_{BW}$-day	picograms per kilogram of body weight per day
pg/kg$_{BW}$-month	picograms per kilogram of body weight per month
ppm	parts per million
(ppm)$^{-1}$	per part per million

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