Note To Readers:

The following errors were identified after publication.

The units for selenium and molybdenum are presented in µg/kg-d in Table 1. To convert the units to mg/kg-d, the values in the Table need to be divided by 1,000.

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Part II:

Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors, Version 2.0

Federal Contaminated Site Risk Assessment in Canada

Canada

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FEDERAL CONTAMINATED SITE RISK ASSESSMENT IN CANADA

PART II:
HEALTH CANADA TOXICOLOGICAL REFERENCE VALUES (TRVs) AND CHEMICAL-SPECIFIC FACTORS

Version 2.0

September 2010

Prepared by:
Contaminated Sites Division
Safe Environments Directorate

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PREFACE

The Federal Contaminated Sites Action Plan (FCSAP) is a program of the Government of Canada designed to ensure improved and continuing federal environmental stewardship as it relates to contaminated sites located on federally owned or operated properties. Guidance documents on human health risk assessment (HHRA) prepared by the Contaminated Sites Division of Health Canada, in support of the FCSAP, are available on our website and may also be obtained by contacting the Contaminated Sites Division at cs-sc@hc-sc.gc.ca.

This guidance document (*Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors, Version 2.0*) is a companion to *Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA)*, *Version 2.0*, and was prepared to provide guidance for custodial departments.

As is common with any national guidance, this document will not satisfy all of the requirements presented by contaminated sites, custodial departments, or risk assessors in every case. As the practice of risk assessment advances and the 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. Health Canada should be consulted at the address below to confirm that the version of the document in your possession is the most recent edition, and that the most recent assumptions and parameters are being used.

In addition, Health Canada requests that any questions, comments, criticisms, suggested additions, or revisions to this document be directed to Contaminated Sites Division, Safe Environments Directorate, Health Canada, 99 Metcalfe Street, 11th Floor, Address Locator: 4111A, Ottawa, ON, K1A 0K9. E-mail: cs-sc@hc-sc.gc.ca.

See also: http://www.hc-sc.gc.ca/ewh-semt/contamsite/index-eng.php.

SUMMARY OF REVISIONS

Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors, Version 2.0 reflects numerous revisions to text and tables, relative to Version 1.0. Significant technical revisions to this document include:

- significant additions to the text to enhance background and contextual information, including links to sources of toxicological reference values (TRVs) from other agencies;
- new procedures for establishing TRVs for essential trace elements, with explanatory text;
- additions of new or revised TRVs to Table 1. Toxicological Reference Values (TRVs) Recommended for use in Human Health Risk Assessments of Federal Contaminated Sites:
  - arsenic (revised oral slope factor)
  - benzene (revised oral slope factor)
  - benzo[*a*]pyrene (dermal slope factor)
  - carbon tetrachloride (revised tolerable daily intake)
  - fluoride (revised tolerable daily intake)
  - n-hexane (provisional tolerable daily intake)
  - nickel sulphate (revised tolerable daily intake)
  - non-dioxin-like polychlorinated biphenyls (PCBs) (revised tolerable daily intake)
  - trichloroethylene (TCE) (new tolerable daily intake, new oral slope factor)
- addition of Table 2. Toxicological Reference Values (TRVs) for Pesticides Recommended for Use in Human Health Risk Assessments of Federal Contaminated Sites;
- addition of Table 3. Soil Dermal Relative Absorption Factors (RAF_{Derm}) of Selected Chemical Substances; and
- addition of Table 4. Sources of Physical–Chemical Property Data in the Health Canada PQRA Spreadsheet Tool.

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ABBREVIATIONS AND ACRONYMS

AROI	acceptable range of oral intake
ATSDR	Agency for Toxic Substances and Disease Registry (United States)
DRI	dietary reference intake
DQRA	detailed quantitative risk assessment
ETE	essential trace element
FCSAP	Federal Contaminated Sites Action Plan
IOM	Institute of Medicine of the National Academies
IRIS	Integrated Risk Information System (U.S. EPA)
LOAEL	lowest observable adverse effect level
NOAEL	no observable adverse effect level
OMOE	Ontario Ministry of the Environment
PMRA	Pest Management Regulatory Agency (Canada)
PQRA	preliminary quantitative risk assessment
RAF	relative absorption factor
RDA	recommended dietary allowance
RfD	reference dose
SF	slope factor
TDI	tolerable daily intake
TRV	toxicological reference value
UF	uncertainty factor
UL	tolerable upper intake level
UR	unit risk
U.S. EPA	United States Environmental Protection Agency
VOCs	volatile organic compounds
WHO	World Health Organization

1.0 INTRODUCTION

Toxicological reference values (TRVs) are prescribed by a variety of national and international agencies for the purpose of characterizing risks associated with exposure to environmental contaminants. For chemicals and substances that are not carcinogenic or germ cell mutagens, the TRV is the daily dose that is deemed to be tolerable or acceptable (i.e. the dose that is "safe"), based on the assumption that a threshold dose exists at or below which toxic effects do not occur. For substances that are genotoxic (certain carcinogens and germ cell mutagens), the TRV represents an upper bound estimate of the slope between exposure and the occurrence of effect (cancer, in most cases). The slope of the dose-response relationship is referred to as the slope factor (SF) (relating to exposure dose) or unit risk (UR) (relating to exposure concentration, typically in air or in some cases in water) and, when multiplied by the exposure level (dose or concentration as appropriate), it provides an upper bound estimate of the probability of occurrence of cancer or germ cell mutation in a chronically exposed population. For the assessment of risks posed by federal contaminated sites in Canada, that negligible risk level for cancer and germ cell mutation is 1 in 100,000 persons exposed (1×10^{-5}; see *Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA)*, *Version 2.0* (HC, 2010a) for more discussion of negligible risk).

Sources of TRVs include, but may not be limited to

- Health Canada – various sources including:
  - http://www.hc-sc.gc.ca/ewh-semt/pubs/contamsite/index-eng.php
  - http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/eval-prior/index-eng.php
  - http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/index-eng.php
- United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS)
  - www.epa.gov/iris/

  TRVs are generally identified by the U.S. EPA as reference doses (RfDs), reference concentrations (RfCs), oral slope factors (SF_{Oral}), inhalation slope factors (SF_{Inh}), and inhalation unit risks (UR_{Inh}),
- California Environmental Protection Agency http://www.oehha.ca.gov/risk/ChemicalDB/index.asp

The Agency employs the same general terminology as the U.S. EPA.

- World Health Organization (WHO) and the International Programme on Chemical Safety (IPCS) – various sources including:
  - http://www.inchem.org/; http://www.who.int/ipcs/en/
  - http://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) or acceptable daily intakes (ADIs). Although carcinogenic effects are evaluated, TRVs for carcinogenic substances are not routinely prescribed as SFs or URs.
- United States Agency for Toxic Substances and Disease Registry (ATSDR)
  - http://www.atsdr.cdc.gov/toxprofiles/index.asp

  TRVs are generally identified by the ATSDR as minimal risk levels (MRLs). MRLs are not generally prescribed by the ATSDR on the basis of carcinogenic effects or risks.

2.0 HEALTH CANADA TOXICOLOGICAL REFERENCE VALUES (TRVS)

2.1 Toxicological Reference Values for Environmental Contaminants

For the assessment of risks posed by chemicals and substances found at federal contaminated sites in Canada, Health Canada TRVs should be employed, when available, for the characterization of potential health risks. Health Canada TRVs for environmental contaminants, excluding those that are also considered as essential trace elements (ETEs) or that are, or have been registered pesticides in Canada, are presented in Table 1. The means by which Health Canada establishes these TRVs are described elsewhere (see *Federal Contaminated Site Risk Assessment in Canada, Part V: Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals ($DQRA_{Chem}$)* (HC, 2010b); see also HC, 1994, 1995).

The TRVs presented in Table 1 are recommended for exposures of chronic duration. At this time, Health Canada does not prescribe TRVs for exposures of less-than-chronic (acute, subchronic) duration. Short-term TRVs from other regulatory jurisdictions may be used in risk assessments of federal contaminated sites, with technical rationale provided in the report.

2.2 Toxicological Reference Values for Essential Trace Elements

Recommended TRVs for ETEs are also presented in Table 1.

The Contaminated Sites Division of Health Canada has adopted an approach for establishing TRVs for ETEs that better reflects the understanding of the benefits and risks posed by these substances; this approach is consistent with their designation and assessment as essential elements. For potential risks posed at federal contaminated sites in Canada from exposure to contaminants also considered to be ETEs, the Contaminated Sites Division recommends the use of the tolerable upper intake level (UL) as the reference exposure level for contaminated site risk assessment. In other words, the UL is to be interpreted and applied as the TDI or the RfD for ingestion exposure. UL values published by the Institute of Medicine of the National Academies (IOM) (IOM, 2000, 2001) are used. Adjustments for relative bioavailability may be necessary when considering exposure via foods for the UL versus exposure via soil and/or water ingestion for the contaminant dose; gastrointestinal absorption of an ETE may be more or less efficient from soil or water than from food. Absorption may also be subject to physiological regulation.

Please be aware that use of the UL to assess the non-carcinogenic risks of an ETE does not preclude or nullify the need to quantify cancer risks for ETEs that may also be considered carcinogenic.

2.2.1 Rationale for essential trace element toxicological reference values

Some elemental contaminants found at federal contaminated sites are also considered to be ETEs by nutritionists. For example, the World Health Organization (WHO) considers the following trace elements as essential in human nutrition: iron (FAO/WHO, 1988), zinc, copper, chromium, iodine, cobalt, molybdenum, and selenium (WHO, 1996, 2002). Manganese is now fully recognized as essential to human health (IOM, 2001). There is also a growing body of evidence that silicon (Si), boron (B), nickel (Ni), and vanadium (V) play essential metabolic roles in some species, possibly in humans, and these have been considered to be probable ETEs by the WHO (1996). Arsenic (As) was also added to this list by the IOM (2001). At the present time, however, there is a paucity of human data on the ULs for probable ETEs. Therefore, until further notice by Health Canada, exposure to the probable ETEs should be assessed using the typical approach for contaminants in environmental samples from contaminated sites, and their toxicological evaluations should be based on the TRVs presented in Table 1 or elsewhere.

An absence or a deficiency of an ETE in the diet produces functional or structural abnormalities associated with biochemical changes that can be reversed by an adequate supplementation of the ETE (e.g. WHO, 1996; Mertz, 1980). Conversely, an excess of intake of an ETE may present risks of toxicity as demonstrated with well-established TDIs or RfDs. For both the RfD and the TDI, the underlying assumption that a zero intake is without risk is an inappropriate proposition for ETEs (WHO, 2002). Moreover, it has been recently demonstrated that TDIs or RfDs for ETEs can be overly conservative when compared to dietary reference intakes (DRIs) established by the Food and Nutrition Board of the IOM (IOM, 2000, 2001). In some instances, when the same data sets are used to develop both TDIs and DRIs, the TDI values tend to overestimate risk (Goldhaber, 2003). Hence, overestimating the toxicity of ETEs at contaminated sites may become costly when ETEs are drivers for site management, including remediation.

A framework for dietary allowances and recommendations has been developed by the Expert Advisory Committee on Dietary Reference Intakes (DRI Committee) in close collaboration with Health Canada (IOM, 2000, 2001). Thus, the DRIs are applicable to healthy Canadian (and American) populations. The DRIs for ETEs consider bioavailability as well as all nutrient and dietary interactions (e.g. Mertz, 1995; WHO, 2002; IOM, 2000, 2001). DRIs are normally developed for specific age and gender groups and physiological states for almost all population groups (IOM, 2000, 2001). Hence, different values can protect subpopulation groups at risk without being overprotective for the rest of the general population (Mertz, 1998; Munro, 1999).

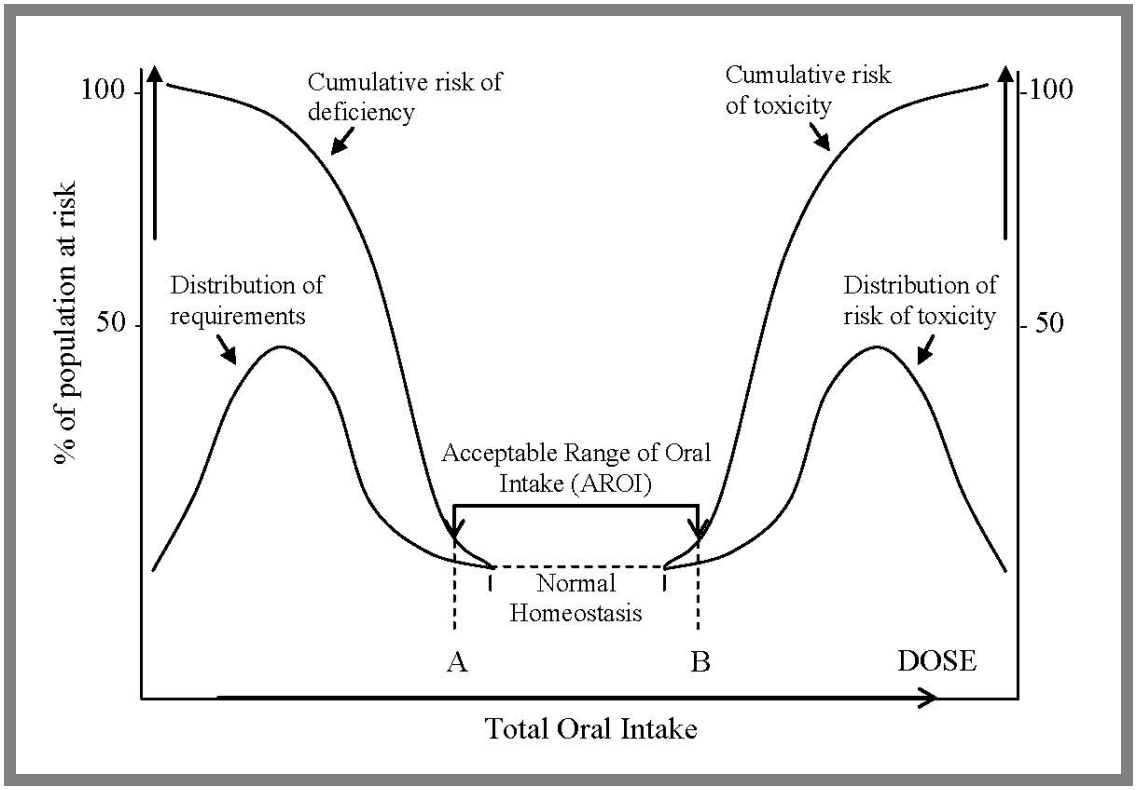
For each ETE, there is a safe range of intakes between deficiency and toxicity that is generally represented by a U-shaped “dose-response” curve as shown in Figure 1 (WHO, 1996; Abernathy, 1999; Becking, 1998). However, this curve is more a risk probability curve derived from a series of curves from various population groups (Becking, 1998). The area under the curve between points A and B represents an acceptable range of oral intake (AROI), including food and water, which is maintained under homeostasis in healthy populations (IOM, 2000, 2001). However, it should be noted that values below point A or above point B are not absolute values where deficiency or toxicity are necessarily encountered in a population group; nutrient needs vary considerably among individuals (Abernathy, 1999; Becking, 1998). The DRI values within the AROI include the following, as defined by the IOM (2000, 2001):

- 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 (AI): 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 (EAR): average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group

- 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.

ULs are not specific data points from any particular dose-response study, but are derived using well-established principles of the risk assessment methodology (WHO, 2002). Various data sources, such as epidemiological studies with excessive ETE intake, clinical trials, and experimental studies, can be all used in the risk characterization to derive ULs (WHO, 1996, 2002; IOM, 2000, 2001). Adverse health effects of endpoints from excessive nutrient intakes such as a no observable adverse effect level (NOAEL) and/or a lowest observable adverse effect level (LOAEL) are identified and used for the derivation of ULs for chronic daily intake of ETEs (IOM, 2000, 2001). Uncertainty factors (UFs) are applied to NOAELs and/or LOAELs in the calculation of ULs (WHO, 2002). However, these UFs tend to be much lower than those traditionally used to establish TDIs or RfDs while remaining fully protective (Mertz, 1995). UFs used to establish ULs are usually much less than 10 owing to the availability of reliable human data (Becking, 1998; Dourson et al., 2001; Munro, 1999). ULs must consider risks from both nutrient deficiencies and toxicity, as well as variability among individuals (WHO, 2002). The use of large UFs may conceivably lead to a reference intake potentially associated with nutritional deficiencies. ULs are not recommended levels of intake; there are generally no benefits observed in individuals ingesting ETEs at levels above the RDA (e.g. WHO, 2002; Munro, 1999).

Figure 1 Percentage of Population at Risk of Deficiency or Toxic Effects from Oral Intake



Source: WHO, 2002.

As discussed previously, a traditional TDI or RfD for an ETE can be overly conservative when compared to the UL value. This problem is demonstrated with zinc as an example in Figure 2.

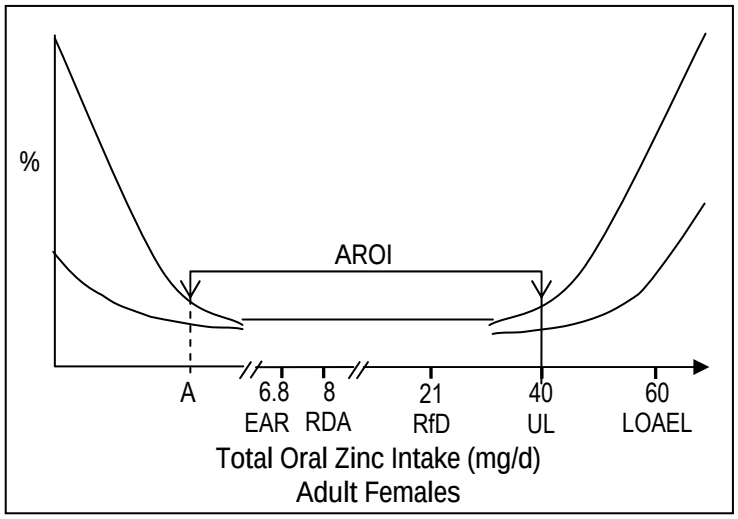
Figure 2 Comparison of the Tolerable Upper Intake Level (UL) and the Reference Dose (RfD) for Zinc

Zinc RDA:
Adult males: 11 mg/d
Adult females: 8 mg/d

Zinc AI:
not available

Zinc EAR:
Adult males: 9.4 mg/d
Adult females: 6.8 mg/d

Zinc median content of U.S. diet:
Adult males: 14 mg/d
Adult females: 9 mg/d



Total Daily Intake (mg/d)
Adult Women

Zinc UL:
Adults: 40 mg/d (0.6 mg/kg bw/d; assumed adult bw = 70 kg), based on a study on the effect of zinc gluconate supplementation on the copper balance status of 18 healthy adult females for 10 weeks; LOAEL: 60 mg/d, based on significantly lower erythrocyte superoxide dismutase (ESOD) activity; UF: 1.5, to account for inter-individual sensitivity and for extrapolation from a LOAEL to a NOAEL; a higher UF could not be justified because reduced copper status is rare in humans (IOM, 2001).

Zinc U.S. EPA RfD:
Adults: 21 mg/d (0.3 mg/kg bw/d), based on a clinical study on the effects of oral supplementation on copper and zinc balance; LOAEL: 1 mg/kg bw/d, based on a 47% decrease in ESOD concentration in adult females after 10 weeks of supplementation; UF: 3, based on duration of study (moderate) and sensitive humans] (IRIS database).

Note: AROI, acceptable range of oral intake; EAR, estimated average requirement; IA, adequate intake; LOAEL, lowest observable adverse effect level; RDA, recommended dietary allowance; RfD, reference dose; UF, uncertainty factor; UL, tolerable upper intake level.

Source: after Sandstead, 1995.

2.3 Toxicological Reference Values for Pesticides

In Canada, the Pest Management Regulatory Agency (PMRA) is responsible for the evaluation and approval of pesticides used in Canada. To that end, evaluations are routinely completed on new and existing pesticides. TRVs are established by that agency, or are endorsed and adopted from other agencies with which PMRA has harmonized their pesticide evaluation process.

Table 2 presents ADIs or other TRVs (as appropriate) for pesticides or former pesticides that may no longer be used or approved for use in Canada. Those derived by or endorsed by PMRA are indicated; TRVs for former pesticides are drawn from other sources (as indicated in Table 2) because they are no longer evaluated by PMRA.

3.0 RELATIVE ABSORPTION FACTORS (RAF_{ORAL}, RAF_{INH}, RAF_{DERM})

A relative absorption factor (RAF) may be used to account for differences in the efficiency of chemical absorption from different exposure media (food, soil, or water) and exposure routes (ingestion, skin contact, and inhalation) in a human exposure scenario as compared to the toxicity study used to derive the TRV. A RAF of 1 (i.e. 100%) does not therefore indicate absorption is complete, but rather absorption from environmental exposure is considered equivalent to absorption in the principal study upon which the TRV is based. RAFs depend on the unique physical–chemical properties of each contaminant and the exposure scenario; therefore, they are contaminant specific, exposure pathway specific, and chemical species specific.

Where route-specific TRVs are available, the fraction of soil-borne, foodborne, or drinking waterborne chemical absorbed will generally be assumed to be equivalent to the fraction absorbed in the principal toxicological study upon which the TRV for that route was based (i.e. relative absorption is assumed to be 1). Adjustments may be applied for dermal exposure (see section 3.3) or where site-specific bioavailability and/or bioaccessibility data are available (see *Federal Contaminated Site Risk Assessment in Canada, Part V: Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals (DQRA$_{Chem}$)*(HC, 2010b).

3.1 Oral Exposures

Unless site-specific data have been collected, oral exposures should be assumed to have a relative absorption factor of 1 for comparison with an oral TRV:

$$RAF_{Oral} = \frac{\text{fraction of chemical absorbed orally}}{\text{fraction absorbed in principal study}} = 1$$

Similarly, where oral exposures are characterized with inhalation TRVs, a $RAF_{Oral} = 1$ will generally be assumed unless there is evidence (with references provided) that oral absorption is significantly greater ($RAF_{Oral} > 1$) or less ($RAF_{Oral} < 1$) than that for inhalation exposure in the TRV principal study.

3.2 Inhalation Exposures

A comprehensive set of RAF values for inhalation exposures is not currently available. The inhalation RAF (RAF_{Inh}) will therefore default to 1 in all cases when inhalation exposures are being compared to an inhalation-specific TRV:

$$RAF_{Inh} = \frac{\text{fraction of chemical absorbed by inhalation}}{\text{fraction absorbed in principal study}} = 1$$

Where inhalation exposures are being summed with oral exposures for risk characterization using an oral-specific TRV, the inhalation RAF (RAF_{Inh}) will generally default to 1 unless there is evidence (with references provided) that respiratory absorption is significantly greater ($RAF_{Inh} > 1$) or less ($RAF_{Inh} < 1$) than for oral exposure in the TRV principal study.

3.3 Dermal Exposures

At the present time, a route-specific TRV for dermal exposure is only available for benzo[*a*]pyrene. The dermal TRV (see Table 1) should be used to characterize health risk from dermal exposure to benzo[*a*]pyrene in soil. The dermal relative absorption factor (RAF_{Derm}) for benzo[*a*]pyrene (see Table 3) accounts for the difference in absorption efficiency in humans from soil and in animals in the principal study used to derive the dermal TRV, and should be applied in the exposure estimation.

The dermal relative absorption factor (RAF_{Derm}) is calculated as follows:

$$RAF_{Derm} = \frac{\text{fraction of chemical absorbed through the skin}}{\text{fraction absorbed in principal study}} = 1$$

For chemicals with no dermal TRV, it is a common practice to characterize health risk from dermal exposure to soil by estimating the systemically absorbed dose and combining this with ingestion exposure for comparison to an oral TRV. The dermal absorption of many contaminants is typically 10% or less, whereas absorption following ingestion of the same contaminants may be at or near 100%. As a result, adjustments leading to RAF_{Derm} of < 1 will normally be applied to account for the differences in absorption between dermal exposure to soil and the principal toxicity study used to derive the oral TRV.

The RAF_{Derm} can be calculated using the same equation. Note that for these chemicals, the denominator represents the chemical absorption efficiency in the principal study used to derive the oral TRV. For example, if dermal absorption was 10% and oral absorption in the principal study was 100%, the RAF_{Derm} would be 10% ÷ 100% = 10%. However, if oral absorption in the principal study was only 50%, then the RAF_{Derm} would be 10% ÷ 50% = 20%.

After adjusting for absorption efficiency relative to the TRV principal study, the dermal exposure doses are generally summed with oral exposure doses, and the resulting combined value is compared to the oral TRV for risk characterization.

Recommended RAF_{Derm} values (dermal absorption of chemical from soil relative to oral absorption in the principal study used to derive oral TRV) are provided in Table 3. Unless otherwise indicated, the RAF_{Derm} values were obtained from the Ontario Ministry of the Environment (OMOE) (OMOE, 2009); RAF_{Derm} values for the petroleum hydrocarbon fractions were obtained from the Canadian Council of Ministers of the Environment (CCME, 2008). The OMOE (2009) identified estimates of absorption for the animal species and the dosing medium used in the TRV principal study, and compared these values to dermal absorption data for soil. Reviews from agencies and/or organizations such as the U.S. EPA, in particular *Risk Assessment Guidance for Superfund (RAGS), Volume I: Human Health Evaluation Manual* (Part E, Supplemental Guidance for Dermal Risk Assessment) (U.S. EPA, 2004), National Environmental Policy Institute (NEPI, 2000a, 2000b), the California Environmental Protection Agency (Cal EPA, 2000), the Massachusetts Department of Environmental Protection (MassDEP, 1992), and the ATSDR Toxicological Profiles database (http://www.atsdr.cdc.gov/toxprofiles/index.asp)) were used to obtain literature-derived advice and estimates

of absorption. If absorption estimates were not sufficient or available from reviews, primary literature was consulted.

The OMOE (2009) calculated RAF_{Derm} values using the preceding RAF_{Derm} equation, with the following modifications applied as necessary:

- A default of 100% oral absorption in the TRV principal study was applied to all organic compounds not reviewed by the major agencies.
- Oral absorption in the principal study was assumed to be complete (100%) for any contaminant if estimated to be near complete (>50%) in the literature.
- The default of 10% dermal absorption for semi-volatile organic compounds was based upon representative experimental values for this chemical class, as obtained from the U.S. EPA (2004, Exhibit 3-4).
- The default value of 3% dermal absorption from soil was used for all volatile organic compounds (VOCs), based on the analysis of the U.S. EPA (1995). Oral absorption in the principal study (upon which the TRV is based) was estimated to be 100% for most VOCs.
- For several inorganics, the quantitative data were considered insufficient to estimate chemical-specific dermal absorption fractions. The value of 1% was assigned to these inorganics, based on an analysis of other inorganics deemed to have sufficient data. The assigned value is equal to the geometric mean of the midpoints of the range of dermal absorption values that the U.S. EPA (2004), the California Environmental Protection Agency (Cal EPA, 2000), New York State (NYS, 2006), and the Massachusetts Department of Environmental Protection (MassDEP, 1992) have estimated for dermal absorption for arsenic, cadmium, chromium, mercury, nickel, and silver from chemical-specific data.
- An order-of-magnitude approach was sometimes used to determine a dermal RAF of 1%, 10%, or 100% where:
    - the dermal absorption of a contaminant could be significant but is not quantified;
    - the dermal absorption is not quantified, but is qualified relative to oral absorption;
    - the range of reported absorption factors is considerably wide; or
    - a dermal absorption rate has been determined by default and is approximately an order of magnitude lower than the estimated oral absorption.

The OMOE (2009) has not provided a value for *n*-hexane. However, applying the OMOE process to determine RAF_{Derm} for VOCs results in an estimated value of 3% for *n*-hexane.

For polycyclic aromatic hydrocarbons (PAHs), the OMOE (2009) adopted the recommendation of the U.S. EPA (2004, Exhibit 3-4) for a dermal absorption of 13%, based on Wester et al. (1990). However, research has been conducted by Health Canada (Moody et al., 2007), specifically on the dermal absorption of benzo[*a*]pyrene from soil by viable human skin. The value of total absorption (receiver + skin depot) of 14.8% determined by Moody et al. (2007) is recommended herein for the dermal absorption of soil-borne benzo[*a*]pyrene. Consistent with the approach applied to other PAHs by the OMOE (2009), the default RAF_{Derm} for all PAHs was set to the same value as for benzo[*a*]pyrene .

For nickel (Ni) and mercury (Hg), research has been conducted by Health Canada (Moody et al., 2009), specifically on the dermal absorption of these elements from soil by viable human skin. Values of total absorption (receiver + skin depot) of 1.0% for Ni and 46.6% for Hg were determined. For Ni, a recommended RAF_{Derm} value of 0.091 was calculated by dividing 1% (absolute dermal absorption value: Moody et al., 2009) by 11% (oral bioavailability: Ishimatsu et al., 1995). For Hg, a RAF_{Derm} of 1 was recommended; this value was based on the absolute dermal absorption (46.6%) determined in the Moody et al. (2009) study on viable human skin—a value similar to the range of oral absorption of $HgCl_2$ in water (30%–40%) in male rats (Morcillo and Santamaria, 1995).

Additional RAF_{Derm} values for substances that are not listed in Table 3 may be obtained from the sources listed at the beginning of this section, as well as the Risk Assessment Information System (RAIS; http://rais.ornl.gov) or other authoritative sources. Where alternate data sources are used, they must be clearly cited and fully referenced.

Dermal absorption of contaminants from contact with water during activities such as bathing, swimming, and showering should be derived employing dermal permeability constants (P_{Derm}) and methods described by the U.S. EPA (1992). Values for P_{Derm} can be found in U.S. EPA (2004).

4.0 PHYSICAL–CHEMICAL PROPERTIES OF CONTAMINANTS

Environmental fate models, or other predictive models, are often employed within preliminary quantitative risk assessments (PQRAs) and detailed quantitative risk assessments (DQRAs) to predict contaminant concentrations in various media down-gradient of the site or in the future. Likewise, models may be employed to predict the concentration of a contaminant in one environmental medium based on the measured concentration in soil or groundwater, when direct measurements for the medium of interest (such as plants, indoor air, etc.) have not been made. Other uses of models include:

- to predict the environmental fate of contaminants;
- to predict the concentration of a contaminant in groundwater as a result of leaching from contaminated soil;
- to predict the concentration of a contaminant in indoor air as a result of vapour migration from contaminated soil and/or groundwater;
- to predict the concentration of a contaminant in vegetation and/or terrestrial animals resulting from contaminated soil; and
- to predict the concentration of a contaminant in fish or other aquatic organism resulting from contaminated surface water and/or contaminated sediment.

Such modelling employs the physical–chemical properties of the contaminant as input variables to an equation. A variety of published and on-line sources of physical–chemical properties of contaminants are available. Physical–chemical property values routinely employed by the Contaminated Sites Division of Health Canada for selected chemical substances are presented in the PQRA Spreadsheet Tool for Human Health Preliminary Quantitative Risk Assessment (HC, unpublished). If a chemical of interest is not listed in the PQRA Spreadsheet Tool for Human Health Preliminary Quantitative Risk Assessment, sources of additional information on physical–chemical properties are presented in Table 4.

5.0 SUMMARIES OF TOXICOLOGICAL REFERENCE VALUE STUDIES

A brief summary of the key health concern(s) associated with exposure to each contaminant should be provided within the PQRA or DQRA report. The summary should discuss both cancer and non-cancer endpoints, and differentiate effects by exposure route (oral, dermal, inhalation), as appropriate.

To facilitate preparation of text summarizing the toxicology of each contaminant of potential concern and the basis for each TRV, a summary of the key toxicological endpoint(s) for Health Canada's TRVs and the general toxicology of each of these substances are available in Appendix A. This information may be used (and combined with information from other Health Canada sources and the original principal studies) when preparing toxicological summaries for risk assessment reports of contaminated sites being submitted to Health Canada.

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Table 1 Toxicological Reference Values (TRVs) Recommended for Use in Human Health Risk Assessments of Federal Contaminated Sites

Name	Non-Carcinogenic TRVs*		Carcinogenic TRVs*		
	Health Canada Tolerable daily intake (TDI) (mg/kg bw/d)	Health Canada Tolerable concentration (TC) (mg/m^3)	Oral slope factor $(mg/kg\ bw\text{-}d)^{-1}$	Inhalation slope factor $(mg/kg\ bw\text{-}d)^{-1}$	Inhalation unit risk $(mg/m^3)^{-1}$
Aniline	0.0072				
Arsenic			1.80	27	6.4
Barium	0.2				
Benzene			0.0834	0.0145	0.0033
Benzo[a]pyrene†			2.3	0.13	0.031
Bis(2-ethyl-hexyl) phthalate	0.044				
Bis(chloro-methyl) ether				40	9.4
Boron	0.0175				
Cadmium	0.001‡			42	9.8
Carbon tetrachloride	0.00071				
Chlorobenzene	0.43	0.01‡			
Chromium, hexavalent				320	76
Chromium, total	0.001			46	11
Copper§ 0–0.5 years	0.091				
0.6–4 years	0.091				
5–11 years	0.11				
12–19 years	0.126				
20+ years	0.141				
Cyanide, free	0.02				
Dibromoethane, 1,2-	0.009	0.0093	2		0.6
Dibutyl phthalate	0.063				
Dichlorobenzene, 1,2-	0.43				
Dichlorobenzene, 1,4-	0.11	0.095			
Dichlorobenzidine, 3,3'-			0.068		
Dichloroethane, 1,2-			0.0081		
Dichloroethylene, 1,1	0.003				
Dichloromethane	0.05		0.000079	0.000097	0.000023
Dichlorophenol, 2,4-	0.1				
Ethylbenzene	0.100	1			
Fluoride, inorganic	0.105				

Name	Non-Carcinogenic TRVs*		Carcinogenic TRVs*		
	Health Canada Tolerable daily intake (TDI) (mg/kg bw/d)	Health Canada Tolerable concentration (TC) (mg/m^3)	Oral slope factor $(mg/kg\ bw\text{-}d)^{-1}$	Inhalation slope factor $(mg/kg\ bw\text{-}d)^{-1}$	Inhalation unit risk $(mg/m^3)^{-1}$
n-Hexane	0.1‡	0.7‡			
Isopropylbenzene	0.10	0.4			
Lead	Under review				
Manganese§ 0–0.5 years	0.136				
0.6–4 years	0.136				
5–11 years	0.122				
12–19 years	0.142				
20+ years	0.156				
Mercury, inorganic	0.0003				
Methylmercury general adult population	0.00047				
women of child-bearing age, and children < 12 years	0.0002				
Methylnaphthalene, 2-	0.004				
Methyl *tertiary*-butyl ether (MTBE)	0.01	0.037			
Molybdenum§ 0–0.5 years	23				
0.6–4 years	23				
5–11 years	23				
12–19 years	27				
20+ years	28				
Naphthalene	0.02	Under review			
Nickel chloride	0.0011				
Nickel oxide		0.00002			
Nickel subsulphide		0.000018			
Nickel sulfate	0.011	0.0000035			
Nickel, metallic		0.000018			
Nickel, oxidic#, sulphidic**, soluble		0.00002		5.3	1.3
Nickel, soluble††	0.011			3.0	0.71
Nitrilotriacetic acid (NTA)	0.01				
Pentachlorobenzene	0.001				
Phenol	0.06				
Polychlorinated biphenyls (PCBs), dioxin-like	To be evaluated with dioxins, using appropriate toxic equivalence factors (TEFs) (see *Federal Contaminated Site Risk Assessment in Canada, Part I*: *Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0*, Table 8)				

Name	Non-Carcinogenic TRVs*		Carcinogenic TRVs*		
	Health Canada Tolerable daily intake (TDI) (mg/kg bw/d)	Health Canada Tolerable concentration (TC) (mg/m^3)	Oral slope factor $(mg/kg\ bw\text{-}d)^{-1}$	Inhalation slope factor $(mg/kg\ bw\text{-}d)^{-1}$	Inhalation unit risk $(mg/m^3)^{-1}$
PCBs (total of non-coplanar)	0.00013				
Polychlorinated dibenzo-*p*-dioxins/ Polychlorinated dibenzofurans (PCDDs/PCDFs)	2.3E-09				
Pyrene	0.03				
Selenium§ 0–0.5 years	5.5				
0.6–4 years	6.2				
5–11 years	6.3				
12–19 years	6.2				
20+ years	5.7				
Styrene	0.12	0.092			
Tetrachlorobenzene, 1,2,3,4-	0.0034				
Tetrachlorobenzene, 1,2,3,5-	0.00041				
Tetrachlorobenzene, 1,2,4,5-	0.00021				
Tetrachloroethylene	0.014	0.36			
Tetrachlorophenol, 2,3,4,6-	0.01				
Toluene	0.22	3.75			
Tributyltin oxide (TBTO)	0.00025				
Trichlorobenzene, 1,2,3-	0.0015				
Trichlorobenzene, 1,2,4-	0.0016	0.007			
Trichlorobenzene, 1,3,5-	0.0015	0.0036			
Trichloroethylene (TCE)‡‡	0.00146		0.000811	0.0026	0.00061
Trichlorophenol, 2,4,6-			0.020		
Trichloropropane, 1,2,3-	0.006				
Uranium (non-radiological)	0.0006				
Vinyl chloride			0.26		
Xylene, mixed isomers	1.5	0.18‡			
Zinc§ 0–0.5years	0.49				
0.6–4 years	0.48				
5–11 years	0.48				
12–19 years	0.54				
20+ years	0.57				

* Extracted from a variety of sources, including HC (1996) and HC (2002). A summary of key information used in the derivation of the TRVs is provided in Appendix A.
† A dermal slope factor of 3.5 $(\mu g/cm^2\text{-}d)^{-1}$ has also been derived for benzo[*a*]pyrene (Knafla et al., in preparation).
‡ Provisional.
§ For these essential trace elements, TDIs are defined on an age-group specific basis.
# Oxidic Ni includes nickel oxide, nickel–copper oxide, nickel silicate oxides, and complex oxides.
** Sulphidic Ni includes nickel subsulphide
†† Soluble Ni includes water-soluble forms of nickel (primarily nickel sulphate and nickel chloride) as well as other more stable forms (e.g. nickel-bearing sulphide minerals and nickel oxide) that can dissolve under certain conditions of pH (e.g. acidic mine tailings) or redox potential (e.g. buried reducing sediment) in the environment.
‡‡ Exposure to TCE via oral, inhalation, and dermal routes may lead to developmental effects, the most sensitive endpoint for TCE toxicity. The doses from all exposure routes should be summed and compared to the oral TDI to evaluate non-cancer effects. The inhalation and oral doses should also be evaluated separately, in relation to the respective cancer slope factors.

Table 2 Toxicological Reference Values (TRVs) for Pesticides Recommended for Use in Human Health Risk Assessments of Federal Contaminated Sites

Pesticide	Acceptable Daily Intake (ADI) (mg/kg bw/d)	Source
Aldicarb	0.001	a
Aldrin + dieldrin	0.0001	a
Cyanazine	0.0013	a
DDT	0.01	b
Dinoseb	0.001	a
Methoxychlor	0.1	a
Parathion	0.005	a

Sources: a From *Canadian Guidelines for Drinking Water Quality, Supporting Documentation* (Health Canada, 2002, and as updated from time to time), unless otherwise noted.
b From Food and Agriculture Organization and World Health Organization Joint Meetings on Food Contaminants and Pesticide Residues.

Table 3 Dermal Relative Absorption Factors (RAF_{Derm}) of Selected Substances*

Chemical Name	RAF_{Derm}	Chemical Name	RAF_{Derm}
Arsenic	0.03	Methyl *tert*-butyl ether (MTBE)	0.03
Barium	0.1	Methylene chloride (dichloromethane)	0.03
Benzene	0.03	Methylnaphthalene, 2-	0.148†
Benzo[*a*]pyrene	0.148†	Molybdenum	0.01
Bis(2-ethyl-hexyl)phthalate	0.1	Naphthalene	0.148†
Boron	0.01	Nickel	0.091**
Cadmium	0.01	PCBs	0.14
Carbon tetrachloride	0.03	PCDDs/PCDFs	0.03
Chromium (total)	0.1	Petroleum hydrocarbons (PHCs)	0.2††
Chromium (VI)	0.1	Phenol	0.13
Copper	0.06	Pyrene	0.148†
Cyanide	0.1	Selenium	0.01
Dichlorobenzene, 1,2- (*o*-DCB)	0.03	Styrene	0.03
Dichlorobenzene, 1,4- (*p*-DCB)	0.03	Tetrachloroethylene	0.03
Dichlorobenzidine, 3,3'-	0.1	Toluene	0.03
Dichloroethane, 1,2-	0.03	Trichlorobenzene, 1,2,4-	0.03
Dichloroethylene, 1,1-	0.03	Trichloroethylene	0.03
Dichlorophenol, 2,4-	0.03	Trichlorophenol, 2,4,6-	0.1
Ethylbenzene	0.03	Uranium	0.1
Ethylene dibromide (dibromoethane, 1,2-)	0.03	Vinyl chloride (chloroethylene)	0.03
n-hexane	0.03‡	Xylenes (mixed isomers)	0.03
Mercury	1#	Zinc	0.1
Methyl mercury	0.06		

Note: PCBs, polychlorinated biphenyls; PCDDs polychlorinated dibenzo-*p*-dioxins; PCDFs polychlorinated dibenzofurans.

* RAF_{Derm} based on Ontario Ministry of the Environment (OMOE, 2009), unless otherwise noted.
† After Moody et al. (2007).
‡ Assigned the default value of 3% for VOCs as per OMOE (2009) process used to determine RAFs.
\# RAF_{Derm} for mercury is based on the absolute dermal absorption (46.6%) determined in the Moody et al. (2009) study on viable human skin, a value similar to the range of oral absorption of $HgCl_2$ in water (30%–40%) in male rats (Morcillo and Santamaria, 1995).
** RAF_{Derm} for Ni was determined by dividing 1.0% (absolute dermal absorption value from Moody et al., 2009) by 11% (oral bioavailability from Ishimatsu et al., 1995)
†† From CCME (2008).

Table 4 Sources of Physical–Chemical Property Data in the Health Canada PQRA Spreadsheet tool*

Data Sources	Octanol/Water Partition Coefficient (Kow)	Henry's Law Constant (H)	Water Solubility (S)	Molecular Weight (MW)	Diffusivity in Air (Di)	Diffusivity in Water (Dw)	Vapour Pressure (V)	Melting Point (MP)	Boiling Point (BP)	Critical Temperature (Tc)	Enthalpy of Vapourization
1. Mackay et al., 2006	✓	✓	✓	✓	✓		✓	✓	✓		
2. U.S. EPA,2005 (Johnson & Ettinger model)		✓	✓		✓	✓	✓	✓	✓	✓	✓
3. U.S. EPA, 1994 (RSL)		✓	✓	✓	✓	✓					
4. U.S. DOE (RAIS)	✓	✓	✓	✓	✓	✓	✓	✓	✓		
5. NIST, 2005		✓								✓	✓
6. Montgomery, 2000	✓	✓		✓			✓	✓	✓		
7. CRC, 2009	✓	✓	✓	✓					✓		
8. U.S. EPA, 2009a (EPI Suite™)	✓	✓	✓				✓				
9. U.S. EPA, 2009b (diffusion coefficient tool)					✓	✓					
Recommended Order of Preference	1 6 8	1 2 3 4 8	1 2 3 4 8	1 3 4 6 8	2 3 4 8 9	2 3 4 8 9	1 2 4 6 8	1 4 6 7 8	1 4 6 7 8	2 5 8	2 5 8

* Physical–chemical property values routinely employed by the Contaminated Sites Division of Health Canada for selected chemical substances are presented in the PQRA Spreadsheet Tool for Human Health Preliminary Quantitative Risk Assessment (HC, unpublished).

Appendix A Summary of the key toxicological endpoint(s) for Toxicological Reference Values (TRVs)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
aniline	oral TDI	7.2E-03 mg/kg-d	Study Type: chronic Species: rats Mode of administration: diet Dosing Regime: 0, 10, 30, or 100 mg/kg-d Duration: 104 weeks Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for use of LOAEL vs. NOAEL)	LOAEL = 7.2 mg/kg-d (LOAEL of 10 mg/kg-d is equivalent to 7.2 mg/kg-d free base.)	TDI = NOAEL/UF	LOAEL = increased splenic hemosiderin deposition, extramedullary hematopoiesis, and congestion in male rats NOAEL = methemoglobin in female rats	Group III: CEPA (possibly carcinogenic to humans)	PSL1: HC, 1996a (based on CIIT, 1982)
arsenic	oral SF	1.80 $(mg/kg\text{-}d)^{-1}$	Morales et al., 2000 Study Type: epidemiological (natural exposure) Species: human Exposure: oral, drinking water [As] in drinking water: 10 to > 600 µg/L, mean 300–590 µg/L (natural groundwater As concentrations) Duration: ≤ 60 years Uncertainty Factors: N/A	MAC = 0.01mg/L UR (1%) = 3.06E-06 to 3.85E-05 $(µg/L)^{-1}$ (95% upper bound 6.49E-06 to 4.64E-05)	Poisson model by U.S. EPA, 2001, fit by Morales et al., 2000; neither linear nor non-linear; TRV based on upper end of range of mean unit risks	carcinogenic: bladder, lung, liver	Group I: CEPA (carcinogenic to humans)	GCDWQ: HC, 2006 (based on Morales et al., 2000; Chen et al., 1985; Wu et al., 1989)
	inhalation SF	27 $(mg/kg\text{-}d)^{-1}$	Study Type: epidemiological (occupationally exposed cohort) Species: human Exposure: inhalation	TC_{05} = 7.83 µg/m³	relative risk model	lung cancer	Group I: CEPA (carcinogenic to humans)	PSL1: HC/EC, 1993a (based on Higgins et al., 1986)
	inhalation UR	6.4 $(mg/m^3)^{-1}$	Dosing Regime: N/A Duration: N/A Uncertainty Factors: N/A					
barium	oral TDI	2E-01	Study Type: chronic Species: rats and mice	$BMDL_{05}$ = 63 mg/kg-d	TDI = $BMDL_{05}$/UF	renal lesions in mice	Group VA : CEPA (inadequate data for evaluation)	U.S. EPA, 2005a

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
		mg/kg-d	Exposure: oral, drinking water					
			[Ba] in drinking water: barium chloride dehydrate in drinking water					
			Duration: 2years					
			Uncertainty Factors: 300 (intraspecies, intraspecies variation, 3x for database deficiencies)					
benzene	oral SF	8.34E-02 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic	MAC = 0.005 mg/L	multistage model and an allometric scaling factor	carcinogenic: malignant lymphomas (female mice); bone marrow hematopoietic hyperplasia (male mice)	Group I: CEPA (carcinogenic to humans)	GCDWQ: HC, 2009 (based on NTP, 1986a)
			Species: rats and mice					
			Mode of administration: gavage					
			Dosing Regime: 0, 50, 100, and 200 mg/kg-bw (male rats); 0, 25, 50, and 100 mg/kg-bw (female rats, male and female mice), 5 d/week	Unit Lifetime Risk = 2.03E-6 to 4.17E-6				
			Duration: 103 weeks					
			Uncertainty Factors: N/A					
	inhalation SF	1.45E-02 $(mg/kg\text{-}d)^{-1}$	Study Type: epidemiological (occupational, cohort)	TC_{05} = 14.7 mg/m³	linear quadratic model of exposure-response relationship	non-cancer endpoint = hematoxicity	Group I: CEPA (carcinogenic to humans)	PSL: HC/EC, 1993b (based on Rinsky et al., 1987)
			Species: human					
			Exposure: inhalation					
	inhalation UR	3.3E-03 $(mg/m^3)^{-1}$	Dosing Regime: N/A					
			Duration: 8.7 years, cases 2.6 years, controls (average)					
			Uncertainty Factors: N/A					
benzo[*a*]pyrene*	oral SF	2.3 $(mg/kg\text{-}d)^{-1}$	Study Type: subchronic	MAC = 0.00001 mg/L	linear extrapolation and surface-area correction	gastric tumours (mostly squamous cell papillomas, with a few carcinomas)	Group II: CEPA (probably carcinogenic to humans)	GCDWQ: HC, 1988 (based on Neal and Rigdon, 1967)
			Species: mice					
			Mode of administration: diet					
			Dosing Regime: 0, 0.001, 0.01, 0.02, 0.03, 0.04, 0.045, 0.05, 0.10, and 0.25 (mg/g food)	Unit Lifetime Risk = 5E-5				
			Duration: 110 d					
			Uncertainty Factors: N/A					
	inhalation SF	1.3E-01	Study Type: subchronic–chronic	TC_{05} = 1.6 mg/m³	multistage	respiratory tract	Group II: CEPA	PSL1: HC,

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
		(mg/kg-d)$^{-1}$	Species: hamsters		modelling	tumours		1996a (based onThysson et al., 1981)
	inhalation U R	3.1E-02 (mg/m^3)$^{-1}$	Mode of administration: inhalation (nose only) Dosing Regime: 0, 2.2, 9.5, and 45.6 mg/m^3, 4.5 h/d, 7d/week for 10 weeks; 3 h/d, 7 d/week for remaining exposure period (up to 96 weeks) Duration: 10–106 weeks Uncertainty Factors: N/A				(probably carcinogenic to humans)	
bis(2-ethyl-hexyl)phthalate	oral TDI	4.4E-02 mg/kg-d	Study Type: developmental (single generation) Species: mice Mode of administration: diet Dosing Regime: 0, 250, 500, 1000, and 1500 ppm Duration: gestational days 0–17 Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for potential teratogenicity)	NOAEL = 44 mg/kg-d (250 ppm)	TDI = NOAEL/UF	developmental toxicity: maternal rough fur coat and lethargy, increased number of resorptions, malformed and dead fetuses	Group IV: CEPA (unlikely to be carcinogenic to humans)	PSL1: HC/EC, 1994a (based on Wolkowski-Tyl et al., 1984)
bis(chloro-methyl)ether (BCME)	inhalation SF	4.0E+01 (mg/kg-d)$^{-1}$	Study Type: chronic Species: rats	TC_{05} = 0.139 mg/m^3 (0.0053 mg/m^3 adjusted for continuous exposure)	multistage modelling	respiratory tract tumours (primarily nasal esthesio-neuroepitheliomas)	Group I: CEPA (carcinogenic to humans)	PSL1: HC/EC, 1993c; HC, 1996a (based on Leong et al., 1981)
	inhalation UR	9.4E+00 (mg/m^3)$^{-1}$	Mode of administration: inhalation Dosing Regime: 1, 10, and 100 ppb (0.0047, 0.047, and 0.47 mg/m^3), 6 h/d, 5 d/week Duration: 6 months of exposure followed by observation for duration of natural lifespan (up to 28 months) Uncertainty Factors: N/A					
boron	oral ADI	1.75E-02 mg/kg-d	Study Type: chronic Species: dogs Mode of administration: diet	NOAEL = 8.75 mg/kg-d	TDI = NOAEL/UF	testicular atrophy, resulting in	Group IVC: CEPA (probably not carcinogenic to humans)	GCDWQ: HC, 1991 (based on Weir and Fisher, 1972)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Dosing Regime: 58, 117, 350 (groups 1, 2, 3), and 1170 ppm (group 4)			infertility and spermatogenic arrest		
			Duration: 2 years (groups 1 to 3), 38 weeks (group 4); all groups: 1 male and 1 female necropsied 1 year after end of exposure, remaining animals necropsied 2 years after end of exposure	MAC = 0.2 mg/L (health based); 5 mg/L (practicable treatment technology)				
			Uncertainty Factors: 500 (10x each for intra- and interspecies variability, 5x for study limitations)					
cadmium	oral TDI (provisional)	1E-03 mg/kg-d	Study Type: epidemiological (occupational exposure)	NOAEL = 2.5 µg Cd/g creatinine in urine	2.5 µg Cd/g creatinine associated with chronic oral intake of 0.5–2.0 µg/kg-d ; pTWI maintained at 7 µg/kg-w [= 1 µg/kg-d	renal tubular dysfunction (proximal tubule epithelial cell damage), manifested by low molecular weight proteinuria	not classified	GCDWQ: HC 1986 (based on WHO, 1972; Friberg et al., 1971)
			Species: human					
			Exposure: various, primarily inhalation (cadmium oxide dusts and/or fumes)					
			Dosing Regime: N/A					
			Duration: chronic					
			Uncertainty Factors: none					
	inhalation SF	4.2E+01 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic	TC_{05} = 0.0029 mg/m³	multistage model	carcinogenic: lung	Group II: CEPA (probably carcinogenic to humans)	PSL1: HC, 1996a; HC/EC, 1994b (based on Takenaka et al., 1983; Oldiges et al., 1984)
			Species: rats					
			Dosing Regime: inhalation of cadmium chloride aerosols	(0.0051 mg/m³ adjusted for continuous exposure, standard lifetime, and difference in inhalation rate and body weight of rats and humans)				
			Dosing Regime: 12.5, 25, and 50 µg/m³, 23 h/d, 7 d/week					
	inhalation UR	9.8 $(mg/m^3)^{-1}$	Duration: 18 months; necropsied 13 months after end of exposure					
			Uncertainty Factors: N/A					
carbon tetrachloride	oral TDI	7.1E-04 mg/kg-d	Study Type: chronic	NOAEL = 0.71 mg/kg-d	TDI = NOAEL/UF	hepatotoxicity	Group III: CEPA (possibly carcinogenic to humans)	GCDWQ: HC, 2010a (based on Bruckner et al., 1986)
			Species: rats					
			Mode of administration: gavage in corn oil					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Dosing Regime: 0, 20, 40, or 80 mg/kg-bw per day) for 5 consecutive days, allowed 2 days without dosing, and dosed once daily for 4 additional days. In a second study, five rats per dose level were gavaged with 0, 20, 80, or 160 mg/kg-bw per day according to the same dosing schedule. In both studies, one group of rats at each dosage level was sacrificed 1, 4, and 11 days after initiation of dosing. Duration: 11 days Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for major database deficiencies, including lack of adequate chronic studies)	MAC = 0.002 mg/L				
chlorobenzene	oral TDI	4.3E-01 mg/kg-d	Study Type: chronic Species: rats and mice Mode of administration: gavage Dosing Regime: 60 or 120 mg/kg-d (male and female rats, and female mice); 30 or 60 mg/kg-d (male mice), 5x per week Duration: 103 weeks Uncertainty Factors: 100 (10x each for intra- and interspecies variability)	NOAEL = 60 mg/kg-d (43 mg/kg-d adjusted for continuous exposure)	TDI = NOAEL/UF	neoplastic nodules in the liver	Group III: CEPA (possibly carcinogenic to humans)	PSL1: HC, 1996a; HC/EC, 1992a (based on NTP, 1983a; Kluwe et al., 1985)
	inhalation TC (provisional)	1E-02 mg/m³	Study Type: subchronic Species: rats Mode of administration: inhalation Dosing Regime: unspecified; 5x per week Duration: 24 weeks Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for less than chronic and limited study, 5x for use of LOAEL rather than NOAEL)	LOAEL = 341 mg/m³ (50.2 mg/m³ adjusted for continuous exposure and inhalation volume /body weight between rats and the human child (5–11 years))	TC = LOAEL/UF	nephrotoxic	Group III: CEPA (possibly carcinogenic to humans)	PSL1: HC, 1996a; HC/EC, 1992a (based on Dilley, 1977)
chromium† (total)	oral TDI	1E-03	Study Type: weight of evidence	MAC = 0.05 mg/L	TDI = MAC x	hepatotoxicity,	not classified	GCDWQ: HC,

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
		mg/kg-d	Species: unknown		water consumption rate (1.5 L/d)/bw(70 kg)	irritation, or corrosion of the gastrointestinal mucosa, encephalitis		1979 (updated 1986)
			Mode of administration: Cr(IV) in drinking water					
			Dosing Regime: unknown					
			Duration: unknown					
			Uncertainty Factors: unknown Note: Cr(III) is considered an essential element; TDI for total chromium is based on Cr(IV) toxicity					
	inhalation SF	4.6E+01 $(mg/kg\text{-}d)^{-1}$	Study Type: epidemiological(chronic, occupational)	TC_{05} = 4.6 µg/m³		carcinogenic: lung	Group I: CEPA (carcinogenic to humans)	PSL1: HC, 1996a; HC/EC, 1994c (based on Mancuso, 1975)
			Species: human					
			Exposure: inhalation					
	inhalation UR	1.1E+01 $(mg/m^3)^{-1}$	Dosing Regime: N/A					
			Duration: at least 1 year, up to 8 years					
			Uncertainty Factors: N/A					
chromium (hexavalent)	inhalation SF	3.20E+02 $(mg/kg\text{-}d)^{-1}$	Study Type: epidemiological (chronic, occupational)	TC_{05} = 0.66 µg/m3		carcinogenic: lung	Group I: CEPA (carcinogenic to humans)	PSL: HC, 1996a (based on Mancuso, 1975)
			Species: human					
			Exposure: inhalation					
	inhalation UR	7.6E+01 $(mg/m^3)^{-1}$	Dosing Regime: N/A					
			Duration: at least 1 year, up to 8 years					
			Uncertainty Factors: N/A					
copper	UL (IOM)	µg/d	Pratt et al., 1985	NOAEL = 10 mg/d	UL (IOM) = NOAEL/UF UL (HC) = UL (IOM) adjusted for age group and body weight	hepatotoxicity, gastrointestinal effects	IOM, 2001 ("There is little convincing evidence indicating that copper is causally associated with the development of cancer in humans.")	IOM, 2001 (based on Pratt et al., 1985; O'Donohue et al., 1993)
	0–6 months	NA	Study Type: clinical (double blind)					
	7 months–1 year	NA	Species: human					
	1–3 years	1E+03	Mode of administration: ingestion of copper gluconate capsules					
	4–8 years	3E+03						
	9–13 years	5E+03	Dosing Regime: 10 mg/d					
	14–18 years	8E+03	Duration: 12 weeks					
	≥ 19 years	1E+04	Uncertainty Factors: none					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
	(76 kg male, 61 kg female)		O'Donohue et al., 1993			hepatotoxicity, gastrointestinal effects		
			Study Type: case report of chronic self-intoxication					
			Species: human					
	UL (HC)	µg/kg-d	Mode of administration: ingestion of copper tablets					
	0–6 months‡	9.1E+01						
	7 months–4 years	9.1E+01	Dosing Regime: 30 mg/d followed by 60 mg/d					
	5–11 years	1.1E+02						
	12–19 years	1.26E+02	Duration: 2 years, unspecified duration at increased dose					
	20+ years (70.7 kg)	1.41E+02						
			Uncertainty Factors: N/A					
cyanide (free)	oral TDI	2E-02 mg/kg-d (provisional)	Study Type: chronic	NOAEL = 10.8 mg/kg-d	TDI = NOAEL/UF	decreased weight gain, thyroxin levels and myelin degeneration (note no significant adverse effects observed at highest dose in critical study)	Group VIB: CEPA (unclassifiable with respect to carcinogenesis in humans)	CSQG: CCME, 1996a, (summarized in CCME,1997a) ; RfD from U.S. EPA, 1993a (based on Howard and Hanzal, 1955)
			Species: rats					
			Mode of administration: diet (fumigated food)					
			Dosing Regime: 4.3 and 10.8 mg/kg					
			Duration: 2 years					
			Uncertainty Factors: 500 (10x each for intra- and interspecies variability, 5x for differences in cyanide tolerance depending on mode of ingestion)					
dibromoethane,1,2-	oral TDI	9E-03 mg/kg-d	Study Type: chronic	LOAEL = 38 mg/kg-d	TDI = LOAEL/UF	testicular atrophy, liver peliosis, adrenal cortical degeneration	IRIS (likely to be carcinogenic to humans)	IRIS: U.S. EPA, 2004 (based on NCI, 1978a)
			Species: rats					
			Mode of administration: gavage					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Dosing Regime: 40 and 80 mg/kg-d, 5 d/week; TWA low- and high-doses were 38 and 41 mg/kg-d (male rats), and 37 and 39 mg/kg-d (female rats); note intubation of high-dose group suspended at week 16 and resumed at low dose at week 30 because of high mortality	(27 mg/kg-d adjusted for continuous exposure)				
			Duration: 49 weeks (male) and 61 weeks (female)					
			Uncertainty Factors: 3000 (10x each for intra- and interspecies variability, 10x for LOAEL, and 10x for the extent and quality of the database)					
	inhalation TC	9.3E-3 mg/m^3	Study Type: chronic	LOAEL = 76.8 mg/m^3 $BMDL_{10}$(HEC) = 2.8 mg/m^3 (BMDL of 80.1 mg/m^3 adjusted for continuous exposure and human equivalent)	TC = $BMDL_{10}$(HEC)/ UF	nasal inflammation, hepatic necrosis, testicular and retinal atrophy, adrenal cortical degeneration, splenic hematopoiesis		IRIS: U.S. EPA, 2004 (based on NTP, 1982)
			Species: mice					
			Mode of administration: inhalation					
			Dosing Regime: 0, 77, or 307 mg/m^3, 6 h/d, 5 d/week					
			Duration: low dose: 104–106 weeks, high dose: 78 and 91 weeks (because of high mortality rate)					
			Uncertainty Factors: 300 (3x for interspecies and 10x for intraspecies variability, 10x for database uncertainty)					
	oral SF	2E+00 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic	6.E-05 $(\mu g/L)^{-1}$ drinking water UR		fore-stomach squamous cell carcinoma, hemangiosarcoma, thyroid follicular cell adenoma, hepatocellular carcinoma, lung adenomas		IRIS: U.S. EPA 2004 (based on NCI, 1978a)
			Species: rats					
			Mode of administration: gavage					
			Dosing Regime: 40 and 80 mg/kg-d, 5 d/week; TWA low- and high-doses were 38 and 41 mg/kg-d (male rats), and 37 and 39 mg/kg-d (female rats); note intubation of high-dose group suspended at week 16 and resumed at low dose at week 30 because of high mortality					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Duration: 49 weeks (male) and 61 weeks (female)					
			Uncertainty Factors: N/A					
	inhalation UR	6E-01 $(mg/m^3)^{-1}$	Study Type: chronic		multistage model amortized for continuous exposure	nasal cavity tumours, hemangiosarcomas, mesotheliomas		IRIS: U.S. EPA 2004 (based on NTP, 1982)
			Species: rats (male)					
			Mode of administration: inhalation					
			Dosing Regime: 0, 77, or 307 mg/m^3, 6 h/d, 5 d/week					
			Duration: low dose: 104–106 weeks, high dose: 78 and 91 weeks (because of high mortality rate)					
			Uncertainty Factors: N/A					
dibutyl phthalate	oral TDI	6.3E-02 mg/kg-d	Study Type: developmental (single generation)	NOAEL = 62.5 mg/kg-d	TDI = NOAEL/UF	fetotoxic and possible teratogenic: decreased number of live offspring, increased incidence of external defects and skeletal anomalies	Group VI: CEPA (unclassifiable with respect to its carcinogenicity to humans)	PSL: HC/EC, 1994d (based on Hamano et al., 1977)
			Species: rats					
			Mode of administration: diet					
			Dosing Regime: 6.25, 62.5, or 625 mg/kg-d					
			Duration: throughout 18 d of gestation					
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for severity of the effect at the LOAEL in the critical study)					
dichlorobenzene, 1,2-	oral TDI	4.3E-01 mg/kg-d	Study Type: chronic	NOAEL = 60 mg/kg-d	TDI = NOAEL/UF	increase in tubular regeneration in the kidney	Group V: CEPA (probably not carcinogenic to humans)	PSL: HC, 1996a (based on NTP, 1983b)
			Species: rats and mice					
			Mode of administration: gavage					
			Dosing Regime: 60 and 120 mg/kg (male and female rats, female mice), 30 and 60 mg/kg (male mice) 5x per week	(43 mg/kg-d adjusted for continuous exposure)				
			Duration: 103 weeks					
			Uncertainty Factors: 100 (each for intra- and interspecies variability)					
dichlorobenzene, 1,4-	oral TDI	1.1E-01	Study Type: chronic	LOAEL =	TDI =	nephrotoxic,	Group III: CEPA	PSL: HC,

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
		mg/kg-d	Species: rats and mice	150 mg/kg-d	NOAEL/UF	nephropathy, parathyroid hyperplasia	(possibly carcinogenic to humans)	1996a (based on NTP, 1987)
			Mode of administration: gavage					
			Dosing Regime: 0,150, 300 mg/kg bw/d (male rats), and 0, 300 and 600 mg/kg bw/d (female rats, male and female mice), 5 d/week	(107 mg/kg-d adjusted for continuous exposure)				
			Duration: 103 weeks					
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for use of LOAEL vrs. NOAEL).					
	inhalation TC	9.5E-02 mg/m^3	Study Type: chronic	NOAEL = 75 ppm or 450 mg/m^3	TC = NOAEL/UF	increases in liver and kidney weights, urinary protein, and coproporphyrin	Group III: CEPA (possibly carcinogenic to humans)	PSL: HC, 1993 (based on Loeser and Litchfield, 1983)
			Species: rats and mice					
			Mode of administration: inhalation	(47.35 mg/m^3 adjusted for continuous exposure and difference in inhalation and body weights of rats and the human child: 5–11 years)				
			Dosing Regime: 75 and 500 ppm 5 h/d, 5 d/week					
			Duration: 76 weeks, 36 weeks before necropsied					
			Uncertainty Factors: 500 (10x each for intra- and interspecies variability, 5x for less than lifetime exposure)					
dichlorobenzidine, 3,3'-	oral SF	6.8E-02 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic	TD_{05} range: 0.74 (mammary tumours, females) to 1.4 mg/kg-d (granulocytic leukemias, males)	linear interpolation, with corrections for body weight, surface area, and duration of exposure	mammary tumours (fibroadenomas and adenocarcinomas), granulocytic leukemia, Zymbal gland carcinomas	Group II: CEPA (probably carcinogenic to humans)	PSL1: HC/EC, 1993d (based on Stula et al., 1975)
			Species: rats					
			Mode of administration: diet					
			Dosing Regime: 0 and 1000 ppm (0.1 % w/w)					
			Duration: 2 years (up to 488 d)					
			Uncertainty Factors: N/A					
dichloroethane,1,2-	oral SF	8.1E-03 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic	TD_{05} range: 6.2 to 34 mg/kg-d	multistage model amortized for continuous	tumours in fore stomach, hemangio sarcoma of the	Group II: CEPA (probably carcinogenic to humans)	PSL: HC/EC, 1994e (based on NCI, 1978b)
			Species: rats and mice					
			Mode of administration: gavage					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Dosing Regime: 47 and 95 mg/kg-d male and female rats; 97 and 195 mg/kg-d for male mice, and 149 and 299 mg/kg-d for female mice Duration: 78 weeks (necropsied after 104 weeks) Uncertainty Factors: N/A		exposure	circulatory system, others		
dichloroethylene, 1,1	oral ADI	3E-03 mg/kg-d	Study Type: chronic Species: rats Mode of administration: drinking water Dosing Regime: TWA daily doses: 0, 7, 10, and 20 mg/kg-bw (males); 0, 9, 14, and 30 mg/kg-bw (females) Duration: 2 years Uncertainty Factors: 3000 (10x each for intra- and interspecies variability, 10x for LOAEL, and 3x for limited evidence of carcinogenicity)	LOEAL = 9 mg/kg-d	ADI = LOAEL/UF	hepatocellular swelling with mid-zonal fatty changes	Group IIIB (possibly carcinogenic to humans, limited evidence of carcinogenicity)	GCDWQ: HC, 1984 (based on Quast et al., 1983)
dichloromethane (methylene chloride)	oral TDI	5E-02 mg/kg-d	Study Type: chronic Species: rats Mode of administration: drinking water Dosing Regime: 0, 5, 50, 125, and 250 mg/kg-d; and 250 mg/kg-d (additional group) Duration: 2 years and 78 weeks (additional group) + 26 weeks recovery period Uncertainty Factors: 100 (10x each for intra- and interspecies variability)	NOAEL = 5 mg/kg-d	TDI = NOAEL/UF	increased incidences of foci/areas of cellular alterations and fatty change in liver	Group II: CEPA (probably carcinogenic to humans)	PSL1: HC, 1996a; EC/HC, 1993e (based on Serota et al., 1986)
	inhalation SF	9.7E-05 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic Species: rats and mice	TC_{05} = 2200 mg/m^3	PBPK multistage modelling	pulmonary and hepatic adenomas and carcinomas	Group II: CEPA (probably carcinogenic to humans)	PSL: HC, 1996a; HC/EC, 1993e (based on NTP, 1986b)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
	inhalation UR	2.3E-05 $(mg/m^3)^{-1}$	Mode of administration: inhalation Dosing Regime: 0, 3600, 7200, and 14400 mg/m^3, 6 h/d, 5 d/week (rats); 0, 7200, and 14400 mg/m^3, 6 h/d, 5 d/week (mice) Duration: 102 weeks Uncertainty Factors: N/A					
	oral SF	7.9E-05 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic Species: rats and mice Mode of administration: inhalation Dosing Regime: 0, 3600, 7200, and 14400 mg/m^3; 6 h/d, 5 d/week (rats); 0, 7200, and 14400 mg/m^3; 6 h/day, 5 d/week (mice) Duration: 102 weeks Uncertainty Factors: N/A	MAC = 0.05 mg/L UR = 1.7E-09	linear extrapolation of PBPK model	carcinogenic: hepatocellular adenoma and carcinoma	Group II: CEPA (probably carcinogenic to humans)	GCDWQ: HC, 1987a (based on NTP, 1986b)
dichlorophenol, 2,4-	oral ADI	1E-01 mg/kg-d	Study Type: subchronic Species: mice Mode of administration: diet Dosing Regime: 0, 45, 100, or 230 mg/kg-d Duration: 6 months Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less-than-lifetime study and limitations of the study design)	NOAEL = 100 mg/kg-d	TDI = NOAEL/UF	hepatic cellular hyperplasia	Group VA (inadequate data for evaluation)	GCDWQ: HC, 1987b (based on Kobayashi et al., 1972)
ethylbenzene	oral TDI	1.00E-01 mg/kg-d	Study Type: subchronic Species: rats (female) Mode of administration: gavage Dosing Regime: 13.6, 136, 408, or 680 mg/kg-d, 5 d/week Duration: 182 d	NOAEL = 136 mg/kg-d (97.1 mg/kg-d adjusted for continuous	TDI = NOAEL/UF	histopathologic changes in liver and kidney	Group D: IRIS (not classifiable as to human carcinogenicity) Group 2B: IARC	CSQG: CCME, 1996b (summarized in CCME, 2004) from U.S. EPA (IRIS), 1991

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic)	exposure)			(possibly carcinogenic to humans)	(based on Wolf et al., 1956) GCDWQ: HC, 1986 (reaffirmed 2005)
	inhalation TC	1 mg/m^3	Study Type: subchronic, developmental Species: rabbits and rats Mode of administration: inhalation Dosing Regime: 0, 100, and 1000 ppm (0, 434, and 4342 mg/m^3), 7 h/d Duration: days 1–24 (rabbits) and 1–19 (rats) of gestational period Uncertainty Factors: 300 (10x for intraspecies and 3x for interspecies variation, 10x for absence of multigenerational reproductive studies)	NOAEL = 434 mg/m^3 (not adjusted for continuous exposure)	TC = NOAEL/UF	reduced litter size; increased relative liver, kidney, and spleen weights of dams; skeletal variations	Group D: IRIS (not classifiable as to human carcinogenicity) Group 2B: IARC (possibly carcinogenic to humans)	CSQG: CCME, 1996b (summarized in CCME, 2004), from U.S. EPA (IRIS), 1991 (based on Andrew et al., 1981; Hardin et al., 1981)
fluoride	oral TDI	1.05E-01 mg/kg-d	Study Type: Epidemiological studies Species: human (children) Mode of administration: drinking water, soil, food, air Dosing Regime: N/A Duration: N/A Uncertainty Factors: N/A	MAC = 1.5 mg/L NOAEL = 0.105 mg/kg-d	TDI = NOAEL/UF	moderate dental fluorosis	CEPA (Although there is some evidence for the carcinogenicity of inorganic fluoride, available data are inconclusive.)	GCDWQ: HC, 2010c
n-hexane (synonym: cumene)	inhalation TC (provisional)	7E-01 mg/m^3	Study Type: subchronic Species: rats Mode of administration: inhalation Dosing Regime: 0, 500, 1200, or 3000 ppm (0, 1762, 4230, 10,574 mg/m^3)	NOAEL = 1762 mg/m^3 ($BMCL_{HEC}$ = 215 mg/m^3)	TC = $BMCL_{HEC}$/UF	peripheral neuropathy	U.S. EPA (inadequate information to assess the carcinogenic potential)	IRIS: U.S. EPA, 2005b (based on Huang et al., 1989)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Duration: 12 h/d, 7 d/week for 16 weeks Uncertainty Factors: 300 (10x for intraspecies variation, 3x for interspecies variation, 3x for use of a subchronic study, 3x database deficiencies)					
	oral TDI (provisional)	1E-01 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: gavage Dosing Regime: 66, 132, or 264 mg/d Duration: 7 d/wk for 4 weeks Uncertainty Factors: 90 (10x for sensitive individuals, 3x for toxicokinetic difference, 3x for deficiencies in the database)	POD = 8 mg/kg-d	TDI= POD/UF	motor nerve conduction velocity, mixed nerve conduction velocity	IARC (has not classified regarding carcinogenic potential)	Environmental Equilibrium Inc., 2008 (based on Ono et al., 1979, 1982)
isopropyl benzene	oral TDI	1.0E-01 mg/kg-d	Study Type: chronic Species: rats Mode of administration: gavage Dosing Regime: 139 doses at 154, 462, or 769 mg/kg-d Duration: 194 d Uncertainty Factors: 1000 (rounded: 10x each for intra- and interspecies variability, 3x for less than chronic, and 3x for deficiencies in the database)	NOAEL = 154 mg/kg-d (110 mg/kg-d adjusted for daily exposure)	TDI = NOAEL/UF	increased average kidney weight in female rats	Group D: IRIS (not classifiable as to human carcinogenicity)	IRIS: U.S. EPA, 1997 (based on Wolf et al., 1956)
	inhalation TC	4E-01 mg/m^3	Study Type: subchronic Species: rats Mode of administration: gavage Dosing Regime: group 1: 0, 492, 2438, or 5909 mg/m^3, 6 h/d, 5 d/week; group 2: 0, 44, 492, 2438, or 5909 mg/m^3, 6 h/d, 5 d/week Duration: 13 weeks (group 1), 13 weeks + 4 week post-exposure recovery period (group 2)	NOAEL = 2438 mg/m^3 (435 mg/m^3 adjusted for continuous exposure and human equivalent)	TC = NOAEL/UF	increased kidney weights in female rats and adrenal weights in male and female rats	Group D: IRIS (not classifiable as to human carcinogenicity)	IRIS: U.S. EPA, 1997 (based on Cushman et al., 1995)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Uncertainty Factors: 1000 (10x for intraspecies variability, 10x for less than chronic, and 3x each for interspecies extrapolation and deficiencies in the database)					
manganese	UL (IOM)	mg/d	Study Type: weight of evidence from epidemiological and experimental studies	NOAEL (food) = 11 mg/kg-d	UL (IOM) = NOAEL/UF UL (HC) = UL (IOM) adjusted for life stage and body weight	Parkinsonian-like neurotoxicity	IOM does not consider manganese carcinogenic to humans.	IOM, 2001 (based on Greger, 1999)
	0–6 months	N/A						
	7 months–1 year	N/A	Species: human epidemiological studies					
	1–3 years	2.E+00	Expsoure/Mode of administration: food and water					
	4–8 years	3.E+00						
	9–13 years	6.E+00	Dosing Regime: not specified					
	14–18 years	9.E+00	Duration: N/A					
	≥ 19years (76 kg male, 61 kg female)	1.1E+01	Uncertainty Factors: deemed unnecessary					
	UL (HC)	mg/kg-d						
	0–6 months‡	1.36E-01						
	7 months–4 years	1.36E-01						
	5–11 years	1.22E-01						
	12–19 years	1.42E-01						
	20+ years (70.7 kg)	1.56E-01						
mercury (inorganic)	oral TDI	3E-04 mg/kg-d	Druet et al., 1978	LOAEL = 0.226 mg/kg-d (converted from subcutaneous to	TDI = LOAEL (0.3 mg/kg-d)/UF	nephrotoxicity	Group 3 : IARC (not classifiable as to its carcinogenicity to humans)	CSQG: CCME, 1999a,b; RfD from U.S. EPA, 1995 (based on several studies,
			Study Type: subchronic					
			Species: rats					
			Mode of administration: sub-cutaneous injection					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Dosing Regime: 0, 5, 10, 25, 50, 100, and 200 µg/100 g-bw ; 1, 2 or 3 injections/week (various groups)	oral route)			Group C: IRIS (possible human carcinogen)	including Druet et al., 1978; Bernaudin et al., 1981; Andres, 1984)
			Duration: 1, 2, 6, 8 weeks (various groups)					
			Bernaudin et al., 1981	LOAEL = 0.317 mg/kg-d				
			Study Type: subchronic					
			Species: rats					
			Mode of administration: gavage					
			Dosing Regime: 3 mg $HgCl_2$ (equivalent to 2.22 mg Hg)/kg-bw per week					
			Duration: 2 months					
			Andres, 1984	LOAEL = 0.633 mg/kg-d				
			Study Type: subchronic					
			Species: rats					
			Mode of administration: gavage					
			Dosing Regime: 3 mg $HgCl_2$ (equivalent to 2.22 mg Hg)/kg body weight, 2x per week					
			Duration: 2 months					
			Uncertainty Factors: 1000 (10x for use of subchronic studies, 10x for interspecies varibility, 10x for LOAEL)	drinking water equivalent level = 0.01 mg/L				
mercury (methylmercury)	oral TDI	4.7E-4 mg/kg-d (general adult population)	Study Type: epidemiological (epidemic accidental poisoning and chronic low-level exposure in populations with high consumption of fish)		see Health Canada, 2007	neurotoxicity	Group 2B: IARC (possibly carcinogenic to humans)	HC Food Directorate, 2007

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
		2E-4 mg/kg-d (women of child-bearing age, children < 12 years)	Study Type: epidemiological prospective studies of neurodevelopmental effects Uncertainty Factors: 5 (see Health Canada, 2007, for details) Note: Exposure to mercury through consumption of fish, seafood, and marine mammals should be compared to the TRV for methylmercury, the predominant form of mercury in these foods.	(approximate threshold of 10 ppm in maternal hair equivalent to 0.001mg/kg-d)	approximate threshold dose/UF	neurodevelopmental toxicity		
methylnaphthalene, 2-	oral TDI	4E-03 mg/kg-d	Study Type: chronic Species: mice Mode of administration: diet Dosing Regime: 0, 54.3 or 113.8 mg/kg-d (males); 0, 50.3, or 107.6 mg/kg-d (females) Duration: 81 weeks Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for deficiencies in the database)	$BMDL_{05}$ 3.5 mg/kg-d	TDI = $BMDL_{05}$/UF	pulmonary alveolar proteinosis	IRIS (inadequate data to assess human carcinogenic potential)	IRIS: U.S. EPA, 2003 (based on Murata et al., 1997)
methyl *tertiary*-butyl ether (MTBE)	oral TDI	1E-02 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: gavage Dosing Regime: 100, 300, 900, and 1200 mg/kg-d Duration: 90 d Uncertainty Factors: 10,000 (10x each for intra- and interspecies variability, 100x for less than chronic study, lack of data on carcinogenicity, minimal effects observed at the NOAEL)	NOAEL = 100 mg/kg-d	TDI = NOAEL/UF	increase in relative kidney weight; decrease in blood urea nitrogen, serum calcium and glucose	Group VIA: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL: HC/EC1992b (based on Robinson et al., 1990)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
	inhalation TC	3.7E-02 mg/m^3	Study Type: subchronic Species: rats Mode of administration: inhalation Dosing Regime: 0, 800, 4000, and 8000 ppm, 6 h/d, 5 d/week Duration: 13 weeks Uncertainty Factors: 10,000 (10x each for intra- and interspecies variability, 100x for less than chronic study, lack of data on carcinogenicity, minimal effects observed at the NOAEL)	NOAEL = 2915 mg/m^3 (368 mg/m^3 adjusted for continuous exposure, and human equivalent; 5–11 years)	TC = NOAEL/UF increased relative weights of kidney and liver at this dose indicate it may be more appropriate to consider this NOAEL as a LOAEL	neurobehavioral effects, kidney lesions	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL1: HC/EC, 1992b; HC, 1996a [(based on Dodd and Kintigh, 1989)
molybdenum	UL (IOM) 0–6 months 7 months–1 year 1–3 years 4–8 years 9–13 years 14–18 years ≥ 19 years UL (HC) 0–6 months‡ 7 months–4 years 5–11 years 12–19 years 20+ years	µg/d N/A N/A 3E+02 6E+02 1.1E+03 1.7E+03 2E+03 µg/kg-d 2.3E+01 2.3E+01 2.3E+01 2.7E+01 2.8E+01	Study Type: subchronic, developmental/reproductive Species: rats Mode of administration: drinking water Dosing Regime: 0, 5, 10, 50, and 100 mg/L + 0.025mg/kg in diet (equivalent to 0, 0.91, 1.6, 8.3, and 16.7 mg Mo/kg-bw-d) Duration: 9 weeks (including 3 weeks of gestation) Uncertainty Factors: 30 (10x for interspecies variability, 3x for intraspecies variability)	NOAEL = 0.9 mg/kg-d LOAEL = 1.6 mg/kg-d	UL (IOM) = NOAEL/UF x bw (adult female, 61 kg) UL (HC) = UL (IOM) adjusted for age group and body weight	reproductive effects	IOM does not consider molybdenum carcinogenic to humans.	IOM, 2001 (based on Fungwe et al., 1990)
naphthalene	oral TDI	2E-02 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: gavage	NOAEL = 100 mg/kg-d	TDI = NOAEL/UF	decreased mean terminal body weight in males	Group C: IRIS (a possible human carcinogen)	IRIS: U.S. EPA, 1998 (based on BCL, 1980)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Dosing Regime: 0, 25, 50, 100, 200, or 400 mg/kg, 5 d/week Duration: 13 weeks Uncertainty Factors: 3000 (10x each for intra- and interspecies variability, 10x for less than chronic, 3x for database deficiencies including lack of chronic oral exposure and reproductive toxicity studies)	(71 mg/kg-d adjusted for continuous exposure)				
nickel soluble (nickel chloride and nickel sulphate)	oral TDI	1.10E-02 mg/kg-d	Study Type: two-generation reproductive toxicity Species: rats Mode of administration: drinking water Dosing Regime: 0, 0.22, 0.55, 1.1, and 2.2 mg/kg-d Duration: F0: prior to and during mating (males and females) and throughout gestation lactation; F1: from weaning through reproduction until weaning of F2 pups Uncertainty Factors: 100 (10x each for intra- and interspecies variability)	NOAEL = 1.1 mg/kg-d	TDI = NOAEL/UF	post-implantation perinatal lethality	Group I: CEPA (carcinogenic to humans)	WHO, 2005 (based on SLI, 2000)
nickel soluble (primarily nickel chloride and nickel sulphate)	inhalation SF inhalation UR	3.0 $(mg/kg\text{-}d)^{-1}$ 0.71 $(mg/m^3)^{-1}$	Study Type: epidemiological (chronic occupational expsoure, cohort) Species: human Exposure: inhalation Dosing Regime: N/A Duration: ≥ 12 months occupational exposure Uncertainty Factors: N/A	TC_{05} = 0.07 mg/m^3		carcinogenic: lung and nasal cancer; kidney, prostate, and mouth cavity cancers	Group I: CEPA (carcinogenic to humans)	HC/EC, 1994f; HC, 1996a (based on Doll et al., 1990)
nickel (combined oxidic, sulphidic and soluble nickel)	Inhalation SF	5.3 $(mg/m^3)^{-1}$	Study Type: epidemiological (chornic occupational exposure, cohort) Species: human	TC_{05} = 0.04 mg/m^3		carcinogenic: lung and nasal cancer, also kidney,	Group I: CEPA (carcinogenic to humans)	PSL: HC/EC, 1994, HC 1996a (based

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
	inhalation UR	1.3 $(mg/m^3)^{-1}$	Mode of administration: inhalation Dosing Regime: N/A Duration: > 6 months occupational exposure Uncertainty Factors: N/A			prostrate, bucal cavity cancers		on Doll et al. 1990)
nickel oxide	inhalation TC	2.0E-05 mg/m^3	Study Type: subchronic Species: rats Mode of administration: inhalation Dosing Regime: 0.025 and 0.150 mg/m^3, 24 h/d, 7 d/week Duration: 4 months Uncertainty Factors: 1000 (10x for intraspecies variability, 10x for interspecies variation, and 10x for less than chronic)	LOEL = 0.025 mg/m^3	TC= LOEL/UF	increases in lung granulocytes and multi-nucleated counts	Group I: CEPA (carcinogenic to humans)	HC, 1996a (based on Spiegelberg et al., 1984)
nickel subsulphide (sulphidic nickel)	inhalation TC	1.8E-05 mg/m^3	Study Type: subchronic Species: rats and mice Mode of administration: inhalation Dosing Regime: 0, 0.11, 0.2, 0.4, 0.9, and 1.8 mg/m^3, 6 h/d, 5 d/week Duration: 13 weeks Uncertainty Factors: 1000 (10x for intraspecies and 10x for interspecies variation, 10x for less than chronic)	NOAEL (mice), LOAEL (rats) = 0.1 mg/m^3	TC = LOAEL/UF	respiratory track effects: alveolar macrophages, hyperplasia	Group I: CEPA (carcinogenic to humans)	HC/EC, 1994f; HC, 1996a (based on Benson et al., 1990; Dunnick et al., 1989)
nickel sulphate	oral TDI	1.10E-02 mg/kg-d	Study Type: two-generation reproductive toxicity Species: rats Mode of administration: drinking water Dosing Regime: 0, 0.22, 0.55, 1.1, and 2.2 mg/kg-d	NOAEL = 1.1 mg/kg-d	TDI = NOAEL/UF	post-implantation perinatal lethality	Group I: CEPA (carcinogenic to humans)	WHO, 2005 (based on SLI, 2000)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Duration: F0: prior to and during mating (males and females) and throughout gestation lactation; F1: from weaning through reproduction until weaning of F2 pups					
			Uncertainty Factors: 100 (10x each for intra- and interspecies variability)					
	inhalation TC	3.5E-06 mg/m^3	Study Type: subchronic	LOAEL = 0.02 mg/m^3	TC = LOAEL/UF	respiratory effects, lesions in lung, nasal epithelium, others	Group I: CEPA (carcinogenic to humans)	HC/EC, 1994f; HC 1996a (based on Dunnick et al., 1989)
			Species: rats					
			Mode of administration: inhalation					
			Dosing Regime: 0, 0.02, 0.05, 0.1, 0.2, and 0.4 mg/m^3, 6 h/d, 5 d/week					
			Duration: 13 weeks					
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic)					
nickel (metallic)	inhalation TC	1.8E-05 mg/m^3	Study Type: subchronic	LOAEL = 0.1 mg/m^3 (0.018 mg/m^3 adjusted for continuous exposure)	TC = LOAEL/UF	respiratory effects, morphological and biological effects	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	HC/EC, 1994f; HC, 1996a (based on various studies; TDI from Johansson et al., 1983)
			Species: rabbits					
			Mode of administration: inhalation					
			Dosing Regime: 0.13 ± 0.05 mg/m^3,6 h/d, 5 d/week					
			Duration: 4 and 8 months					
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic and inadequate data on carcinogenicity)					
nitrilotriacetic acid (NTA)	oral TDI	1E-02 mg/kg-d	Study Type: chronic	NOAEL = 0.03% Na_3NTA 10 mg/kg-d	TDI = NOAEL/UF	nephritis, nephrosis	Group IIIB: (possibly carcinogenic to humans)	GCDWQ: HC, 1990 (based on Nixon et al., 1972)
			Species: rats					
			Mode of administration: diet					
			Dosing Regime: 0.03, 0.15, or 0.5% Na_3NTA					
			Duration: 2 years (sacrificed at 6, 12, 18, and 24 months)					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for carcinogenic potential at high doses)					
pentachlorobenzene	oral TDI	1E-03 mg/kg-d	Study Type: subchronic Species: rats and mice Mode of administration: diet Dosing Regime: 0, 33, 100, 330, 1000, and 2000 ppm Duration: 13 weeks Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for less than chronic, 5x for lack of data on carcinogenicity)	LOAEL (mice) = 5.2 mg/kg-d	TDI = LOAEL/UF	hepatotoxicity, hepatocellular hypertrophy	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL: HC/EC, 1993f; HC, 1996a (based on NTP, 1991a)
phenol	oral TDI	6E-02 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: gavage Dosing Regime: 0, 4, 12, 40, and 120 mg/kg-d Duration: 14 d Uncertainty Factors: 200 (10x each for intra- and interspecies variability, 2x for limited animal toxicity data)	NOAEL = 12 mg/kg-d	TDI = NOAEL/UF	neurotoxic, nephrotoxic, hepatotoxic	no adequate data to characterize in terms of carcinogenicity	CSQG: CCME, 1997b (based on WHO, 1994; Schlicht et al., 1992; Berman et al., 1995)
polychlorinated biphenyls (PCBs), (dioxin-like)			To be evaluated with dioxins, using appropriate TEFs (see Table 8, HC, 2010b).					TEFs: HC, 2010b (based on van den Berg et al., 2006)
polychlorinated biphenyls (PCBs), (non dioxin-like)	oral TDI	1.3E-01 µg/kg-d	Study Type: chronic Species: rhesus monkeys Mode of administration: diet Dosing Regime: 0.5 and 1.0 ppm, 3 d/week (6 and 13 µg/kg-d) Duration: 65–102 weeks	NOAEL = 13 µg/kg-d	TDI = NOAEL/UF		IARC (inadequate data for evaluation of carcinogenicity to humans)	HC , 2003 (NOAEL from Bowman et al., 1981)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Uncertainty Factors: 100 (10x each for intra- and interspecies variability)					
polychlorinated dibenzo-*p*-dioxins/ polychlorinated dibenzofurans (PCDDs/PCDFs)	oral TDI	2.3E-09 (mg/kg-d)	Study Type: subchronic, developmental Species: rats Mode of administration: diet (Oshako et al., 2001); subcutaneous injection (Faqi et al., 1998) Duration and Dosing Regime: single bolus dose (0, 12.5, 50, 200, or 800 ng 2,3,7,8-TCDD)/kg-bw) on day 15 of gestation (Oshako et al., 2001); subcutaneous loading dose 25, 60, or 300 ng TCDD/kgbw) followed by weekly maintenance doses (5, 12, or 60 ng TCDD/kgbw) beginning 2 weeks prior to mating, and continuing through mating, gestation and lactation (Faqi et al., 1998) Uncertainty Factors: 3.2 (applied to NOAEL for intraspecies variability) and 9.6 (applied to LOAEL: 3x for use of a LOAEL rather than a NOAEL and 3.2 for intraspecies variability)		pTMI = EHMI/UF Mid-point of the range of pTMI (40–100 pg/kg bw) estimated from Faqi et al., 1998; Ohsaka et al., 2001) was selected as the PTMI.	developmental effects: immune and reproductive effects in offspring of exposed dams	Group 2B: IARC (possibly carcinogenic to humans	FAO/WHO, 2002 (based on Faqi et al., 1998; Ohsako et al., 2001)
pyrene	oral TDI	3E-02 mg/kg-d	Study Type: subchronic Species: mice Mode of administration: gavage Dosing Regime: 0, 75, 125, or 250 mg/kg-d Duration: 13 weeks Uncertainty Factors: 3000 (10 each for intra- and interspecies variability, 10x for less than chronic, 3x for the lack of toxicity studies in a second species and developmental/ reproductive studies)	NOAEL = 75 mg/kg-d	TDI = NOAEL/UF	nephrotoxic: renal tubular pathology, decreased kidney weights	Group D: IRIS (not classifiable as to human carcinogenicity)	IRIS: U.S. EPA, 1993b (based on U.S. EPA, 1989)
selenium	UL (IOM)	µg/d	Yang and Zhou, 1994	NOAEL (adults) = 800 µg/	UL (IOM) = NOAEL/UF UL (HC) = UL (IOM) adjusted	selenosis	IOM does not consider selenium carcinogenic to humans.	IOM 2000; CCME, 2009 (based on Yang and Zhou, 1994; Shearer
	0–6 months	4.5E+01	Study Type: epidemiological (cohort)					
	7 months–1year	6E+01	Species: human					
	1–3 years	9E+01	Mode of administration: diet					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
	4–8 years	1.5E+02	Dosing Regime: N/A		for age group and body weight		Group 3: IARC (not classifiable as to human carcinogenicity) Group B2: U.S. EPA (probable human carcinogen) for selenium sulphide	and Hadjimarkos, 1975)
	9–13 years	2.8E+02	Duration: N/A					
	14–18 years	4E+02	Uncertainty Factors: 2 (severity of irreversible results)					
	≥ 19 years (76 kg male, 61k g female)	4E+02						
	UL (HC)	(µg/kg-d)	Shearer and Hadjimarkos, 1975	NOAEL (infants and children) =7 µg/kg-d				
			Study Type: chronic, epidemiological					
	0–6 months‡	5.5	Species: human (infants)					
	7 months–4 years	6.2	Mode of administration: diet					
	5–11 years	6.3	Dosing Regime: N/A					
	12–19 years	6.2	Duration: N/A					
	20+ years(70.7kg)	5.7	Uncertainty Factors: 1					
styrene	oral TDI	1.2E-01 mg/kg-d	Study Type: chronic	NOAEL = 12 mg/kg-d	TDI = NOAEL/UF	reproductive effects: reduced gestational survival, pup survival, pup body weight	Group III: CEPA (possible germ cell mutagen, and possibly carcinogenic to humans)	PSL: HC 1996a; HC/EC 1993g (based on Beliles et al., 1985)
			Species: rats					
			Mode of administration: drinking water					
			Dosing Regime: 125 and 250 ppm; 7.7 and 14 mg/kg-d (males), 12 and 21 mg/kg-d (females)					
			Duration: 2 years, 3 generations					
			Uncertainty Factors: 100 (10x each for intra- and interspecies variability)					
	inhalation TC	9.2E-02 mg/m^3	Study Type: chronic	LOAEL = 260 mg/m^3	TC = LOAEL/UF	decreased pup body weight, decreased neuroamines, neurological/behavioural changes	Group III: CEPA (possible germ cell mutagen; possibly carcinogenic to humans)	PSL: HC/EC, 1993g (based on Kishi et al., 1992)
			Species: rats					
			Mode of administration: inhalation					
			Dosing Regime: 0, 50, and 300 ppm; 260 and 1280 mg/m^3, 6 h/d for days 7–21 of gestation; postnatal exposure of pups to 217mg/m^3, 7 h/d for 48 d from birth	(46 mg/m^3$ adjusted for continuous exposure and human equivalent: 5–11 years)				

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Duration: 1 gestational period, 48 d post-natal exposure Uncertainty Factors: 500 (10x each for intra- and interspecies variability, 5x for use of LOAEL)					
tetrachlorobenzene, 1,2,3,4-	oral TDI	3.4E-03 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: diet Dosing Regime: 0, 0.5, 5.0, 50, or 500 ppm Duration: 13 weeks Uncertainty Factors: 10,000 (10x each for intra- and interspecies variability, 10x for subchronic, 10x for limited database)	NOAEL = 34 mg/kg-d (males) 41 mg/kg-d (females)	TDI = NOAEL/UF	histological changes in the liver and kidney	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL1: HC/EC, 1993h (based on Chu et al., 1984)
tetrachlorobenzene, 1,2,3,5-	oral TDI	4.1E-04 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: diet Dosing Regime: 0, 0.5, 5.0, 50, or 500 ppm Duration: 13 weeks Uncertainty Factors: 10,000 (10x each for intra- and interspecies variability, 10x for subchronic, 10x for limited database)	NOAEL = 4.1 mg/kg-d	TDI = NOAEL/UF	histopathological lesions in the liver	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL: HC/EC, 1993h (based on Chu et al., 1984)
tetrachlorobenzene, 1,2,4,5-	oral TDI	2.1E-04 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: diet Dosing Regime: 0, 30, 100, 1000, or 2000 ppm Duration: 13 weeks Uncertainty Factors: 10,000 (10x each for intra- and interspecies variability, 10x for subchronic, 10x for limited database)	NOAEL = 2.1 mg/kg-d	TDI = NOAEL/UF	thyroid follicular cell hypertrophy	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL: HC/EC, 1993h (based on NTP, 1991b)
tetrachlorophenol, 2,3,4,6-	oral ADI	1E-02 mg/kg-d	Study Type: subchronic, reproductive Species: rats	NOAEL = 10 mg/kg-d	ADI = NOAEL/UF	delayed ossification of	Group VA: (inadequate data	GCDWQ: HC, 1987b (based

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Mode of administration: gavage (corn oil)			skull bones of rat fetuses	for evaluation)	on Schwetz et al., 1974)
			Dosing Regime: 10 and 30 mg/kg-d					
			Duration: 10 d (days 6–15 of gestation)					
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for subchronic study)					
tetrachloroethylene	oral TDI	1.4E-02 mg/kg-d	Study Type: subchronic	NOAEL = 14 mg/kg-d	TDI = NOAEL/UF	reduced weight gain, increased liver to body weight ratio, increased kidney to body weight ratio	Group III: CEPA (possibly carcinogenic to humans)	GCDWQ: HC, 1996b (based on Hayes et al., 1986)
			Species: rats					
			Mode of administration: drinking water					
			Dosing Regime: 14, 400, and 1400 mg/kg-d					
			Duration: 90 d	MAC = 0.03 mg/L				
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic)					
	inhalation TC	3.6E-01 mg/m^3	Study Type: chronic	LOAEL = 678 mg/m^3 (363 mg/m^3 adjusted for continuous exposure and human equivalent: 5–11 years)	TC = LOAEL/UF	nephrotoxic, hepatotoxic, lung congestion, mononuclear cell leukemia	Group IV: CEPA (unlikely to be carcinogenic to humans) Group 2A: IARC (probably carcinogenic to humans)	PSL: HC, 1996b; HC/EC, 1993i (based on NTP, 1986c)
			Species: rats and mice					
			Mode of administration: inhalation					
			Dosing Regime: 0, 200 and 400 ppm (rats); 0, 100, and 200 ppm (mice); 6 h/d, 5 d/week					
			Duration: 103 weeks					
			Uncertainty Factors: 1000 (10x for intraspecies and 10x for interspecies variation, 10x for LOAEL vrs. NOAEL)					
toluene	oral TDI	2.2E-01 mg/kg-d	Study Type: subchronic	NOAEL = 312 mg/kg-d (222.8 mg/kg-d adjusted for continuous exposure)	TDI = NOAEL/UF	increased relative liver and kidney weight neurotoxic, irritation of the respiratory tract	Group IV: CEPA (unlikely to be carcinogenic to humans)	PSL: HC, 1996a, (based on NTP, 1990a)
			Species: rats and mice					
			Mode of administration: gavage					
			Dosing Regime: 0, 312, 625, 1250, 2500, and 5000 mg/kg-d, 5 d/week					
			Duration: 13 weeks					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic)					
	inhalation TC	3.75 mg/m^3	Study Type: acute	NOAEL = 150 mg/m^3	TC = NOAEL/UF			PSL: HC, 1996a; HC/EC 1992c (based on Andersen et al., 1983)
			Species: human volunteers					
			Mode of administration: inhalation	(37.5 mg/m^3 adjusted for continuous exposure)				
			Dosing Regime: 0, 10, 40, and 100 ppm, 6 h/d (each group assigned 1 dose/d)					
			Duration: 4 d					
			Uncertainty Factors: 10 (10x intraspecies variation)					
tributyltin oxide (TBTO)	oral TDI	2.5E-04 mg/kg-d	Study Type: chronic	NOAEL = 0.025 mg/kg-d	TDI = NOAEL/UF	decreased host resistance to nematode *Trichinella spiralis* (depressed serum IgE, increased muscle larvae); (thymus-dependent immunosuppression; suppressed natural killer cell activity in spleen cells; non-specific immunosupression (Vos et al., 1990) increased food and water consumption (behavioural), and lymphocytopenia (immune) (Wester et al., 1990)	Group D: IRIS (not classifiable as to human carcinogenicity)	HC Food Directorate (based on Vos et al., 1990; Wester et al., 1990
			Species: rats (Wistar strain for both studies)					
			Mode of administration: diet					
			Dosing Regime: 0, 0.5, 5, and 50 mg TBTO/kg feed; equivalent to 0.025, 0.25, and 2.5 mg/kg-d	(calculated from 0.5 mg TBTO/kg feed and study feed ingestion rates and body weights)				
			Duration: endpoint specific: up to 17 months (Vos et al., 1990); up to 106 weeks (Wester et al., 1990)					
			Uncertainty Factors: 100 (10x each for intra- and interspecies variability)					

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
trichlorobenzene, 1,2,3-	oral TDI	1.5E-03 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: diet Dosing Regime: 1, 10, 100, or 1000 ppm Duration: 13 weeks Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)	NOAEL = 100 ppm (7.7 mg/kg-d)	TDI = NOAEL/UF	reduced weight gain, increased relative liver and kidney weight, histological changes in liver and thyroid	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL: HC/EC, 1993j (based on Côté et al., 1988)
trichlorobenzene, 1,2,4-	oral TDI	1.6E-03 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: diet Dosing Regime: 1, 10, 100, or 1000 ppm Duration: 13 weeks Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)	NOAEL = 100 ppm (7.8 mg/kg-d)	TDI = NOAEL/UF	increased relative liver and kidney weights, and absolute kidney weight; histopathological changes in liver and thyroid	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL: HC/EC, 1993j (based on Côté et al., 1988)
	inhalation TC	7E-03 mg/m^3	Study Type: subchronic Species: rats Mode of administration: inhalation Dosing Regime: 0, 223 or 746 mg/m^3, 7 h/d, 5 d/week Duration: 44 d Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)	NOAEL = 223 mg/m^3 (32.9 mg/m^3 adjusted for continuous exposure and human equivalent: 5–11 years)	TC = NOAEL/UF	increased liver weight and relative kidney weight		PSL1: HC/EC, 1993j (based on Kociba et al., 1981)
trichlorobenzene, 1,3,5-	oral TDI	1.5E-03 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: diet Dosing Regime: 1, 10, 100, or 1000 ppm Duration: 13 weeks	NOAEL = 100 ppm (7.6 mg/kg-d)	TDI = NOAEL/UF	increased relative liver and kidney weight; histological changes in liver, kidney, and thyroid	Group VI: CEPA (unclassifiable with respect to carcinogenicity to humans)	PSL1: HC/EC, 1993j (based on Côté et al., 1988)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)					
	inhalation TC	3.6E-03 mg/m^3	Study Type: subchronic Species: rats Mode of administration: inhalation Dosing Regime: 0, 10, 100, and 1000 mg/m^3, 6 h/d, 5 d/week Duration: 13 weeks Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)	NOAEL = 100 mg/m^3 (17.9 mg/m^3 adjusted for continuous exposure)	TC = NOAEL/UF	squamous metaplasia and hyperplasia in the respiratory epithelium of the nasal passage		PSL1: HC/EC, 1993j (based on Sasmore et al., 1988)
trichloroethylene[§] (TCE)	oral TDI	1.46E-03 mg/kg-d	Study Type: subchronic, developmental Species: rats Mode of administration: drinking water Dosing Regime: 0, 0.18, and 132 mg/kg-d Duration: 3 dosing regimes: for 3 months before pregnancy, for 2 months before and 21 d during pregnancy, or for 21 d during pregnancy only Uncertainty Factors: 100 (10x each for intra- and interspecies variability)	LOAEL = 0.18 mg/kg-d $BMDL_{10}$ = 0.146 mg/kg-d (NOAEL estimate)	TDI = $BMDL_{10}$/UF	fetal heart defect, nephrotoxic effect	Group II: CEPA (probably carcinogenic to humans) Group 2A: IARC (probably carcinogenic to humans)	GCDWQ: HC, 2005; PSL1: HC/EC, 1993k (based on Dawson et al., 1993)
	oral SF	8.11E-04 $(mg/kg-d)^{-1}$	Study Type: chronic Species: rats Mode of administration: gavage Dosing Regime: 0, 500 and 1000 mg/kg-d, 5 d/week Duration: 103 weeks Uncertainty Factors: N/A	SF range: 5.8E-04 to 8.1E-04 $(mg/kg-d)^{-1}$	linearized multistage method, including allometric scaling	carcinogenic: tubular cell adenomas and adenocarcinomas of the kidneys	Group II: CEPA (probably carcinogenic to humans)	GCDWQ: HC, 2005, (based on NTP, 1988, 1990b)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
	inhalation SF inhalation UR	2.6E-03 $(mg/kg\text{-}d)^{-1}$ 6.1E-04 $(mg/m^3)^{-1}$	Study Type: chronic Species: rats Mode of administration: inhalation Dosing Regime: 0, 546, 1638, and 3276 mg/m^3, 7 h/d, 5 d/week Duration: 104 weeks Uncertainty Factors: N/A	TC_{05} = 101.9 ppm (82 mg/m^3 adjusted for continuous exposure and human equivalent: child 5–11 years)	multistage modelling	carcinogenic: Leydig cell tumours in testes	Group II: CEPA (probably carcinogenic to humans)	PSL1: HC, 1996a; HC/EC,1993k (based on Maltoni et al., 1986, 1988)
trichlorophenol, 2,4,6-	oral SF	2E-02 $(mg/kg\text{-}d)^{-1}$	Study Type: chronic Species: rats Mode of administration: diet Dosing Regime: 5,000 or 10,000 ppm (10,000 or 20,000 ppm for 38 weeks followed by 2,500 and 5,000 ppm for remainder of study for females) Duration: 105 to 107 weeks Uncertainty Factors: N/A	drinking water UR (1 µg/L) range: 1.8E-8 to 4.3E-7	robust linear extrapolation model incorporating a surface-area correction	lymphomas, leukemia, hepatocellular caracinomas and adenomas	Group II: CEPA (probably carcinogenic to humans)	GCDWQ: HC, 1987b (based on NCI, 1979)
trichloropropane, 1,2,3-	oral TDI	6E-03 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: gavage Dosing Regime: 8, 16, 32, 63, 125, or 250 mg/kg-d, 5 d/week Duration: 120 d Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic)	NOAEL = 8 mg/kg-d (5.71 mg/kg-d adjusted for daily dosing schedule)	TDI = NOAEL/UF	alterations in clinical chemistry, reduction in red cell mass	IRIS (inadequate data for evaluation of carcinogenicity) Group 2A: IARC (probably carcinogenic to humans)	IRIS: U.S. EPA, 1990 (based on NTP, 1983c)
uranium	oral TDI	6E-04 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: drinking water Dosing Regime: 0.06, 0.31, 1.52, 7.54, and 36.73 mg/kg-d (males); 0.09, 0.42, 2.01, 9.98, and 53.56 mg/kg-d (females)	LOAEL = 0.06 mg/kg-d IMAC = 0.02 mg/L	TDI = LOAEL/UF	nephrotoxic, hepatotoxic effects	Group V (inadequate data for evaluation of carcinogenicity)	CSQG: CCME,2006, 2007b, 2008; GCDWQ: HC, 2001 (based on Gilman, 1998)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Duration: 91 d Uncertainty Factors: 100 (10x each for intra- and interspecies variability)					
vinyl chloride	oral SF	2.6E-01 $(mg/kg\text{-}d)^{-1}$	Til et al., 1991 Study Type: chronic Species: rats Mode of administration: diet Dosing Regime: 0.017, 0.17, and 1.7 mg/kg-d Duration: 149 weeks Uncertainty Factors: N/A Feron et al., 1981 Study Type: Chronic Species: rats Mode of administration: diet; highest dose by gavage as a positive control Dosing Regime: 0, 1.7, 5.0, 14.1, and 300 mg/kg-d Duration: lifetime (up to 140 weeks) Uncertainty Factors: N/A	UR range: 5.6E-06 to 5.8E-07 MAC = 0.002 mg/L	model-free extrapolation with surface-area correction	carcinogenic: hepatocellular angiosarcomas and carcinomas	Group I: CEPA (carcinogenic to humans)	GCDWQ: HC, 1992 (based on Til et al., 1983,1991; Feron et al., 1981)
xylene	oral TDI	1.5E+00 mg/kg-d	Study Type: subchronic Species: rats Mode of administration: gavage Dosing Regime: 0, 150, 750, and 1500 mg/kg-d Duration: 90 d Uncertainty Factors: 100 (10x each for intra- and interspecies variability)	NOAEL = 150 mg/kg-d	TDI = NOAEL/UF	enlarged livers and kidneys	Group IV: CEPA (unlikely to be carcinogenic to humans)	PSL1: HC, 1996a (based on Condie et al., 1988)
	inhalation TC	1.8E-01 mg/m^3 (provisional)	Study Type: subchronic, developmental Species: rats Mode of administration: inhalation Dosing Regime: 0, 250, 1900, and 3400 mg/m^3, 24 h/d	LOAEL = 250 mg/m^3 (180 mg/m^3	TC = LOAEL/UF	maternal effects, fetal retardation, increased proportion of fetal mortality and	Group IV: CEPA (unlikely to be carcinogenic to humans)	PSL1: HC, 1996a (based on Ungvary and Tantrai, 1985)

Substance	Type of TRV	TRV value	Study details	Threshold/ non-threshold endpoint	TRV derivation	Critical health effect	Carcinogenicity classification	TRV source
			Duration: 8 d, on gestational days 7–15	adjusted for human equivalent: 7–11 years)		resorbed fetuses		
			Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, and 10x LOAEL vs. NOAEL and limitations of the study)					
zinc	UL (IOM) 0–6 months 7 months–1 year 1–3 years 4–8 years 9–13 years 14–18 years ≥ 19years (76 kg male, 61 kg female)	mg/d 4 5 7 12 23 34 40	Yadrick et al., 1989 Study Type: subchronic prospective supplementation trial Species: human (adults) Mode of administration: dietary supplements Dosing Regime: 10 mg/d (dietary intake) + 50 mg/d (supplement) Duration: 10 weeks Uncertainty Factors: 1.5 (intraspecies variability and extrapolation of LOAEL to NOAEL)	LOAEL (adult) = 60 mg/d	UL (IOM) = LOAEL/UF UL (HC) = UL (IOM) adjusted for age group and body weight	reduced iron and copper status	IOM does not consider zinc carcinogenic to humans.	IOM, 2001 (adult data based on Yadrick et al., 1989; infants and children data based on Walravens and Hambidge, 1976)
	UL (HC) 0–6 months 7 months–4 years 5–11 years 12–19 years 20+ years (70.7 kg)	mg/kg-d 5E-01 5E-01 5E-01 5E-01 6E-01	Walravens and Hambidge, 1976 Study Type: subchronic prospective supplementation trial Species: human (infants) Mode of administration: dietary supplements Dosing Regime: 1.8 mg/L (formula concentration, control group), 5.8 mg/L (formula concentration + 4mg/L supplement) Duration: 6 months Uncertainty Factors: none	NOAEL (infants and children) = 4.5 mg/d	UL_{infant} adjusted for body weight of other receptors	increased growth of infant: length, weight, and head circumference		

Note: For TRVs based on a TC_{05}, inhalation unit risks were derived as $UR_{Inh} = 0.05/TC_{05}$; inhalation slope factor was derived as $SF_{Inh} = 0.05/(TC_{05} \times$ inhalation rate [16.6 m^3/d]/bw [70.7 kg]); oral slope factor was derived as $SF_{Oral} = 0.05/TD_{05}$; SF = UR $\times$ bw (70.7 kg)/drinking water consumption rate (1.5 L/d).

* A dermal slope factor of 3.5 $(\mu g/cm^2\text{-}d)^{-1}$ together with a relative absorption factor (RAF_{derm}) of 0.084 were derived for benzo[*a*]pyrene (Knafla et al., 2006). See text for details.

† U.S. EPA, 1985 (draft, subsequently published in 1987) indicates that there are inadequate data to conclude that chromium is carcinogenic via oral ingestion.

‡ No data, assumed equivalent to the toddler.

§ Exposure to TCE via oral, inhalation, and dermal routes may lead to developmental effects, which is the most sensitive endpoint for TCE toxicity. The doses from all exposure routes should be summed and compared to the oral TDI in order to evaluate non-cancer effects. The inhalation and oral doses should be evaluated separately, however, in relation to the respective cancer slope factors.

GLOSSARY FOR APPENDIX A

BMDL	benchmark dose lower limit
$BMDL_{05}$ or $BMDL_{10}$	benchmark dose lower limit associated with an incidence of 5% or 10% of induced tumors
DQRA	detailed quantitative risk assessment
HEC	human equivalent concentration
IMAC	interim maximal acceptable concentration (drinking water)
LOAEL	lowest observable adverse effect level
LOEL	lowest observable adverse effect level
MAC	maximum acceptable concentration in drinking water
N/A	not applicable
NOAEL	no observable adverse effect level
PBPK	physiologically-based pharmacokinetic (model)
POD	point of departure
pTMI	provisional tolerable monthly intake
pTWI	provisional tolerable weekly intake
RfD	reference dose
SF	slope factor
TC	tolerable concentration
TC_{05} or TC_{10}	tumorigenic concentration found to induce a 5% or 10% increase in the incidence of, or deaths due to, tumours considered to be associated with exposure
TD_{05} or TD_{10}	tumorigenic dose found to induce a 5% or 10% increase in the incidence of, or deaths due to, tumours considered to be associated with exposure
TDI	tolerable daily intake
TRV	toxicological reference value
TWA	time-weighted average
UF	uncertainty factor
UL	tolerable upper limit (for essential elements)
UR	unit risk

SOURCES

CCME	Canadian Council of Ministers of the Environment
CEPA	Canadian Environmental Protection Act
CIIT	Chemical Industry Institute of Toxicology
CSD	Contaminated Sites Division (Health Canada)
CSQG	Canadian Soil Quality Guidelines
GCDWQ	Guidelines for Canadian Drinking Water Quality
HC	Health Canada
EC	Environment Canada
EU	European Union
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 (U.S. EPA)
NTP	National Toxicology Program
NCI	National Cancer Institute
PSL	Priority Substance List
SLI	Springborn Laboratories, Inc.
U.S.	EPA United States Environmental Protection Agency
WHO	World Health Organization

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