



Part II:

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



**Federal
Contaminated
Site Risk
Assessment
in Canada**

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. We assess the safety of drugs and many consumer products, help improve the safety of food, and provide information to Canadians to help them make healthy decisions. We provide health services to First Nations people and to Inuit communities. We work with the provinces to ensure our health care system serves the needs of Canadians.

Published by authority of the Minister of Health.

Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors, Version 2.0

is available on Internet at the following address:

www.healthcanada.gc.ca

Également disponible en français sous le titre :

L'évaluation des risques pour les sites contaminés fédéraux au Canada, Partie II : Valeurs toxicologiques de référence (VTR) de Santé Canada et paramètres de substances chimiques sélectionnées, version 2.0.

This publication can be made available on request in a variety of alternative formats.

For further information or to obtain additional copies, please contact:

Publications

Health Canada

Ottawa, Ontario K1A 0K9

Tel.: 613-954-5995

Fax: 613-941-5366

E-mail: info@hc-sc.gc.ca

© Her Majesty the Queen in Right of Canada,
represented by the Minister of Health, 2010

This publication may be reproduced without permission provided the source is fully acknowledged.

Cat.: H128-1/11-638E-PDF

ISBN: 978-1-100-17925-4

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

TABLE OF CONTENTS

| | |
|---|----|
| PREFACE | iv |
| SUMMARY OF REVISIONS..... | v |
| ABBREVIATIONS AND ACRONYMS | vi |
| 1.0 INTRODUCTION | 1 |
| 2.0 HEALTH CANADA TOXICOLOGICAL REFERENCE VALUES (TRVs)..... | 1 |
| 2.1 Toxicological Reference Values for Environmental Contaminants | 1 |
| 2.2 Toxicological Reference Values for Essential Trace Elements..... | 2 |
| 2.2.1 Rationale for essential trace element toxicological reference values..... | 2 |
| 2.3 Toxicological Reference Values for Pesticides | 4 |
| 3.0 RELATIVE ABSORPTION FACTORS (RAF _{ORAL} , RAF _{INH} , RAF _{DERM}) | 4 |
| 3.1 Oral Exposures | 5 |
| 3.2 Inhalation Exposures | 5 |
| 3.3 Dermal Exposures | 5 |
| 4.0 PHYSICAL-CHEMICAL PROPERTIES OF CONTAMINANTS..... | 7 |
| 5.0 SUMMARIES OF TOXICOLOGICAL REFERENCE VALUE STUDIES | 7 |
| 6.0 REFERENCES | 7 |
| APPENDIX A Summary of the key toxicological endpoint(s) for Toxicological Reference Values (TRVs)..... | 17 |

LIST OF FIGURES

| | | |
|----------|--|---|
| Figure 1 | Percentage of Population at Risk of Deficiency or Toxic Effects from Oral Intake..... | 3 |
| Figure 2 | Comparison of the Tolerable Upper Intake Level (UL) and the Reference Dose (RfD) for Zinc..... | 4 |

LIST OF TABLES

| | | |
|---------|---|----|
| Table 1 | Toxicological Reference Values (TRVs) Recommended for Use in Human Health Risk Assessments of Federal Contaminated Sites | 10 |
| Table 2 | Toxicological Reference Values (TRVs) for Pesticides Recommended for Use in Human Health Risk Assessments of Federal Contaminated Sites | 14 |
| Table 3 | Dermal Relative Absorption Factors (RAF _{Derm}) of Selected Substances | 15 |
| Table 4 | Sources of Physical–Chemical Property Data in the Health Canada PQRA Spreadsheet Tool | 16 |

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.

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):

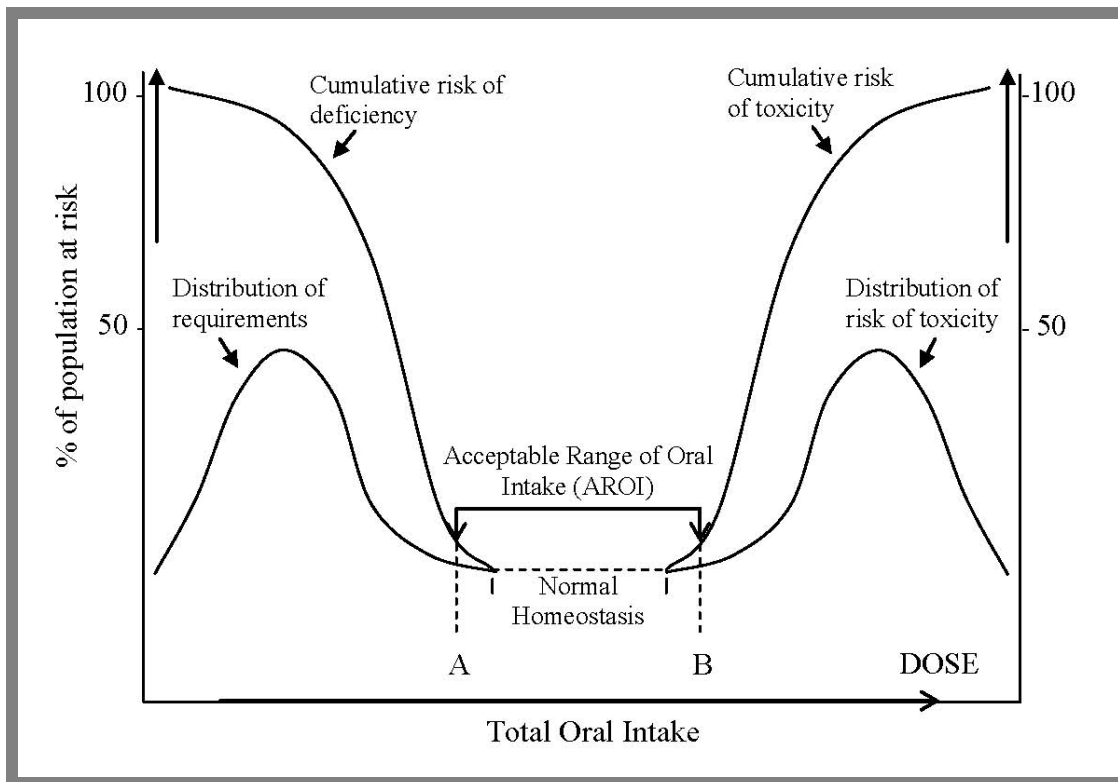
- **Recommended Dietary Allowance (RDA):** average daily nutrient intake level sufficient to meet the nutrient requirement of nearly all (97% to 98%) healthy individuals in a particular life stage and gender group
- **Adequate Intake (AI):** recommended average daily intake level based on observed or 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.

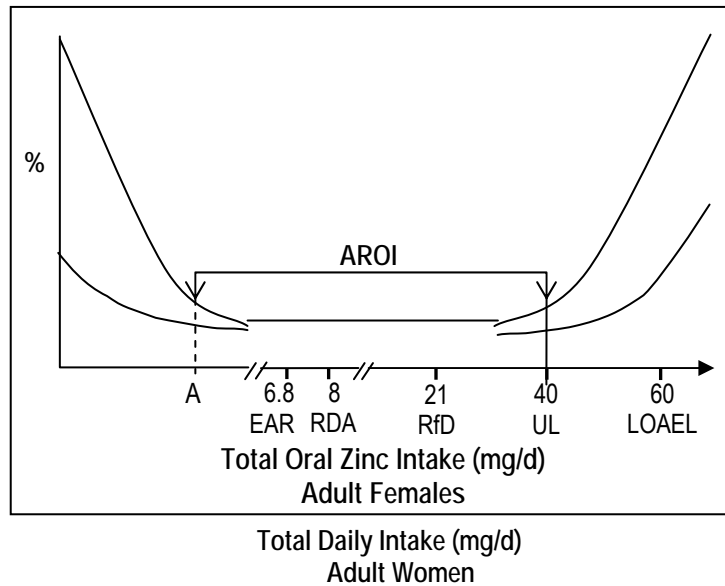
Figure 2 Comparison of the Tolerable Upper Intake Level (UL) and the Reference Dose (RfD) for Zinc

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



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:

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

Similarly, where oral exposures are characterized with inhalation TRVs, a $\text{RAF}_{\text{Oral}} = 1$ will generally be assumed unless there is evidence (with references provided) that oral absorption is significantly greater ($\text{RAF}_{\text{Oral}} > 1$) or less ($\text{RAF}_{\text{Oral}} < 1$) 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:

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

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 ($\text{RAF}_{\text{Inh}} > 1$) or less ($\text{RAF}_{\text{Inh}} < 1$) 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:

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

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 $10\% \div 100\% = 10\%$. However, if oral absorption in the principal study was only 50%, then the RAF_{Derm} would be $10\% \div 50\% = 20\%$.

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.

6.0 REFERENCES

- Abernathy, C. 1999. *Risk Assessment of Essential Trace Elements – An International Approach*. Proceedings of the Annual Summer Meeting of the Toxicology Forum, July 12–16, Aspen, CO.
- Becking, G.C. 1998. The effect of essentiality on risk assessment. *Biol. Trace Elem. Res.* 66(1–3): 423–438.
- California Environmental Protection Agency (Cal EPA). 2000. *Air Toxics Hot Spots Program Risk Assessment Guidelines. Part IV. Technical Support Document for Exposure Assessment and Stochastic Analysis*. Appendix F: Dermal Absorption Factors. Cal EPA, Office of Environmental Health Hazard Assessment.
- Canadian Council of Ministers of the Environment (CCME). 2008. *Canada-Wide Standards for Petroleum Hydrocarbons (PHCs) in Soil: Scientific Rationale* (Supporting Technical Document). CCME, Winnipeg.
- CRC. 2009. *CRC Handbook of Chemistry and Physics*. CRC Press, Boca Raton, FL.
- Dourson, M.L., M.E. Andersen, L.S. Erdreich, and J.A. MacGregor. 2001. Using human data to protect the public's health. *Reg. Toxicol. Pharmacol.* 33(2): 234–256.
- Food and Agriculture Organization and World Health Organization (FAO/WHO). 1988. *Requirements of Vitamin A, Iron, Folate and Vitamin B₁₂*. Report of the Joint FAO/WHO Expert Consultation, Rome. Food and Agriculture Organization of the United Nations. FAO Food and Nutrition Series, No. 23.
- Goldhaber, S.B. 2003. Trace element risk assessment: Essentiality vs. toxicity. *Reg. Toxicol. Pharmacol.* 38(2): 232–242.
- Health Canada (HC). 1994. *Human Health Risk Assessment for Priority Substances*. Priority Substances List Assessment Report. Health Canada, Ottawa.

- HC. 1995. Part I: Approach to the derivation of drinking water guidelines. In: *Guidelines for Canadian Drinking Water Quality – Supporting Documentation*. Health Canada, Ottawa.
- HC. 1996. *Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/Concentrations for Priority Substances*. Report no. 96-EHD-194. Ottawa.
- HC. 2002 (and later revisions). *Guidelines for Canadian Drinking Water Quality, Supporting Documentation*. Ottawa. Available in two sections. Accessed December 10, 2009, from <http://www.hc-sc.gc.ca/ewh-semt/water-eau/drink-potab/guide/index-eng.php> and http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/index-eng.php#tech_doc.
- HC. unpublished. *Spreadsheet Tool for Human Health Preliminary Quantitative Risk Assessment*. Version dated October 31st, 2008. Contaminated Sites Division, Safe Environments Directorate, Health Canada, Ottawa.
- HC. 2010a. *Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0*. Contaminated Sites Division, Safe Environments Directorate, Health Canada, Ottawa, Ontario.
- HC. 2010b. *Federal Contaminated Site Risk Assessment in Canada, Part V: Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals (DQRA_{chem})*. Contaminated Sites Division, Safe Environments Directorate, Health Canada, Ottawa, Ontario.
- Institute of Medicine of the National Academies (IOM). 2000. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of DRIs, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board of the Institute of Medicine of the National Academies. National Academy Press, Washington, DC.
- IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. A Report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of the Interpretation and Uses of Dietary Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board of the Institute of Medicine of the National Academies. National Academy Press, Washington, DC.
- Ishimatsu, S., T. Kawamoto, K. Matsuno, and Y. Kodama. 1995. Distribution of various nickel compounds in rat organs after oral administration. *Biol. Trace Element Res.* 49: 43–52.
- Knafla, A., S. Petrovic, M. Richardson, J. Carey, and C. Rowat. In press. *Development and Application of a Skin Cancer Slope Factor for Exposures to benzo[a]pyrene in Soil*. *Regulatory Toxicology and Pharmacology* (2010). doi: <http://dx.doi.org/10.1016/j.yrtph.2010.09.011>
- MacKay, D., W.Y. Shiu, K.-C. Ma, and S.C. Lee. 2006. *Physical, Chemical Properties and Environmental Fate for Organic Chemicals, 2nd ed.* CRC Press: Boca Raton, FL.
- Massachusetts Department of Environmental Protection (MassDEP). 1992. *Documentation for the Risk Assessment Shortform Residential Scenario, Version 1.6 a and b*. Appendix C: Relative Absorption Factors. MassDEP, Office of Research and Standards and the Bureau of Waste Site Cleanup. Policy WSC/ORS-142-92.
- Mertz, W. 1980. Mineral elements: New perspectives. *J. Am. Diet. Assoc.* 77(3): 258–263.
- Mertz, W. 1995. Risk assessment of essential trace elements: New approaches to setting recommended dietary allowances and safety limits. *Nutr. Rev.* 53(7): 179–185.
- Mertz, W. 1998. A perspective on mineral standards. *J. Nutr.* 128(2 Suppl): 375S–378S.
- Montgomery, J.H. 2000. *Groundwater Chemicals Desk Reference, 3rd ed.* CRC Press: Boca Raton, FL.
- Moody, R.P., J. Joncas, M. Richardson, and I. Chu. (2007). Contaminated soils (I): *In vitro* dermal absorption of benzo[a]pyrene in human skin. *J. Toxicol. Environ. Health. Part A.* 70(21) 1858–1865.
- Moody, R.P., J. Joncas, M. Richardson, S. Petrovic, and I. Chu. (2009). Contaminated soils (II): *In vitro* dermal absorption of nickel (Ni-63) and mercury (Hg-203) in human skin. *J. Toxicol. Environ. Health. Part A.* 72(8): 551–559.
- Morcillo, M.A., and J. Santamaria. 1995. Whole-body retention, and urinary and fecal excretion of mercury after subchronic oral exposure to mercuric chloride in rats. *Biomaterials* 8(4): 301–308.
- Munro, I. 1999. *Perspective of the Food and Nutrition Board Subcommittee on Upper Reference Levels of Nutrients*. Proceedings of the Annual Summer Meeting of the Toxicology Forum, July 12–16, Aspen, CO.
- National Institute of Standards and Technology (NIST). 2005. *NIST Chemistry WebBook, Standard Reference*

Database Number 69, June 2005 Release. Accessed December 9, 2009, from <http://webbook.nist.gov/chemistry/>.

National Environmental Policy Institute (NEPI). 2000a. *Assessing the Bioavailability of Metals in Soil for Use in Human Health Risk Assessments*. Bioavailability Policy Project Phase II, Metals Task Force Report. NEPI.

NEPI. 2000b. *Assessing the Bioavailability of Organic Chemicals in Soil for Use in Human Health Risk Assessments*. Bioavailability Policy Project Phase II, Organics Task Force Report. NEPI.

New York State (NYS). 2006. *New York State Brownfield Cleanup Program. Development of Soil Cleanup Objectives*. Technical Support Document. New York State Department of Health and New York State Department of Environmental Conservation. Accessed December 9, 2009, from http://www.dec.ny.gov/docs/remediation_hudson_pdf/techsu_ppdoc.pdf.

Ontario Ministry of Environment (OMOE). 2009. *Rationale for the Development of Soil and Groundwater Standards for Use at Contaminated Sites in Ontario*. Standards Development Branch, OMOE, Toronto. Accessed January 18, 2010, from http://www.ene.gov.on.ca/environment/en/resources/STDPR_OD_081485.html.

Sandstead, H.H. 1995. Requirements and toxicity of essential trace elements, illustrated by zinc and copper. *Am. J. Clin. Nutr.* 61(3 Suppl): 621S–624S.

United States Department of Energy (U.S. DOE). Risk Assessment Information System (RAIS). *Chemical-Specific Factors*. Oak Ridge Operations Office (ORO). Accessed December 9, 2009, from http://rais.ornl.gov/cgi-bin/tools/TOX_search?select=chem_spef.

U.S. EPA. 1992. *Dermal Exposure Assessment: Principles and Applications*. Interim Report (DEA). Accessed December 9, 2009, from <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188>.

U.S. EPA. 1994. Region 9 *Regional Screening Levels (RSL) for Chemical Contaminants at Superfund Sites*. Chemical Specific Parameters. Accessed December 9, 2009, from <http://www.epa.gov/region09/superfund/prgl/>.

U.S. EPA. 1995. *Region 3 Technical Guidance Manual, Risk Assessment: Assessing Dermal Exposure from Soil*. U.S. Environmental Protection Agency Region III, Hazardous Waste Management Division. EPA/903-K-95-003.

U.S. EPA. 2004. *Risk Assessment Guidance for Superfund (RAGS), Volume 1: Human Health Evaluation Manual*. Part E, Supplemental Guidance for Dermal Risk Assessment.

United States Environmental Protection Agency (U.S. EPA). 2005. Johnson & Ettinger (1991) Model for Subsurface Vapour Intrusion into Buildings. Accessed December 9, 2009, from http://www.epa.gov/oswer/riskassessment/airmodel/johnson_ettinger.htm.

U.S. EPA. 2009a. *Office of Pollution Prevention and Toxics, Syracuse Research Corporation. Estimations Programs Interface (EPI) Suite™*. version 4.0. Accessed December 9, 2009, from <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm>.

U.S. EPA. 2009b. *EPA On-line Tools for Site Assessment Calculation. On-Site: the On-line Site Assessment Tool*. Diffusion Coefficient Estimation – Extended Input Range. Office of Research and Development. Accessed December 9, 2009, from <http://www.epa.gov/athens/learn2model/part-two/onsite/estdiffusion-ext.htm>.

Wester, R.C., H.I. Maibach, D.A.W. Bucks, L. Sedik, J. Melendres, C.L. Laio, and S. DeZio. 1990. Percutaneous absorption of [¹⁴C]DDT and [¹⁴C]benzo(a)pyrene from soil. *Fund. Appl. Toxicol.* 15: 510–516.

World Health Organization (WHO). 1996. *Trace Elements in Human Nutrition and Human Health*. Prepared in collaboration with the Food and Agriculture Organization of the United Nations and the International Atomic Energy. Geneva.

WHO. 2002. *Principles and Methods for the Assessment of Risk from Essential Trace Elements*. International Programme on Chemical Safety. Environmental Health Criteria 228. Geneva.

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-d) ⁻¹ | Inhalation slope factor (mg/kg bw-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[<i>a</i>]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-d) ⁻¹ | Inhalation slope factor (mg/kg bw-d) ⁻¹ | Inhalation unit risk (mg/m ³) ⁻¹ |
| <i>n</i> -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 | 0.00047 | | | | |
| | general adult population | | | | |
| | women of child-bearing age, and children < 12 years | 0.0002 | | | |
| Methylnaphthalene, 2- | 0.004 | | | | |
| Methyl <i>tertiary</i> -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 |
| Nitilotriacetic 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 <i>Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0, Table 8</i>) | | | | |

| 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-d) ⁻¹ | Inhalation slope factor (mg/kg bw-d) ⁻¹ | Inhalation unit risk (mg/m ³) ⁻¹ |
| PCBs (total of non-coplanar) | 0.00013 | | | | |
| Polychlorinated dibenzo- <i>p</i> -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 [§] | | | | | |
| 0–0.5 years | 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 $3.5 (\mu\text{g}/\text{cm}^2\text{-d})^{-1}$ 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 <i>tert</i> -butyl ether (MTBE) | 0.03 |
| Barium | 0.1 | Methylene chloride (dichloromethane) | 0.03 |
| Benzene | 0.03 | Methylnaphthalene, 2- | 0.148† |
| Benzo[<i>a</i>]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- (<i>o</i> -DCB) | 0.03 | Styrene | 0.03 |
| Dichlorobenzene, 1,4- (<i>p</i> -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 |
| <i>n</i> -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 HgCl₂ 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 | LOAEL = 7.2 mg/kg-d | 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) | |
| | | | Species: rats | | | | | | |
| | | | Mode of administration: diet | | | | | | |
| | | | Dosing Regime: 0, 10, 30, or 100 mg/kg-d | (LOAEL of 10 mg/kg-d is equivalent to 7.2 mg/kg-d free base.) | | | | | |
| | | | Duration: 104 weeks | | | | | | |
| Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for use of LOAEL vs. NOAEL) | | | | | | | | | |
| arsenic | oral SF | 1.80 (mg/kg-d) ⁻¹ | Morales et al., 2000 | MAC = 0.01mg/L | 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) | |
| | | | 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) | UR (1%) = 3.06E- 06 to 3.85E-05 (µg/L) ⁻¹ (95% upper bound 6.49E-06 to 4.64E- 05) | | | | | |
| | | | Duration: ≤ 60 years | | | | | | |
| | Uncertainty Factors: N/A | | | | | | | | |
| | inhalation SF | 27 (mg/kg-d) ⁻¹ | Study Type: epidemiological (occupationally exposed cohort) | TC ₀₅ = 7.83 µg/m ³ | | relative risk model | lung cancer | Group I: CEPA (carcinogenic to humans) | PSL1: HC/EC, 1993a (based on Higgins et al., 1986) |
| | Species: human | | | | | | | | |
| | Exposure: inhalation | | | | | | | | |
| 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 | 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 | |
| | | | Species: rats and mice | | | | | | |

| 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-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 | | | | | |
| | | | Duration: 103 weeks | | | | | |
| | | | Uncertainty Factors: N/A | | | | | |
| Unit Lifetime Risk = 2.03E-6 to 4.17E-6 | | | | | | | | |
| benzene | inhalation SF | 1.45E-02 (mg/kg-d) ⁻¹ | Study Type: epidemiological (occupational, cohort) | TC ₀₅ = 14.7 mg/m ³ | linear quadratic model of exposure- response relationship | non-cancer endpoint = hematotoxicity | Group I: CEPA (carcinogenic to humans) | PSL: HC/EC, 1993b (based on Rinsky et al., 1987) |
| | | | Species: human | | | | | |
| | | | Exposure: inhalation | | | | | |
| benzene | inhalation UR | 3.3E-03 (mg/m ³) ⁻¹ | Dosing Regime: N/A | Unit Lifetime Risk = 5E-5 | 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) |
| | | | Duration: 8.7 years, cases 2.6 years, controls (average) | | | | | |
| | | | Uncertainty Factors: N/A | | | | | |
| benzo[<i>a</i>]pyrene* | oral SF | 2.3 (mg/kg-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) | | | | | |
| | | | Duration: 110 d | | | | | |
| | | | Uncertainty Factors: N/A | | | | | |
| Unit Lifetime Risk = 5E-5 | | | | | | | | |
| benzo[<i>a</i>]pyrene* | inhalation SF | 1.3E-01 | Study Type: subchronic-chronic | TC ₀₅ = 1.6 mg/m ³ | 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 |
|--|----------------|---|--|---|-------------------------|--|---|---|
| | inhalation U R | (mg/kg-d) ⁻¹ | Species: hamsters | | modelling | tumours | (probably carcinogenic to humans) | 1996a (based onThysson et al., 1981) |
| | | 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 | | | | | |
| bis(2-ethyl- hexyl)phthalate | oral TDI | 4.4E-02 mg/kg-d | Study Type: developmental (single generation) | 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) |
| | | | 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) | | | | | | | | |
| bis(chloro-methyl)ether (BCME) | inhalation SF | 4.0E+01 (mg/kg-d) ⁻¹ | Study Type: chronic | 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) |
| | | | Species: rats | | | | | |
| | 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 | 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) |
| | | | Species: dogs | | | | | |
| | | | 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 |
|---|---------------------------|--|--|--|---|--|---|--|
| | | | 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-d) ⁻¹ | Study Type: chronic | TC ₀₅ = 0.0029 mg/m ³ | 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 | | | | | |
| | inhalation UR | 9.8 (mg/m ³) ⁻¹ | Dosing Regime: 12.5, 25, and 50 µg/m ³ , 23 h/d, 7 d/week | (0.0051 mg/m ³ adjusted for continuous exposure, standard lifetime, and difference in inhalation rate and body weight of rats and humans) | | | | |
| 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/m ³ | 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/m ³ (50.2 mg/m ³ 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 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 | | water consumption rate (1.5 L/d)/bw(70 kg) | irritation, or corrosion of the gastrointestinal mucosa, encephalitis | | 1979 (updated 1986) | |
| | inhalation SF | 4.6E+01 (mg/kg-d) ⁻¹ | Study Type: epidemiological(chronic, occupational) Species: human Exposure: inhalation | TC ₀₅ = 4.6 µg/m ³ | | carcinogenic: lung | Group I: CEPA (carcinogenic to humans) | PSL1: HC, 1996a; HC/EC, 1994c (based on Mancuso, 1975) | |
| | 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-d) ⁻¹ | Study Type: epidemiological (chronic, occupational) Species: human Exposure: inhalation | TC ₀₅ = 0.66 µg/m ³ | | carcinogenic: lung | Group I: CEPA (carcinogenic to humans) | PSL: HC, 1996a (based on Mancuso, 1975) |
| | | 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 | | | | | |
| 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) | |
| copper | 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 | Dosing Regime: 10 mg/d | | | | | | |
| | 9–13 years | 5E+03 | Duration: 12 weeks | | | | | | |
| | 14–18 years | 8E+03 | Uncertainty Factors: none | | | | | | |
| | ≥ 19 years | 1E+04 | | | | | | | |

| 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 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) | 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) |
| | oral SF | 2E+00 (mg/kg-d) ⁻¹ | Study Type: chronic 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 | 6.E-05 (µg/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) |

| 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 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 | | multistage model amortized for continuous exposure | nasal cavity tumours, hemangiosarcomas, mesotheliomas | | IRIS: U.S. EPA 2004 (based on NTP, 1982) |
| dibutyl phthalate | oral TDI | 6.3E-02 mg/kg-d | Study Type: developmental (single generation) 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) | 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) |
| dichlorobenzene, 1,2- | oral TDI | 4.3E-01 mg/kg-d | Study Type: chronic 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 Duration: 103 weeks Uncertainty Factors: 100 (each for intra- and interspecies variability) | NOAEL = 60 mg/kg-d (43 mg/kg-d adjusted for continuous exposure) | 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) |
| 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 (107 mg/kg-d adjusted for continuous exposure) | 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 | | | | | |
| | | | 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 (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) | 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 | | | | | |
| | | | 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-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-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-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-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) | | | | (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 |
| <i>n</i> -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 | 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) |
| | | | 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) | | | | | |
| isopropyl benzene | oral TDI | 1.0E-01 mg/kg-d | Study Type: chronic | NOAEL = 154 mg/kg-d | 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) |
| | | | Species: rats | (110 mg/kg-d adjusted for daily exposure) | | | | |
| | | | 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) | | | | | |
| | inhalation TC | 4E-01 mg/m ³ | Study Type: subchronic | NOAEL = 2438 mg/m ³ | 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) |
| | | | Species: rats | (435 mg/m ³ adjusted for continuous exposure and human equivalent) | | | | |
| | | | 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) | | | | | |

| 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 | Species: human epidemiological studies | | | | | |
| | 7 months–1 year | N/A | Exposure/Mode of administration: food and water | | | | | |
| | 1–3 years | 2.E+00 | Dosing Regime: not specified | | | | | |
| | 4–8 years | 3.E+00 | Duration: N/A | | | | | |
| | 9–13 years | 6.E+00 | Uncertainty Factors: deemed unnecessary | | | | | |
| | 14–18 years | 9.E+00 | | | | | | |
| | ≥ 19 years (76 kg male, 61 kg female) | 1.1E+01 | | | | | | |
| | 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) Duration: 1, 2, 6, 8 weeks (various groups) | oral route) | | | Group C: IRIS (possible human carcinogen) | including Druet et al., 1978; Bernaudin et al., 1981; Andres, 1984) |
| | | | Bernaudin et al., 1981 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 | LOAEL = 0.317 mg/kg-d | | | | |
| | | | Andres, 1984 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 | LOAEL = 0.633 mg/kg-d | | | | |
| | | | Uncertainty Factors: 1000 (10x for use of subchronic studies, 10x for interspecies variability, 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) | <p>Study Type: epidemiological prospective studies of neurodevelopmental effects Uncertainty Factors: 5 (see Health Canada, 2007, for details)</p> <p>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.</p> | (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 | <p>Study Type: chronic</p> <p>Species: mice</p> <p>Mode of administration: diet</p> <p>Dosing Regime: 0, 54.3 or 113.8 mg/kg-d (males); 0, 50.3, or 107.6 mg/kg-d (females)</p> <p>Duration: 81 weeks</p> <p>Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for deficiencies in the database)</p> | 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 <i>tertiary</i> -butyl ether (MTBE) | oral TDI | 1E-02 mg/kg-d | <p>Study Type: subchronic</p> <p>Species: rats</p> <p>Mode of administration: gavage</p> <p>Dosing Regime: 100, 300, 900, and 1200 mg/kg-d</p> <p>Duration: 90 d</p> <p>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 NOEL)</p> | 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 | <p>Study Type: subchronic</p> <p>Species: rats</p> <p>Mode of administration: inhalation</p> <p>Dosing Regime: 0, 800, 4000, and 8000 ppm, 6 h/d, 5 d/week</p> <p>Duration: 13 weeks</p> <p>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)</p> | <p>NOAEL = 2915 mg/m³</p> <p>(368 mg/m³ adjusted for continuous exposure, and human equivalent; 5–11 years)</p> | <p>TC = NOAEL/UF</p> <p>increased relative weights of kidney and liver at this dose indicate it may be more appropriate to consider this NOAEL as a LOAEL</p> | 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 | <p>UL (IOM)</p> <p>0–6 months</p> <p>7 months–1 year</p> <p>1–3 years</p> <p>4–8 years</p> <p>9–13 years</p> <p>14–18 years</p> <p>≥ 19 years</p> <p>UL (HC)</p> <p>0–6 months†</p> <p>7 months–4 years</p> <p>5–11 years</p> <p>12–19 years</p> <p>20+ years</p> | <p>µg/d</p> <p>N/A</p> <p>N/A</p> <p>3E+02</p> <p>6E+02</p> <p>1.1E+03</p> <p>1.7E+03</p> <p>2E+03</p> <p>µg/kg-d</p> <p>2.3E+01</p> <p>2.3E+01</p> <p>2.3E+01</p> <p>2.7E+01</p> <p>2.8E+01</p> | <p>Study Type: subchronic, developmental/reproductive</p> <p>Species: rats</p> <p>Mode of administration: drinking water</p> <p>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)</p> <p>Duration: 9 weeks (including 3 weeks of gestation)</p> <p>Uncertainty Factors: 30 (10x for interspecies variability, 3x for intraspecies variability)</p> | <p>NOAEL = 0.9 mg/kg-d</p> <p>LOAEL = 1.6 mg/kg-d</p> | <p>UL (IOM) = NOAEL/UF x bw (adult female, 61 kg)</p> <p>UL (HC) = UL (IOM) adjusted for age group and body weight</p> | 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 | <p>Study Type: subchronic</p> <p>Species: rats</p> <p>Mode of administration: gavage</p> | 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 | 3.0 (mg/kg-d) ⁻¹ | Study Type: epidemiological (chronic occupational exposure, cohort) Species: human | 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) |
| | inhalation UR | 0.71 (mg/m ³) ⁻¹ | Exposure: inhalation Dosing Regime: N/A Duration: ≥ 12 months occupational exposure Uncertainty Factors: N/A | | | | | |
| nickel (combined oxidic, sulphidic and soluble nickel) | Inhalation SF | 5.3 (mg/m ³) ⁻¹ | Study Type: epidemiological (chronic 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 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) | 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) |
| nickel (metallic) | inhalation TC | 1.8E-05 mg/m ³ | Study Type: subchronic 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) | 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) |
| nitrilotriacetic acid (NTA) | oral TDI | 1E-02 mg/kg-d | Study Type: chronic Species: rats Mode of administration: diet Dosing Regime: 0.03, 0.15, or 0.5% Na ₃ NTA Duration: 2 years (sacrificed at 6, 12, 18, and 24 months) | NOAEL = 0.03% Na ₃ NTA 10 mg/kg-d | TDI = NOAEL/UF | nephritis, nephrosis | Group IIIB: (possibly carcinogenic to humans) | GCDWQ: HC, 1990 (based on Nixon et al., 1972) |

| 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- <i>p</i> -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) | 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, 61 kg female) | 4E+02 | | | | | | |
| | UL (HC) | (µg/kg-d) | Shearer and Hadjimarkos, 1975 | NOAEL (infants and children) =7 µg/kg-d | | | Group B2: U.S. EPA (probable human carcinogen) for selenium sulphide | |
| | | | 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/behav- ioural 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 | TC = LOAEL/UF | nephrotoxic, hepatotoxic, lung congestion, mononuclear cell leukemia | Group IV: CEPA (unlikely to be 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 | (363 mg/m ³ adjusted for continuous exposure and human equivalent: 5–11 years) | | | | |
| | | | Duration: 103 weeks | | | | | |
| | | | Uncertainty Factors: 1000 (10x for intraspecies and 10x for interspecies variation, 10x for LOAEL vrs. NOAEL) | | | | Group 2A: IARC (probably carcinogenic to humans) | |
| toluene | oral TDI | 2.2E-01 mg/kg-d | Study Type: subchronic | NOAEL = 312 mg/kg-d | 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 | (222.8 mg/kg-d adjusted for continuous exposure) | | | | |
| | | | 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 |
|-----------------------------|---------------|---------------------------|---|---|----------------|--|--|--|
| | inhalation TC | 3.75 mg/m ³ | <p>Uncertainty Factors: 1000 (10x each for intra- and interspecies variability, 10x for less than chronic)</p> <p>Study Type: acute</p> <p>Species: human volunteers</p> <p>Mode of administration: inhalation</p> <p>Dosing Regime: 0, 10, 40, and 100 ppm, 6 h/d (each group assigned 1 dose/d)</p> <p>Duration: 4 d</p> <p>Uncertainty Factors: 10 (10x intraspecies variation)</p> | <p>NOAEL = 150 mg/m³</p> <p>(37.5 mg/m³ adjusted for continuous exposure)</p> | TC = NOAEL/UF | | | PSL: HC, 1996a; HC/EC 1992c (based on Andersen et al., 1983) |
| tributyltin oxide (TBTO) | oral TDI | 2.5E-04 mg/kg-d | <p>Study Type: chronic</p> <p>Species: rats (Wistar strain for both studies)</p> <p>Mode of administration: diet</p> <p>Dosing Regime: 0, 0.5, 5, and 50 mg TBTO/kg feed; equivalent to 0.025, 0.25, and 2.5 mg/kg-d</p> <p>Duration: endpoint specific: up to 17 months (Vos et al., 1990); up to 106 weeks (Wester et al., 1990)</p> <p>Uncertainty Factors: 100 (10x each for intra- and interspecies variability)</p> | <p>NOAEL = 0.025 mg/kg-d</p> <p>(calculated from 0.5 mg TBTO/kg feed and study feed ingestion rates and body weights)</p> | TDI = NOAEL/UF | <p>decreased host resistance to nematode <i>Trichinella spiralis</i> (depressed serum IgE, increased muscle larvae); (thymus-dependent immunosuppression; suppressed natural killer cell activity in spleen cells; non-specific immunosuppression (Vos et al., 1990)</p> <p>increased food and water consumption (behavioural), and lymphocytopenia (immune) (Wester et al., 1990)</p> | Group D: IRIS (not classifiable as to human carcinogenicity) | HC Food Directorate (based on Vos et al., 1990; Wester et al., 1990) |

| 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 | 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) |
| | | | 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) | | | | | | | | |
| trichlorobenzene, 1,2,4- | oral TDI | 1.6E-03 mg/kg-d | Study Type: subchronic | 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) |
| | | | 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) | | | | | | | |
| | inhalation TC | 7E-03 mg/m ³ | Study Type: subchronic | NOAEL = 223 mg/m ³ | TC = NOAEL/UF | increased liver weight and relative kidney weight | | PSL1: HC/EC, 1993j (based on Kociba et al., 1981) |
| | | | Species: rats | (32.9 mg/m ³ adjusted for continuous exposure and human equivalent: 5–11 years) | | | | |
| | | | 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) | | | | | | | | |
| trichlorobenzene, 1,3,5- | oral TDI | 1.5E-03 mg/kg-d | Study Type: subchronic | 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) |
| | | | Species: rats | | | | | |
| | | | Mode of administration: diet | | | | | |
| | | | Dosing Regime: 1, 10, 100, or 1000 ppm | | | | | |
| | | | Duration: 13 weeks | | | | | |

| Substance | Type of TRV | TRV value | Study details | Threshold/ non-threshold endpoint | TRV derivation | Critical health effect | Carcinogenicity classification | TRV source |
|---|---------------|-------------------------------------|---|---|--|--|--|--|
| | inhalation TC | 3.6E-03 mg/m ³ | <p>Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)</p> <p>Study Type: subchronic</p> <p>Species: rats</p> <p>Mode of administration: inhalation</p> <p>Dosing Regime: 0, 10, 100, and 1000 mg/m³, 6 h/d, 5 d/week</p> <p>Duration: 13 weeks</p> <p>Uncertainty Factors: 5000 (10x each for intra- and interspecies variability, 10x for use of subchronic study, 5x for inadequate data on carcinogenicity)</p> | 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 | <p>Study Type: subchronic, developmental</p> <p>Species: rats</p> <p>Mode of administration: drinking water</p> <p>Dosing Regime: 0, 0.18, and 132 mg/kg-d</p> <p>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</p> <p>Uncertainty Factors: 100 (10x each for intra- and interspecies variability)</p> | LOAEL = 0.18 mg/kg-d | TDI = BMDL ₁₀ /UF | fetal heart defect, nephrotoxic effect | Group II: CEPA (probably carcinogenic to humans) | GCDWQ: HC, 2005; PSL1: HC/EC, 1993k (based on Dawson et al., 1993) |
| | | | <p>BMDL₁₀ = 0.146 mg/kg-d (NOAEL estimate)</p> | | | | | |
| | oral SF | 8.11E-04 (mg/kg-d) ⁻¹ | <p>Study Type: chronic</p> <p>Species: rats</p> <p>Mode of administration: gavage</p> <p>Dosing Regime: 0, 500 and 1000 mg/kg-d, 5 d/week</p> <p>Duration: 103 weeks</p> <p>Uncertainty Factors: N/A</p> | 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 | 2.6E-03 (mg/kg-d) ⁻¹ | Study Type: chronic Species: rats | 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) |
| | inhalation UR | 6.1E-04 (mg/m ³) ⁻¹ | 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 | | | | | |
| trichlorophenol, 2,4,6- | oral SF | 2E-02 (mg/kg-d) ⁻¹ | Study Type: chronic | 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 carcinomas and adenomas | Group II: CEPA (probably carcinogenic to humans) | GCDWQ: HC, 1987b (based on NCI, 1979) |
| | | | 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 | | | | | | | | |
| trichloropropane, 1,2,3- | oral TDI | 6E-03 mg/kg-d | Study Type: subchronic | 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) | IRIS: U.S. EPA, 1990 (based on NTP, 1983c) |
| | | | 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) | | | | | | | | |
| uranium | oral TDI | 6E-04 mg/kg-d | Study Type: subchronic | 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) |
| | | | 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) | | | | | |

| 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-d) ⁻¹ | Til et al., 1991 | 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) |
| | | | 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 | | | | | | | | |
| xylene | oral TDI | 1.5E+00 mg/kg-d | Study Type: subchronic | 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) |
| | | | 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) | | | | | | | |
| | inhalation TC | 1.8E-01 mg/m ³ (provisional) | Study Type: subchronic, developmental | 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) |
| | | | Species: rats | | | | | |
| | | | Mode of administration: inhalation | | | | | |
| | | | Dosing Regime: 0, 250, 1900, and 3400 mg/m ³ , 24 h/d | | | | | |
| | | | | | | | | |

| 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) | mg/d | Yadrick et al., 1989 | 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) |
| | 0–6 months | 4 | Study Type: subchronic prospective supplementation trial | | | | | |
| | 7 months–1 year | 5 | Species: human (adults) | | | | | |
| | 1–3 years | 7 | Mode of administration: dietary supplements | | | | | |
| | 4–8 years | 12 | Dosing Regime: 10 mg/d (dietary intake) + 50 mg/d (supplement) | | | | | |
| | 9–13 years | 23 | Duration: 10 weeks | | | | | |
| | 14–18 years | 34 | Uncertainty Factors: 1.5 (intraspecies variability and extrapolation of LOAEL to NOAEL) | | | | | |
| | ≥ 19 years (76 kg male, 61 kg female) | 40 | | | | | | |
| | UL (HC) | mg/kg-d | Walravens and Hambidge, 1976 | 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 | | |
| | 0–6 months | 5E-01 | Study Type: subchronic prospective supplementation trial | | | | | |
| | 7 months–4 years | 5E-01 | Species: human (infants) | | | | | |
| | 5–11 years | 5E-01 | Mode of administration: dietary supplements | | | | | |
| | 12–19 years | 5E-01 | Dosing Regime: 1.8 mg/L (formula concentration, control group), 5.8 mg/L (formula concentration + 4mg/L supplement) | | | | | |
| | 20+ years (70.7 kg) | 6E-01 | Duration: 6 months | | | | | |
| | | | Uncertainty Factors: none | | | | | |

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 $SF_{inh} = 0.05/(TC_{05} \times \text{inhalation rate [16.6 m}^3\text{/d]}/bw [70.7 \text{ kg}])$; oral slope factor was derived as $SF_{oral} = 0.05/TD_{05}$; $SF = UR \times bw (70.7 \text{ kg})/\text{drinking water consumption rate (1.5 L/d)}$.

* A dermal slope factor of $3.5 (\mu\text{g}/\text{cm}^2\text{-d})^{-1}$ 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 |

REFERENCES FOR APPENDIX A

- Canadian Council of Ministers of the Environment (CCME). 1996a. "Canadian Soil Quality Guidelines for Contaminated Sites. Human Health Effects: Free Cyanide." Prepared for CCME by Air and Waste Section, Environmental Health Directorate, Health Canada (unpublished document).
- CCME. 1996b. *Canadian Soil Quality Guidelines for Contaminated Sites. Human Health Effects: Ethylbenzene*. Prepared for CCME by Air and Waste Section, Environmental Health Directorate, Health Canada.
- CCME. 1997a. *Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Cyanide*. Fact sheet.
- CCME. 1997b. *Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Phenol*. Fact sheet. Winnipeg.
- CCME. 1999a. *Canadian Soil Quality Guidelines for Contaminated Sites. Human Health Effects: Inorganic Mercury*. Prepared for CCME by UMA Engineering Ltd., with further revisions by Health Canada and Environment Canada.
- CCME. 1999b. *Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Inorganic Mercury*. Fact sheet.
- CCME. 2004. *Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Ethylbenzene*. Fact sheet.
- CCME. 2006. *Canadian Soil Quality Guidelines for Contaminated Sites. Human Health Effects: Uranium*. Prepared for CCME by Air and Waste Section, Environmental Health Directorate, Health Canada.
- CCME. 2007. *Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Uranium*. Fact sheet.
- CCME. 2008. *Canadian Soil Quality Guidelines for Uranium: Environmental and Human Health*. Scientific Supporting Document (PN 1371) (2007 document revised December 2008).
- CCME. 2009. *Canadian Soil Quality Guidelines: Selenium*. Environmental and Human Health. Scientific Supporting Document. Winnipeg.
- Equilibrium Environmental Inc. 2008. *Tolerable Daily Concentration/Tolerable Daily Intake (TDC/TDI) Section of the Scientific Supporting Document for a Human Health-Based Soil Quality Guideline for n-Hexane (n-HX)*. Report prepared under contract to Health Canada's Contaminated Sites Division.
- Health Canada (HC). 1979 (updated 1986). *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Chromium*. Ottawa.
- HC. 1984. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – 1,1-Dichloroethylene*. Ottawa.
- HC. 1986 (reaffirmed 2005). *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Ethylbenzene*. Ottawa.
- HC. 1987a. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Dichloromethane*. Ottawa.
- HC. 1987b. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Chlorophenols*. Ottawa.
- HC. 1988. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Benzo(a)pyrene*. Ottawa.
- HC. 1990. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Nitrotriacetic Acid*. Ottawa.
- HC. 1991. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Boron*. Ottawa.
- HC. 1992b. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Vinyl Chloride*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa.
- HC. 1996a. *Canadian Environmental Protection Act, Priority Substances List, Supporting Documentation: Health-Based Tolerable Daily Intakes/Concentrations and Tumourigenic Doses/Concentrations for Priority Substances* (unedited version).
- HC. 1996b. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Tetrachloroethylene*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa.
- HC. 2001. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Uranium*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa.
- HC. 2003. *Summary: Provisional Re-Evaluation of PCBs by the Health Canada Food Directorate (2003)*. Ottawa.
- HC. 2005. *Guidelines for Canadian Drinking Water Quality: Supporting Documentation—Trichloroethylene*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa.

- HC. 2006. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Arsenic*. Ottawa.
- HC. 2007. Human Health Risk Assessment of Mercury in Fish and Health Benefits of Fish Consumption. Bureau of Chemical Safety Food Directorate Health Products and Food Branch, Health Canada, Ottawa.
- HC. 2009. *Guidelines for Canadian Drinking Water Quality, Supporting Documents – Benzene*. Ottawa.
- HC. 2010a. *Carbontetrachloride in Drinking Water*. Document for public comment prepared by the Federal-Provincial-Territorial Committee on Drinking Water. Ottawa.
- HC. 2010b. *Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0*. Contaminated Sites Division, Safe Environments Directorate, Health Canada, Ottawa.
- HC. 2010c. *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Fluoride*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa.
- HC/EC. 1992a. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Chlorobenzene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1992b. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Methyl Tertiary-Butyl Ether*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1992c. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Toluene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993a. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Arsenic and Its Compounds*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993b. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Benzene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993c. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Bis(chloromethyl)ether*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993d. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for 3,3'-dichlorobenzidine*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993e. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Dichloromethane*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993f. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Pentachlorobenzene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993g. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Styrene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993h. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Tetrachlorobenzenes*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993i. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Tetrachloroethylene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993j. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Trichlorobenzenes*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1993k. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Trichloroethylene*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1994a. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Bis(2-ethylhexyl)phthalate*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1994b. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Cadmium*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1994c. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Chromium and Its Compounds*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1994d. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Dibutyl Phthalate*. Canada Communication Group Publishing, Ottawa.
- HC/EC. 1994e. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for 1,2-Dichloroethane*. Canada Communication Group Publishing, Ottawa.

HC/EC. 1994f. *Canadian Environmental Protection Act. Priority Substances List Assessment Report for Nickel and Its Compounds*. Canada Communication Group Publishing, Ottawa.

Institute of Medicine (IOM). 2000. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of DRIs, and Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board of the Institute of Medicine of the National Academies. National Academy Press, Washington, DC.

IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. A Report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of the Interpretation and Uses of Dietary Intakes, and Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board of the Institute of Medicine of the National Academies. National Academy Press, Washington, DC.

Joint FAO/WHO Expert Committee on Food Additives. 2002. *Evaluation of Certain Food Additives and Contaminants: Fifty-Seventh Report of the Joint FAO/WHO Expert Committee on Food Additives* (in Rome, Italy, 2001). WHO Technical Report Series No. 909.

U.S. EPA. 1990. *Toxicological Review of 1,2,3-Trichloropropane in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 1991. *Toxicological Review of Ethylbenzene in Support of Summary Information on the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 1993a. *Toxicological Review of Cyanide (free) in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 1993b. *Toxicological Review of Pyrene in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 1995 (last revised). *Toxicological Review of Mercuric Chloride in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 1997. *Toxicological Review of Cumene in Support of Summary Information on the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 1998. *Toxicological Review of Naphthalene in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 2001. *National Primary Drinking Water Regulations: Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring – Final Rule*. 40 CFR Parts 9, 141, and 142. U.S. EPA, Washington, DC.

U.S. EPA. 2003. *Toxicological Review of 2-Methylnaphthalene in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 2004. *Toxicological Review of 1,2-Dibromoethane in Support of Summary Information on the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 2005a. *Toxicological Review of Barium in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

U.S. EPA. 2005b. *Toxicological Review of n-Hexane in Support of Summary Information for the Integrated Risk Information System (IRIS)*. U.S. EPA, Washington, DC.

van den Berg, M., L.S. Birnbaum, M. Denison, M. De Vito, W. Farland, M. Feeley, H. Fiedler, H. Hakansson, A. Hanberg, L. Haws, M. Rose, S. Safe, D. Schrenk, C. Tohyama, A. Tritscher, J. Tuomisto, M. Tysklind, N. Walker and R.E. Peterson. 2006. The 2005 World Health Organization re-evaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicol. Sci.* 93(2): 223–241.

WHO. (World Health Organization). 1972. Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyro-carbonate, and octyl gallate. WHO Food Additive Series, No. 4. Geneva: World Health Organization.

WHO. 2005. *Nickel in Drinking-Water. Background Document for Development of WHO Guidelines for Drinking-Water Quality*. WHO, Geneva.

REFERENCES FOR APPENDIX A. PRIMARY LITERATURE

- Andersen, I., G.R. Lundqvist, L. Molhave, O.F. Pedersen, D.F. Procter, M. Vaeth, and D.P. Wyon. 1983. Human response to controlled levels of toluene in six-hour exposures. *Scand. J. Work Environ. Health* 9: 405–418.
- Andres, P. 1984. IgA-IgG disease in the intestine of Brown Norway rats ingesting mercuric chloride. *Clin. Immunol. Immunopathol.* 30: 488–494.
- Andrew, F.D., R.L. Buschbom, W.C. Cannon, R.A. Miller, L.F. Montgomery, D.W. Phelps et al. 1981. *Teratologic Assessment of Ethylbenzene and 2-Ethoxyethanol*. Battelle Pacific Northwest Laboratory, Richland, WA. PB 83- 208074, 108.
- Battelle's Columbus Laboratories (BCL). 1980. "Subchronic Toxicity Study: Naphthalene (C52904), Fischer 344 Rats." Unpublished. Prepared by Battelle Laboratories under NTP Subcontract No. 76-34-106002.
- Beliles, R.P., J.H. Butala, C.R. Stack, and S. Makris. 1985. Chronic toxicity and three-generation reproduction study of styrene monomer in the drinking water of rats. *Fund. Appl. Toxicol.* 5: 855–868.
- Benson, J.M., D.G. Burt, Y.S. Cheng, A.F. Eidson, D.K. Gulati, F.F. Hahn, C.H. Hobbs, and J.A. Pickrell. 1990. Subchronic inhalation toxicity of nickel subsulfide to rats and mice. *Inhalation Toxicol.* 2: 1–19.
- Berman, E., M. Schlicht, V.C. Moser, and R.C. MacPhail. 1995. A multidisciplinary approach to toxicological screening: I. Systemic toxicity. *J. Toxicol. Environ. Health* 45: 127–143.
- Bernaudin, J.F., E. Druet, P. Druet, and R. Masse. 1981. Inhalation or ingestion of organic or inorganic mercurials produces auto-immune disease in rats. *Clin. Immunol. Immunopathol.* 20: 129–135.
- Bowman, R.E., M.P. Heiromimus, and D.A. Barsotti. 1981. Locomotor hyperactivity in PCB-exposed rhesus monkeys. *Neurotoxicol.* 2(2): 251–268.
- Bruckner, J.V., W.F. Mackenzie, S. Muralidhara, R. Luthra, G.M. Kyle, and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. *Fund. Appl. Toxicol.* 6: 16–34.
- Chen, C.J., Y.C. Chuang, T.M. Lin, and H.Y. Wu. 1985. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. *Cancer Res.* 45: 5895.
- Chu, I., D.C. Villeneuve, V.E. Valli, and V.E. Secours. 1984. Toxicity of 1,2,3,4-, 1,2,3,5- and 1,2,4,5- tetrachlorobenzene in the rat: Results of a 90-day feeding study. *Drug. Chem. Toxicol.* 7: 113–127.
- Chemical Industry Institute of Toxicology (CIIT). 1982. *Final Report: 104-Week Chronic Toxicity Study in Rats: Aniline, Volume 1*. CIIT, Research Triangle Park, NC.
- Condie, L.W., J.R. Hill, and J.F. Borzelleca. 1988. Oral toxicology studies with xylene isomers and mixed xylenes. *Drug Chem. Toxicol.* 11(4): 329–354.
- Côté, M., I. Chu, D.C. Villeneuve, V.E. Secours, and V.E. Valli. 1988. Trichlorobenzene: Results of a thirteen week feed study in the rat. *Drug Chem. Toxicol.* 11(1): 11–28.
- Cushman, J.R., J.C. Norris, D.E. Dodd, K.I. Darmer, and C.R. Morris. 1995. Subchronic inhalation toxicity assessment of cumene in Fischer 344 rats. *J. Am. Coll. Toxicol.* 14(2): 129–147.
- Dawson, B.V., P.D. Johnson, S.J. Goldberg, and J.G. Ulreich. 1993. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. *J. Am. Coll. Cardiol.* 21: 1466–1472.
- Dilley, J.V. 1977. *Toxic Evaluation of Inhaled Chlorobenzene (Monochlorobenzene)*. National Technical Information Service, U.S. Department of Commerce (PB-276 623).
- Dodd, D., and W. Kintigh, 1989. *Methyl Tertiary Butyl Ether (MTBE): Repeated (13-Week) Vapor Inhalation Study in Rats with Neurotoxicity Evaluation*. Union Carbide, Bushy Run Research Center. Project Report 52-507. Export, PA. NTIS Publication No. NTIS/OTS0528043.
- Doll, R., A. Andersen, W.C. Cooper et al. 1990. Report of the International Committee on Nickel Carcinogenesis in Man, *Scand. J. Work Environ. Health* 16: 1–82.
- Druet, P., E. Druet, F. Potdevin, and C. Sapin. 1978. Immune type glomerulonephritis induced by HgCl₂ in the Brown Norway rat. *Ann. Immunol.* 129C: 777–792.
- Dunnick, J.K., M.R. Elwell, J.M. Benson, C.H. Hobbs, F.F. Hahn, P.J. Haley, Y.S. Cheng, and A.F. Eidson. 1989. Lung toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate in F344/N rats and B6C3F1 mice. *Fund. Appl. Toxicol.* 12: 584–594.

- Faqi, A.S., and I. Chahoud. 1998. Antiestrogenic effects of low doses of 2,3,7,8-TCDD in offspring of female rats exposed throughout pregnancy and lactation. *Bull. Environ. Contam. Toxicol.* 61: 462–469.
- Feron, V.J., C.F.M. Hendriksen, A.J. Speek et al. 1981. Lifespan oral toxicity study of vinyl chloride in rats. *Food Cosmet. Toxicol.* 19(3): 317–333.
- Friberg, L., M. Piscator, and G. Nordberg. 1971. *Cadmium in the Environment*. The Chemical Rubber Co (CRC) Press, Cleveland, OH.
- Fungwe, T.V., F. Buddingh, D.S. Demick, C.D. Lox, M.T. Yang, and S.P. Yang. 1990. The role of dietary molybdenum on estrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats. *Nutr. Res.* 10: 515–524.
- Gilman, A.P., D.C. Villeneuve, V.E. Secours, A.P. Yagminas, B.L. Tracy, J.M. Quinn, V.E. Valli, R.J. Willes, and M.A. Moss. 1998. Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. *Fund. Appl. Toxicol.* 41: 117–128.
- Greger, J.L. 1999. Nutrition versus toxicology of manganese in humans: Evaluation of potential biomarkers. *Neurotoxicol.* 20: 205–212.
- Hamano, Y., A. Kuwano, K. Inoue, Y. Oda, H. Yamamoto, B. Mitsuda, and N. Kunita. 1977. Studies on toxicity of phthalic acid esters. Part I: Teratogenic effects after oral administration to mice. *Osaka-furitsu Koshu Eiseikenkyusho Kenkyu Hokada Shokukhim Eisei Hen.* 8: 29–33.
- Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles, and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. *Scand. J. Work Environ. Health* 7(suppl 4): 66–75.
- Hayes, J.R., L.W. Condie, and J.F. Borzelleca. 1986. The subchronic toxicity of tetrachloroethylene (perchloroethylene) administered in the drinking water of rats. *Fund. Appl. Toxicol.* 7: 119–125.
- Higgins, I.T.T., M.S. Oh, K.L. Kryston, C.M. Burchfiel, and N.M. Wilkinson. 1986. "Arsenic Exposure and Respiratory Cancer in a Cohort of 8 044 Anaconda Smelter Workers. A 43-Year Follow-Up Study." Prepared for the Chemical Manufacturers' Association and the Smelters Environmental Research Association (unpublished).
- Howard, J.W., and R.F. Hanzal. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. *J. Agric. Food Chem.* 3: 325.
- Huang, J., K. Kato, E. Shibata et al. 1989. Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. *Arch. Toxicol.* 63: 381–385.
- Johansson, A., P. Camner, C. Jarstrand, and A. Wiernik. 1983. Rabbit lungs after long-term exposure to low nickel dust concentration. II. Effects on morphology and function. *Environ. Res.* 30(1): 142–151.
- Kishi, R., Y. Katakura, T. Ikeda, B.Q. Chen, and H. Miyake. 1992. Neurochemical effects in rats following gestational exposure to styrene. *Toxicol. Lett.* 63: 141–146.
- Kluwe, W.M., G. Dill, A. Persing, and A. Peters. 1985. Toxic response to acute, subchronic, and chronic oral administrations of monochlorobenzene to rodents. *J. Toxicol. Environ. Health* 15(6): 745–767.
- Knafila, A., K.A. Phillipps, R.W. Brecher, S. Petrovic, and M. Richardson. 2006. Development of a dermal cancer slope factor for benzo[a]pyrene. *Reg. Toxicol. Pharmacol.* 45: 159–168.
- Kobayashi, S., S. Toida, H. Kawamura, H.S. Chang, T. Fukuda, and K. Kawaguchi. 1972. Chronic toxicity of 2,4-dichlorophenol in mice: A simple design for the toxicity of residual metabolites of pesticides. *J. Med. Soc. Toho (Japan)*, 19(3–4): 356.
- Kociba, R.J., B.J.K. Leong, and R.E. Hefner. 1981. Subchronic toxicity study of 1,2,4-trichlorobenzene in the rat, rabbit and beagle dog. *Drug Chem. Toxicol.* 4(3): 229–249.
- Leong, B.K.J., R.J. Kociba, and G.C. Jersey. 1981. A lifetime study of rats and mice exposed to vapours of bis(chloromethyl) ether. *Toxicol. Appl. Pharmacol.* 58: 269–281.
- Loeser, E., and M.H. Litchfield. 1983. Review of recent toxicology studies on p-dichlorobenzene. *Food Chem. Toxicol.* 21(6): 825–832.
- Maltoni, C., G. Lefemine, and G. Cotti. 1986. *Experimental Research on Trichloroethylene Carcinogenesis. Archives of Research on Industrial Carcinogenesis, Volume V*. Princeton Scientific Publishing, Princeton, NJ. 393 p.
- Maltoni, C., G. Lefemine, G. Cotti, and G. Perino. 1988. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss mice and B6C3F mice. *Ann. New York Acad. Sci.* 534: 316–342.
- Mancuso, T.F. 1975. *Consideration of Chromium as an Industrial Carcinogen*. International Conference on Heavy Metals in the Environment. Symposium Proceedings. Toronto, Ontario, October 27–31, 1975. Toronto: Institute for Environmental Studies. pp. 343–356.

- Morales, K.H., L. Ryan, T.L. Kuo, M.M. Wu, and C.J. Chen. 2000. Risk of internal cancers from arsenic in drinking water. *Environ. Health Perspect.* 108: 655–661.
- Murata, Y, A. Denda, H. Maruyama, D. Nakae, M. Tsutsumi, T. Tsujuchi, and Y. Konishi. 1997. Short communication. Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. *Fundam. Appl. Toxicol.* 36: 90–93.
- National Cancer Institute (NCI). 1978a. *Bioassay of 1,2-Dibromoethane for Possible Carcinogenicity*. NTIS No. PB 288428. National Cancer Institute, Bethesda, MD.
- NCI. 1978b. *Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity*. Technical Report No. TR-55. National Technical Information Service Publication No. PB 285 968.
- NCI. 1979. *Bioassay of 2,4,6-Trichlorophenol for Possible Carcinogenicity*. Technical Report Series Number 155. DHEW Publication No. (NIH) 79-1711. U.S. Department of Health, Education and Welfare.
- Neal, J., and R.H. Rigdon. 1967. Gastric tumours in mice fed benzo[a]pyrene: A quantitative study. *Tex. Rep. Biol. Med.* 25: 553.
- Nixon, G.A., E.V. Buehler, and R.J. Niewenhuis. 1972. Two-year rat feeding study with trisodium nitrilotriacetate and its calcium chelate. *Toxicol. Appl. Pharmacol.* 21: 244.
- National Toxicology Program (NTP). 1982. *Carcinogenesis Bioassay of 1,2-Dibromoethane (CAS No. 106-93-4) in F344 Rats and B6C3F1 Mice (Inhalation Study)*. NTP-80-28, NIH Publication No. 82-1766. Available from National Technical Information Service, Springfield, VA; PB82-181710.
- NTP. 1983a. *NTP Technical Report on the Carcinogenesis Studies of Chlorobenzene (CAS No. 108-90-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. NTP Technical Report No. TR 261. Research Triangle Park, NC. National Technical Information Service (NTIS) Publication No. PB86-144888.
- NTP. 1983b. *NTP Technical Report on the Carcinogenesis Studies of 1,2-Dichlorobenzene (CAS No. 95-50-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. NTP Technical Report No. TR 255. Research Triangle Park, NC. NTIS Publication No. PB86-144888.
- NTP. 1983c. "120-Day Gavage Study in Mice and Rats with 1,2,3-Trichloropropane." Unpublished report prepared by Hazleton Laboratories.
- NTP. 1986a. *Draft Carcinogenesis Bioassay of Benzene in F344/N Rats and B6C3F1 Mice (Gavage Study)*. NTP-84-072. U.S. Department of Health and Human Services, Research Triangle Park, NC.
- NTP. 1986b. *Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)*. U.S. Department of Health and Human Services. Technical Report No. 306. National Institutes of Health Publication No. 86-2562. 208 p. NTIS Publication No. PB86-187903.
- NTP. 1986c. *Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)*. Technical Report No. 311. U.S. Department of Health and Human Services. NTIS Publication No. PB87-147054.
- NTP. 1987. *Toxicology and Carcinogenesis Studies of 1,4-Dichlorobenzene in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. NTP Technical Report Series 319. NIH Publication No. 87-2575.
- NTP. 1988. *Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies)*. NTP Technical Report Series No. 273. NIH Publication No. 88-2525. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC.
- NTP. 1990a. *Toxicology and Carcinogenesis Studies of Toluene (CAS No. 108-88-3) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)*. Technical Report No. 371. U.S. Department of Health and Human Services. NTIS Publication No. PB90-256371.
- NTP. 1990b. *Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. NTP Technical Report Series No. 243. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC.
- NTP. 1991a. *Toxicology and Carcinogenesis Studies of Pentachlorobenzene (CAS No. 608-93-5) in F344/N Rats and B6C3F1 Mice (Feed Studies)*. NTP Tox 6, NIH Publication No. 91-3125. U.S. Dept. of Health and Human Services, Research Triangle Park, NC.
- NTP. 1991b. *NTP Report on the Toxicity Studies of 1,2,4,5-Tetrachlorobenzene in F344/N Rats and B6C31 Mice (Feed Studies)*. NTP Tox 7. U.S. Department of Health and Human Services, Research Triangle Park, NC.
- O'Donohue, J., M.A. Reid, A. Varghese, B. Portmann, and R. Williams. 1993. Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur. J. Gastroenterol. Hepatol.* 5: 561–562.

- Ohsako, S., Y. Miyabara, N. Nishimura, S. Kurosawa, M. Sakaue, R. Ishimura, M. Sato, K. Takeda, Y. Aoki, H. Sone, C. Tohyama, and J. Yonemoto. 2001. Maternal exposure to a low dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) suppressed the development of reproductive organs of male rats: Dose-dependent increase of mRNA levels of 5-reductase type 2 in contrast to decrease of androgen receptor in the pubertal ventral prostate. *Toxicol. Sci.* 60: 132–143.
- Oldiges H., D. Hochrainer, Sh. Takenaka, G. Oberdörster, and H. König. 1984. Lung carcinomas in rats after low level cadmium inhalation. *Toxicol. Environ. Chem.* 9: 41–51.
- Ono Y, Y. Takeuchi, and N. Hisanaga. 1979. Studies on the method of measuring nerve conduction velocity in the rat's tail and on the comparative toxicity of n-hexane, methyl nbutyl ketone and 2,5-hexanedione. *Jap. J. Ind. Health* 21: 528–538.
- Ono Y, Y. Takeuchi, N. Hisanaga, and M. Iwata. 1982. Neurotoxicity of petroleum benzene compared with n-hexane. *Int. Arch. Occup. Environ. Health* 50: 219–229.
- Pratt, W.B., J.L. Omdahl, and J.R. Sorenson. 1985. Lack of effects of copper gluconate supplementation. *Am. J. Clin. Nutr.* 42: 681–682.
- Quast, J.F., C.G. Humiston, C.E. Wade, J. Ballard, J.E. Beyer, R.W. Schwetz, and J.M. Norris. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. *Fundam. Appl. Toxicol.* 3: 55.
- Rinsky, R.A., A.B. Smith, R. Hornung, T.G. Filloon, R.J. Young, A.H. Okun, and P.J. Landrigan. 1987. Benzene and leukemia—An epidemiologic risk assessment. *N. Eng. J. Med.* 316: 1044–1050.
- Robinson, M., R.H. Bruner, and G.R. Olson. 1990. Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats. *J. Am. Coll. Toxicol.* 9: 525–540.
- Sasmore, D.P., C. Mitoma, C.A. Tyson, and J.S. Johnson. 1983. Subchronic inhalation toxicity of 1,3,5-trichlorobenzene. *Drug Chem. Toxicol.* 6(3): 241–258.
- Schlicht, M.P., V.P. Moser, B.M. Sumrell, E. Berman, and R.C. McPhail. 1992. Systematic and neurotoxic effects of acute and repeated phenol administration. *Toxicologist* 12(1): 274.
- Schwetz, B.A., P.A. Keeler, and P.J. Gehring. 1974. Effect of purified and commercial grade tetrachlorophenol on rat embryonal and fetal development. *Toxicol. Appl. Pharmacol.* 28(1): 146.
- Serota, D.G., A.K. Thakur, B.M. Ulland, J.C. Kirschman, N.M. Brown, R.H. Coots, and K. Morgareidge. 1986a. A two-year drinking-water study of dichloromethane in rodents II. Mice. *Food Chem. Toxicol.* 24(9): 959–963.
- Shearer, R.R., and D.M. Hadjimarkos. 1975. Geographic distribution of selenium in human milk. *Arch. Environ. Health* 30: 230–233.
- Springborn Laboratories, Inc. (SLI). 2000. *An Oral (Gavage) Two-Generation Reproduction Toxicity Study in Sprague-Dawley Rats with Nickel Sulphate Hexahydrate*. Prepared by Springborn Laboratories, Inc., Spencerville, OH, for Nickel Producers Environmental Research Association, Durham, NC (Study No. 3472.2).
- Spiegelberg, T., W. Kordel, and D. Hochrainer. 1984. Effects of NiO inhalation on alveolar macrophages and the humoral immune systems of rats. *Ecotox. Environ. Safety* 8: 516–525.
- Stula, E.F., H. Sherman, J.A. Zapp, and J.W. Clayton. 1975. Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). *Toxicol. Appl. Pharmacol.* 31: 159–176.
- Takenaka, S., H. Oldiges, H. König, D. Hochrainer, and G. Oberdorster. 1983. Carcinogenicity of cadmium chloride aerosols in W rats. *J. Natl. Cancer Inst.* 70: 367–373.
- Thyssen, J., J. Althoff, G. Kimmerle, and U. Mohr. 1981. Inhalation studies with benzo[a]pyrene in Syrian golden hamsters. *J. Natl. Cancer Inst.* 66: 575–577.
- Til, H.P., H.R. Immel, and V.J. Feron. 1983. *Lifespan Oral Carcinogenicity Study of Vinyl Chloride in Rats*. Final report. CIVO Institutes. TNO Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.
- Til, H.P., V.J. Feron, and H.R. Immel. 1991. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem. Toxicol.* 29: 713–718.
- U.S. EPA. 1989. *Mouse Oral Subchronic Toxicity of Pyrene*. Study conducted by Toxicity Research Laboratories, Muskegon, MI for the Office of Solid Waste, Washington, DC.
- Ungvary, G., and E. Tatrai. 1985. On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. *Arch. Toxicol.* (suppl. 8): 425–430.
- Vos, J.G., A. DeKlerk, E.I. Krajnc, V. Van Loveren, and J. Rozing. 1990. Immunotoxicity of bis(tri-n-butyltin)oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young versus aged rats. *Toxicol. Appl. Pharmacol.* 105: 144–155.

- Walravens, P., and K.M. Hambidge. 1976. Growth of infants fed a zinc supplemented formula. *Am. J. Clin. Nutr.* 29: 1114–1121.
- Weir, R.J., Jr., and R.S. Fisher. 1972. Toxicologic studies on borax and boric acid. *Toxicol. Appl. Pharmacol.* 23: 351.
- Wester, P.W., E.I. Krajnc, F.X.R van Leeuwen, J.G. Loeber, C.A. van der Heijden, H.A.M.G. Vaessen, and P.W. Helleman. 1990. Chronic toxicity and carcinogenicity of bis(tri- n-butyltin)oxide (TBTO) in the rat. *Food Chem. Toxicol.* 28: 179–196.
- World Health Organization (WHO). 1994. *Phenol. Environ. Health Criteria* 161.
- WHO. 2001. *Evaluation of Certain Food Additives and Contaminants: Fifty-Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives*. WHO Technical Report Series No. 901. Geneva. Accessed December 15, 2007, from http://whqlibdoc.who.int/trs/WHO_TRS_901.pdf.
- WHO. 2004. *Evaluation of Certain Food Additives and Contaminants: Sixty-First Report of the Joint FAO/WHO Expert Committee on Food Additives*. WHO Technical Report Series No. 922, Geneva. Accessed December 15, 2007, from http://whqlibdoc.who.int/trs/WHO_TRS_922.pdf.
- Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth, and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. *Arch. Ind. Health* 14: 387–398.
- Wolkowsky-Tyl, R., C. Jones-Price, M.C. Marr, and C.A. Kinmel. 1984. *Teratologic Evaluation of Diethylhexyl Phthalate in CD-1 Mice. Final Report*. National Center for Toxicological Research, Jefferson, AZ. NTIS Publication No. PB85-105674.
- Wu, M.-M., T.-L. Kuo, Y.-H. Hwang, and C.-J. Chen. 1989. Dose–response relation between arsenic concentration in well water and mortality from cancers and cardiovascular diseases. *Am. J. Epidemiol.* 130: 1123.
- Yadrick, M.K., M.A. Kenney, and E.A. Winterfeldt. 1989. Iron, copper, and zinc status: Response to supplementation with zinc or zinc and iron in adult females. *Am. J. Clin. Nutr.* 49: 145–150.
- Yang, G.-Q., and R.-H. Zhou. 1994. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. *J. Trace Elem. Electrolytes Health Dis.* 8:159–165.