APPENDIX B

Toxicity Assessment

Table of Contents

List of Tables

GLOSSARY AND ACRONYMS

Absolute bioavailability	Absolute bioavailability is the fraction or percentage of an administered dose that reaches systemic circulation (blood) irrespective of via the gastrointestinal tract, skin or lungs
Ah	Aryl hydrocarbon
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMDL	Benchmark Dose (lower confidence limit)
Bioavailability	The degree to which a substance becomes available to the target tissue after administration or exposure.
CEPA	Canadian Environmental Protection Act
COPC	Contaminants of Potential Concern
ESOD	Erythrocyte Superoxide Dismutase
FAO	Food and Agriculture Organization. An organization of the United Nations.
IARC	International Agency for Research on Cancer. An organization of the WHO.
IOC	Intake of concern
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System. A database maintained by the US EPA.
LOAEL	Lowest-observed-effects-level. A term that describes the benchmark on a threshold dose-response curve at which the lowest dose results in observed adverse health effects. May be used in place of a NOAEL where a NOAEL cannot be determined.
MAC	Maximum Allowable Concentration
MADEP	Massachusetts Department of Environmental Protection
MOE	Ontario Ministry of the Environment

GLOSSARY AND ACRONYMS

MRL	Minimal Risk Level. A term used by the ATSDR to describe an estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.
NATO	North Atlantic Treaty Organization
NCEA	National Center for Environmental Assessment
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-effects-level. A term that describes the benchmark on a threshold dose-response curve at which the highest dose does not result in adverse effects.
NRC	National Research Council
OEHHA	Office of Environmental Health Hazard Assessment
ORD	Office of Research and Development
PCB	Polychlorinated biphenyls
PCDD	Polychlorinated dibenzo-p-dioxins
PCDF	Polychlorinated dibenzofurans
PTWI	Provisional Tolerable Weekly Intake
RAF	Relative absorption factor
RDA	Recommended Dietary Allowance
REL	Reference Exposure Level is a NIOSH time-weighted average concentration for up to a 10-hour workday during a 40-hour work week.
Relative bioavailability	A comparative fraction which predicts bioavailability in one medium or form in relation to the medium for which the TRV was derived.
RfC	Reference Concentration. The RfC is an estimate of lifetime daily exposure to a non-carcinogen in air for the general human population that appears to be without appreciable risk of deleterious effects expressed in mg

	chemical/kg body weight-day.
RfD	Reference Dose. The RfD is an estimate of lifetime daily exposure to a non-carcinogen for the general human population that appears to be without appreciable risk of deleterious effects expressed in mg chemical/kg body weight-day.
SF	Slope factor. The SF is a plausible upper bound estimate of the probability of a response per unit intake of a chemical over a lifetime expressed as (mg chemical/kg body weight-day)$^{-1}$ and is used to express carcinogenic effects.
STSC	Superfund Health Risk Technical Support Center
TC	Tolerable Concentration. A term used by Health Canada to describe concentrations in air that a person may be continuously exposed to over a lifetime without adverse effects.
TC_{05}	Tumorigenic concentration that will induce a 5% increase in the incidence of tumors or deaths due to tumors following exposure to that chemical in air.
TD	Tumorigenic Dose. A term used to describe a dose that will induce an increase in the incidence of tumors or deaths due to tumours as calculated from a non-threshold dose-response curve.
TD_{05}	Tumorigenic Dose that will induce a 5% increase in the incidence of tumors or deaths due to tumors.
TDI	Tolerable Daily Intake. A term used by Health Canada in place of RfD.
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalent
TRV	Toxicity Reference Value
UF	Uncertainty Factor. A factor that is applied to NOAELs or LOAELs to yield a RfC or RfD. For example, the UF can be used to account for intra-species and inter-species extrapolations.
UL	Tolerable upper intake level. A term used by the IOM to describe the highest daily nutrient intake that will not result in adverse health effects.
Unit Risk	Units risks estimate the upper bound probability of an individual developing cancer following exposure to a particular level (usually as 1 µg/L in water or

	1 µg/m^3) of a potential carcinogen. For example, if the unit risk is 1.2 x 10^{-6} µg/L then it is expected that 1.2 excess tumours are expected to occur per 1,000,000 people exposed to 1 µg of that chemical in 1 L of drinking water.
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

1.0 INTRODUCTION

For the purpose of this assessment, toxicity reference values (TRVs) were obtained for each of the identified chemicals of potential concern (CoPC). Toxicological information was obtained, as necessary, from various sources including Health Canada, the US EPA Integrated Risk Information System (IRIS) database, and the Agency for Toxic Substances and Disease Registry (ATSDR).

TRVs are values used to describe maximum acceptable doses of chemicals that will not result in the development of adverse health effects. TRVs can be used to describe non-carcinogenic and carcinogenic effects and can express effects in different terms based on magnitude of the dose, length of exposure and route of exposure.

1.1 Non-Carcinogenic TRVs

Non-carcinogenic chemicals exhibit threshold effects following exposure. Threshold effects are defined by the observation of adverse effects at a given dose or concentration. Given these threshold effects, two measures of interest can describe the dose-response curve: the no-adverse-effects-level (NOAEL) and lowest-adverse-effects-level (LOAEL). The NOAEL is the benchmark at which the highest dose does not result in observed adverse effects. The LOAEL may be used when a NOAEL is not available and is the lowest dose at which adverse effects are observed.

The reference dose (RfD) is used for the assessment of non-carcinogenic endpoints. The RfD is the estimate of lifetime daily exposure to a non-carcinogenic substance for the general human population that appears to be without appreciable risk of deleterious effects. It is expressed as mg chemical/kg body weight/day (*i.e*., mg/kg-day). The RfD is derived from either the NOAEL or the LOAEL determined in a laboratory study. Uncertainty factors (UF) are applied to the NOAEL or LOAEL to account for interspecies variability and interspecies variability (*i.e*., sensitive sub-populations). Additionally, uncertainty factors are applied to extrapolate from subchronic exposure to chronic exposure or where there is a paucity of data available for a chemical (*i.e*., no data regarding effects on reproduction).

Other regulatory agencies have substituted the term RfD to be reflective of objectives and toxicological endpoints. Health Canada replaces the term RfD with tolerable daily intake (TDI), also expressed in mg/kg-day. The Institute of Medicine (IOM) uses the tolerable upper intake level (UL) expressed as mg chemical/day to describe the highest daily nutrient intake that will not result in adverse health effects. The ATSDR uses a minimal risk level (MRL) similar to the IOM's UL that estimates daily human exposure to a substance that, over a specified duration, will not cause an appreciable risk of adverse effects.

Health Canada uses a tolerable concentration (TC) to express concentrations in air that a person can be continuously exposed to over their lifetime without adverse effects. The reference concentration (RfC) is also used as a non-carcinogenic endpoint specific to inhalation exposure.

1.2 Carcinogenic TRVs

Carcinogenic chemicals exhibit non-threshold effects following exposure. Non-threshold effects are defined by the observation of adverse effects regardless of concentration and length of exposure. Primarily, two TRVs are used to describe carcinogenic effects: the slope factor and unit risk.

A slope factor (SF) is used for assessment of carcinogenic effects of a chemical. The SF is a plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime, expressed as $(mg/kg\ body\ weight/day)^{-1}$. It is used to estimate an upper bound probability of an individual developing cancer as a result of exposure to a particular level of a potential carcinogen.

Unit risks are used to estimate an upper bound probability of an individual developing cancer as a result of exposure to a particular level (usually as 1 µg/L in water, or 1 $\mu g/m^3$ in air) of a potential carcinogen. Unit risks are calculated by dividing the SF by body weight and multiplying that product by the inhalation or drinking rate as applicable.

Health Canada used tumorigenic doses and concentrations to develop SF or unit risks for substances that are considered to have non-threshold or carcinogenic effects. The potency is expressed as a dose or concentration that will induce a 5% increase in the incidence of tumours or deaths due to tumours as calculated from a dose-response curve. The TRVs that defined the 5% increased are tumorigenic concentration 05 (TC_{05}) primarily used as a benchmark for exposure to a certain chemical in air or tumorigenic dose 05 (TD_{05}).

1.3 Bioavailability

The definition of bioavailability varies with the source and context in which the term is used. The simplest and broadest definition of bioavailability describes the extent or rate that a chemical enters a receptor or is made available at the target site (*i.e.*, blood). The importance of bioavailability in risk assessment is illustrated by comparison TRVs as toxicity measures that are usually defined by laboratory studies. The fraction of a dose which is absorbed during an animal study may differ from the fraction that is available to a receptor in the environment due to several factors including weathering.

There are two specific types of bioavailability that are applicable to risk assessment: absolute and relative bioavailability. Absolute bioavailability is the fraction or percentage of an administered dose that reaches systemic circulation (blood) irrespective of via the gastrointestinal tract, skin or lungs. Relative bioavailability is the absolute bioavailability in one medium divided by the absolute bioavailability of the chemical under the conditions used to derive the TRV. Therefore, the relative bioavailability is a comparative fraction which predicts bioavailability in one medium or form in relation to the medium for which the TRV was derived. Relative bioavailability can be expressed as a relative absorption fraction (RAF).

2.0 ANTIMONY

Antimony is a silvery-white metal that is found in the earth's crust. Exposure to antimony at high levels can result in a variety of adverse health effects. Chronic inhalation of high levels of antimony can irritate the eyes and lungs as well as cause heart and lung problems as well as digestive problems. Ingesting large doses of antimony can cause vomiting. Chronic animal studies have reported that ingesting antimony can cause liver damage and blood changes. (ATSDR, 1992)

2.1 Assessment of Carcinogenicity

The US EPA's IRIS program has not evaluated the carcinogenicity of antimony. The Agency for Toxic Substances and Disease Registry (ATSDR, 1992) state that no information is available on the carcinogenic potential of antimony. The International Agency for Research on Cancer (IARC, 1989) found that there is insufficient supporting evidence to list antimony trioxide or antimony trisulphide as carcinogenic agents at this time.

2.2 Susceptible Populations

Individuals with existing chronic respiratory or cardiovascular disease or problems would probably be at special risk, since antimony probably exacerbates one or both types of health problems. Because antimony is excreted in the urine, individuals with kidney dysfunction may be unusually susceptible (ATSDR, 1992).

2.3 Selection of Toxicity Values

2.3.1 Non-Cancer Oral Toxicity Reference Values

An oral reference dose (RfD) of 0.0004 mg/kg-day was provided for antimony by the U.S. EPA (1991) based on a chronic study examining ingestion by rats. The main endpoints of concern were a decrease in longevity, a decrease in blood glucose levels and an alteration in cholesterol levels. The U.S. EPA (1991) reported a LOAEL of 0.35 mg/kg-day, and applied an uncertainty factor of 1000 (10 for interspecies conversion, 10 to protect sensitive individuals, and 10 because the effect level was a LOAEL) to the LOAEL to derive the RfD.

For this assessment, the US EPA RfD of 0.0004 mg/kg-day was used. Health Canada does not provide a non-cancer oral TRV for antimony.

2.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor or unit risk for antimony.

2.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore for this assessment, the inhalation TRV was set equal to the oral TRV.

2.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an inhalation slope factor or unit risk for antimony.

2.4 Bioavailability

2.4.1 Oral Bioavailability

The relative oral absorption factor for antimony has been conservatively assumed to be 1.0.

2.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for antimony has been conservatively assumed to be 1.0.

2.4.3 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.1 for antimony. Therefore, a relative dermal bioavailability of 0.1 was adopted for this assessment.

2.5 Conclusion

The following tables present the TRV and bioavailability summaries for antimony.

Table 1 Selected Toxicity Reference Values for Antimony

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	4.0×10^{-4} mg/kg-day	RfD	US EPA, 1991
Inhalation	4.0×10^{-4} mg/kg-day	RfD	US EPA, 1991
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 2 Selected Bioavailabilities for Antimony

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004

2.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 1992. Toxicological Profile for Antimony. September 1992.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Screening Level Risk Assessment (SLRA). October 3, 2003.

International Agency for Research on Cancer (IARC). 1989. "Antimony Trioxide And Antimony Trisulfide". *Monographs.* Vol. 47, p. 291. World Health Organization.

US EPA (Environmental Protection Agency). 1991. Integrated Risk Information System (IRIS) Database – Antimony. Available on-line at: http://www.epa.gov/iris/

Last reviewed: June 2007 (RJ)

3.0 ARSENIC

Arsenic is a natural, ubiquitous element found in soils and minerals. Arsenic can occur in both organic and inorganic forms in the environment with substantially different toxicological effects. Inorganic arsenic is considered to be more toxic then arsenic in its organic form. The most common form of inorganic arsenic in air is arsenic trioxide (As_2O_3), while a variety of arsenites (the trivalent form, As III) and arsenates (the pentavalent form, As V) occur in water, soil and food (ATSDR, 2000). Organic arsenic tends to be less extensively metabolized and more rapidly eliminated in both humans and laboratory animals. In addition, no conclusive evidence has been found on the carcinogenicity of organic arsenic (ATSDR, 2000; EHC, 1981; EHC, 2001). Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic; therefore for the purposes of this assessment the total concentrations of arsenic are believed to be in the inorganic form.

3.1 Assessment of Carcinogenicity

Exposure to high levels of arsenic has been shown to cause both carcinogenic and non-carcinogenic effects in humans. Inorganic arsenic is a known human carcinogen (Environment Canada and Health Canada, 1993; US EPA, 1998; US EPA, 2002). Arsenic is listed as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC, 1987).

3.2 Susceptible Populations

No studies were located regarding unusual susceptibility of any human subpopulation to arsenic; however, since the degree of arsenic toxicity may be influenced by the rate and extent of methylation in the liver, it is likely that members of the population with lower than normal methylating capacity might be more susceptible (ATSDR, 2000).

3.3 Selection of Toxicity Values

The following section describes various studies conducted to establish arsenic toxicity values via ingestion, inhalation and dermal routes of exposure.

3.3.1 Oral Non-Cancer Toxicity Reference Values

Chronic oral exposure to inorganic arsenic in humans has resulted in gastrointestinal effects, anemia, peripheral neuropathy, skin lesions, hyper pigmentation, gangrene of the extremities, vascular lesions, and liver or kidney damage (ATSDR, 2000).

The United States Environmental Protection Agency (US EPA, 1993) provides an oral RfD for non-carcinogenic effects from inorganic arsenic of 3×10^{-4} mg/kg-day. This value is based on the extensive data set of both non-cancerous and carcinogenic health effects of Taiwan residents that were exposed to inorganic arsenic (predominately as arsenate (As[V]) in their drinking water. Tseng (1977) studied the prevalence blackfoot disease in 40,421 inhabitants of an area on the Southwest coast of Taiwan where well water with a high concentration of arsenic was used for over 60 years. The rates of

blackfoot disease were recorded for three ranges of arsenic concentrations in well water. The low range (<0.3 ppm arsenic) from the Tseng (1977) study was taken as a LOAEL of 0.17 mg/L (converted to 0.014 mg/kg-day) (Tseng *et al*., 1968; US EPA, 1993).

In an earlier study (Tseng *et al*., 1968), prevalence of hyper pigmentation, keratosis, skin cancer and blackfoot disease were observed. A control population of 7,500 individuals was also examined. In the control population, 4,978 persons used water with non-detectable levels of arsenic and 2,522 persons used water with 0.001 to 0.017 ppm of arsenic. Not a single case of keratosis, hyper pigmentation or skin cancer was observed in these populations. The US EPA (1993) adopted a NOAEL of 0.009 mg/L based on this study (converted to 0.0008 mg/kg-day).

The RfD was developed based on the NOAEL of 0.8 µg/kg-day of arsenic divided by an uncertainty factor of 3. The uncertainty factor of 3 was to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals; therefore, this RfD is appropriate for comparison to exposures averaged over an entire lifetime (US EPA, 2003). The US EPA (1993) weights the selected study as medium given the poor characterization of doses, the presence of other contaminants despite the large sample population.

The US EPA RfD of $3x10^{-4}$ mg/kg-day was used for non-carcinogenic effects from inorganic arsenic as Health Canada does not provide an RfD.

3.3.2 Oral Cancer Toxicity Reference Values

The US EPA (1998) provides an oral cancer SF of 1.5 $(mg/kg\text{-}day)^{-1}$. The slope factor was based on data provided by the US EPA (2002) from increased incidence of skin cancer in Taiwanese populations orally exposed to arsenic in drinking water (Tseng, 1977; Tseng *et al*., 1968). These studies did not examine rates of internal cancers (*i.e.,* bladder and lung cancer) and are thus considered to underestimate total carcinogenic risks from arsenic. Arsenic is being reassessed under the Integrated Risk Information System (IRIS) program (US EPA, 1998).

Based on the same data set Health Canada (2003) recommends an oral SF of 2.8 $(mg/kg\text{-}day)^{-1}$ based on a TD_{05}.

For this assessment, the US EPA (1998) SF of 1.5 $(mg/kg\text{-}day)^{-1}$ will be used.

3.3.3 Non-Cancer Inhalation Toxicity Reference Values

A non-cancer inhalation TRV has not been selected for this assessment because arsenic is carcinogenic by inhalation.

3.3.4 Cancer Inhalation Toxicity Reference Values

Health Canada (1996) made TD_{05} estimates for inhalation carcinogenic risk for the Anaconda, Tacoma and Ronnskar (Sweden) cohorts of 7.83, 10.2, and 50.5 µg/m^3, respectively. These equate to unit risks of 6.4 x10^{-3} per µg/m^3, of 4.9 x10^{-3} per µg/m^3, and of 0.99x10^{-3} per µg/m^3 for the Anaconda, Tacoma and Ronnskar cohorts, respectively. Health Canada reviewed only one follow-up study for the Anaconda cohort. The Health Canada TD_{05} is based on only the Anaconda smelter data as being the most conservative. Recently, Health Canada (2004) has recommended an inhalation SF of 28.0 (mg/kg-day)$^{-1}$ based on a TC_{05} of 7.8 µg/m^3 for arsenic and its inorganic compounds (Health Canada, 1996).

The US EPA has developed a unit risk of 4.3 per mg/m^3 for carcinogenic risk from inhalation of inorganic arsenic, based on incidence of lung cancer. This is based on unit risk estimates derived for the Anaconda, Montana smelter cohort (3 studies yielding average unit risk of 2.6x10^{-3} per µg/m^3) and the ASARCO (Tacoma, Washington) smelter cohort (average of two estimates of 7.2x10 ^{3} per µg/m^3) (US EPA, 1998). The midpoint of average unit risk estimated for the two cohorts was adopted by the US EPA for use in developing the unit risk.

The US EPA (1998) inhalation unit risk of 4.3 (mg/m^3)$^{-1}$ was used in this assessment as it corresponds with proposed MOE (2007) standards for arsenic.

3.4 Bioavailability

Distribution of arsenic within the body is affected by the route through which exposure occurs. Arsenic tends to be evenly distributed amongst tissues within the body (Environment Canada and Health Canada, 1993). The interaction of arsenic with various tissues is dependent on the chemical form of the arsenic. The primary pathway of elimination of inorganic arsenic is excretion within the urine (ATSDR, 2000).

3.4.1 Oral Bioavailability

For this assessment, the oral bioavailability factor for soil can be conservatively assumed to be 1.0, in accordance with guidance from Health Canada (2004).

3.4.2 Inhalation Bioavailability

For this assessment, the inhalation bioavailability factor for soil was conservatively assumed to be 1.0, in accordance with guidance from Health Canada (2004).

3.4.3 Dermal Bioavailability

Arsenic is not very bioavailable when it is on the skin in a soil-bound matrix. Wester *et al.* (1993) administered arsenic in water topically to rhesus monkeys in vivo over 24 hours. The amount recovered in urine was 6.4% at the low dose and 2.0% at the high dose. Using human skin in vitro, 1.9% was recovered after 24 hour administration (combined receptor fluid accumulation of 0.93% and skin concentration of 0.98%).

Dutkiewicz (1977) applied pentavalent inorganic arsenic dermally to rats. Wistar rats tails were submerged in solution for one hour. An absorption rate of 1.14 to 33.1 µg/cm^2-hour was recorded for concentrations ranging from 0.01 to 0.2M.

Soil was also applied to human skin. The in vitro application to human skin yielded 0.43% receptor fluid accumulation and 0.33% skin concentration for a total absorption of 0.8%. The in vivo application of soil to rhesus monkeys yielded absorption estimates of 3.2% to 4.5%. Based on this study, the US EPA (2001) recommends a dermal absorption fraction for soil of 3%. This value was used to assess the bioavailable fraction of arsenic that would be absorbed through exposure to the skin.

Health Canada (2004) recommends the application of a relative dermal absorption fraction (RAF) of 0.03 to the estimation of daily dose; this value was used in this assessment.

3.5 Conclusion

Table 3 summarizes the selected toxicity reference values and Table 4 summarizes the selected relative bioavailabilities.

Table 3 Selected Toxicity Reference Values for Arsenic

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	3 x 10^{-4} mg/kg-day	RfD	US EPA, 1993
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	1.5 $(mg/kg\text{-}day)^{-1}$	SF	US EPA, 1998
Inhalation	4.3 $(mg/m^3)^{-1}$	UR	US EPA, 1998

Notes: NA: Not Applicable

Table 4 Selected Relative Bioavailabilities for Arsenic

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.03	Health Canada, 2004

3.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 2000. *Toxicological Profile for Arsenic*. September 2000.

Dutkiewicz T, 1977. Experimental studies on arsenic absorption routes in rats. *Environmental Health Perspectives* 19:173-177.

Environment Canada and Health Canada, 1993. Priority substances list assessment report, Arsenic and its compounds. Canadian Environmental Protection Act. Government of Canada, Ottawa, Ontario.

EHC (Environmental Health Criteria 18). 1981. Arsenic. IPCS International Programme on Chemical Safety. World Health Organization, Geneva.

EHC (Environmental Health Criteria 224). 2001. Arsenic and Arsenic Compounds. IPCS International Programme on Chemical Safety. World Health Organization, Geneva.

Health Canada. 1996. Health based Tolerable daily intakes/concentrations and tumorigenic doses/concentrations for priority substances. Minister of Supply and Services Canada, Ottawa.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs). October 3, 2003.

IARC (International Agency for Research on Cancer), 1987. Summaries & Evaluations – Arsenic. Supplement 7.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

Tseng WP. 1977. Effects and dose-response relationships of skin cancer and Blackfoot disease with arsenic. *Environmental Health Perspectives*. 19:109-119.

Tseng WP, Chu HM, How SW, Fong JM, Lin CS and Yeh S. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J. Natl. Cancer Inst*. 40: 453-463.

US EPA (United States Environmental Protection Agency), 1993. Integrated Risk Information System (IRIS) Database: Arsenic, inorganic (Oral RfD Assessment). Last revised 02/01/1993. Available on-line at: http://www.epa.gov/iris/.

US EPA (United States Environmental Protection Agency), 1998. Integrated Risk Information System (IRIS) Database: Arsenic, inorganic (Carcinogenicity Assessment). Last revised 04/10/1998. Available on-line at: http://www.epa.gov/iris/.

US EPA (United States Environmental Protection Agency), 2001. Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). Office of Emergency and Remedial Response, EPA/540/R/99/005, Interim, Review Draft, September. United States Environmental Protection Agency.

US EPA (United States Environmental Protection Agency), 2002. *Implementation Guidance for the Arsenic Rule, Drinking Water Regulations for Arsenic and Clarification to Compliance and New Source Contaminants Monitoring.* August 2002. United States Environmental Protection Agency.

US EPA (United States Environmental Protection Agency), 2003. Integrated Risk Information System (IRIS) Glossary. Revised September 2003. Available http://www.epa.gov/iris/ gloss8.htm.

Wester RC, Maibach HI, Sedik L, Melendres J, and Wade M. 1993. In vivo and in vitro percutaneous absorption and skin decontamination of arsenic from water and soil. *Fundamental and Applied Toxicology* 20: 336-340.

Last reviewed: May 2007 (RJ)

4.0 BARIUM

Barium is a silvery-white metal that takes on a silver-yellow color when exposed to air. Barium occurs in nature in many different forms called compounds. These compounds are solids, existing as powders or crystals, and they do not burn well. Two forms of barium, barium sulfate and barium carbonate, are often found in nature as underground ore deposits. Barium is sometimes found naturally in drinking water and food. Because certain barium compounds (barium sulfate and barium carbonate) do not mix well with water, the amount of barium usually found in drinking water is small.

Barium and barium compounds are used for many important purposes. Barium sulfate ore is mined and used in several industries. It is used mostly by the oil and gas industries to make drilling muds. Some barium compounds, such as barium carbonate, barium chloride, and barium hydroxide, are used to make ceramics, insect and rat poisons, and additives for oils and fuels; in the treatment of boiler water; in the production of barium greases; as a component in sealants, paper manufacturing, and sugar refining; in animal and vegetable oil refining; and in the protection of objects made of limestone from deterioration (ATSDR, 2005).

4.1 Assessment of Carcinogenicity

Barium is not classified as a carcinogenic compound. It is considered a class D carcinogen (i.e., not classifiable as to human carcinogenicity) due to lack of human data and a limited amount of animal studies (US EPA, 2005).

4.2 Susceptible Populations

The limited data available suggest that certain subgroups of the population may be more susceptible to barium exposure than the general population. These include people with cardiovascular problems or lung disease, those taking certain prescription drugs, children, pregnant women, and smokers.

Animal studies suggest that the kidney may be a sensitive target of barium toxicity; thus, individuals with impaired renal function may have a higher risk of developing barium-induced kidney damage. There is suggestive evidence that barium may affect blood pressure; therefore, humans with hypertension could be at increased risk from chronic, intermediate, or acute barium exposure (ATSDR, 2005).

4.3 Selection of Toxicity Values

4.3.1 Non-Cancer Oral Toxicity Reference Values

U.S. EPA (2005) provides an oral TRV of 0.2 mg/kg-day for barium based on a 2-year NTP (1994) drinking water study in mice. The kidney was the most sensitive target of toxicity resulting from repeated ingestion of soluble barium salts. The TRV was derived by benchmark dose approach using renal lesions in mice as the critical effect from the NTP (1994) study; a total uncertainty factor of 300 was also applied.

Alternatively, Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.016 mg/kg-day, which was used as the oral TRV in this assessment. This TDI value is derived from the barium drinking water quality MAC guideline of 0.73 mg/L (Health Canada, 2002), which is based on the results of an

epidemiological study by Brenniman and Levy (1985). This study showed adverse effects on blood pressure and increases in the prevalence of cardiovascular disease were not observed in a population ingesting water containing a mean concentration of 7.3 mg/L barium. This NOAEL was then divided by an uncertainty factor of 10, resulting in a MAC 0.73 mg/L. To convert to a TDI, 0.73 mg/L was multiplied by the adult daily water intake rate (1.5 L/day) and divided by a body weight of 70 kg, resulting in a value of 0.0016 mg/kg-day.

The US EPA (2005) TRV of 0.2 mg/kg-day was used in this assessment as it is based on more current data and corresponds to proposed MOE (2007) standards for barium.

4.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify barium as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

4.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore for this assessment, the inhalation TRV was set equal to the oral TRV.

4.3.4 Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify barium as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

4.4 Bioavailability

4.4.1 Oral Bioavailability

The relative oral absorption factor for barium has been conservatively assumed to be 1.0.

4.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for barium has been conservatively assumed to be 1.0.

4.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.1 for barium.

4.5 Conclusion

The following tables summarize the selected toxicity reference values and bioavailabilities.

Table 5: Selected Toxicity Values for Barium

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.2 mg/kg-day	RfD	US EPA (2005)
Inhalation	0.2 mg/kg-day	RfD	US EPA (2005)
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 6: Selected Relative Bioavailabilities for Barium

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	NA
Dermal	0.1	Health Canada, 2004a

4.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 2005. Toxicological Profile for Barium. September 2005.

Brenniman, G.R. and Levy, P.S. 1985. Epidemiological study in Illinois drinking water supplies. In: Advances in modern environmental toxicology. Vol. IX. Princeton Publishing Co., Princeton, NJ. p. 231.

Health Canada. 2002. *Guidelines for Canadian Drinking Water Quality, Supporting Documentation*. Ottawa, Ontario. Available online at: http://www.hc-sc.gc.ca/hecs-sesc/water/dwgsup.htm

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment. Environmental Health Assessment Services, Safe Environments Programme.

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

NTP (National Toxicology Program) 1994, Public Health Service, U.S. Department of Health and Human Services. NTP technical report on the toxicology and carcinogenesis studies of barium chloride dihydrate (CAS no. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). NTP TR 432. Research Triangle Park, NC. NIH pub. no. 94-3163. NTIS pub PB94-214178.

US EPA. 2005. Integrated Risk Information System (IRIS) Database, Barium. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

Last reviewed: May 2007 (RJ)

5.0 BENZENE

Benzene is a colourless liquid with a sweet odour. It is highly flammable and evaporates into air very quickly and dissolves into water slightly. Benzene is commonly found in the environment and enters the environment mainly through industrial processes, such as burning coal and oil, motor vehicle exhaust, evaporation from gas service stations and in the manufacturing of rubbers, lubricants, dyes, detergents and pesticides (ATSDR, 2005). Natural emissions are discharged from volcanic gases, forest fires and present in crude oil and gasoline (ATSDR, 2005).

5.1 Assessment of Carcinogenicity

Benzene is a known human carcinogen (Category A, US EPA, 2003) and is listed as a Group 1 carcinogen by IARC (1987). Health Canada (1996; CEPA 1993) has also classified benzene as carcinogenic to humans (Group I).

5.2 Susceptible Populations

Individuals expressing certain genetic polymorphisms, such as mutations in alleles responsible for the enzymes NQ01 and CYP2E1, may be at greater risk of benzene poisoning than those not expressing these polymorphisms (ATSDR, 2005). Also at risk for increased benzene toxicity include individuals with reduced bone marrow function or decreased levels of certain blood factors, and individuals who consume alcohol (ATSDR, 2005). No definitive human data were discovered on the effects of gender, or age at exposure, on rate or extent of benzene metabolism, although theories have been advanced on these subjects (ATSDR, 2005).

5.3 Selection of Toxicity Values

Chronic exposure to benzene vapours may damage bone marrow leading to anemia and blood disorders, such as leukemia (ATSDR, 2005). Benzene exposure may also harm reproductive organs in females. Exposure to benzene in food or water can also damage blood and the immune system and cause cancer (ATSDR, 2005). Dermal exposure causes general irritation redness and sores.

The following section describes various studies conducted to establish benzene toxicity reference values via ingestion and inhalation routes of exposure. Benzene was evaluated as both a carcinogen and non-carcinogen via oral and inhalation exposure pathways.

5.3.1 Non-Cancer Oral Toxicity Reference Values

The RfD recommended by US EPA (2003) IRIS database, 0.004 mg/kg-day, was selected for use in this assessment. The RfD is based on route-to-route extrapolation of the results of benchmark dose (BMD) modeling of the absolute lymphocyte count data from the occupational epidemiological study by Rothman et al. (1996), in which workers were exposed to benzene by inhalation. A comparison analysis based on BMD modeling of data from the National Toxicology Program's (NTP) experimental animal gavage study (NTP, 1986) was also conducted. In addition, comparison analyses using the

lowest-observed-adverse-effect levels (LOAELs) from the Rothman et al. (1996) and NTP (1986) studies were performed. Rothman et al. (1996) monitored 44 workers exposed to benzene in the workplace. Benzene was monitored by organic vapor passive dosimetry badges worn by each worker for a full workshift on 5 days within a 1–2 week period prior to collection of blood samples. Rothman et al. (1996) yielded a benchmark concentration (BMC) of 13.7 with an adjusted statistical lower confidence limit benchmark ($BMCL_{ADJ}$) of 8.2 mg/m^3. This yields a bench mark dose (BMDL) of 1.2 mg/kg-d. A LOAEL of 7.6 ppm was calculated.

NTP (1986) in one study exposed male mice (five/group) to 0, 8, 40, or 180 mg/kg-day benzene in drinking water for 28 days. Hematological effects were observed at all exposure levels. BMD modeling of the ALC yielded a BMD of 2.2 mg/kg-day and a BMDL of 1.4 mg/kg-day. In a second study, female mice were exposed to 0, 12, 195, or 350 mg/kg-day benzene in drinking water for 30 days. BMD modeling of the ALC (five to six mice/group) resulted in a BMD of 11.6 mg/kg-day and a BMDL of 5.3 mg/kg-day. A LOAEL of 25 mg/kg identified for hematological effects in the NTP (1986) study, there was no NOAEL.

An uncertainty factor of 300 (3 for BMD extrapolation, 10 for intraspecies differences, 3 for sub-chronic to chronic exposure and 3 to account for database deficiencies) was applied to the BMDL from Rothman et al. (1996). A modifying factor of 1 was used.

Health Canada does not provide a non-cancer oral TRV.

5.3.2 Cancer Oral Toxicity Reference Values

An oral slope factor of 0.31 $(mg/kg\text{-}day)^{-1}$ has been reported by Health Canada (2004b) for the assessment of benzene carcinogenicity via oral exposure. This slope factor was based on the Drinking Water Quality Guideline (DWQG). The DWQG was itself partly based on an endpoint of oral squamous cell carcinomas in male rats, and partly based on detection considerations (Health Canada, 1987)

The US EPA provides a slope factor of 0.055 $(mg/kg\text{-}day)^{-1}$ as the upper limit of a range of slope factors for oral exposure to benzene. This value is extrapolated from an inhalation dose-response prepared from several occupational studies of workers' exposures to benzene (Rinsky et al., 1981, 1987; Paustenbach et al., 1993; Crump 1994; U.S. EPA, 1998; U.S. EPA, 1999; all cited in US EPA, 2003). The selected critical effect from the studies was leukemia. An range of inhalation unit risks was developed from these studies, 2.2×10^{-6} $(\mu g/m^3)^{-1}$ to 7.8×10^{-6} $(\mu g/m^3)^{-1}$, and this range was converted to a range of oral slope factors using an assumed 100% oral absorption of benzene (whereas 50% of inhalation benzene was assumed to be absorbed), an assumed inhalation rate of 20 m^3/day, and an assumed body weight of 70 kg. The resulting slope factors were 1.5×10^{-2} $(mg/kg\text{-}day)^{-1}$ to 5.5×10^{-2} $(mg/kg\text{-}day)^{-1}$.

The US EPA (2003) slope factor has been selected for use in this assessment and corresponds with proposed MOE (2007) standards for benzene.

5.3.3 Non-Cancer Inhalation Toxicity Reference Values

A reference concentration (RfC) of 0.03 mg/m^3 was used in this study. It was derived by the US EPA (2003) IRIS database based on benchmark dose modeling of absolute lymphocyte data in humans occupationally exposed to benzene (Rothman et al. 1996). The non-carcinogenic endpoint used in the development of the RfC was decreased lymphocyte count. The study yielded a statistical lower limit benchmark concentration (BMCL) of 8.2 mg/m^3. An uncertainty factor of 300 was applied with a modifying factor of 1.

Health Canada does not provide a non-cancer inhalation TRV.

5.3.4 Cancer Inhalation Toxicity Reference Values

A TC_{05} of 14.7 mg/m^3 was developed by Health Canada (CEPA 1993; Health Canada 1996). This value was derived from epidemiological studies of humans following occupational exposure. In humans, chronic inhalation exposure to benzene in the workplace resulted in an increased incidence of leukemia. The US EPA (2003) gives a unit risk range of 2.2×10^{-6} (µg/m^3)$^{-1}$ to 7.8×10^{-6} (µg/m^3)$^{-1}$ based on several occupational studies demonstrating this critical effect. The unit risk derived from the TC_{05}, 0.0033 (mg/m^3)$^{-1}$ (Health Canada, 2004b), falls within the US EPA range, and was selected for use in this assessment.

5.4 Bioavailability

5.4.1 Oral Bioavailability

The oral bioavailability was assumed to be 100% for the purpose of this assessment.

5.4.2 Inhalation Bioavailability

The inhalation bioavailability was assumed to be 100% for the purpose of this assessment.

5.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.08 for dermal exposure to benzene.

5.5 Conclusion

The following tables present the TRV and bioavailability summaries for benzene.

Table 7 Selected Toxicity Reference Values for Benzene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.004 mg/kg-day	RfD	US EPA, 2003
Inhalation	0.03 mg/m^3	RfC	US EPA, 2003
Cancer Effects			
Ingestion	0.055 $(mg/kg\text{-}day)^{-1}$	SF	US EPA, 2003
Inhalation	0.0033 $(mg/m^3)^{-1}$	UR	HC, 2004b

NA – Not Applicable

Table 8 Selected Bioavailabilities for Benzene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.08	Health Canada, 2004a

5.6 References

ATSDR, 2005. *Toxicological Profile for Benzene.* Prepared by Syracuse Research Corporation. U.S. Department of Health and Human Services, September. Agency for Toxic Substances and Disease Registry.

CEPA 1993. *Benzene*. Canadian Environmental Protection Act, Priority Substances List Assessment Report. Environment Canada and Health Canada, Ottawa. Government of Canada.

Crump, KS. (1994) Risk of benzene-induced leukemia: a sensitivity analysis of the Pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42:219-242.

Health Canada. 1987. Canadian Drinking Water Quality Guidelines: Benzene. Available at: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/doc-sup-appui/benzene/benzene_e.pdf. Updated October 1987.

Health Canada, 1996. Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/ Concentrations for Priority Substances. Ministry of Supply and Services Canada.

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment. Environmental Health Assessment Services, Safe Environments Programme.

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

IARC 1987. "Benzene". IARC Monographs, Supplement 7: (1987) (p. 120). International Agency for Research on Cancer.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP, Research Triangle Park, NC.

Paustenbach, D; Bass, R; Price, P. (1993) Benzene toxicity and risk assessment, 1972-1992: implications for future regulation. Environ Health Perspect 101 (Suppl 6):177-200.

Rinsky, RA; Young, RJ; Smith, AB. (1981) Leukemia in benzene workers. Am J Ind Med 2:217-245.

Rinsky, RA; Smith, AB; Horning, R; et al. (1987) Benzene and leukemia: an epidemiologic risk assessment. N Engl J Med 316:1044-1050.

Rothman, N., G.L. Li, M. Dosemeci, W.E. Bechtold, G.E. Marti, Y.Z. Wang, M. Linet, L.Q. Xi, W. Lu, M.T. Smith, N. Titenko-Holland, L.P. Zhang, W. Blot, S.N. Yin, and R.B. Hayes. 1996. Hematotoxicity among Chinese workers heavily exposed to benzene. *Am. J. Ind. Med*. 29: 236-246.

U.S. EPA. (1998). Carcinogenic effects of benzene: an update. Prepared by the National Center for Environmental Health, Office of Research and Development. Washington, DC. EPA/600/P-97/001F.

US EPA. 1999. Extrapolation of the Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure. US Environmental Protection Agency. Washington DC, NCEA-W-0517.

US EPA. 2003. Integrated Risk Information System (IRIS) Database, Benzene (CASRN 71-43-2). Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

Last reviewed: May 2007 (RJ)

6.0 BERYLLIUM

According to the ATSDR (2002), beryllium is a hard, grayish metal naturally found in mineral rocks, coal, soil, and volcanic dust. Beryllium compounds are commercially mined, and the beryllium is purified for use in nuclear weapons and reactors, aircraft and space vehicle structures, instruments, x-ray machines, and mirrors. Beryllium ores are used to make specialty ceramics for electrical and high-technology applications. Beryllium alloys are used in automobiles, computers, sports equipment (golf clubs and bicycle frames), and dental bridges.

6.1 Assessment of Carcinogenicity

The Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have determined that beryllium is a human carcinogen. The U.S. EPA (1998) has determined that beryllium is a probable human carcinogen.

6.2 Susceptible Populations

There are no studies on the health effects of children exposed to beryllium. It is likely that the health effects seen in children exposed to beryllium will be similar to the effects seen in adults. We do not know whether children differ from adults in their susceptibility to beryllium (ATSDR, 2002).

It is not known if exposure to beryllium will result in birth defects or other developmental effects in people: the studies on developmental effects in animals are not conclusive.

6.3 Selection of Toxicity Values

6.3.1 Non-Cancer Oral Toxicity Reference Values

The oral reference dose (RfD) for beryllium published by the US EPA (1998) is 0.002 mg/kg-d. The US EPA oral RfD is based on a long-term study of dogs fed diets containing beryllium by Morgareidge, *et al* (1976). The oral RfD is based on the development of intestinal lesions. A BMD_{10} (the lower 95% confidence limit on the dose from the maximum likelihood estimate [MLE] of a 10% relative change) of 0.46 mg/kg-day (MLE = 1.4 mg/kg-day) was derived for the lesions and used for further quantitation in this assessment in the US EPA's assessment. (U.S. EPA, 1998). An uncertainty factor of 300 was applied: 10 for extrapolation for interspecies differences, 10 for consideration of intraspecies variation, and 3 for database deficiencies.

An oral RfD of 0.002 mg/kg-day has been adopted in this assessment based on the US EPA's recommended oral RfD. No non-cancer oral TRV was provided by Health Canada.

6.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic oral data precludes the derivation of an oral slope factor or unit risk for beryllium.

6.3.3 Non-Cancer Inhalation Toxicity Reference Values

The inhalation reference concentration (RfC) for beryllium used for this assessment was published by the US EPA (1998) is 2E-5 mg/m^3. The RfC is based on beryllium sensitization and progression to chronic beryllium disease (CBD) identified in the co-principal studies by Kreiss, *et al.* (1996) and Eisenbud, *et al.* (1949). The Kreiss, *et al.* (1996) occupational exposure study identified a lowest observed adverse effects level (LOAEL) for beryllium sensitization in workers exposed to 0.55 µg/m^3 (median of average concentrations). The Eisenbud, *et al.* (1949) study, using relatively insensitive screening methods, suggests a no observed adverse effects level (NOAEL) of 0.01-0.1 µg/m^3 in community residents living near a beryllium plant. The LOAEL from the Kreiss, *et al*. study was used for the operational derivation of the RfC because the screening method used in the Eisenbud, *et al.* (1949) study was less sensitive than the method used in the Kreiss, *et al*. (1996) study.

Because individuals developing beryllium sensitization and CBD are the most sensitive subpopulation, an uncertainty factor of 1 was used to account for human variability. An uncertainty factor of 1 was also used to adjust for the less-than-chronic exposure duration of the Kreiss, *et al.* (1996) study; use of this uncertainty factor is supported by the evidence that the occurrence of CBD does not appear to be related to exposure duration. A database uncertainty factor of 3 was used to account for the poor quality of exposure monitoring in the co-principal studies and other epidemiology studies that assessed the incidence of beryllium sensitization and CBD among exposed workers and community residents.

No non-cancer inhalation TRV was provided by Health Canada.

6.3.4 Cancer Inhalation Toxicity Reference Values

The US EPA (1998) has published an inhalation unit risk for beryllium of 2.4 (mg/m^3)$^{-1}$. The unit risk value is based on an occupational exposure epidemiological study by Wagoner, *et al.* (1980) which was used to estimate the lifetime cancer risk from exposure to beryllium oxide based on the estimated lower and upper bounds of exposure estimated by the National Institute of Occupational Safety and Health (NIOSH); namely, 100 and 1,000 µg/m^3.

For this assessment, the US EPA inhalation unit risk of 2.4 (mg/m3)$^{-1}$ was used. No cancer inhalation TRV was provided by Health Canada.

6.4 Bioavailability

6.5 Oral Bioavailability

The relative oral absorption factor for beryllium has been conservatively assumed to be 1.0.

6.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for beryllium has been conservatively assumed to be 1.0.

6.5.2 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.03 for beryllium.

6.6 Conclusion

The following tables present the TRV and bioavailability summaries for beryllium.

Table 9 Selected Toxicity Reference Values for Beryllium

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	2.00E-03 mg/kg-day	RfD	US EPA, 1998
Inhalation	2.00E-05 mg/m^3	RfC	US EPA, 1998
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	2.4 $(mg/m^3)^{-1}$	UR	US EPA, 1998

NA – Not Applicable

Table 10 Selected Bioavailabilities for Beryllium

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.03	Health Canada, 2004

6.7 References

ATSDR (Agency for Toxic Substances and Disease Registry), 2002. Toxicological Profile for Beryllium. September 2002. Available on-line at: http://www.atsdr.cdc.gov/toxpro2.html.

Eisenbud, M; Wanta, RC; Dustan, C; *et al*., 1949. Non-occupational berylliosis. J Ind Hyg Toxicol 31:282-294. Cited In: US EPA, 1998.

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment. Environmental Health Assessment Services, Safe Environments Programme.

Kreiss, K; Mroz, MM; Newman, LS; *et al*,. 1996. Machining risk of beryllium disease and sensitization with median exposures below 2 MU-G/M(3). Am J Ind Med 30(1):16-25. Cited In: US EPA, 1998.

Morgareidge, K; Cox, GE; Gallo, MA. 1976. Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America, Alcan Research & Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc. Cited In: US EPA, 1998.

US EPA (United States Environmental Protection Agency), 1998. Integrated Risk Information System (IRIS) Database. Beryllium and compounds (inorganic). Confirmed current as of December 2004. Available on-line at: http://www.epa.gov/iris/

Wagoner, JK; Infante, PF; Bayliss, DL. (1980) Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. Environ Res 21:15-34. Cited In: US EPA, 1998.

Last reviewed: May 2007 (RJ)

7.0 BORON

Boron is a solid substance that widely occurs in nature. It usually does not occur alone, but is often found in the environment combined with other substances to form compounds called borates. Common borate compounds include boric acid, salts of borates, and boron oxide. Boron and salts of borate have been found at hazardous waste sites. Boron alone does not dissolve in water nor does it evaporate easily, but it does stick to soil particles (ATSDR, 1992).

Borates are used mostly in the production of glass. They are also used in fire retardants, leather tanning and finishing industries, cosmetics, photographic materials, with certain metals, and for high-energy fuel. Pesticides for cockroach control and wood preservatives also contain borates (ATSDR, 1992).

7.1 Assessment of Carcinogenicity

Boron has not been classified as a carcinogen by any of the major regulatory review agencies including the IARC, US EPA or Health Canada.

7.2 Susceptible Populations

According to ATSDR (1992), neonatal children are unusually susceptible to boron exposure.

7.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to boron.

7.3.1 Non-Cancer Oral Toxicity Reference Values

The oral toxicity reference value used for boron in this assessment is 0.2 mg/kg-d (US EPA, 2004). According to US EPA (2004) this dose was derived as a BMDL05 (i.e., the 95 percent lower confidence limit) from the combination of two studies Price et al. (1996) and Heindel et al. (1992) relating to developmental toxicity. The measurement endpoint chosen was a BMR (i.e., benchmark response) of a 5% decrease in fetal weight relative to control samples. The dose response data from Price et al (1996) showed a statistically significant ($P < 0.05$) decrease in fetal weights with increasing exposure to boron over a range of exposures. The exposure associated with the 5% weight decrease fell well within the range of the experimental data. From this an experimental dose of 10.3 mg/kg-day was calculated, with an uncertainty factor of 66 applied to account for animal-to-human and sensitive-human uncertainty.

The Health Canada (2004) non-cancer oral TRV is 0.0175 mg/kg-day; no information on the derivation of this value could be located.

For this assessment, the US EPA (2004) value of 0.2 mg/kg-day was used as it corresponds with proposed MOE (2007) standards for boron.

7.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify boron as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

7.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data a non-cancer inhalation TRV has not been selected for this assessment; therefore the inhalation TRV has been set to equal the oral TRV.

7.3.4 Carcinogenic Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify boron as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

7.4 Bioavailability

7.4.1 Oral Bioavailability

The oral absorption factor for boron has been conservatively assumed to be 1.0.

7.4.2 Inhalation Bioavailability

The inhalation absorption factor for boron has been conservatively assumed to be 1.0.

7.4.3 Dermal Bioavailability

The dermal absorption factor for boron is assumed to be equal to the inorganic default of 0.1.

7.5 Conclusion

Table 11: Selected Toxicity Values for Boron

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.2 mg/kg-day	RfD	US EPA, 2004
Inhalation	0.2 mg/kg-day	RfD	US EPA, 2004
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 12: Selected Bioavailabilities for Boron

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Assumed

7.6 References

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological Profile for Boron and Compounds. Available on-line at: http://www.atsdr.cdc.gov/toxprofiles/tp26.pdf

Heindel, JJ; Price, CJ; Field, EA; et al. 1992. Developmental toxicity of boric acid in mice and rats. Fund Appl Toxicol 18:266-277.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

Price, CJ; Strong, PL; Marr, MC; Myers, CB; Murray, FJ. (1996) Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fund Appl Toxicol 32:179.

US EPA (United States Environmental Protection Agency). 2004. Integrated Risk Information System (IRIS) Database, Boron. United States Environmental Protection Agency. Available on-line at: http://www.epa.gov/iris/subst/0410.htm.

Last reviewed: May 2007 (RJ)

8.0 CADMIUM

Cadmium is a naturally occurring element that is commonly found as a mineral combined with other elements. Cadmium has many uses in industry and consumer products, mainly in batteries, pigments, metal coatings, plastics, and some metal alloys (ATSDR, 1999).

8.1 Assessment of Carcinogenicity

Several occupational studies have reported an excess risk of lung cancer in humans from exposure to inhaled cadmium; however, the evidence is limited rather than conclusive due to confounding factors (US EPA, 1994; ATSDR, 1999). Animal studies have reported cancer resulting from inhalation exposure to several forms of cadmium, while animal ingestion studies have not demonstrated carcinogenicity (US EPA, 1994; ATSDR, 1999). The US EPA (1994) considers cadmium to be a probable human carcinogen and has classified it as Group B1. Health Canada (Environment Canada and Health Canada, 1994) has classified cadmium as a Group II carcinogen – probably carcinogenic to humans. IARC classifies cadmium as a Group 1 carcinogen (1993).

8.2 Susceptible Populations

Populations which may be unusually susceptible to cadmium exposure are those with a genetic predisposition to lower inducibility of metallothionein, the enzyme which sequesters cadmium (ATSDR, 1999). Dietary deficiencies which lead to depleted levels of calcium or iron in individuals may result in increased absorption of cadmium from the gastrointestinal tract (ATSDR, 1999). Infants and children may have increased uptake of cadmium via the gastrointestinal tract and higher concentrations of cadmium in the bone (ATSDR, 1999).

8.3 Selection of Toxicity Values

Chronic inhalation and oral exposure of humans to cadmium results in a build-up of cadmium in the kidneys that can cause kidney disease, including proteinuria, a decrease in glomerular filtration rate, and an increased frequency of kidney stone formation (ATSDR, 1999). The following section describes various studies conducted to establish cadmium toxicity values via ingestion, inhalation and dermal routes of exposure.

8.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) has adopted the value of 0.0008 mg/kg-day as a tolerable daily intake (TDI). The Health Canada TDI is based upon the Canadian Guidelines for Drinking Water Quality, Supporting Documentation (2003). The Canadian drinking water maximum allowable concentration (MAC) of 0.005 mg/L was calculated based on the joint FAO/WHO expert committee's proposed upper limit provisional tolerable weekly intake (PTWI) of 0.5 mg for adults (WHO, 1992; Health Canada, 2003). The PTWI was based on the estimation that a daily intake of 0.05 mg would lead to 0.1% of the population reaching the "critical" concentration of 0.2 mg/g of cadmium in the renal cortex after

50 years. The WHO (1992) derived a PTWI range of 0.4 to 0.5 mg for cadmium. The kidney is believed to be the target organ of cadmium, specifically affecting the renal cortex.

The US EPA (1994) has developed oral RfDs for cadmium in food and water also based on kidney effects. The RfD for food is 1.0×10^{-3} mg/kg-day and for water is 5.0×10^{-4} mg/kg-day (US EPA, 1994). Both RfDs are based on significant proteinuria in humans with an assumed 2.5% absorption of cadmium from food and 5% from water. The NOAELs for chronic cadmium exposure were determined to be 5.0 and 10 µg/kg-day for food and water, respectively. An uncertainty factor of 10 to account for human variability was applied to the NOAELs to develop the reference doses for food and water.

The Health Canada TDI of 8.0×10^{-4} mg/kg-day was selected to assess non-carcinogenic effects from oral cadmium exposure.

8.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor or unit risk for cadmium.

8.3.3 Non-Cancer Inhalation Reference Toxicity Values

A non-cancer inhalation TRV has not been selected for this assessment because cadmium is carcinogenic by inhalation.

8.3.4 Cancer Inhalation Reference Toxicity Values

The US EPA (1994) has developed an inhalation unit risk of 1.8 $(mg/m^3)^{-1}$ to be used only if the air concentration does not exceed 6 $\mu g/m^3$. This unit risk is based on lung and upper respiratory tract cancers in cadmium production workers (Thun *et al*., 1985) and was selected over another study that yielded a more conservative unit risk because it was based on human data which involved a large cohort and took into consideration the effects of arsenic and smoking.

Health Canada (2004b) has calculated an inhalation unit risk of 9.8 $(mg/m^3)^{-1}$ which is equivalent to an inhalation slope factor of 4.29E+01 $(mg/kg\text{-}day)^{-1}$, which was based on a TC_{05} of 5.1 $\mu g/m^3$ (Health Canada, 1996). The estimated TD_{05} for cadmium chloride based on multistage model of lung tumour incidences observed in rats by Takenaka *et al*. (1983). The TD_{05} of 2.9 µg of cadmium/m^3 was amortized to be constant over the entire life of the rat, adjusted for longer than lifetime duration of the experiment and converted to an equivalent concentration for humans using standard breathing rates and body weights which yielded a TC_{05} of 5.1 $\mu g/m^3$ (Environment Canada and Health Canada, 1994).

The Health Canada TC_{05} provides a more conservative unit risk estimate of the potency of inhaled cadmium, therefore an inhalation unit risk of 9.8 $(mg/m^3)^{-1}$ was used in this assessment.

8.4 Bioavailability

Cadmium compounds have varying degrees of solubility ranging from very soluble to nearly insoluble. The solubility affects their absorption and toxicity. Exposure to cadmium and cadmium compounds may occur in both occupational and environmental settings, the latter primarily via the diet and drinking water (ATSDR, 1999).

8.4.1 Oral Bioavailability

Cadmium bound in a soil matrix is expected to be less bioavailable than cadmium in drinking water, as in the study from which the oral RfD was derived. Other studies have reported the oral absorption of cadmium to range from 0.027 (Newton *et al*., 1984) to 0.06 (Rahola *et al*., 1975).

The selected oral RfD for cadmium is based on kidney effects following water consumption. Water consumption was assumed to be 5% absorbed in humans (US EPA, 1994). Falling within the range of the above studies. For this assessment, an oral relative bioavailability of 1.0 in soil was used.

8.4.2 Inhalation Bioavailability

Cadmium in air exists primarily as fine suspended particulate matter. When inhaled, some fraction of the larger particles (*i.e*., greater than 10 microns in diameter) is deposited in the airways or lungs, and the rest is exhaled. Finer particles tend to penetrate into the alveoli. While some soluble cadmium compounds may be absorbed from the airways or lungs, the major site of absorption is the alveoli (ATSDR, 1999). Comprehensive modelling of the kinetics of cadmium in the respiratory tree indicates that 5 to 50% of particles will be deposited, and that 50 to 100% of cadmium deposited in the alveoli will be absorbed (Nordberg *et al*., 1985). An inhalation relative bioavailability factor of 1.0 was used in this assessment.

8.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.14 for dermal exposure to cadmium.

8.5 Conclusion

The following tables present the TRV and bioavailability summaries for cadmium.

Table 13 Selected Toxicity Reference Values for Cadmium

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	8.0×10^{-4} mg/kg-day	TDI	Health Canada, 2004b
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	$9.8\ (mg/m^3)^{-1}$	UR	Health Canada, 2004b

NA – Not Applicable

Table 14 Selected Relative Bioavailabilities for Cadmium

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.14	Health Canada, 2004a

8.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 1999. Toxicological Profile for Cadmium. July 1999.

Environment Canada and Health Canada, 1994. Priority Substances List Assessment Report, Cadmium and its Compounds. Canadian Environmental Protection Act. Government of Canada, Ottawa, Ontario.

Health Canada. 1996. Health based Tolerable daily intakes/concentrations and tumorigenic doses/concentrations for priority substances. Minister of Supply and Services Canada, Ottawa.

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment. Environmental Health Assessment Services, Safe Environments Programme.

Health Canada, 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs). October 3, 2003.

Health Canada, 2003. Cadmium in Guidelines for Canadian Drinking Water Quality – Supporting Documents. Confirmed current as of December, 2004. Available online at: http://www.hc-sc.gc.ca/hecs-sesc/water/dwgsup.htm.

IARC. 1993. "Arsenic and Arsenic Compounds". *Monographs.* Vol. 23 Suppl. 7. World Health Organization. International Agency for Research on Cancer.

Newton D, Johnson P, Lally AE, *et al*. 1984. The uptake by man of cadmium ingested in crab meat. *Hum Toxicol* 3:23-28. Cited In: ATSDR, 1999.

Nordberg GF, Kjellstrom T, and Nordberg M, 1985. Kinetics and Metabolism. In: Friberg *et al*., eds. Cadmium and health: A toxicological and epidemiological appraisal. Volume I: Exposure, dose, and metabolism. Boca Roton, FL: CRC Press, 103-178. Cited In: ATSDR, 1999.

Rahola T, Aaran RK, and Miettinen JK, 1973. Retention and Elimination of Cd in Man. In: Health Physics Problems of International Contamination, Bujdoso, Ed. Akademiai Kiado Budapest, 1973, 213pp. Cited In: ATSDR, 1999.

Takenaka S, Oldiges H, Konig H, *et al*., 1983. Carcinogenicity of cadmium chloride aerosols in Wistar rats. *Journal of the Nationa1 Cancer Institute* 70:367-373. Cited In: ATSDR, 1999.

Thun MJ, Schnorr TM, Smith AB, and Halperin WE, 1985. Mortality Among a Cohort of US Cadmium Production Workers: An update. *J. Natl. Cancer Inst.* 74(2): 325-333. Cited In: US EPA, 1994.

US EPA (United States Environmental Protection Agency). 1994. Integrated Risk Information System (IRIS) Database – Cadmium. Confirmed current as of December 2004. Available: http://www.epa.gov/iris/.

WHO (World Health Organization). 1992. Toxicological Evaluation of Certain Food Additives and Contaminants – Food Additives Series 24. Prepared by the 33rd meeting of the Joint FAO/WHO Expert Committee on Food Additives, March 21-30, 1989, Geneva. Cambridge University Press, New York. pp. 163-219. Cited In: Health Canada, 1996.

Last reviewed: June 2007 (RJ)

9.0 CHLOROFORM

Chloroform is a colorless liquid with a pleasant, nonirritating odor and a slightly sweet taste (ATSDR, 1997). It will burn only when it reaches very high temperatures. In the past, chloroform was used as an inhaled anesthetic during surgery, but it isn't used that way today. Today, chloroform is used to make other chemicals and can also be formed in small amounts when chlorine is added to water (ATSDR, 1997). Chloroform is also known as trichloromethane and methyl trichloride.

9.1 Assessment of Carcinogenicity

The Department of Health and Human Services (DHHS) has determined that chloroform may reasonably be anticipated to be a carcinogen. Rats and mice that ate food or drank water with chloroform developed cancer of the liver and kidneys (ATSDR, 1997).

Under the 1986 U.S. EPA Guidelines for Carcinogen Risk Assessment, chloroform has been classified as Group B2, *probable human carcinogen*, based on "sufficient evidence" of carcinogenicity in animals (U.S. EPA, 1998a). However, under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996; U.S. EPA, 1999), chloroform is *likely to be carcinogenic to humans by all routes of exposure* under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b). Chloroform is *not likely to be carcinogenic to humans by any route of exposure* under exposure conditions that do not cause cytotoxicity and cell regeneration.

The IARC lists chloroform as a Group 2B chemical: describing it as a possibly carcinogenic to humans. This determination is based on the fact that there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals (IARC, 1999).

9.2 Susceptible Populations

Because the liver and kidney are the two main organs responsible for chloroform metabolism, individuals who have hepatic or renal impairment may be more susceptible to chloroform toxicity; one such population would be those who abuse alcohol (Wang et al. 1994; Kutob and Plaa 1962).

9.3 Selection of Toxicity Values

The following section describes various studies conducted to establish chloroform toxicity values via the inhalation route of exposure.

9.3.1 Non-Cancer Oral Toxicity Reference Values

An oral reference dose (RfD) of 0.01 mg/kg-day was provided for chloroform by the U.S. EPA (1991) based on a chronic study on beagle dogs by Heywood et al. (1979). From this study moderate-to-marked fatty cyst formation was seen in the liver along with elevated levels of serum glutamate-

pyruvate transaminase. The RfD of 0.01 mg/kg-day was derived from a LOAEL of 12.9 mg/kg-day divided by an uncertainty factor of 1000.

For this assessment the US EPA RfD value of 0.01 mg/kg-day was selected. No Health Canada value was available for chloroform.

9.3.2 Cancer Oral Toxicity Reference Values

Due to the lack of sufficient data a cancer oral TRV has not been selected for this assessment.

9.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, MOE values were used. MOE (2001) provides a inhalation toxicity reference value of 0.001 mg/m^3; no back-up information on the derivation of this TRV is available.

9.3.4 Cancer Inhalation Toxicity Reference Values

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, MOE values were used. MOE (2001) provides a cancer inhalation toxicity reference value of 5.00E-03 mg/m^3; no back-up information on the derivation of this TRV is available.

9.4 Bioavailability

9.5 Oral Bioavailability

The oral absorption factor for chloroform has been conservatively assumed to be 1.0.

9.5.1 Inhalation Bioavailability

The inhalation absorption factor for chloroform has been conservatively assumed to be 1.0.

9.5.2 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.1 for dermal exposure to chloroform.

9.6 Conclusion

The following tables present the TRV and bioavailability summaries for chloroform.

Table 15 Selected Toxicity Reference Values for Chloroform

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	1.00E-02 mg/kg-d	RfD	US EPA, 1991
Inhalation	1.00E-03 mg/m^3	AAQC	MOE, 2001
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	5.00E-03 (mg/m^3)$^{-1}$	UR	MOE, 2001

NA – Not Applicable

Table 16 Selected Bioavailabilities for Chloroform

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada (2004)

9.7 References

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological Profile for Chloroform.* US Department of Health and Human Services, Public Health Service. September, 1997

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada. Part I: Guidance on Human Health Screening Level Risk assessment (SLRA). Version 1.1, October 3, 2003

IARC (International Agency for Research on Cancer). 1999. IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans, Chloroform, Volume 73, p.131.

Kutob SD, Plaa GL. 1962. The effect of acute ethanol intoxication on chloroform-induced liver damage. J Pharmacol Exp Ther 135:245-251. Cited in: ASTDR, 1997.

MOE (Ontario Ministry of the Environment). 2001. Ontario Air Standards for Chloroform. Standards Development Branch.

Roe, FJC; Palmer, AK; Worden, AN; et al. (1979) Safety evaluation of toothpaste containing chloroform: I. Long-term studies in mice. J Environ Pathol Toxicol 2:799-819. Cited in: US EPA, 2005.

Wang P-Y, Kaneko T, Tsukada H, et al. 1994. Dose and route dependency of metabolism and toxicity of chloroform in ethanol-treated rats. Arch Toxicol 69:18-23. Cited in: ASTDR, 1997.

US EPA (United States Protection Agency), 1996. Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960-18011. Cited in: US EPA, 2005.

US EPA (United States Protection Agency), 1998a. Health risk assessment/characterization of the drinking water disinfection byproduct chloroform. Prepared for Health and Ecological Criteria Division, Office of Science and Technology, Washington, DC, by Toxicology Excellence for Risk Assessment, Cincinnati, OH, under Purchase Order No. 8W-0767-NTLX. November 4, 1998. Cited in: US EPA, 2005.

US EPA (United States Protection Agency), 1998b. National primary drinking water regulations: disinfectants and disinfection byproducts. Notice of data availability; proposed rule. 40 CFR Parts 141-142:15674. Cited in: US EPA, 2005.

US EPA (United States Protection Agency), 1999. Guidelines for Carcinogenic Risk Assessment. Review Draft. July 1999. US Environmental Protection Agency, Risk Assessment Forum. Cited in: US EPA, 2005.

Last reviewed: May 2007 (RJ)

10.0 CHROMIUM (TOTAL)

Chromium (Cr) is a naturally occurring element that is often found complexed with oxygen, iron or lead. Although chromium has nine different oxidation states it is often found either in its trivalent (III) or hexavalent (VI) states. Total chromium represents a mixture of these compounds.

Chromium (III) is an essential nutrient that aids the human body in utilizing sugars, proteins, and fats. Allergic reactions consisting of severe redness and swelling of the skin have been noted. Although chromium (III) is an essential nutrient, the ATSDR recommends that one should avoid excessive use of dietary supplements containing chromium (ATSDR, 2000).

10.1 Assessment of Carcinogenicity

Epidemiological studies of leather tannery workers exposed to chromium (III) have consistently shown that exposures to chromium (III) compounds are not associated with an increased incidence of cancer. Epidemiological studies of people living in the vicinity of chromium (III) industries have shown no link between environmental exposure to chromium (III) and cancer rates in the population (ATSDR, 2000). Oral and dermal exposures to chromium (III) compounds are not associated with the development of cancers (ATSDR, 2000). The US EPA (2002) IRIS database has assessed chromium (III) as not carcinogenic to humans (Category D, Not Classifiable as to Human Carcinogenicity) based on inadequate evidence to support carcinogenicity. The International Agency for Research on Cancer (IARC, 1990) lists chromium (III) as a Group 3 chemical, not classifiable as to human carcinogenicity. Health Canada (2004b) has not evaluated chromium (III) for human carcinogenicity. Health Canada (2004b) has, however, evaluated total chromium as an inhalation carcinogen but not an oral carcinogen. Inhalation carcinogenicity of total chromium may be a result of chromium (VI), a known carcinogen, being a component of total chromium.

Occupational exposures to chromium (VI) compounds have been associated with increased risks of respiratory system cancers (ATSDR, 2000). Epidemiological studies of workers exposed to chromium (VI) compounds in the plating and chromate pigment industries have consistently shown an association between occupational inhalation exposures and respiratory tract cancers (primarily nasal and bronchogenic cancers) (ATSDR, 2000). These studies have been used by both the US EPA and Health Canada to develop cancer slope factors for inhalation exposures to chromium (VI) (Health Canada, 2004a, US EPA, 1998).

There are no reports of cancer associated with oral exposure to chromium (VI) compounds in humans (ATSDR, 2000). Further, studies with animals found no evidence of carcinogenicity in animals exposed to chromium (VI) compounds in drinking water (ASTDR, 2000). Based on the lack of evidence of carcinogenic activity for chromium (VI) by ingestion, the US EPA and Health Canada have determined that chromium (VI) is not carcinogenic when ingested (US EPA, 2002, Health Canada, 2004a).

10.2 Susceptible Populations

People who have developed contact dermatitis may be more sensitive to exposure to chromium (III) compounds than the general population.

10.3 Selection of Toxicity Values

Breathing chromium (III) does not cause an irritation to the mouth or nose in most people (ATSDR, 2000). Although orally ingesting small amounts is essential for proper nutrition and bodily function, ingesting larger amounts may be harmful to health. Whereas chromium (VI) is readily transportable through biological membranes, chromium (III) is not. However the rapid reduction of chromium (VI) to chromium (III) once inside the cells may be an important mechanism of toxicity (ATSDR, 2000).

The following section describes various studies conducted to establish chromium (total) toxicity reference values via ingestion, inhalation and dermal routes of exposure.

10.3.1 Non-Cancer Oral Toxicity Reference Values

The US EPA have developed separate TRVs for chromium (III) and chromium (VI). A chronic oral reference dose (RfD) of 0.003 mg chromium (VI)/kg-day has been derived and verified by EPA for soluble salts of chromium (VI) (e.g., potassium chromate, sodium chromate, potassium dichromate, and sodium dichromate) (US EPA 2000b). The RfD is based on a NOAEL for systemic effects in rats exposed to 2.5 mg chromium (VI)/kg-day as potassium chromate in the drinking water for 1 year in the study by MacKenzie *et al.* (1958).

A chronic oral RfD of 1.5 mg chromium (III)/kg-day has been derived and verified by EPA for insoluble salts of chromium (III) (e.g., chromium oxide and chromium sulfate) (US EPA 2000a). The RfD is based on a NOAEL for systemic effects in rats fed 1,800 mg chromium (III)/kg-day for 5 days/week for 600 feedings (840 total days) in the study by Ivankovic and Preussmann (1975). An uncertainty factor of 100 was applied to the lowest dose in the study to account for inter-species variability and variability within the human population (US EPA, 2000a).

Health Canada has not developed an oral toxicity value for chromium (III) compounds, but Health Canada (2004b) has released a TDI of 0.001 mg/kg-day for total chromium, based on Canadian Drinking Water Quality Guidelines (Health Canada, 2002). It is based on a NOAEL of 0.05 mg/L, which is itself based on several other studies, all of which are referenced in the Health Canada (2002) supporting documentation for the Canadian Guidelines for Drinking Water Quality. Health Canada (2004b) also developed a TRV for chromium (VI) of 0.001 mg/kg-day.

The Canadian Council of Ministers of the Environment (CCME) developed TDIs of 0.0062 mg/kg-day and 0.0029 mg/kg-day for toddlers and adults, respectively, as part of the CCME soil quality guideline development process (CCME, 1996).

As the Health Canada (2004b) TDI for total chromium includes both species of chromium, and it is more conservative than the other TRVs proposed, it has been selected for use in the risk assessment.

10.3.2 Cancer Oral Toxicity Reference Values

The US EPA (2002) has not established an oral slope factor (SF) for chromium (III), chromium (VI), or total chromium under the IRIS database, and Health Canada (2004b) does not recommend a TD_{05} for any of these compounds. A cancer oral toxicity value was therefore not selected for this risk assessment.

10.3.3 Non-Cancer Inhalation Toxicity Reference Values

A non-cancer inhalation TRV has not been selected for this assessment because chromium (total) is carcinogenic by inhalation.

10.3.4 Cancer Inhalation Toxicity Reference Values

Health Canada developed a TC_{05} of 4.6 µg/m^3 for total chromium that includes consideration for the presence of chromium (III) and chromium (VI) compounds (Health Canada, 2004b). This quantity is the concentration that corresponded to a 5% increase in lung cancer mortality in a cohort of chromate production workers (Mancuso *et al.*, 1975, cited in CEPA, 1994). Based on the TC_{05}, Health Canada (2004b) provides an inhalation slope factor for total chromium of 47.6 $(mg/kg\text{-}day)^{-1}$ based on this TC_{05}, as well as a unit risk of 10.9 $(mg/m^3)^{-1}$.

Health Canada (2004b) also provides an inhalation slope factor for chromium (VI) of 331 $(mg/kg\text{-}day)^{-1}$ and an equivalent unit risk of 75.8 $(mg/m^3)^{-1}$, but these values do not pertain to total chromium, so were not used in this risk assessment.

The Health Canada (2004b) cancer inhalation TRVs for exposure to total chromium were selected for use in the risk assessment. No US EPA value was available.

10.4 Bioavailability

10.4.1 Oral Bioavailability

The oral bioavailability was assumed to be 1.0 for the purpose of this assessment.

10.4.2 Inhalation Bioavailability

The inhalation bioavailability was assumed to be 1.0 for the purpose of this assessment.

10.4.3 Dermal Bioavailability

The Health Canada (2004a) dermal absorption value of 0.04 was used to assess the bioavailable fraction of chromium that would be absorbed through soil exposure to the skin.

10.5 Conclusion

The following tables present the TRV and bioavailability summaries for total chromium.

Table 17 Selected Toxicity Reference Values for Total Chromium

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.001 mg/kg-day	TDI	Health Canada, 2004b
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	47.6 $(mg/kg\text{-}day)^{-1}$	SF	Health Canada, 2004b
Inhalation	10.9 $(mg/m^3)^{-1}$	UR	Health Canada, 2004b

NA – Not Applicable

Table 18 Selected Bioavailabilities for Chromium III

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	NA	NA
Dermal	0.04	Health Canada, 2004

10.6 References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for Chromium. Atlanta, Georgia, US Department of Health and Human Services, Public Health Service.

Canadian Council of Ministers of the Environment (CCME), 1996. Canadian Soil Quality Guidelines for Contaminated Sites. Human Health Effects: Chromium. Final Report, March 1996. The National Contaminated Sites Remediation Program.

CEPA, 1994. Canadian Environmental Protection Act Priority Substances List Assessment Report: Chromium and its Compounds. Available at: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/chromium_chrome/chromium_chrome_e.pdf

Health Canada. 2002. Canadian Guidelines for Drinking Water Quality, Supporting Documentation. Health Canada.

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment. Environmental Health Assessment Services, Safe Environments Programme.

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

IARC. 1990. “Chromium (III) Compounds”. *Monographs.* Vol. 31, Suppl. 7. World Health Organization. International Agency for Research on Cancer.

US EPA. 2000a. Integrated Risk Information System (IRIS) Database, Chromium (III), insoluble salts, (CASRN 16065-83-1). Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA. 2000b. Integrated Risk Information System (IRIS) Database, Chromium (IV). Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

Last reviewed: June 2007 (RJ)

11.0 COBALT

Cobalt is a naturally-occurring element that is found in small amounts in rocks, soil, water, plants, and animals often combined with other elements such as oxygen, sulfur, and arsenic. Cobalt is even found in water in dissolved or ionic form, typically in small amounts.

A biochemically important cobalt compound is vitamin B-12 or cyanocobalamin, which is essential for good health in animals and humans (ATSDR, 2001). Vitamin B-12 cannot be synthesized by humans and must be ingested via dietary sources (IOM, 2000). Cobalt is essential in the human body only because it is an integral component of Vitamin B-12 and functions as a co-enzyme for several enzymes critical in the synthesis of hemoglobin and the prevention of pernicious anemia (IOM, 2000). The RDA for vitamin B-12 is 2.4 µg/day for a 76 kg adult (IOM, 2000). No essential biological function of inorganic cobalt in the human body has been identified (ATSDR, 2001). TDIs of inorganic cobalt in humans varies greatly with Canadian adults ingesting between 9 and 15 µg/day from dietary sources (ATSDR, 2001).

11.1 Assessment of Carcinogenicity

The ATSDR (2001) discusses carcinogenicity data in its toxicological profile for cobalt, however it does not currently assess cancer potency. Human occupational studies of cancer from cobalt inhalation have been confounded by exposures to nickel and arsenic. Injection of cobalt compounds in a number of animal studies have produced local tumours in some cases (IARC, 1991). There is insufficient evidence available to classify cobalt or cobalt compounds as carcinogens since cobalt has not been shown to cause cancer in humans by inhalation, oral or dermal routes of administration (ATSDR 2001). The US EPA and Health Canada have not classified cobalt for carcinogenicity. The International Agency for Research on Cancer (IARC, 1991), however, has classified cobalt and cobalt compounds as Group 2B, possibly carcinogenic to humans.

11.2 Susceptible Populations

Individuals that are already sensitized to cobalt may be unusually susceptible to cobalt-triggered asthmatic attacks. Allergic dermatitis was reported in some cobalt-sensitized individuals following oral challenge with cobalt and dermal patch test. Exposure levels associated with sensitization to cobalt have not been established (ATSDR, 2001).

11.3 Selection of Toxicity Values

Major non-carcinogenic adverse effects observed in humans after exposure to high concentrations of cobalt include cardiomyopathy, respiratory irritation, polycythemia, contact dermatitis, rhinitis and asthma. Cardiomyopathy has been caused by the excessive, prolonged intake of cobalt (IARC, 1991), particularly intake of beer to which 1 mg/L of cobalt (Co) was added as a foam stabilizer (this practice has been discontinued). Nausea and vomiting occurred prior to cardiac effects. The effects observed depend upon the dose and length of exposure, species of cobalt to which humans are exposure and the route of administration (Hostynek, 1993; ATSDR, 2001).

11.3.1 Non-Cancer Oral Toxicity Reference Values

There is little information regarding toxicity values for cobalt. A RfD of 0.02 mg/kg-day was developed by US EPA's (2001) Office of Research and Development (ORD)/National Center for Environmental Assessment (NCEA)/Superfund Health Risk Technical Support Center (STSC). This value is based on the upper range of the average intake of cobalt in the diet of children. No Health Canada TRV was available.

ATSDR (2001) has developed an intermediate exposure duration MRL of 1.0E-02 mg/kg-day. This is based on a LOAEL of 150 mg/day cobalt as cobalt chloride (1 mg Co/kg-day) exposure for polycuthemia as reported in (ATSDR, 2001). Six men were exposed for up to 22 days, which resulted in the development of polycythemia in all six patients. An uncertainty factor of 100 was applied (10 for use of a LOAEL and 10 for human variability).

For this assessment the ATSDR MRL of 1.0E-02 mg /kg-day was used as it is more conservative to the US EPA value and corresponds with proposed MOE (2007) standards for cobalt.

11.3.2 Cancer Oral Toxicity Reference Values

The carcinogenic potential of cobalt has not been adequately assessed, therefore oral SFs are not available.

11.3.3 Non-Cancer Inhalation Toxicity Reference Values

ATSDR (2001) has established an intermediate inhalation MRL of 1.0×10^{-4} mg/m^3 based on respiratory effects in diamond polishers (Nemery *et al*., 1992). The Nemery *et al*. (1992) study group consisted of 194 diamond polishers in 10 workshops. Personal air samplers and air samplers were used and urinary cobalt was monitored. Exposures were divided into low and high groups. Comparison of control, low and high workers groups showed a NOAEL for the low exposure group. The air samplers for this group showed a mean exposure concentration of 1.6 µg/m^3 while the personal air samplers indicated a mean concentration of 5.3 µg/m^3. Complaints of respiratory effects, cough and irritation to eyes, nose and throat were prevalent in the high group exposed to 10.2 µg/m^3 to 15.1 µg/m^3 based on air and personal air samplers, respectively.

The US EPA Region III (2001) provides a provisional inhalation RfD of 5×10^{-6} mg/kg-day. No Health Canada TRV was available.

The ATSDR MRL of 1.0×10^{-4} mg/m^3 for cobalt was selected for this assessment as it corresponds with proposed MOE (2007) standards for cobalt.

11.3.4 Cancer Inhalation Toxicity Reference Values

The carcinogenic potential of cobalt has not been adequately assessed therefore inhalation SFs and unit risks are not available.

11.4 Bioavailability

11.4.1 Oral Bioavailability

According to ATSDR (2001) the oral bioavailability of cobalt varies from 18-97% depending on dose, form of cobalt compound and nutritional status of the subjects. Cobalt absorption into the gastrointestinal tract has been shown to increase if the body is deficient in iron (Valberg *et al*., 1969; Sorbie *et al*., 1971).

Christensen *et al*. (1993) compared the bioavailability of soluble and insoluble cobalt compounds in humans, measuring uptake based on levels in blood and urine. The measured absorption was <0.17 to 4373 nmol/mmol for cobalt chloride and <0.17 to 14.6 nmol/mmol for cobalt oxide. This suggests that cobalt, in its inorganic form in soils may be significantly less bioavailable than cobalt from dietary intake and could indicate a relative bioavailability in the order of 0.3% would be appropriate for cobalt oxide or other inorganic forms of cobalt.

Since the selected toxicity reference value is based on dietary cobalt, an adjustment for relative oral bioavailability of cobalt in soil of 1.0 has been adopted for this assessment.

11.4.2 Inhalation Bioavailability

Inhaled cobalt particles are deposited in the upper and lower respiratory tract (Casarett & Doull, 1986). Fractional deposition of inhaled cobalt oxide particles in humans varies from approximately 50 to 75%, depending on particle size (Foster *et al*., 1989).

For this assessment, a relative bioavailability of 1.0 for inhalation was used.

11.4.3 Dermal Bioavailability

Scansetti *et al*. (1994) measured cobalt in air and cobalt in urine at two medium size plants and one small factory. No relationship between levels in air and urine was observed. They concluded that the substantial dermal exposure could be contributing significantly to the observations. Four volunteers were exposed to freshly mixed powder containing about 5 to 15% cobalt or waste powder dermally, resulting in a ten-fold increase in urinary excretions over the first 48 to 60 hours. The mean particle diameter of the waste dry powder was 1.5 µm. Volunteers held one hand in a box of the exposure medium for 90 minutes. Urine concentrations were measured over the three days following exposure, but were not presented in the literature.

A dermal absorbed fraction of 0.0004 is cited by Paustenbach (2000) for cobalt chloride (0.04%) in aqueous solution. The dermal bioavailability factor of 0.01 is based on the recommendations of the US EPA Region III (1995). Health Canada (2004) recommends a RAF_{dermal} of 0.1 for cobalt based on an arbitrary value selected by the MOE (1996). The Health Canada relative dermal bioavailability of 0.1 has been adopted for this assessment.

11.5 Conclusion

The following tables present the TRV and bioavailability summaries for cobalt.

Table 19 Selected Toxicity Reference Values for Cobalt

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	1.0E-02 mg/kg-day	MRL	ATSDR, 2001
Inhalation	1.0×10^{-4} mg/m^3	MRL	US EPA Region III, 1995
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 20 Selected Bioavailabilities for Cobalt

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004

11.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 2001. *Toxicological Profile for Cobalt.* September 2001.

Casarett and Doull. 1986. Toxicology: The basic science of poisons. 3rd ed. New York, NY: Macmillan Publishing Company, 56-57. As cited in ATSDR, 2001.

Christensen JM, OM Poulsen and M Thomsen, 1993. "A short term cross-over study on oral administration of soluble and insoluble cobalt compounds: sex differences in biological levels." *Int Arch Occup Environ Health.* 65:233-240.

Foster PP, Pearman I and Ramsden D, 1989. An interspecies comparison of the lung clearance of inhaled monodisperse cobalt oxide particles – Part II: Lung clearance of inhaled cobalt oxide in man. *J Aerosol Sci*. 20:189-204.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Screening Level Risk Assessment (SLRA)..

Hostynek JJ, Hinz RS, Lorence CR, Price M and Guy RH, 1993. Metals and the skin. *Crit Rev Toxicol.* 23: 171-235.

IARC (International Agency for Research on Cancer), 1991. IARC Monograph, Volume 52: Chlorinated Drinking-Water; Chlorination By-products; Some Other Halogenated Compound; Cobalt and Cobalt Compounds. Available at: http://193.51.164.11/ monoeval/allmonos.html.

IOM (Institute of Medicine), 2000. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Panthothenic Acid, Biotin and Choline. National Academy Press, Washington, DC.

MOE (Ontario Ministry of the Environment), 1996. Rationale for the Development and Application of Generic Soil, Groundwater and Sediment Criteria for Use at Contaminated Sites in Ontario. Standards Development Branch, 1996.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

Nemery B, Casier P and Roosels D, 1992. Survey of cobalt exposure and respiratory health in diamond polishers. *Am Rev Respir Dis* 145: 610-616.

Paustenbach DJ, 2000. "The practice of exposure assessment: A state-of-the-art review." *J.Toxicol.Environ. Health. Part B.* 3:179-291.

Scansetti G, Botta GC, Spinelli P, Reviglione L and Ponzetti C, 1994. Absorption and excretion of cobalt in the hard metal industry. *Sci Tot Environ.* 150:141-144.

Sorbie J, Olatunbosun D, Corbett WE and Valberg LS, 1971. Cobalt excretion test for the assessment of body iron stores. *CMAJ.* 104: 777-782.

US EPA (United States Environmental Protection Agency), 2001. "Risk-Based Concentration Table." EPA Region III, Revised 09/25/2001. On: http://www.epa.gov/reg3hwmd/risk/ riskmenu.htm.

US EPA (United States Environmental Protection Agency) Region III, 1995. Risk Assessment: Technical Guidance Manual. Assessing Dermal Contact with Soil. http://www.epa.gov/ reg3hwmd/risk/solabsg2.htm

Valberg LS, Ludwig J and Olatunbosun D, 1969. Alteration in Cobalt Absorption in Patients with Disorders of Iron Metabolism. *Gastroenterology* 56(2):241-251. Cited In: ATSDR, 2001.

12.0 DICHLOROMETHANE

Dichloromethane, also known as methylene chloride, is a colorless liquid that has a mild sweet odor, evaporates easily, and is non-flammable. Most applications are based on its solvent capacity for grease, plastics and paint binding agents, in combination with its volatility and stability. It can be found in certain aerosol and pesticide products and is used in the manufacture of photographic film. The chemical may be found in some spray paints, automotive cleaners and other household products (ATSDR, 2000; INCHEM, 1996).

Dichloromethane does not appear to occur naturally in the environment. It is made from methane gas or wood alcohol. Most of the methylene chloride released to the environment results from its use as an end product by various industries and the use of aerosol products and paint removers in the home (ATSDR, 2000).

12.1 Assessment of Carcinogenicity

Dichloromethane is classified as a possible human carcinogen by IARC (1989), US EPA (1995) and Health Canada (1996) because there is sufficient evidence for carcinogenicity in animal tests; however there is inadequate human data.

12.2 Susceptible Populations

Certain subgroups of the general population may be more susceptible to dichloromethane than others; of concern are potential health effects of carboxyhemoglobin (COHb). COHb is a chemical formed in blood as dichloromethane metabolizes in the body into carbon monoxide. COHb generated from exposure to dichloromethane would be expected to be additive to COHb from other sources, such as smoking and those with existing cardiovascular disease. Smokers maintain significantly constant levels of COHb. Furthermore, varying susceptibility to dichloromethane may be correlated with polymorphism in its metabolizing enzymes, GSTT1 and CYP2E1 (ATSDR, 2000).

12.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to dichloromethane.

12.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.05 mg/kg-day, which was used as the oral TRV in this assessment. A LOEL of 50 mg/kg bw/day caused non-neoplastic effects after ingestion of dichloromethane by F344 rats (Serota et al., 1986). At this LOEL, fully reversible cellular proliferation and partially reversible fatty change in livers was observed. A TDI was derived from the NOEL of 5 mg/kg bw/day (Serota et al., 1986), with an uncertainty factor of 100 applied for interspecies and intraspecies variability.

The US EPA (1995) provides a RfD of 0.06 mg/kg-day. The RfD value is based on a study (National Coffee Association, 1982) that included a 24-Month chronic toxicity and oncogenicity study of methylene chloride in rats. 85 rats per sex at four dose groups (5, 50, 125 and 250 mg/kg-day) were observed for 2 years. Treatment-related histological alterations of the liver were evident at doses of 50

mg/kg-day or higher. The low dose of 5 mg/kg-day was a NOAEL. Supporting studies are limited. A NOAEL of 28 mg/kg bw/day was reported in one inhalation study (Haun et al., 1972).

For this assessment, the Health Canada TRV of 0.05 mg/kg-day was chosen because it was more conservative to the US EPA value.

12.3.2 Cancer Oral Toxicity Reference Values

An oral slope factor of 7.90E-05 $(mg/kg\text{-}day)^{-1}$ has been reported by Health Canada (2004b) for the assessment of dichloromethane carcinogenicity via oral exposure. This slope factor was based on the Drinking Water Quality Guideline (DWQG). The DWQG for dichloromethane is 0.05 mg/L (Health Canada, 2002).

An Oral Slope Factor of 7.5E-03 $(mg/kg\text{-}day)^{-1}$ for the assessment of dichloromethane carcinogenicity via oral exposure has been reported by the US EPA (1995). The slope factor is an arithmetic mean of slope factors, 2.6E-3 $(mg/kg\text{-}day)^{-1}$ and 1.2E-2 $(mg/kg\text{-}day)^{-1}$, derived from two studies, NTP(1986) and the National Coffee Association (1983). The National Coffee Association study (1983) consisted of rats and/or mice exposed to dichloromethane in drinking water. The NAP (1986) was a gavage bioassay of dichloromethane in mice.

For this assessment, the US EPA (1995) oral slope factor of 7.5E-03 $(mg/kg\text{-}day)^{-1}$ was selected as it corresponds with proposed MOE (2007) standards for dichloromethane.

12.3.3 Non-Cancer Inhalation Toxicity Reference Values

A non-cancer inhalation TRV has not been selected for this assessment because dichloromethane is carcinogenic by inhalation.

12.3.4 Carcinogenic Cancer Inhalation Toxicity Reference Values

In the most extensive inhalation bioassays in experimental animals exposed to dichloromethane conducted to date, there have been increases in the incidence of benign and malignant tumors in the lungs of both male and female mice, benign (females only) and malignant tumors in the liver (both male and female) of mice and benign mammary tumors in male and female rats. There has also been a borderline increase in malignant liver tumours in female rats (ITER, 2007).

For dichloromethane, Health Canada has determined two tumourigenic concentrations (5%; TC05) by multistage modeling of the incidence of (1) pulmonary adenomas and carcinomas (combined) and (2) hepatic adenomas and carcinomas (combined) in male and female mice (NTP, 1986). To take into account interspecies variations in the rates of metabolism by PBPK modeling of the delivered dose for the putatively carcinogenic pathway, "PBPK modified TC05s" were then determined by multistage modeling of the incidence of pulmonary adenomas and carcinomas (combined) and hepatic adenomas and carcinomas (combined) in male and female mice in the NTP bioassay, versus amortized delivered dose by the GST pathway. The resulting values of the "PBPK modified TC05s" range from 645 ppm (2238 mg/m^3 - rounded to 2200 mg/m^3) for adenomas and carcinomas (combined) of the lung in females to 4106 ppm (14,248 mg/m^3 - rounded to 14,200 mg/m^3) for adenomas and carcinomas (combined) of the liver in males (ITER, 2007).

To calculate an inhalation unit risk factor, as per Health Canada (1996) guidance, 0.05 is divided by TC05; thus the inhalation unit risk is equivalent to 2.30E-05 $(mg/m^3)^{-1}$.

The US EPA (1995) cancer inhalation unit risk factor is 4.70E-04 $(mg/m^3)^{-1}$, based on increased incidence of both hepatocellular adenomas and carcinomas in mice from exposure to dichloromethane. Mammary adenomas and fibroadenomas were significantly increased in male and female rats. In addition, there were significant dose-related increases in the number of lung tumours in both sexes of mice.

For this assessment, the US EPA (1995) inhalation unit risk value of 4.70E-04 $(mg/m^3)^{-1}$ was selected and corresponds with proposed MOE (2007) standards for dichloromethane.

12.4 Bioavailability

12.4.1 Oral Bioavailability

The relative oral absorption factor for dichloromethane has been conservatively assumed to be 1.0.

12.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for dichloromethane has been conservatively assumed to be 1.0.

12.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.1 for dichloromethane.

12.5 Conclusion

Table 21: Selected Toxicity Values for Dichloromethane

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.05 mg/kg-day	TDI	Health Canada, 2004b
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	7.90E-05 $(mg/kg\text{-}day)^{-1}$	SF	US EPA, 1995
Inhalation	4.70E-04 $(mg/m^3)^{-1}$	SF	US EPA, 1995

NA – Not Applicable

Table 22: Selected Relative Bioavailabilities for Dichloromethane

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004a

12.6 References

ATSDR (Agency for Toxic Substances and Disease Registry). 2000. Toxicological Profile for Methylene chloride. Available on-line at: http://www.atsdr.cdc.gov/toxprofiles/tp14.pdf.

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA). September, 2004.

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

Health Canada. 1996. Health based Tolerable daily intakes/concentrations and tumorigenic doses/concentrations for priority substances. Minister of Supply and Services Canada, Ottawa.

Health Canada. 2002. Guidelines for Canadian Drinking Water Quality, Supporting Documentation. Dichloromethane. Ottawa, Ontario. Available online at: http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/doc_sup-appui/dichloromethane/index_e.html

IARC (International Agency for Research on Cancer). 1989. " Dichloromethane". IARC - Summaries & Evaluations, Volume 71. Available on-line at: http://www.inchem.org/documents/iarc/vol71/004-dichloromethane.html

INCHEM (International Programme on Chemical Safety). 1996. Environmental Health Criteria 164: Methylene Chloride**.** Available online at: http://www.inchem.org/documents/ehc/ehc/ehc128.htm.

ITER (International Toxicity Estimates for Risk Database). 2007. Dichloromethane. Available online at: http://iter.ctcnet.net/publicurl/pub_view_list.cfm?crn=75%2D09%2D2

MacEwen, J.D., E.H. Vernot and C.C. Haun. 1972. Continuous animal exposure to dichloromethane. AMRL-TR-72-28, Systems Corporation Report No. W-71005. Wright Patterson Air Force Base, Ohio, Aerospace Medical Research. AD746295.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

NCA (National Coffee Association). 1982. Twenty-four-month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories, America, Inc., Vienna, VA. Unpublished.

NCA (National Coffee Association). 1983. Twenty-four month oncogenicity study of methylene chloride in mice. Final Report. Prepared by Hazleton Laboratories, America, Inc., Vienna, VA.

NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). US Department of Health and Human Services. Technical Report No. 306. NIH Publication No. 86-2562. 208 p. [NTIS Publication No. PB86-187903.]

Serota DG, Thakur AK, Ulland BM, Kirschman JC, Brown NM, Coots RH, Morgareidge K. 1986. A two-year drinking-water study of dichloromethane in rodents. I. Rats. Fd. Chem. Toxicol. 24(9), 951-958.

US EPA (United States Environmental Protection Agency). 1995. Integrated Risk Information System (IRIS) Database, Dichloromethane. Available on-line at: http://www.epa.gov/iris/subst/0070.htm

13.0 FORMALDEHYDE

At room temperature, formaldehyde is a colourless, highly reactive, highly flammable gas with a pungent, irritating odour (Health Canada, 2001). It polymerizes easily in air and water to form a variety of other compounds (Health Canada, 2001). Because of its reactivity, formaldehyde is one of the most widely-used organic chemicals in the world (ATSDR, 1999). It is used as a preservative in a variety of consumer goods, and as an intermediate in a large number of chemical syntheses (ATSDR, 1999). It has also been used as a disinfectant, as a biocide, and in the manufacture of fertilizers (ATSDR, 1999).

13.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC, 2004), classifies formaldehyde as Group 1, "carcinogenic to humans." The US EPA (1991) classifies formaldehyde as Group B1, a probable human carcinogen, based on limited evidence in humans, and sufficient evidence in animals. Health Canada (2001) notes, however, that formaldehyde appears to be carcinogenic only at concentrations high enough to produce cytotoxicity, a non-carcinogenic effect, for which the cellular proliferative response is itself carcinogenic.

13.2 Susceptible Populations

The ATSDR (1999) indicates that two segments of the general population are potentially susceptible to toxic effects of formaldehyde, although the data are not always consistent: those suffering from asthma, and those with dermal sensitization to formaldehyde.

13.3 Selection of Toxicity Values

The following sections describe the toxicity reference values chosen for formaldehyde.

13.3.1 Non-Cancer Oral Toxicity Reference Values

The US EPA (1990) provides an oral reference dose (RfD) of 0.2 mg/kg-day for formaldehyde, based on a two-year study of Wistar rats (Til *et al.*, 1989, cited in US EPA, 1990). Same-sex groups of rats were fed doses of 0, 1.2, 15, or 82 mg/kg-day formaldehyde for males, or 0, 1.8, 21, or 109 mg/kg-day formaldehyde for females, in their drinking water. A maximum of 10 rats per sex per dose were sacrificed after 12 months and 18 months, with the remainder being sacrificed after 24 months. The dose of 15 mg/kg-day was designated the No Observed Adverse Effects Level (NOAEL), with reduced weight gain and histopathology as the end points. An uncertainty factor of 100 – a factor of 10 for interspecies variation, and a factor of 10 for intraspecies variation – was applied to this NOAEL to derive the RfD, 0.2 mg/kg-day.

Health Canada (2001) remarks that due to the high reactivity of formaldehyde, non-cancer effects of ingestion would more likely be a function of the concentration of formaldehyde in the immediately ingested medium, instead of a function of cumulative dose administered. For this reason, a tolerable concentration (TC) of formaldehyde is provided by Health Canada (2001) instead of a tolerable daily intake (TDI). This value, 2.6 mg/L, is based on a No Observed Effects Level (NOEL) of 260 mg/L from

the same Til *et al.* (1989, cited in Health Canada, 2001) study used by the US EPA (1990). The endpoint chosen by Health Canada was histopathological changes in the gastrointestinal system. An uncertainty factor of 100 – 10 for interspecies variation, and 10 for intraspecies variation – was applied to the NOEL to derive the TC.

For this assessment, the US EPA (1990) RfD of 0.2 mg/kg-day was used.

13.3.2 Cancer Oral Toxicity Reference Values

Limited information on the carcinogenic effects of oral exposure to formaldehyde is available, and no toxicity reference values were found for the assessment of any oral cancer effects. As such, no TRVs in this category have been selected for use in the risk assessment.

13.3.3 Non-Cancer Inhalation Toxicity Reference Values

Health Canada (2001) does not provide a toxicity reference value (TRV) for non-cancer effects of formaldehyde inhalation, but it is noted in the review of the literature that very few members of the general population experience irritation of the eyes, nose, and throat at levels of formaldehyde less than 0.12 mg/m^3. Health Canada does, however, warn that irritation of the eyes, nose, and throat has been shown to occur even at the lowest concentrations tested experimentally (Health Canada, 2001).

There is no US EPA non-cancer inhalation toxicity reference value.

A non-cancer inhalation TRV has not been selected for this assessment because formaldehyde is carcinogenic by inhalation.

13.3.4 Cancer Inhalation Toxicity Reference Values

CEPA (2001) provides an inhalation toxicity reference value of 5.26E-03 (mg/m3)-1, where both nasopharyngeal and sinonasal cancers were seen; no further information on the derivation of this TRV is available.

The US EPA (1990) gives an inhalation unit risk of 1.3E-2 $(mg/m3)^{-1}$. This value comes from a study (Kerns et al., 1983) of the effects of inhalation exposure to formaldehyde in rats and mice. The study was positive in both sexes all showing squamous cell carcinomas. About 120 animals/sex/species were exposed to 0, 2, 5.6 or 14.3 ppm, 6 hours/day, 5 days/week for 24 months. Five animals per group were sacrificed at 6 and 12 months and 20 per group were killed at 18 months. At 24 and 27 months the number sacrificed is unclear. The studies were terminated at 30 months.

No Health Canada cancer inhalation TRV was available.

For this assessment, the more conservative, CEPA (2001) inhalation toxicity reference value of 5.26E-03 $(mg/m3)^{-1}$ was selected.

13.4 Bioavailability

13.4.1 Oral Bioavailability

The relative oral absorption factor for formaldehyde has been conservatively assumed to be 1.0.

13.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for formaldehyde has been conservatively assumed to be 1.0.

13.4.3 Dermal Bioavailability

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, RAIS values were used. RAIS (2007) recommends a relative dermal absorption factor of 0.01 for formaldehyde.

13.5 Conclusion

The following tables present the TRV and bioavailability summaries for formaldehyde.

Table 23 Selected Toxicity Reference Values for Formaldehyde

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.2 mg/kg-day	RfD	US EPA, 1990
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	5.26E-03 $(mg/m^3)^{-1}$	UR	CEPA, 2001

NA – Not Applicable

Table 24 Selected Bioavailabilities for Formaldehyde

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.01	RAIS (2007)

13.6 References

ATSDR, 1999. *Toxicological Profile for Formaldehyde.* Prepared by Syracuse Research Corporation. U.S. Department of Health and Human Services, September. Agency for Toxic Substances and Disease Registry.

CEPA (Canadian Environmental Protection Act). 2001. Priority Substances List Assessment Report: Formaldehyde.

Health Canada. 2001. Priority Substances List Assessment Report: Formaldehyde. Available at: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/formaldehyde/formaldehyde_e.pdf. Environment Canada / Health Canada. February 2001.

IARC. 2004. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 88: Formaldehyde, 2-Butoxyethanol, and 1-*tert*-Butoxy-2-propanol. Available at: http://monographs.iarc.fr/ENG/Monographs/vol88/volume88.pdf. Last updated 07/09/2004.

Kerns, W.D., K.L. Pavkov, D.J. Donofrio, E.J. Gralla and J.A. Swenberg. 1983. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res. 43: 4382-4392.

RAIS (Risk Assessment Information System). 2007. Oak Ridge National Laboratory. U.S. Department of Energy. Available online at: http://rais.ornl.gov/cgi-bin/tox/TOX_select?select=nrad

US EPA. 1990. Integrated Risk Information System (IRIS) Database, Formaldehyde (RfD). Available at: http://www.epa.gov/iris/. United States Environmental Protection Agency

US EPA. 1991. Integrated Risk Information System (IRIS) Database, Formaldehyde (Carcinogenicity Assessment). Available at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

Last reviewed: May 2007 (RJ)

14.0 HEXACHLOROBENZENE

Chlorobenzenes are cyclic aromatic compounds formed by the addition of 1-6 atoms of chlorine to the benzene ring. This yields 12 compounds, including hexachlorobenzene. At room temperature, chlorobenzenes are white crystalline solids. In general, the water solubility of chlorobenzene compounds is low, decreasing with increased chlorination. Flammability is low, the octanol/water partition coefficients are moderate to high, increasing with increasing chlorination, and the vapour pressures are low to moderate, decreasing with increasing chlorination (INCHEM, 1991).

Until 1965, hexachlorobenzene was widely used as a pesticide to protect the seeds of onions and sorghum, wheat, and other grains against fungus. It was also used to make fireworks, ammunition, and synthetic rubber. Currently, there are no commercial uses of hexachlorobenzene in the United States (ATSDR, 2002). Hexachlorobenzene is formed as a by-product while making other chemicals, in the waste streams of chloralkali and wood-preserving plants, and when burning municipal waste (ATSDR, 2002).

14.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer states that there is inadequate evidence in humans for the carcinogenicity of hexachlorobenzene, but that there is sufficient evidence in experimental animals for the carcinogenicity of hexachlorobenzene (IARC, 2001). Overall it rates hexachlorobenzene as a possibly carcinogenic to humans (Group 2B).

14.2 Susceptible Populations

According to the ATSDR (2002), a study has showed that the young children of mothers who it ate bread accidentally contaminated with hexachlorobenzene or young children who ate it themselves can have lower survival rates. Nursing infants can be exposed to hexachlorobenzene through breast milk if their mothers have been exposed, likewise unborn children may also be affected if their mother have been exposed (ATSDR, 2002).

14.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to hexachlorobenzene.

14.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004) provides a tolerable daily intake (TDI) of 0.0005 mg/kg-day, which was used as the oral TRV in this assessment. Health Canada based their TDI on results from studies conducted by den Tonkelaar et al. (1978), Arnold et al. (1985) and Mollenhauer et al. (1975, 1976) on pigs and rats.

Based on the lowest reported NOEL [0.05 mg/kg bw/day based primarily on hepatic effects in two species observed at higher doses (den Tonkelaar et al., 1978; Arnold et al., 1985; Mollenhauer et al., 1975, 1976)], a tolerable daily intake (TDI) of 500 ng/kg bw/day was derived. An uncertainty factor of 100 (x10 for intraspecies variation and x10 for interspecies variation) was used to derive the TDI.

The US EPA toxicity reference value is 0.0008 mg/kg-day. The derivation of the oral RfD is based on a 130-week study (Arnold et al., 1985). The study involved feeding male and female rats diets containing

0, 0.32, 1.6, 8.0, or 40 ppm of hexachlorobenzene for 90 days prior to mating and until 21 days after parturition (at weaning).

For this assessment, the Health Canada value of 0.0005 mg/kg-day was selected because it is more conservative than the US EPA value.

14.3.2 Cancer Oral Toxicity Reference Values

Health Canada (2004) provides a tumerogenic dose (TD_{05}) of 8.3E-01 $(mg/kg\text{-}d)^{-1}$, which was used as the oral slope factor in this assessment.

The oral slope factor for hexachlorobenzene was derived from the results of the study by Arnold et al. (1985). The tumor incidences in the pups were analyzed in the same manner as data from a single generation study due to the lack of information on individual litters. Owing to the lack of information about the extent of metabolism to unidentified active metabolite(s) and the possible role of such metabolites in carcinogenicity, a surface area to body weight correction was incorporated into a multistage model. The TD_{05} values calculated in this manner from the results of the study in rats by Arnold et al. (1985) range from 0.06 mg/kg bw/day for hepatic neoplastic nodules in females to 0.17 mg/kg bw/day for parathyroid adenomas in males.

The US EPA (1996) cancer oral toxicity reference value provded is 1.6 $(mg/kg\text{-}day)^{-1}$ based on a linearized multistage extrapolation from data collected by Ertuk et al. (1986). Ertuk et al (1986) saw an increased incidence of heptocellular carcinoma and bile duct tumour in female rats after oral exposure through diet to hexachlorobenzene.

The Health Canada value of 8.3E-01 $(mg/kg\text{-}day)^{-1}$ was used because it is more conservative than the US EPA value.

14.3.3 Non-Cancer Inhalation Toxicity Reference Values

A non-cancer inhalation TRV has not been selected for this assessment because hexachlorobenzene is carcinogenic by inhalation.

14.3.4 Carcinogenic Cancer Inhalation Toxicity Reference Values

US EPA (1996) provides an inhalation unit risk of 4.6E-04 $(\mu g/m^3)^{-1}$ for hexachlorobenzene based on a linearized multistage extrapolation from data collected by Ertuk et al. (1986). Ertuk et al (1986) saw an increased incidence of heptocellular carcinoma and bile duct tumour in female rats after oral exposure through diet to hexachlorobenzene.

For this assessment the US EPA inhalation unit risk of 4.6E-04 $(\mu g/m^3)^{-1}$ was selected. No Health Canada TRV was available.

14.4 Bioavailability

14.4.1 Oral Bioavailability

The relative oral absorption factor for hexachlorobenzene has been conservatively assumed to be 1.0.

14.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for hexachlorobenzene has been conservatively assumed to be 1.0.

14.4.3 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.13 for hexachlorobenzene.

14.5 Conclusion

Table 25: Selected Toxicity Values for Hexachlorobenzene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.0005 mg/kg-day	TDI	Health Canada, 2004
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	8.30E-05 $(mg/kg\text{-}day)^{-1}$	SF	Health Canada, 2004
Inhalation	4.6E-04 $(\mu g/m^3)^{-1}$	UR	US EPA (1996)

NA – Not Applicable

Table 26: Selected Relative Bioavailabilities for Hexachlorobenzene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.13	Health Canada, 2004

14.6 References

Arnold, D.L., C.A. Moodie, S.M. Charbonneau, H.C. Grice, P.F. McGuire, F.R. Bryce, B.T. Collins, Z.Z. Zwadizka, D.R. Krewski, E.A. Nera and I.C. Munro. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. Food Chem. Toxicol. 23: 779-793.

ATSDR, 2002. ToxFAQs for Hexachlorobenzene. Agency for Toxic Substances and Diseases Registry. September 2002. Available at: http://www.atsdr.cdc.gov/tfacts90.html

den Tonkelaar, E.M., H.G. Verschueren, J. Bankovska, T. de Vries, R. Kroes and G.J. van Esch. 1978. Hexachlorobenzene toxicity in pigs. Toxicol. Appl. Pharmacol. 43: 137-145.

Erturk, E., R.W. Lambrecht, H.A. Peters, D.J. Cripps, A. Gocmen, C.R. Morris and G.T. Bryan. 1986. Oncogenicity of hexachlorobenzene. In: Hexachlorobenzene: Proc. Int. Symp., C.R. Morris and J.R.P. Cabral, Ed. IARC Scientific Publ. No. 77, Oxford University Press, Oxford. p. 417-423.

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA). September, 2004.

IARC (International Agency for Research on Cancer) 2001. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Volume 79. September 2001. Available at: http://monographs.iarc.fr/ENG/Monographs/vol79/volume79.pdf

INCHEM (International Programme on Chemical Safety). 1991. Environmental Health Criteria 128: Chlorobenzenes other than Hexachlorobenzene**.** Available online at: http://www.inchem.org/documents/ehc/ehc/ehc128.htm.

Mollenhauer, H.H., J.H. Johnson, R.L. Younger and D.E. Clark. 1975. Ultrastructural changes in liver of the rat fed hexachlorobenzene. Am. J. Vet. Res. 36: 1777-1781.

Mollenhauer, H.H., J.H. Johnson, R.L. Younger and D.E. Clark. 1976. A unique intracellular aberration related to hexachlorobenzene ingestion. Am. J. Vet. Res. 37: 847-850.

US EPA (United States Environmental Protection Agency), 1996. Integrated Risk Information System (IRIS) Database. Hexachlorobenzene. Available on-line at: http://www.epa.gov/iris.

15.0 LEAD

Lead is a naturally occurring element found in the earth's crust. Exposure to lead can lead to effects to the central nervous system. In adults, exposure can result in decreased performance, weakness and anemia. Kidney damage and brain damage may also occur at high exposures. In children exposed to lead, central nervous system effects occur at blood lead levels so low as to indicate that there is no threshold level below which effects do not occur (ATSDR, 1999).

15.1 Assessment of Carcinogenicity

Epidemiological studies of occupationally exposed adults were not able to demonstrate an increase in cancers among an exposed population compared to a control group. The US EPA (2004) lists lead as a Group 2B, probable human carcinogen, based on sufficient animal evidence but did not recommend derivation of a quantitative estimate of oral carcinogenic risk due to a lack of understanding of the toxicological and pharmacokinetic characteristics of lead. Neurobehavioural effects of lead in children were considered to be the most relevant endpoints in determining a toxicity value.

Health Canada (1996) classified lead as Group IIIB – possibly carcinogenic to man (inadequate data in humans, limited evidence in animals) according to the classification scheme of the Environmental Health Directorate of Health and Welfare Canada. Chemicals classified in Group IIIB are treated as non-carcinogens and are evaluated against a tolerable daily intake (TDI), based on a no observed adverse effects level (NOAEL).

The International Agency for Research on Cancer (IARC) (1987) lists lead and inorganic lead compounds as Group 2B, possibly carcinogenic to humans. IARC states that there is inadequate evidence of carcinogenicity in humans.

15.2 Susceptible Populations

There is a very large database that documents the effects of acute and chronic lead exposure in adults and children. Extensive summaries of the human health effects of lead are available from a number of sources including Health Canada (1996) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1999). These reviews show that infants, young children up to the age of six, and pregnant women (developing fetuses) are the most susceptible.

15.3 Selection of Toxicity Values

15.3.1 Non-Cancer Oral Toxicity Reference Values

The oral reference dose (RfD) for lead used by Health Canada (1996), is the same as the provisional tolerable weekly intake (PTWI) for children of 25 µg/kg, equivalent to approximately 3.57 µg/kg/day from all sources, established by the World Health Organization (WHO) (1986). The PTWI is considered sufficiently low to protect against effects on the central nervous system and blood (*i.e.,* neurobehavioural effects and anemia). This PTWI was based on the results of metabolic studies

in infants and was used to establish Canadian drinking water standards for lead (CCME, 1987). WHO (1993) has more recently extended this PTWI to all age groups to protect other sensitive population groups, such as women of child-bearing age. The PTWI of 0.025 mg/kg was maintained at the fifty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (WHO, 1999).

The US EPA does not provide and non-cancer oral toxicity reference value for lead.

The MOE (1994) developed an intake of concern (IOC_{pop}) of 1.85 µg/kg-day based on a lowest observed adverse effects level (LOAEL) of 10 µg/dL blood lead level. A transfer factor of 0.21 µg lead per dL blood level per µg/day was applied for a 13kg child aged 6 months to 4 years. An uncertainty factor of 2 was applied. The LOAEL is based on a convergence of data on blood levels of 10 to 15 µg/dL as the level of concern for impairment of neurological behaviour.

For this assessment, the MOE (1994) value of 1.85 was µg/kg-day adopted as an oral TRV as it is the most conservative and corresponds with the proposed MOE (2007) standards for lead.

15.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor for lead.

15.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore for this assessment, the inhalation TRV was set equal to the oral TRV.

15.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an inhalation slope factor or unit risk for lead.

15.4 Bioavailability

15.4.1 Oral Bioavailability

Adult humans absorb 10-15% of ingested lead; however, children absorb up to 50% of ingested lead (ORNL, 1994). Gastrointestinal absorption may vary depending on dietary factors and the chemical form of the lead. Lead is more readily absorbed in fasting individuals (up to 45% for adults) than when ingested with food. Absorption is also increased in children suffering from iron or calcium deficiencies. Gastrointestinal absorption in children may be only 30% for lead present in dust and dirt and 17% for lead in paint chips, compared with 50% for lead in food and beverages (US EPA, 2004).

Oral bioavailability for lead assuming normal feeding habits are 42 to 53% in children (Hrudey *et al.*, 1996) and 4 to 13% in adults (CCME, 1996; Hrudey *et al.*, 1996). Other studies for estimating lead oral bioavailability assuming normal feeding habits are 40 to 50% in children

(Alexander *et al*., 1974; Ziegler *et al*., 1978) and 4 to 13% in adults (Harrison *et al*., 1969; Rabinowitz *et al*., 1980; Blake *et al*., 1983; Chamberlain, 1985). The oral bioavailability is assumed to be 53% since the RfD is based on oral exposure that is protective of children. The absorption of lead in soil and dust by children has been estimated at 30% (CCME, 1996).

For the purpose of this assessment, the relative oral bioavailability from soil exposure was assumed to be 1.0.

15.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for lead has been conservatively assumed to be 1.0.

15.4.3 Dermal Bioavailability

The dermal bioavailability factor of 0.01 is recommended by US EPA Region III (1995).

Health Canada (2004) recommends a relative dermal absorption factor of 0.006 for lead; therefore, this value has been adopted for this assessment.

15.5 Conclusion

The following tables present the TRV and bioavailability summaries for lead.

Table 27 Selected Toxicity Reference Values for Lead

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	1.85 µg/kg-day	LOAEL	MOE, 1994
Inhalation	1.85 µg/kg-day	LOAEL	MOE, 1994
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 28 Selected Bioavailabilities for Lead

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.006	Health Canada, 2004

15.6 References

Alexander YW, Clayton BE, and Delves HT, 1974. Mineral and Trace-Metal Balances in Children Receiving Normal and Synthetic Diets. *Quart. J. Med.* 43: 89. Cited In: ATSDR, 1999.

ATSDR (Agency for Toxic Substances and Disease Registry), 1999. Toxicological Profile for Lead. July 1999. Available on-line at: http://www.atsdr.cdc.gov/toxpro2.html.

Blake KHC, Barbezat GO and Mann M, 1983. Effect of Dietary Constituents on the Gastrointestinal Absorption of ^{203}Pb in Man. *Environ. Res* 30:182. Cited In: ATSDR, 1999.

CCME (Canadian Council of Ministers of the Environment), 1987. Guidelines for Canadian Drinking Water Quality. Supporting Documentation. Health and Welfare Canada.

CCME (Canadian Council of Ministers of the Environment), 1996. Canadian soil quality Guidelines For contaminated Sites. Human Health Effects: Inorganic Lead. Final report. The National Contaminated Sites Remediation Program. Canadian Council of Ministers of the Environment.

Chamberlain AC, 1985. Prediction of Response of Blood Lead to Airborne and Dietary Lead from Volunteer Experiments with Lead Isotopes. *Proc R Soc Lond* B224:149. Cited In: ATSDR, 1999.

Harrison GE, Carr TEF, Sutton A and Humphreys ER, 1969. Effect of Alginate on the Absorption of Lead in Man. *Nature* 224:1115. Cited In: ATSDR, 1999.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Screening Level Risk Assessment (SLRA).

Hrudey SE, Chen W and Rousseaux CG, 1996. Bioavailability in Environmental Risk Assessment. CRC Press, Lewis Publishers, Boca Raton.

IARC (International Agency for Research on Cancer), 1987. Lead and Lead Compounds. *Monographs.* Supplement 7: p. 230. World Health Organization.

MOE (Ontario Ministry of the Environment), 1994. Scientific Criteria Document for Multimedia Environmental Standards Development – Lead.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

ORNL (Oak Ridges National Laboratory), 1994. Toxicity Summary for Lead (Inorganic). December, 1994.

Rabinowitz MB, Kopple JD and Wetherill GW. 1980. Effect of food intake and fasting on gastrointestinal lead absorption in humans. *Am J Clin Nu.* 33:1784. Cited In: ATSDR, 1999.

US EPA (United States Environmental Protection Agency) Region III, 1995. Preliminary Remediation Goals Database.

US EPA (United States Environmental Protection Agency), 2004. Integrated Risk Information System (IRIS) Database. Lead and compounds (inorganic). Available on-line at: http://www.epa.gov/iris.

WHO (World Health Organization), 1986. Evaluation of Certain Food Additives and Contaminants. Thirtieth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 751. The World Health Organization, Geneva, 1986.

WHO (World Health Organization). 1993. Evaluation of Certain Food Additives and Contaminants. Forty-first report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 837. The WHO, Geneva, 1993.

Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, and Fomon SJ, 1978. Absorption and retention of lead by infants. *Pediat Res* 12:29. Cited In: ATSDR, 1999

Last reviewed: May 2007 (RJ)

16.0 MERCURY (ELEMENTAL, INORGANIC, METHYLMERCURY)

Mercury occurs naturally in the environment and exists in several forms. These forms can be organized under three headings: metallic mercury (also known as elemental mercury), inorganic mercury, and organic mercury (e.g., methyl mercury). Inorganic mercury compounds occur when mercury combines with elements such as chlorine, sulfur, or oxygen. These mercury compounds are also called mercury salts. Most inorganic mercury compounds are white powders or crystals, except for mercuric sulfide (also known as cinnabar) which is red and turns black after exposure to light.

Some inorganic mercury compounds are used as fungicides. Inorganic salts of mercury, including ammoniated mercuric chloride and mercuric iodide, have been used in skin-lightening creams. Mercuric chloride is a topical antiseptic or disinfectant agent (ATSDR, 1999).

The most common organic form of mercury is methylmercury. Methylmercury is of particular concern because it can bioconcentrate up in certain edible freshwater and saltwater fish and marine mammals to levels that are many times greater than levels in the surrounding water. Methylmercury is primarily the product of microorganisms (i.e., bacteria and fungi), rather than from anthropogenic sources (ATSDR, 1999).

16.1 Assessment of Carcinogenicity

The US EPA (2006a, 2006c) has classified inorganic mercury and methylmercury as Group C chemicals, indicating that they are possible human carcinogens. Elemental mercury has been classified as a Group D Chemical, not classifiable as a human carcinogen. (US EPA, 2006b) IARC (1997) classifies methylmercury compounds as Group 2B chemicals, possibly carcinogenic to humans; metallic mercury and inorganic mercury as Group 3 chemicals, not classifiable as to their carcinogenicity to humans

16.2 Susceptible Populations

Populations more susceptible to the toxic effects of mercury include: the elderly because of declining organ function, higher levels of persistent heavy metals (e.g., cadmium) that also accumulate in the kidney, and potentially higher brain to liver or kidney mercury concentrations; people with preexisting disease (e.g., renal or neurological disease); and the youngest of the population because of their immature and developing organs (ATSDR, 1999).

Neonates may also be especially susceptible to mercury toxicity. Both inorganic and organic forms of mercury are excreted in the milk (Sundberg and Oskarsson 1992; Yoshida et al. 1992). The transfer of mercury to suckling rats through milk was found to result in greater concentrations of the metal in the brains of the offspring than in the mother (Yang et al. 1973).

Individuals with diseases of the liver, kidneys, lungs, and nerves are considered to be at greater risk of suffering from the toxic effects of both organic and inorganic mercury. Individuals with a dietary insufficiency of zinc, glutathione, antioxidants, or selenium or those who are malnourished may be more susceptible to the toxic effects of mercury poisoning because of the diminished ability of these substances to protect against mercury toxicity (ATSDR, 1999).

16.3 Selection of Toxicity Values

16.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) provides an oral TRV for non-carcinogenic effects from inorganic mercury (i.e., mercuric chloride) of 3.00E-04 mg/kg-day. The Health Canada oral TRV is based on the recommendation of the CCME soil quality guideline for mercury. It recommends using the US EPA (2006c) RfD for mercuric chloride as the basis of the Canadian TDI. This TRV is based on the back calculations from a Drinking Water Equivalent Level (DWEL), recommended to and subsequently adopted by the US EPA, of 0.010 mg/L. A DWEL of 0.010 mg/L was recommended based on the weight of evidence from three studies using Brown Norway rats and limited human tissue data. An uncertainty factor of 1000 was applied to the animal studies using Brown Norway rats accounting for the use of subchronic studies (10), a combined 10 for both animal to human and sensitive human populations and 10 for the use of LOAELs instead of NOAELs.

The US EPA derived oral TRV for methyl mercury of 1.00E-04 mg/kg-day is from studies by Grandjean et al (1997) and Budtz-Jørgensen et al. (1999). Benchmark dose modeling was used to estimate a range of 46–79 ppb in maternal blood for different neuropsychological effects in the offspring at 7 years of age, corresponding to a range of maternal daily intakes of 0.857–1.472 µg/kg-day. An uncertainty factor of 10 was applied to account for pharmacokinetic variability and uncertainty in estimating an ingested mercury dose from cord-blood mercury concentration and pharmacodynamic variability and uncertainty.

The Bureau of Chemical Safety Food Directorate of Health Canada (HC, 2007) has adopted a provisional tolerable daily intake of 0.2 µg/kg-d of methylmercury for pregnant women (or women of child bearing age) and toddlers, and a general population value of 0.47 µg/kg-d of methylmercury exposure of fish in diet. This is consistent with the WHO/FAO Expert Committee on Food Additives (JECFA) recommended a provisional tolerable weekly intake (pTWI) for methylmercury of 1.6 ìg/kg bw/week (equivalent to 0.23 ìg methylmercury/kg bw/day) in order to sufficiently protect the developing fetus (WHO, 2003).

For this assessment, oral TRVs of 3.00E-04 mg/kg-day and 0.2 µg/kg-day were adopted as oral TRVs for inorganic mercury and methylmercury, respectively.

16.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify mercury as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

16.3.3 Non-Cancer Inhalation Toxicity Reference Values

The US EPA (2006b) IRIS database provides an inhalation reference concentration (RfC) of 3.0E-04 mg/m^3 for elemental mercury, based on a LOAEL of 0.025 mg/m^3 as a time-weighted average (TWA), which represents a convergence of a number of studies (Fawer et al., 1983; Piikivi and Tolonen, 1989; Piikivi and Hanninen, 1989; Piikivi, 1989; Ngim et al., 1992; Liang et al., 1993). From this LOAEL a human-equivalent concentration (HEC) of 0.009 mg/m^3 was established and an uncertainty factor of 30

was applied for the protection of sensitive human subpopulations (10) and to account for database deficiencies (3).

Due to the lack of sufficient data for inorganic mercury and methyl mercury, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore for this assessment, the inhalation TRVs for inorganic mercury and methyl mercury were set equal to their respective oral TRVs.

16.3.4 Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify mercury as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

16.4 Bioavailability

16.4.1 Oral Bioavailability

The relative oral absorption factor for all forms of mercury has been conservatively assumed to be 1.0.

16.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for all forms of mercury has been conservatively assumed to be 1.0.

16.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.05 for inorganic mercury and 0.2 for methylmercury.

16.5 Conclusion

The following tables summarize the selected toxicity reference values and bioavailabilities for mercury.

Table 29: Selected Toxicity Values for Mercury

Route of Exposure	Form of Mercury	TRV	TRV Type	Source Agency
Non-Cancer Effects				
Ingestion	Mercury, Inorganic	3.00E-04 mg/kg-day	TDI	Health Canada, 2004b
	Methylmercury	0.2 µg/kg-day	TDI	Health Canada, 2007
Inhalation	Mercury, Inorganic	3.00E-04 mg/kg-day	TDI	Health Canada, 2004b
	Mercury, elemental	3.00E-04 mg/kg-day	RfC	IRIS, 2006b
	Methylmercury	0.2 µg/kg-day	TDI	Health Canada, 2007
Cancer Effects				
Ingestion	NA	NA	NA	NA
Inhalation	NA	NA	NA	NA

NA – Not Applicable

Table 30: Selected Relative Bioavailabilities for Mercury

Route of Exposure	Form of Mercury	Relative Bioavailability	Reference
Ingestion	All	1.0	Assumed
Inhalation	All	1.0	Assumed
Dermal	Mercury, Inorganic	0.05	Health Canada, 2004a
	Methylmercury	0.2	Health Canada, 2004a

16.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 1999. Toxicological Profile for Mercury. March 1999.

Budtz-Jorgensen, E; Keiding, N; Grandjean, P; et al. (1999) Methylmercury neurotoxicity independent of PCB exposure. [Letter]. Environ Health Perspect 107(5):A236-237.

Fawer, R.F., U. DeRibaupierre, M.P. Guillemin, M. Berode and M. Lobe. 1983.Measurement of hand tremor induced by industrial exposure to metallic mercury. J. Ind. Med. 40: 204-208.

Grandjean, P; Weihe, P; White, R; et al. (1997) Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 20:1-12.

Health Canada, 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Screening Level Risk Assessment (SLRA). September, 2004.

Health Canada, 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs). September, 2004.

HC (Health Canada). 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.

IARC (International Agency for Research on Cancer), 1997. Environmental Monograph 58: Mercury and Mercury Compounds. Last revised 08/22/1997.

Liang, Y-X., R-K. Sun, Y. Sun, Z-Q. Chen and L-H. Li. 1993. Psychological effects of low exposure to mercury vapor: Application of a computer-administered neurobehavioral evaluation system. Environ. Res. 60: 320-327.

Ngim, C.H., S.C. Foo, K.W. Boey and J. Jeyaratnam. 1992. Chronic neurobehavioral effects of elemental mercury in dentists. Br. J. Ind. Med. 49: 782-790.

Piikivi, L. 1989. Cardiovascular reflexes and low long-term exposure to mercury vapor. Int. Arch. Occup. Environ. Health. 61: 391-395.

Piikivi, L. and H. Hanninen. 1989. Subjective symptoms and psychological performance of chlorine-alkali workers. Scand. J. Work Environ. Health. 15: 69-74.

Piikivi, L. and U. Tolonen. 1989. EEG findings in chlor-alkali workers subjected to low long term exposure to mercury vapor. Br. J. Ind. Med. 46: 370-375.

Sundberg J, Oskarsson A. 1992. Placental and lactational transfer of mercury from rats exposed to methylmercury in their diet: Speciation of mercury in the offspring. J Trace Elem Exp Med 5(1):47-56.

US EPA. 2006a. Integrated Risk Information System (IRIS) Database, Methylmercury. Available on-line at: http://www.epa.gov/iris/subst/0073.htm. United States Environmental Protection Agency.

US EPA. 2006b. Integrated Risk Information System (IRIS) Database, Mercury, elemental. Available on-line at: http://www.epa.gov/iris/subst/0370.htm. United States Environmental Protection Agency.

US EPA. 2006c. Integrated Risk Information System (IRIS) Database, Mercury, Inorganic. Available on-line at: http://www.epa.gov/iris/subst/0692.htm. United States Environmental Protection Agency.

Yang MG, Wang JHC, Garcia JD, et al. 1973. Mammary transfer of 203 Hg from mothers to brains of nursing rats. Proc Soc Exp Biol Med 142:723-727.

Yoshida M, Satoh H, Kishimoto T. 1992. Exposure to mercury via breast milk in suckling offspring of maternal guinea pigs exposed to mercury vapor after parturition. J Toxicol Environ Health 35(2):135-139.

World Health Organization (WHO). 2003. Joint FAO/WHO Expert Committee on Food Additives, Sixty-first meeting 10-19 June 2003, Summary and Conclusions. Available on-line: ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf

Last reviewed: May 2007 (RJ)

17.0 NICKEL

Nickel (Ni) is a naturally occurring metal existing in various mineral forms, and may be found throughout the environment including rivers, lakes, oceans, soil, air, drinking water, plants and animals. Soil and sediment are the primary receptacles for nickel, but mobilization may occur depending on the physico-chemical characteristics of the soil (ATSDR, 1988). The average worldwide concentration of nickel in soil is 8 parts per million (ppm), however, areas can naturally contain much higher concentrations. Nickel is used in a wide variety of metallurgical processes such as electroplating and alloy production, as well as in nickel-cadmium batteries. Some evidence suggests that nickel may be an essential trace element for mammals (Goyer, 1991). As for most metals, the toxicity of nickel is dependent on the route of exposure and the solubility of the nickel compound (Coogan et al., 1989).

17.1 Assessment of Carcinogenicity

Certain forms of nickel (essentially sulphate and sulphide) are considered to be carcinogenic to humans and are listed as a Group 1 carcinogens by IARC. The US EPA (1991) considers nickel refinery dust to be a human carcinogen via inhalation exposure. Compounds such as nickel sulphide and nickel subsulphide, both present in nickel refinery dusts, have been shown to be carcinogenic in humans (CEPA, 1994; US EPA, 1991). The carcinogenic activity of nickel is dependent upon the specific species of nickel present; the form of nickel most relevant to this assessment is soluble nickel (i.e., nickel chloride) which is not considered to be carcinogenic.

17.2 Susceptible Populations

Sensitized individuals may be unusually susceptible because exposure to nickel by any route may trigger an allergic response (ATSDR, 1997). Persons with kidney dysfunction are also likely to be more susceptible to nickel as the primary route of nickel elimination is via the urine. Increased nickel serum concentrations have been observed in dialysis patients (Hopfer et al., 1989).

17.3 Selection of Toxicity Values

17.3.1 Non-Cancer Oral Toxicity Reference Value

The oral RfD developed by the US EPA (1991) for nickel (soluble salts) is 0.02 mg/kg-day. The RfD was based on decreased body weight and organ weights in rats exposed to nickel in food for two years (Ambrose *et al*., 1976). A NOAEL of 5 mg/kg-day for decreased body and organ weights and a LOAEL of 50 mg/kg-day from a rat chronic oral study was used to derive the RfD. The study by Ambrose *et al*. (1976) was given a low confidence rating by the US EPA (1996) given high mortality observed in controls.

Health Canada (2004b) has established TDIs for soluble nickel including nickel sulphate and nickel chloride of 0.05 mg/kg-day and 1.3×10^{-3} mg/kg-day, respectively. The nickel sulphate TDI was based on the same study as US EPA (1998), using the same established NOAEL of 5 mg/kg-day and

incorporating an uncertainty factor of 10 for each of interspecies variation and intraspecies variation.

The Health Canada (2004b) TDI for nickel chloride, meanwhile, was based on a study of female Long-Evans rats (Smith *et al.*, 1993), which were administered nickel chloride in drinking water for 11 weeks prior to mating, and then throughout two periods of gestating and lactating. A LOAEL of 1.3 mg/kg-day was established for the endpoints of reduced maternal weight gain and proportion of dead pups per litter, but no NOAEL was established for this study. Three uncertainty factors of 10 each were applied to the LOAEL – 10 for interspecies variation, 10 for intraspecies variation, and 10 for the use of a LOAEL instead of a NOAEL – to obtain the TDI.

For this assessment the US EPA oral RfD of 0.02 mg/kg-day was used.

17.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data for soluble nickel precludes the derivation of an oral slope factor.

17.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data a non-cancer inhalation TRV has not been selected for this assessment. The inhalation TRV was therefore set as equal to the oral TRV.

17.3.4 Cancer Inhalation Toxicity Reference Value

The lack of suitable positive carcinogenic data for soluble nickel precludes the derivation of inhalation toxicity reference values.

17.4 Bioavailability

17.4.1 Oral Bioavailability

The relative oral absorption factor for pentachlorobenzene has been conservatively assumed to be 1.0.

17.4.2 Inhalation Bioavailability

There was no data available for inhalation bioavailability, therefore, a inhalation bioavailability factor of 1.0 was used.

17.4.3 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.35 for nickel.

17.5 Conclusion

The following tables present the TRV and bioavailability summaries for nickel.

Table 31 Selected Toxicity Values for Nickel

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	2.0E-02 mg/kg-day	RfD	US EPA, 1996
Inhalation	2.0E-02 mg/kg-day	RfD	US EPA, 1996
Cancer Effects			
Ingestion	N/A	N/A	N/A
Inhalation	N/A	N/A	N/A

N/A Not Available

Table 32 Selected Bioavailabilities for Nickel

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.35	Health Canada, 2004

17.6 References

Ambrose, A.M., Larson, D.S. Borzelleca, J.R. and Hennigar, G.R. 1976. Long term toxicologic assessment of nickel in rats and dogs. J Food Sci Technol 13:181-87. Cited In: US EPA, 1996.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Draft Toxicological Profile for Nickel. Available on-line at: http://www.atsdr.cdc.gov/toxprofiles/

ATSDR (Agency for Toxic Substances and Disease Registry). 1988. Toxicological Profile for Nickel, ATSDR/U.S. Public Health Service, ATSDR/TP-88/19.

CEPA. 1994. Nickel and its Compounds. Canadian Environmental Protection Act. Priority Substances List Assessment Report.

Coogan, T. P., D. M. Latta, E. T. Snow, and M. Costa. 1989. Toxicity and carcinogenicity of nickel compounds, In: Critical Reviews in Toxicology, Vol 19. McClellan, R.O., ed., CRC Press, Boca Raton, FL. pp. 341-384.

Goyer. R. 1991. Toxic effects of metals, In: Casarett and Doull's Toxicology, 4th ed. Amdur, M.O., J.D. Doull and C.D. Klaassen, eds., Pergamon Press, New York. pp.623-680.

Health Canada, 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Screening Level Risk Assessment (SLRA).

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

Hopfer SM, Fay WP, Sunderman FW Jr. 1989. Serum nickel concentrations in hemodialysis patients with environmental exposure. Ann Clin Lab Sci 19:161-167. Cited In: ATSDR, 1997.

Smith MK, George EL, Stober JA, Feng HLA, Kimmel GL. 1993. Perinatal Toxicity Associated with Nickel Chloride Exposure. Environmental Research 61(2), pp. 200-211.

US EPA (Environmental Protection Agency). 1991. Integrated Risk Information System (IRIS) Database – Nickel – soluble salts. Available on-line at: http://www.epa.gov/iris/

Last reviewed: Date (reviewers initials)

18.0 PENTACHLOROBENZENE

Chlorobenzenes are cyclic aromatic compounds formed by the addition of 1-6 atoms of chlorine to the benzene ring. This yields 12 compounds, including pentachlorobenzene. At room temperature, chlorobenzenes are white crystalline solids. In general, the water solubility of chlorobenzene compounds is low, decreasing with increased chlorination. Flammability is low, the octanol/water partition coefficients are moderate to high, increasing with increasing chlorination, and the vapour pressures are low to moderate, decreasing with increasing chlorination (INCHEM, 1991).

18.1 Assessment of Carcinogenicity

Pentachlorobenzene has not been classified as a carcinogen by any of the major regulatory review agencies including the IARC, US EPA or Health Canada.

18.2 Susceptible Populations

No populations have been identified that are unusually susceptible to the effects of pentachlorobenzene; however, a limited number of studies have shown that, on a body weight basis, breast-fed infants may receive a higher dose of chlorobenzenes than members of the adult population (INCHEM, 1991).

18.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to pentachlorobenzene.

18.3.1 Non-Cancer Oral Toxicity Reference Values

An oral TRV of 0.001 mg/kg-day was provided for pentachlorobenzene by the Health Canada (2004) based on a subchronic toxicity study (NTP, 1991), where oral exposure to pentachlorobenzene in diet of mice established a LOEL of 5.2 mg/kg bw/day. Pentachlorobenzene was administered in diet at various doses for 13 weeks (i.e., 5.2 to 410 mg/kg bw/day in mice). Compound-related clinical signs were seen in both male and female mice, including increases in kidney and liver weights and functional effects on the thyroid. Exposure-related histological lesions, centrilobular hepatocellular hypertrophy and minimal necrosis, were seen in both male and female mice. Based on these histopathological lesions, the NOEL in female mice was 22 mg/kg bw/day; while, the LOEL in male mice was 5.2 mg/kg bw/day (NTP, 1991).

To derive a tolerable daily intake (TDI) for pentachlorobenzene of 0.001 mg/kg-day the 5.2 mg/kg bw/day LOEL for male mice was divided by an uncertainty factor of 5000 (i.e., 10 for intraspecies variation; 10 for interspecies variation; 10 for less than chronic study; and 5 for lack of data on carcinogenicity).

The US EPA (1988) non-cancer oral toxicity reference value is 8E-04 mg/kg-day. This US EPA value is based on a study (Linder et al., 1980) that used eight experimental groups of 10 rats each. A statistically significant increase in kidney weights, a decreased heart weight, and an increase in hyaline droplets in proximal kidney tubules was noted in rats receiving 8.3 mg/kg-day. The lowest dose of 8.3 mg/kg-day is considered a LOAEL. This value was divided by 10 000 to account for interspecies and

interhuman variability to the toxicity of this compound in lieu of specific data, extrapolation of the subchronic effect level to its chronic counterpart, dropping the LOAEL into the expected range of a NOAEL.

The Health Canada (2004) value of 0.001 mg/kg-day was selected because uses more recent toxicity data than US EPA (1988).

18.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify pentachlorobenzene as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

18.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data a non-cancer inhalation TRV has not been selected for this assessment. The inhalation TRV was therefore set as equal to the oral TRV.

18.3.4 Carcinogenic Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify pentachlorobenzene as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

18.4 Bioavailability

18.4.1 Oral Bioavailability

The relative oral absorption factor for pentachlorobenzene has been conservatively assumed to be 1.0.

18.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for pentachlorobenzene has been conservatively assumed to be 1.0.

18.4.3 Dermal Bioavailability

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, RAIS values were used. RAIS (2007) recommends a relative dermal absorption factor of 0.01 for pentachlorobenzene.

18.5 Conclusion

Table 33: Selected Toxicity Values for Pentachlorobenzene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.001 mg/kg-day	TDI	Health Canada, 2004
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 34: Selected Relative Bioavailabilities for Pentachlorobenzene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.01	RAIS, 2007

18.6 References

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

INCHEM (International Programme on Chemical Safety). 1991. Environmental Health Criteria 128: Chlorobenzenes other than Hexachlorobenzene**.** Available online at: http://www.inchem.org/documents/ehc/ehc/ehc128.htm.

Linder, R., T. Scotti, J. Goldstein, K. McElroy and D. Walsh. 1980. Acute and subchronic toxicity of pentachlorobenzene. J. Environ. Pathol. Toxicol. 4: 183-196.

NTP (National Toxicology Program). 1991. Toxicology Studies of pentachlorobenzene in F344/N Rats and B6C3F1 Mice (Feed Studies). U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, Research Triangle Park, NC.

RAIS (Risk Assessment Information System). 2007. Oak Ridge National Laboratory. U.S. Department of Energy. Available online at: http://rais.ornl.gov/cgi-bin/tox/TOX_select?select=nrad.

United States Environmental Protection Agency (US EPA), 1988. Integrated Risk Information System (IRIS) Database - Pentachlorobenzene. Available on-line at: http://www.epa.gov/iris/

19.0 PENTACHLOROPHENOL (PCP)

Pentachlorophenol (PCP) is a manufactured chemical that does not occur naturally. Pure pentachlorophenol exists as colorless crystals. Impure pentachlorophenol (the form usually found at hazardous waste sites) is dark gray to brown and exists as dust, beads, or flakes. Humans are usually exposed to impure pentachlorophenol (ATSDR, 2001).

19.1 Assessment of Carcinogenicity

ATSDR (2001) suggests a possible association between inhalation pentachlorophenol exposure and cancer (Hodgkins disease, soft tissue sarcoma, and acute leukemia); however, exposure to other toxic substances may have contributed to the reported carcinogenic effects. The US EPA has classified PCP as a Group B2 - probable human carcinogen (US EPA, 1993).

19.2 Susceptible Populations

Groups possibly at risk include persons laboring in hot environments, persons with an inability or decreased ability to disperse body heat, geriatric and pediatric subpopulations, pregnant women and those who are malnourished or consume an unbalanced diet (ATSDR, 2001). Furthermore, those with impaired liver and kidney functions are also at increased risk to the toxic effects of PCP. There is also evidence to support that young children are at an elevated risk, compared to older children and adults (ATSDR, 2001).

19.3 Selection of Toxicity Values

19.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.006 mg/kg-day, which was used as the oral TRV in this assessment. No back-up information on the derivation of this TRV is available.

The US EPA provides a TRV of 3E-02 mg/kg-day. This value is based on a study (Schwetz et al., 1978) in which twenty-five rats/sex were administered 1 of 3 doses in the diet. At the 30 mg/kg-day level of treatment, a reduced rate of body weight gain and increased specific gravity of the urine were observed in females. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg-day or higher levels and in males exposed to 30 mg/kg-day. The 3 mg/kg-day level of exposure was reported as a chronic NOAEL.

The Health Canada (2004b) value of 0.006 kg/mg/day was selected in this assessment because it is more conservative than the US EPA value.

19.3.2 Cancer Oral Toxicity Reference Values

The US EPA (1993) calculated an oral slope factor of 1.2E-01 $(mg/kg\text{-}day)^{-1}$ based on incidences of liver tumors in mice (NTP, 1989). The US EPA oral slope factor was used in this assessment.

No Health Canada TRV was available.

19.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

19.3.4 Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient inhalation data, an inhalation cancer TRV for pentachlorophenol was not selected.

19.4 Bioavailability

19.5 Oral Bioavailability

The relative oral absorption factor for pentachlorophenol has been conservatively assumed to be 1.0.

19.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for pentachlorophenol has been conservatively assumed to be 1.0.

19.5.2 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.1 for pentachlorophenol.

19.6 Conclusion

The following tables present the TRV and bioavailability summaries for pentachlorophenyl.

Table 35 Selected Toxicity Reference Values for Pentachlorophenyl

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	6.00E-03 mg/kg-day	TDI	Health Canada, 2004b
Inhalation	6.00E-03 mg/kg-day	TDI	Health Canada, 2004b
Cancer Effects			
Ingestion	1.2E-01 $(mg/kg\text{-}day)^{-1}$	SF	US EPA (1993)
Inhalation	NA	NA	NA

NA – Not Applicable

Table 36 Selected Bioavailabilities for Pentachlorophenyl

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004

19.7 References

Agency for Toxic Substances and Disease Registry (ATSDR), 2001. Toxicological Profile for Pentachlorophenol Available on-line at: http://www.atsdr.cdc.gov/toxprofiles/

Health Canada, 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Screening Level Risk Assessment (SLRA).

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

United States Environmental Protection Agency (US EPA), 1993. Integrated Risk Information System (IRIS) Database - Pentachlorophenol. . Available on-line at: http://www.epa.gov/iris/

National Toxicology Program (NTP), 1989. Technical Report on the Toxicology and Carcinogenesis Studies of Pentachlorophenol (CAS No. 87-86-5) in B6C3F1 mice (Feed Studies). NTP Tech. Report No. 349. NIH Publ. No. 89-2804.

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

20.0 PHOSPHORUS

Phosphorus is an essential component of protoplasm that is primarily obtained from dietary sources. In adults, 80% of phosphorus is stored in the bones and the remaining 15% contained in soft tissues. The body's total phosphorus is a combination of organic and inorganic phosphorus with the inorganic phosphorus comprising only a fraction of the total but an important contribution at that. Inorganic phosphorus is mainly present in the blood and extracellular fluid and despite its small amount in comparison to organic phosphorus, it is critical to the human body because it is available for absorption and resorption into the bone (IOM, 1997).

20.1 Assessment of Carcinogenicity

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify phosphorus as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

20.2 Susceptible Populations

No information on potentially susceptible populations to phosphorus was found.

20.3 Selection of Toxicity Values

20.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (1990) provides a tolerable daily intake (TDI) of 14300 mg/kg-day, based on a recommended daily nutrient intake rate. No further information on the derivation of this TRV is available. The US EPA did not provide a non-cancer oral TRV for phosphorus; therefore, the Health Canada (1990) value was used in this assessment.

20.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor for phosphorus.

20.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

20.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an inhalation slope factor or unit risk for phosphorus.

20.4 Bioavailability

20.5 Oral Bioavailability

The relative oral absorption factor for phosphorus has been conservatively assumed to be 1.0.

20.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for phosphorus has been conservatively assumed to be 1.0.

20.5.2 Dermal Bioavailability

The relative dermal absorption factor for phosphorus has been conservatively assumed to be 1.0.

20.6 Conclusion

The following tables present the TRV and bioavailability summaries for phosphorus.

Table 37 Selected Toxicity Reference Values for Phosphorus

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	14300 mg/kg-d	TDI	Health Canada, 1990
Inhalation	14300 mg/kg-d	TDI	Health Canada, 1990
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 38 Selected Bioavailabilities for Phosphorus

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	1.0	Assumed

20.7 References

IOM (Institute of Medicine), 1997. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academies Press, Washington, D.C.

Health Canada (Health and Welfare Canada). 1990. Nutrition Recommendations. The Report of the Scientific Review Committee. Ottawa: Minister of Supply and Services Canada.

Last reviewed: May 2007 (RJ)

21.0 POLYCYCLIC AROMATIC HYDROCARBONS (SELECTED)

Polycyclic aromatic hydrocarbons (PAHs) comprise a group of chemicals that are formed from the incomplete burning of organic substances (ATSDR, 1995; WHO, 1998). Sources of PAHs in the environment include forest fires, and petroleum or coal tar distillation and fractionation. Benzo(a)pyrene has been used in this assessment as a surrogate to represent all carcinogenic PAHs.

21.1 Assessment of Carcinogenicity

The US EPA (2003 a,e,f,g,h) considers benzo(a)pyrene, chrysene, benzo(k)fluoranthene, indeno(1,2,3-c,d)pyrene and dibenz(a,h)anthracene to be a Group B2 – probable human carcinogen. Health Canada (1996) classifies benzo(a)pyrene, benzo(k)fluoranthene, and indeno(1,2,3-c,d)pyrene as Group II - probably carcinogenic to humans. In addition, WHO (1998) also consider benzo(g,h,i)perylene a carcinogenic substance.

The US EPA (2003 b) classifies naphthalene as Group C, a possible human carcinogen. Naphthalene is classified as Group 2B by the International Agency for Research on Cancer (IARC, 2002) possibly carcinogenic to humans.

The US EPA (2003 c,d) IRIS database classifies anthracene and phenanthrene as Group D, not classifiable as to human carcinogenicity.

21.2 Susceptible Populations

People with various conditions such as aryl hydrocarbon hydroxylase (AHH) are at increased risk from the toxic effects of benzo(a)pyrene (ATDSR, 1995). Furthermore, people who smoke, persons with a history of excessive sun exposure, people with liver and skin diseases and women, especially of childbearing age, are all at risk (ATDSR, 1995). Data also indicates that the general population may be at increased risk of developing lung cancer following prolonged inhalation of PAH-contaminated air and skin cancer following skin exposure to PAHs and sunlight (ATDSR, 1995). Also, individuals who undergo a rapid reduction in weight may be at risk because of the systemic release and activation of PAHs that had been stored in body fat (ATSDR 1995). People exposed to PAHs in conjunction with particles from tobacco smoke, fossil fuel combustion, coal fly ash, and asbestos fibres are again at an elevated risk of developing toxic effects, primarily cancer (ATSDR 1995). Women may also be at high risk of reproductive dysfunction and fertility may be reduced by causing ovarian dysfunction (ATSDR 1995).

21.3 Selection of Toxicity Values

21.3.1 Carcinogenic PAHs

Although there is strong evidence of carcinogenicity for several PAH compounds, only benzo(a)pyrene has reliable carcinogenic toxicity values. The most common method for estimating carcinogenic toxicity values for the other PAH compounds is the Toxicity Equivalency Factor (TEF) approach. It is assumed that the carcinogenic PAH compounds each have the same biological mechanism of action and

biological end-point, but differ in their relative potencies or degrees of carcinogenicity. The WHO (1998) used this approach to derive TEF values of 1.0, 0.1, 0.01, 0.01, 1.0 and 0.1 for benzo(a)pyrene, benzo(k)fluoranthene, benzo(g,h,i)perylene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-c,d)pyrene, respectively. WHO TEF values were used to derive oral and inhalation toxicity reference values for the carcinogenic PAHs (Table 39), based upon an oral slope factor of 0.46 $(mg/kg\text{-}day)^{-1}$ and an inhalation unit risk of 87 $(mg/m^3)^{-1}$ provided for benzo(a)pyrene by WHO (2000). No back-up information on the derivation of this TRV is available.

21.3.2 Non-Carcinogenic PAHs

21.3.2.1 Anthracene

An oral TRV of 0.3 mg/kg-day was provided for anthracene by the U.S. EPA (2003c) based on a subchronic toxicity study where oral exposure to mice established a NOEL of 1000 mg/kg-day. No LOAEL was established. A total uncertainty factor of 3000 was applied to the NOEL (10 for interspecies variability, 10 for intraspecies variability, 30 for use of a subchronic study and data inadequacies).

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

21.3.2.2 Naphthalene

An oral TRV of 0.02 mg/kg-day was provided for naphthalene by the U.S. EPA (2003b) based on a subchronic toxicity study (BCL, 1980), where there was a decreased mean terminal body weight in male rats. BCL (1980) established a no observed adverse effects level (NOAEL) of 71 mg/kg-day and a lowest observed adverse effects level of 143 mg/kg-day. An uncertainty factor of 3000 was applied to the NOAEL (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 10 for the use of a subchronic exposure study and 3 for database deficiencies including reproductive and chronic study deficiencies).

An inhalation reference concentration (RfC) of 0.003 mg/m^3 is also provided by the US EPA (2003b) on IRIS. This value is derived from a human equivalent LOAEL of 9.3 mg/m^3 in a chronic mouse inhalation study (NTP, 1991). No NOAEL was established. Effects at the LOAEL included metaplasia in the nasal olfactory epithelium and hyperplasia in the nasal respiratory epithelium. A total uncertainty factor of 3000 was applied to the LOAEL (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 10 for the use of a LOAEL and 3 for database deficiencies including reproductive and chronic study deficiencies).

21.3.2.3 Phenanthrene

RIVM (2000) provides a tolerable daily intake (TDI) of 0.04 mg/kg-day, which was used as the oral TRV in this assessment. No back-up information on the derivation of this TRV is available.

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

21.4 Bioavailability

21.4.1 Oral Bioavailability

There is evidence to suggest that most orally ingested benzo(a)pyrene is absorbed in humans. Oral absorption of benzo(a)pyrene in rats is incomplete, and may be influenced by the presence of oils and fat in the gastrointestinal tract. Studies have estimated the oral absorption of benzo(a)pyrene from animal studies as 23% to 58% (ATSDR, 1995). The oral absorption factor reported by the Oak Ridge National Laboratory (ORNL, 2003) was 0.31. In this assessment, oral bioavailability was assumed to be 1.0.

21.4.2 Inhalation Bioavailability

Absorption of benzo(a)pyrene in humans may be inferred to occur from studies of polycyclic aromatic hydrocarbons (PAHs) as a group (ATSDR, 1995). Animal studies on inhalation absorption of benzo(a)pyrene indicate rapid absorption of benzo(a)pyrene by the lungs; however, the studies also indicate that the absorption may be affected by the size of the carrier particles to which the benzo(a)pyrene is absorbed, and the solubility of the vehicle used in the administration (ATSDR, 1995). The inhalation bioavailability factor used in this assessment was 1.0.

21.4.3 Dermal Bioavailability

Dermal absorption factor varied by PAH, and factors ranged from 0.18 to 1 (Health Canada, 2004).

21.5 Conclusion

The following tables summarize the selected toxicity reference values and bioavailabilities.

Table 39: Selected Toxicity Values for PAHs

Route of Exposure	PAH	TEF	TRV	Source Agency
Carcinogenic				
Ingestion	**Benzo(a)pyrene**	**1.0**	**0.46 (mg/kg-day)$^{-1}$**	**WHO, 2000**
	Benzo(k)fluoranthene	0.1	0.046 (mg/kg-day)$^{-1}$	Applied TEF
	Benzo(ghi)perylene	0.01	0.0046 (mg/kg-day)$^{-1}$	Applied TEF
	Chrysene	0.01	0.0046 (mg/kg-day)$^{-1}$	Applied TEF
	Dibenz(a,h)anthracene	1.0	0.46 (mg/kg-day)$^{-1}$	Applied TEF
	Indeno(1,2,3-c,d)pyrene	0.1	0.046 (mg/kg-day)$^{-1}$	Applied TEF
Inhalation	**Benzo(a)pyrene**	**1.0**	**87 (mg/m^3)$^{-1}$**	**WHO, 2000**
	Benzo(ghi)perylene	0.01	8.7 (mg/m^3)$^{-1}$	Applied TEF
	Benzo(k)fluoranthene	0.1	8.7 (mg/m^3)$^{-1}$	Applied TEF
	Chrysene	0.01	8.7 (mg/m^3)$^{-1}$	Applied TEF
	Dibenz(a,h)anthracene	1.0	87 (mg/m^3)$^{-1}$	Applied TEF
	Indeno(1,2,3-c,d)pyrene	0.1	8.7 (mg/m^3)$^{-1}$	Applied TEF

Route of Exposure	PAH	TEF	TRV	Source Agency
Non-carcinogenic				
Ingestion	Naphthalene	-	0.02 mg/kg-day	U.S. EPA, 2003b
	Anthracene	-	0.3 mg/kg-day	U.S. EPA, 2003c
	Phenanthrene	-	0.04 mg/kg-day	RIVM, 2000
Inhalation	Naphthalene	-	0.003 mg/m^3	U.S. EPA, 2003b
	Anthracene	-	0.3 mg/kg-day	U.S. EPA, 2003c
	Phenanthrene		0.04 mg/kg-day	RIVM, 2000

Table 2: Selected Relative Bioavailabilities for PAHs

Route of Exposure	PAH	Relative Bioavailability	Reference
Ingestion	All	1.0	Assumed
Inhalation	All	1.0	Assumed
Dermal	Anthracene	0.29	Health Canada, 2004
	Naphthalene	0.1	Health Canada, 2004
	Phenanthrene	0.18	Health Canada, 2004

21.6 References

ATSDR 1995. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Benzo(a)pyrene Available on-line at: http://www.atsdr.cdc.gov/toxprofiles/tp69.html

BCL (Battelle's Columbus Laboratories). 1980. Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Batelle Laboratories under NTP Subcontract No. 76-34-106002. Available from the Center for Environmental Research Information, (513) 569-7254.

Health Canada. 1996. Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/Concentrations for Priority Substances. ISBN 0-662-24858-9.

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment. Environmental Health Assessment Services, Safe Environments Programme.

IARC, 2002. International Agency for Research on Cancer (IARC) - Summaries & Evaluations: NAPHTHALENE. Vol. 82. p.367. Available online at: http://www.inchem.org/documents/iarc/vol82/82-06.html.

National Toxicology Program (NTP). 1991. Final report on the developmental toxicity of naphthalene (CAS no. 91-20-3) in Sprague Dawley (CD) rats. #TER91006. NTIS Technical Report (NTIS/PB92-135623).

ORNL. 2003. Risk Assessment Program. Risk Assessment Information System. Toxicity and Chemical-specific Factors Data Base Search. http://risk/lsd.ornl.gov/cgi-bin/tox/TOX_9801. Oak Ridge National Laboratory.

RIVM (The National Institute of Public Health & Environmental Protection, the Netherlands) 2000. Baars AJ et al. 2001. Re-evaluation of human-toxicological maximum permissible risk levels. RIVM report no. 711701025, National Institute of Public Health and the Environment, Bilthoven, The Netherlands, March 2001, p 143-152.

US EPA. 2003a. Integrated Risk Information System (IRIS) Database, Benzo(a)pyrene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003b. IRIS – Integrated Risk Information System, Naphthalene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003c. IRIS – Integrated Risk Information System, Anthracene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003d. IRIS – Integrated Risk Information System, Phenanthrene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003e. IRIS – Integrated Risk Information System, Chrysene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003f. IRIS – Integrated Risk Information System, Benzo(k)fluoranthene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003g. IRIS – Integrated Risk Information System, Indeno(123-cd)pyrene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003h. IRIS – Integrated Risk Information System, Dibenz(ah)anthracene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

US EPA 2003i. IRIS – Integrated Risk Information System, Benzo(ghi)perylene. Available on-line at: http://www.epa.gov/iris/. United States Environmental Protection Agency.

WHO (World Health Organization). 1998. International Programme on Chemical Safety. Environmental Health Criteria 202. Selected non-heterocyclic polycyclic aromatic hydrocarbons. Appendix I. Some approaches to risk assessment for polycyclic aromatic hydrocarbons. Prepared for the United Nations Environment Program

WHO (World Health Organization). 2000. Air Quality Guidelines for Europe: Second Edition. WHO Regional Publications, European Series, No. 91.

22.0 SILVER

Silver is a naturally occurring element. It is found in the environment combined with other elements such as sulfide, chloride, and nitrate. Pure silver is "silver" colored, but silver nitrate and silver chloride are powdery white and silver sulfide and silver oxide are dark-gray to black. Silver is often found as a by-product during the retrieval of copper, lead, zinc, and gold ores.

Silver is used to make jewelry, silverware, electronic equipment, and dental fillings. It is also used to make photographs, in brazing alloys and solders, to disinfect drinking water and water in swimming pools, and as an antibacterial agent. Silver has also been used in lozenges and chewing gum to help people stop smoking (ATSDR, 1999).

22.1 Assessment of Carcinogenicity

Silver is classified as Group D – not classifiable as a human carcinogen due to a lack of human evidence, inadequate animal data from assays of silver compounds, and no evidence of mutagenicity (US EPA, 1991).

22.2 Susceptible Populations

Individuals with a dietary deficiency of vitamin E or selenium, or that may have a genetically based deficiency in the metabolism of these essential nutrients may be more susceptible to exposure to silver (ATSDR, 1999). Individuals with damaged livers may also be susceptible to the effects of silver exposure. Some individuals may exhibit an allergic response to silver (ATSDR, 1999).

22.3 Selection of Toxicity Values

22.3.1 Non-Cancer Oral Toxicity Reference Values

An oral reference dose (RfD) of 5.0E-03 mg/kg-day was provided for silver by the U.S. EPA (1991) based on a 2 to 9 year human study. The main endpoint of concern was argyria, a medically benign but permanent bluish-gray discoloration of the skin. Argyria results from the deposition of silver in the dermis and also from silver-induced production of melanin. No Health Canada TRV was available, therefore, the US EPA value was used in this assessment.

22.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor and unit risk for silver.

22.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore for this assessment, the inhalation TRV was set equal to the oral TRV.

22.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an inhalation slope factor or unit risk for silver.

22.4 Bioavailability

22.5 Oral Bioavailability

The relative oral absorption factor for silver has been conservatively assumed to be 1.0.

22.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for silver has been conservatively assumed to be 1.0.

22.5.2 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.25 for silver.

22.6 Conclusion

The following tables present the TRV and bioavailability summaries for silver.

Table 40 Selected Toxicity Reference Values for Silver

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	5.0E-03 mg/kg-day	RfD	US EPA (1991)
Inhalation	5.0E-03 mg/kg-day	RfD	US EPA (1991)
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 41 Selected Bioavailabilities for Silver

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.25	Health Canada, 2004

22.7 References

ATSDR (Agency for Toxic Substances and Disease Registry), 1999. ToxFAQs for Silver. July 1999.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA). September, 2004.

US EPA (United States Environmental Protection Agency), 1991. Integrated Risk Information System (IRIS) Database – Silver. Available on-line at: http://www.epa.gov/iris/

Last reviewed: May 2007 (RJ)

23.0 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (2,3,7,8-TCDD)

2,3,7,8-Tetrachlorodibenzo-P-Dioxin (2,3,7,8-TCDD) is a member of the chlorinated dibenzo-*p*-dioxins (CDDs), a class of related chlorinated hydrocarbons that are structurally similar. It is insoluble in water, slightly soluble in n-octanol and methanol, and soluble in other organic solvents (e.g., dichlorobenzene, chlorobenzene, benzene, chloroform, and acetone). TCDD is very persistent in the environment, but it can be slowly degraded by sunlight (NTP, 2005).

2,3,7,8-TCDD has no known commercial applications, but it is used as a research chemical. TCDD occurred as a contaminant in chlorophenoxy herbicides, including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), that were widely used in the 1960s and 1970s to control weeds (including controlling weeds on pastureland and food crops) and as a defoliant by the US military during the Vietnam War (NTP, 2005).

23.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer has classified 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (2,3,7,8-TCDD) as carcinogenic to humans (Group 1). Health Canada does not assess 2,3,7,8-TCDD as a carcinogen, it has concluded that there has been no adequate demonstration that human populations exposed to dioxins and furans have suffered excess cancer; therefore for this assessment 2,3,7,8-TCDD is considered a non-carcinogen.

23.2 Susceptible Populations

Dermal lesions and chloracne were observed in a number of children exposed in Seveso, Italy during an accidental release of 2,3,7,8-TCDD (Caputo et al., 1988). Of 187 individuals with chloracne, 88% percent of them were children aged 0 to 14 (Bisanti et al., 1980). Therefore, it is apparent that children are unusually susceptible to the dermal toxicity of 2,3,7,8-TCDD. Experimental data also suggests that the prenatal and postnatal population may be more sensitive to the compound effects. Furthermore, persons who have an aryl hydrocarbon (Ah) receptor with high affinity for 2,3,7,8-TCDD may be at the highest risk for the development of lung tumors (Antilla et al., 1991).

23.3 Selection of Toxicity Values

23.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004) provides a tolerable daily intake (TDI) of 2.3E-09 mg/kg-day, based on a tolerable level of 70 picograms per kilogram body weight per day (JECFA, 2001). No further information on the derivation of this TRV is available. There is no US EPA non-cancer oral TRV available therefore the Health Canada (2004) TDI value was selected for this assessment.

23.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor and unit risk for 2,3,7,8-TCDD.

23.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set to equal to the oral TRV.

23.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of inhalation slope factors or unit risks for 2,3,7,8-TCDD.

23.4 Bioavailability

23.5 Oral Bioavailability

The relative oral absorption factor for of 2,3,7,8-TCDD has been conservatively assumed to be 1.0.

23.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for 2,3,7,8-TCDD has been conservatively assumed to be 1.0.

23.5.2 Dermal Bioavailability

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, RAIS values were used. RAIS (2007) recommends a relative dermal absorption factor of 0.03 for 2,3,7,8-TCDD.

23.6 Conclusion

The following tables present the TRV and bioavailability summaries for 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Table 42 Selected Toxicity Reference Values for 2,3,7,8-TCDD

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	2.0E-09 mg/kg-day	TDI	Health Canada, 2004
Inhalation	2.0E-09 mg/kg-day	TDI	Health Canada, 2004
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 43 Selected Bioavailabilities for 2,3,7,8-TCDD

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.03	RAIS (2007)

23.7 References

Antilla S, Hietanen E, Vainio H, et al. 1991. Smoking and peripheral types of cancer are related to high levels of pulmonary cytochrome P450IA in lung cancer patients. Int J Cancer 47:681-685. Cited In: ATSDR 1998.

Bisanti L., Bonetti F., Caramaschi F., et al., 1980. Experiences from the Accident of Seveso. Acta Morphologica Acad Sci Hung 28:139-157. Cited In: ATSDR, 1998.

Caputo R., Monti M., Ermacora E., et al., 1988. Cutaneous Manifestations of Tetrachlorodibenzo-p-dioxin in Children and Adolescents: Follow-up 10 years after the Seveso, Italy accident. J Am Acad Dermatol 19:812-819. Cited In: ATSDR, 1998.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs). September, 2004.

NTP (National Toxicology Program). 2005. Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service.

RAIS (Risk Assessment Information System). 2007. Oak Ridge National Laboratory. U.S. Department of Energy. Available online at: http://rais.ornl.gov/cgi-bin/tox/TOX_select?select=nrad

24.0 TETRACLOROETHYLENE (PCE)

Tetrachloroethylene is a manufactured chemical that is widely used for dry cleaning of fabrics and for metal-degreasing. It is also used to make other chemicals and is used in some consumer products (ATSDR, 1997).

Other names for tetrachloroethylene include perchloroethylene (PCE) and tetrachloroethene. It is a nonflammable liquid at room temperature. It evaporates easily into the air and has a sharp, sweet odor. Most people can smell tetrachloroethylene when it is present in the air at a level of 1 part tetrachloroethylene per million parts of air (1 ppm) or more, although some can smell it at even lower levels (ATSDR, 1997).

24.1 Assessment of Carcinogenicity

The Department of Health and Human Services (DHHS) has determined that tetrachloroethylene may reasonably be anticipated to be a carcinogen since tetrachloroethylene has been shown to cause liver tumours in mice and kidney tumours in male rats.

The National Institute for Occupational Safety and Health (NIOSH, 2005) recommends that tetrachloroethylene be handled as a potential carcinogen and recommends that levels in workplace air should be as low as possible (NIOSH, 2005).

IARC (1995) has determined that there is evidence for consistently positive associations between exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin's lymphoma. These associations appear unlikely to be due to chance, although confounding cannot be excluded and the total numbers in the cohort studies combined are relatively small. IARC (1995) concluded that tetrachloroethylene is probably carcinogenic in humans based on the limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in laboratory animals.

24.2 Susceptible Populations

Some people may have increased sensitivity to certain systemic effects of tetrachloroethylene (*e.g.*, cardiac sensitization) (ATSDR, 1997). Since high doses of tetrachloroethylene are known to cause kidney and liver effects, persons with clinical or subclinical renal or hepatic disease may be predisposed to the effects of tetrachloroethylene (ATSDR, 1997).

Persons with pre-existing nervous system diseases may also be more sensitive to the neurotoxic effects of tetrachloroethylene (ATSDR, 1997). Similarly, the developing nervous system (i.e., the developing fetus, children) may be particularly susceptible (ATSDR, 1997).

24.3 Selection of Toxicity Values

24.3.1 Non-Cancer Oral Toxicity Reference Values

An oral TRV of 0.014 mg/kg-day was provided for tetrachloroethylene by Health Canada (2004a) based on a subchronic toxicity study (Hayes et al., 1996), where oral exposure to tetrachloroethylene in drinking of rats established a NOEL of 14 mg/kg bw/day. Over the length of the study reduced weight gain and altered liver or kidney to body weight ratios were seen. A TDI of 0.014 mg/kg-day was derived from the rat NOEL by applying an uncertainty factor of 1000 for intraspecies variation (10), interspecies variation (10) and for the use of a subchronic study (10).

The US EPA provides a TRV of 0.01 mg/kg-day. The reference study by Buben and O'Flaherty (1985) exposed Swiss-Cox mice to tetrachloroethylene in corn oil by gavage at doses of 0, 20, 100, 200, 500, 1500, and 2000 mg/kg, 5 days/ week for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight/body weight ratio, hepatic triglyceride concentration, DNA content, histopathological evaluation, and serum enzyme levels. An uncertainty factor of 1000 was used to account for for intraspecies variability, interspecies variability and extrapolation of a subchronic effect level to its chronic equivalent.

The Health Canada (2004) value of 0.014 mg/kg-day was selected for this assessment because based on more recent toxicity data than the US EPA value.

24.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor for tetrachloroethylene.

24.3.3 Non-Cancer Inhalation Toxicity Reference Values

The US EPA (1998) has not developed an inhalation reference concentration for tetrachloroethylene. ATSDR (1997) and Health Canada (2004b) have evaluated the non-cancer inhalation toxicity data for tetrachloroethylene and derived risk values for the general population. Health Canada's tolerable concentration (360 µg/m^3) is based on the NTP (1986) study in mice while ATSDR's chronic minimal risk level (240 µg/m^3) is based on studies in people occupationally exposed to tetrachloroethylene. The resulting values from the two agencies are similar, and are discussed below.

ATSDR

ATSDR developed a minimum risk level (MRL) of 0.2 ppm for acute inhalation exposure (14 days or less) to tetrachloroethylene. The acute MRL was based on a study completed by Altmann et al. (1992) in which human volunteers were subjected to concentrations of 10 or 50 ppm of tetrachloroethylene for 4 hours per day for 4 days. Nervous system effects were observed in volunteers exposed to 50 ppm; however, no adverse effects were observed in volunteers exposed to 10 ppm. Few subjects could identify their exposure levels. The MRL was derived from the NOAEL of 10 ppm for neurological effects by applying an uncertainty factor of 10 for human variability, and multiplying by 4/24 to adjust the intermittent exposure to a continuous exposure.

ATSDR developed a MRL of 0.04 ppm (240 µg/m^3) for chronic inhalation exposure. The chronic MRL is based on a study by Ferronic et al. (1992) of 60 women occupationally exposed to tetrachloroethylene in dry cleaning shops. The women had increased reaction times for a series of simple neurological tests compared to the control group. The medial tetrachloroethylene exposure was 15 ppm. Based on this lowest observed adverse effect level (LOAEL) of 15 ppm, the chronic MRL was derived by applying an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability) and by multiplying by 8/24 hours and 5/7 days to adjust the occupational exposure to a continuous exposure.

Health Canada

The Health Canada assessment was based on data identified prior to April 1992. Health Canada considered the available epidemiological data inadequate to serve as a basis for the development of a tolerable daily intake or tolerable concentration, due to the numerous shortcomings of these investigations (*e.g.*, small population sizes, little or no information concerning the level or duration of exposure to tetrachloroethylene, possible concomitant exposure to other chemicals, and the possible contribution to the observed effects by other confounding factors).

Noting that inhalation is considered the most important route of exposure to tetrachloroethylene for the general population, Health Canada derived an inhalation tolerable daily intake on the basis of results from the longest-term study if adequate design in which tetrachloroethylene was administered by inhalation to laboratory animals (NTP, 1986). In the study, tetrachloroethylene was administered by inhalation for 6 hours per day, 5 days per week for 103 weeks. In this study, the lowest concentration of tetrachloroethylene at which adverse effects (reduced survival in males, hepatotoxicity in males, lung congestion and nephrotoxicity in males and females) were observed in mice (*i.e*., the lowest observed adverse effect level, or LOAEL, was 100 ppm or 678 mg/m^3).

The LOAEL was adjusted from an intermittent exposure to a continuous exposure by multiplying by 6/24 hours and 5/7 days. The LOAEL was also modified to account for the assumed volume of air inhaled by mice (0.043 m^3/day) and the average body weight of the mice in the NTP (1986) study (0.0305 kg). An uncertainty factor of 1000 was applied, resulting in an inhalation tolerable daily intake of 0.170 mg/kg-bw/day. The Health Canada tolerable concentration is based on exposure to a child of 5 to 11 years (*i.e*., the tolerable daily intake of 0.170 mg/kg-bw/day is multiplied by an average body weight of 27 kg for the child and divided by an average inhalation rate of 12 m^3/day for the child, resulting in a tolerable concentration of 0.36 mg/m^3).

For this assessment, the Health Canada value of 360 µg/m^3 was selected and corresponds with proposed MOE (2007) standards for Tetrachloroethylene.

24.3.4 Cancer Inhalation Toxicity Reference Values

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, MOE values were used. MOE (2005) provides an inhalation

unit risk of 4.30E-04 $(mg/m^3)^{-1}$, which was used as the inhalation cancer TRV in this assessment. No back-up information on the derivation of this TRV is available

24.4 Bioavailability

The following sections outline the oral, inhalation, and dermal bioavailabilities of tetrachloroethylene.

24.5 Oral Bioavailability

The relative oral absorption factor for tetrachloroethylene has been conservatively assumed to be 1.0.

24.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for tetrachloroethylene has been conservatively assumed to be 1.0.

24.5.2 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.1 for tetrachloroethylene.

24.6 Conclusion

The following tables present the TRV and bioavailability summaries for tetrachloroethylene.

Table 44 Selected Toxicity Reference Values for Tetrachloroethylene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	1.40E-02 mg/kg-d	TDI	Health Canada, 2004b
Inhalation	360 $\mu g/m^3$	TC	Health Canada, 2004b
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	4.30E-04 $(mg/m^3)^{-1}$	UR	MOE (2005)

NA – Not Applicable

Table 45 Selected Bioavailabilities for Tetrachloroethylene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004a

24.7 References

Agency for Toxic Substances and Disease Registry (ATSDR), 1997. *Toxicological Profile for Tetrachloroethylene.* US Department of Health and Human Services, Public Health Service. September, 1997.

Altmann, L., H. Wiegard, A. Bottger, et al., 1992. Neurological behavioural and neurophysiological outcomes of acute reported perchloroethylene exposure. Applied Pyschologu: An international review. 41(3): 269-279. Cited in ATSDR (1997).

Buben, J.A. and E.J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose- effect study. Toxicol. Appl. Pharmacol. 78: 105-122.

Ferronic, C., L. Selis, A. Mutti, et al., 1994. Neurobehavioural and neuroendocrine effects of occupational exposure to perchloroethylene. Neurotoxicity 13:243-247. Cited in ATSDR (1997).

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.

Health Canada, 2004a. Federal Contaminated Site Risk Assessment in Canada. Part I: Guidance on Human Health Screening Level Risk assessment (SLRA).

Health Canada, 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs). September, 2004.

National Toxicology Program (NTP), 1986. Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in F344/N Rats and B6C3F1 mice (Inhalation Studies). NTP TR311. US Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Cited in Health Canada (1993).

MOE (Ontario Ministry of the Environment). 2005. Summary of Point of Impingement Standards, Point of Impingement Guidelines, and Ambient Air Quality Criteria. Online. Available at: http://www.ene.gov.on.ca/envision/gp/2424e01.htm

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

United States Environmental Protection Agency (US EPA), 1998. Integrated Risk Information System (IRIS). Tetrachloroethylene (CASRN 27-18-4). Available on-line at: http://www.epa.gov/iriswebp/iris/subst/0106.htm#top. Accessed March 28, 2006.

Last reviewed: May 2007 (RJ)

25.0 VANADIUM

Vanadium is found in over 50 different mineral ores in the Earth's crust, as well as in iron ores, phosphate rock, and crude petroleum deposits (ATSDR, 1992). It is used in the manufacture of steel, ferrovanadium alloys, nonferrous titanium alloys, and in various industrial catalysts (ATSDR, 1992).

25.1 Assessment of Carcinogenicity

The ATSDR was unable to locate any studies which reported carcinogenic activity of vanadium following inhalation, oral, or dermal exposures in humans or animals (ATSDR, 1992). Neither Health Canada nor the US EPA provides cancer classifications for vanadium. The International Agency for Research on Cancer (IARC) classifies vanadium pentoxide as Group 2B, "possibly carcinogenic to humans," based on sufficient evidence of carcinogenicity in experimental animals (IARC, 2006). No studies on humans, however, were available to the IARC for their assessment, and the carcinogenicities of other chemical forms of vanadium were not assessed. Based on the lack of evidence of carcinogenic activity in humans, then, vanadium is considered to be non-carcinogenic for the purposes of this assessment.

25.2 Susceptible Populations

No unusually susceptible populations have been identified; however, persons with pre-existing conditions, such as asthma, may be expected to have increased adverse effects when exposed to vanadium dusts in the air (ATSDR, 1992).

25.3 Selection of Toxicity Values

25.3.1 Non-Cancer Oral Toxicity Reference Values

The US EPA has developed an RfD of 0.009 mg/kg-day for exposure to vanadium pentoxide based on a single study in rats. The study authors reported a decrease in hair cystine content in test animals compared to controls during the study (US EPA, 1996). The US EPA applied an uncertainty factor of 100 to the NOAEL from the study to account for interspecies extrapolation and sensitive members of the population (US EPA, 1996).

The US EPA Region III developed an oral RfD of 0.001 mg/kg-day, but this TRV was classified by the US EPA as an "EPA-NCEA Provisional Value" (US EPA Region III, 2006). No derivations are provided by the US EPA Region III for RfDs in this category, so no information on the supporting studies could be found. The US EPA also indicates that RfDs in this category are also likely to be site-specific, so this value may not be appropriate for the current risk assessment.

Given the unsuitability of the US EPA Region III RfD, the US EPA IRIS RfD value for vanadium pentoxide of 9×10^{-3} mg/kg-day was used to assess potential risks associated with oral exposures to vanadium. No Health Canada non-cancer oral TRV was available.

25.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor for vanadium.

25.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

25.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of inhalation slope factors or unit risks for vanadium.

25.4 Bioavailability

25.5 Oral Bioavailability

There was no data available for oral bioavailability of vanadium. The relative oral absorption factor for vanadium has been conservatively assumed to be 1.0.

25.5.1 Inhalation Bioavailability

There was no data available for inhalation bioavailability of vanadium; therefore, the relative inhalation absorption factor for vanadium has been conservatively assumed to be 1.0.

25.5.2 Dermal Bioavailability

Health Canada (2004) recommends a dermal relative absorption factor of 0.1 for vanadium.

25.6 Conclusion

The following tables present the TRV and bioavailability summaries for vanadium.

Table 46 Selected Toxicity Reference Values for Vanadium

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	9.00E-03 mg/kg-day	RfD	US EPA, 1996
Inhalation	9.00E-03 mg/kg-day	RfD	US EPA, 1996
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 47 Selected Bioavailabilities for Vanadium

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004

25.7 References

ATSDR. 1992. Toxicological Profile for Vanadium. Agency for Toxic Substances and Disease Registry. Available at http://www.atsdr.cdc.gov/toxprofiles/tp58.html.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA).

IARC. 2006. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 86: Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Available at: http://monographs.iarc.fr/ENG/Monographs/vol86/volume86.pdf.

US EPA. 1996. Integrated Risk Information System (IRIS): Vanadium Pentoxide. Available at http://www.epa.gov/iris/

US EPA Region III. 2006. EPA Region III Risk Based Concentration Table 4/7/2006. Available at http://www.epa.gov/reg3hwmd/risk/human/rbc/rbc0406.pdf

Last reviewed: May 2007 (RJ)

26.0 VINYL CHLORIDE

Vinyl chloride (VC) is a halogenated aliphatic hydrocarbon used primarily as an intermediate in the manufacture of polyvinyl chloride (PVC); limited quantities are used as a refrigerant and as an intermediate in the production of chlorinated compounds (ATSDR, 2004). VC is also a breakdown product of trichloroethylene.

26.1 Assessment of Carcinogenicity

The US EPA (2000) lists vinyl chloride as group A, a known human carcinogen. This grouping is based on based on based on (1) consistent epidemiologic evidence of a causal association between occupational exposure to VC via inhalation and the development of angiosarcoma, an extremely rare tumor; (2) consistent evidence of carcinogenicity in rats, mice, and hamsters by both the oral and inhalation routes; (3) mutagenicity and DNA adduct formation by VC and its metabolites in numerous in vivo and in vitro test systems; and (4) efficient VC absorption via all routes of exposure tested, followed by rapid distribution throughout the body. In light of the very high percentage of angiosarcomas worldwide that are associated with VC exposure, the evidence for VC carcinogenicity is considered strong.

The IARC lists VC as a Group 1 chemical: describing it as not classifiable as to its carcinogenicity to humans. (IARC, 1987).

26.2 Susceptible Populations

Data has shown that the following groups may be unusually susceptible to the toxic effects of VC: fetuses; infants; young children; people with liver disease, irregular heart rhythms, impaired peripheral circulation or systemic sclerosis (ATSDR, 2004).

26.3 Selection of Toxicity Values

26.3.1 Non-Cancer Oral Toxicity Reference Values

An oral TRV of 0.003 mg/kg-day was provided for VC by US EPA (2000) based on two studies by Til et al. (1983, 1991), where oral exposure to VC in diet established a NOAEL of 0.13 mg/kg-day and a LOAEL of 1.3 mg/kg-day. The critical effect seen during this chronic rat feeding study by Til et al. (1983, 1991) was liver cell polymorphism. The NOAEL from Til et al. (1983, 1991) was converted to a human equivalent dose of 0.09 mg/kg-day and an uncertainty factor of 30 (10 for protection of human subpopulations and 3 for animal-to-human extrapolation) was applied to derive an RfD of 0.003 mg/kg-day.

No Health Canada TRV was available, therefore, the US EPA non-cancer oral TRV was selected for use in this assessment.

26.3.2 Cancer Oral Toxicity Reference Values

US EPA (2000) provides an oral slope factor of 1.4 $(mg/kg\text{-}d)^{-1}$ based on a llinearized multistage extrapolation from oral bioassays conducted by Feron et al. (1981) on Wistar rats. Exposure to VC through diet produced angiosarcoma, hepatocellular carcinoma, and neoplastic nodules. 1.4 $(mg/kg\text{-}d)^{-1}$ corresponds to continue lifetime exposure to VC from birth; continuous lifetime exposure during adulthood produces an oral slope factor of 0.72 $(mg/kg\text{-}d)^{-1}$.

No Health Canada cancer oral TRV was available, therefore, the US EPA value was selected for use in this assessment.

26.3.3 Non-Cancer Inhalation Toxicity Reference Values

The US EPA (2000) has developed an inhalation reference concentration (RfC) of 100 $\mu g/m^3$ from a human equivalent concentration no observable adverse effects level (NOAEL) of 2.5 mg/m^3. Liver cell polymorphism was the critical effect in the chronic rat study used in developing the RfC. An uncertainty factor of 30 was applied (3 for interspecies extrapolation and 10 for intraspecies variability). Overall confidence in the RfC is medium.

No Health Canada non-cancer inhalation TRV was available; therefore, the US EPA value was selected for use in this assessment.

26.3.4 Cancer Inhalation Toxicity Reference Values

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, MOE values were used. MOE (2005) provides an inhalation unit risk of 5.00E-03 $(mg/m^3)^{-1}$ based on the occurrence of liver cancer, which was used as the inhalation cancer TRV in this assessment. No further information on the derivation of this TRV is available.

26.4 Bioavailability

26.5 Oral Bioavailability

The relative oral absorption factor for vinyl chloride has been conservatively assumed to be 1.0.

26.5.1 Inhalation Bioavailability

The relative inhalation absorption factor for vinyl chloride has been conservatively assumed to be 1.0.

26.5.2 Dermal Bioavailability

Health Canada (2004) recommends a dermal relative absorption factor of 0.16 for vinyl chloride.

26.6 Conclusion

The following tables present the TRV and bioavailability summaries for vinyl chloride.

Table 48 Selected Toxicity Reference Values for Vinyl Chloride

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.003 mg/kg-day	RfD	US EPA (2000)
Inhalation	100 µg/m^3	RFC	US EPA (2000)
Cancer Effects			
Ingestion	1.4 (mg/kg-d)$^{-1}$	SF	US EPA (2000)
Inhalation	5.00E-03 (mg/m^3)$^{-1}$	UR	MOE (2005)

NA – Not Applicable

Table 49 Selected Bioavailabilities for Vinyl Chloride

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.16	Health Canada, 2004

26.7 References

ATSDR (Agency for Toxic Substances and Disease Registry). 2004. Toxicological Profile for Vinyl Chloride (Draft for Public Comment). US Public Health Service, Department of Health and Human Services, Atlanta, GA. September, 2004.

Health Canada, 2004. Federal Contaminated Site Risk Assessment in Canada. Part I: Guidance on Human Health Screening Level Risk assessment (SLRA). Version 1.1, October 3, 2003

International Agency for Research on Cancer (IARC). 1987. "Vinyl Chloride". *Monographs.* Supplement 7, p. 373. World Health Organization.

MOE (Ontario Ministry of the Environment). 2005. Summary of Point of Impingement Standards, Point of Impingement Guidelines, and Ambient Air Quality Criteria. Online. Available at: http://www.ene.gov.on.ca/envision/gp/2424e01.htm

Risk Assessment Information System (RAIS). 2005. Toxicity Summary for Vinyl Chloride. Prepared by the Chemical Hazard Evaluation Group, Biomedical and Environmental Information Analysis Section, Health Sciences Research Division, Oak Ridge, Tennessee.

Til, HP; Immel, HR; Feron, VJ. (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, HP; Feron, VJ; Immel, HR. (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.

United States Protection Agency (US EPA), 2000. Integrated Risk Information System (IRIS).Vinyl Chloride (CASRN 75-01-4). .

United States Protection Agency (US EPA) 2000. *Toxicological Review of Vinyl Chloride.* Washington, DC. EPA/635R-00/004.

27.0 ZINC

Zinc is the 23rd most abundant element in the earth's crust and is found in air, soil, water and all foods. It has many commercial uses such as in coatings to prevent rust, in dry cell batteries, and mixed with other metals to make alloys like brass and bronze (ATSDR, 1994). Zinc is an essential element, necessary for sustaining all life. It stimulates the activity of approximately 100 enzymes, supports a healthy immune system, is needed for wound healing, helps maintain the sense of taste and smell, and is needed for DNA synthesis. Zinc also supports normal growth and development during pregnancy, childhood and adolescence. The recommended daily allowance of zinc is 15 mg for adult males, 12 mg for adult females, 10 mg for children older than 1 year, and 5 mg for infants 0-12 months old (NRC, 1989).

27.1 Assessment of Carcinogenicity

Epidemiological studies of workers exposed to zinc have not shown a relationship between zinc exposure and the development of cancer (ATSDR, 1994). Additionally, animal studies have not shown a link between inhalation, oral or dermal exposure to zinc and an increase in the incidence of cancers (ATSDR, 1994). Based on inadequate evidence in humans and animals, the US EPA classified zinc as a Class D substance; not classifiable as to human carcinogenicity (US EPA, 1992).

27.2 Susceptible Populations

There is no specific information regarding the existence of human subpopulations that are sensitive to the toxic effects of zinc (ATSDR, 1994).

27.3 Selection of Toxicity Values

27.3.1 Non-Cancer Oral Toxicity Reference Value

The U.S. EPA (1992) suggested an oral RfD of 0.3 mg/kg-day based on decreased blood enzyme levels (*i.e.*, superoxide dismutase) in females in a diet supplement study (Yadrick *et al.*, 1989).

No Health Canada non-caner oral TRV was available, therefore, the US EPA non-cancer oral TRV was selected for use in this assessment.

27.3.2 Cancer Oral Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor for zinc.

27.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

27.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an inhalation slope factor or unit risk for zinc.

27.4 Bioavailability

27.4.1 Oral Bioavailability

Several studies have measured oral absorption rates of zinc in humans. Absorption ranged from 8% to 81% following short-term exposures to zinc supplement in the diet (ATSDR, 1994). The relative oral absorption factor for zinc has been conservatively assumed to be 1.0.

27.4.2 Inhalation Bioavailability

Quantitative studies regarding absorption of zinc and zinc compounds after inhalation exposure in humans are limited. The absorption of inhaled zinc depends on the particle size and solubility (ATSDR, 1994). Elevated levels of zinc have been found in the blood and urine of workers exposed to zinc oxide fume (Hamdi, 1969). In this assessment, the relative inhalation absorption factor for zinc has been conservatively assumed to be 1.0.

27.4.3 Dermal Bioavailability

Health Canada (2004) recommends a dermal relative absorption factor of 0.02 for zinc.

27.5 Conclusion

The following tables present the TRV and bioavailability summaries for zinc.

Table 50 Selected Toxicity Values for Zinc

Route of Exposure	TRV	Toxicological Basis	Source Agency
Non-Cancer Effects			
Ingestion	3.0E-01 mg/kg-day	Decreased erythrocyte SOD	US EPA, 1992
Inhalation	3.0E-01 mg/kg-day	Decreased erythrocyte SOD	US EPA, 1992
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA - Not Available

Table 51 Selected Bioavailabilities for Zinc

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.02	Health Canada, 2004

27.5.1 References

ATSDR (Agency for Toxic Substances and Disease Registry). 1994. Draft Toxicological Profile for Zinc. Available on-line at: http://www.atsdr.cdc.gov/toxprofiles/.

Hamdi, EA. 1969. Chronic exposure to zinc of furnace operators in a brass foundry. Br J Ind Med 26:126-134.

NRC (National Research Council). 1989. Recommended Dietary Allowances. 10th ed National Academy Press, Washington, DC.

US EPA (Environmental Protection Agency). 1992. Integrated Risk Information System (IRIS) Database – Zinc. Confirmed current as of November, 2005. Available on-line at: http://www.epa.gov/iris/.

United States Environmental Protection Agency. 1995. Supplemental Guidance to RAGS: Region 4 Bulletins, Human Health Risk Assessment (Interim Guidance). Waste Management Division, Office of Health Assessment.

Yadrick, M.K., Kenney, M.A. and Winterfeldt, E.A. 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.

Last reviewed: May 2007 (RJ)

28.0 POLYCHLORINATED BIPHENYLS (PCBS)

Polychlorinated biphenyls (PCBs) were previously manufactured for use as dielectric and heat-exchange fluids, as well as various other applications (IPCS, 1993). PCBs have been produced as mixtures under various trade names including Aroclor, Pyranol, Pyroclor, Phenoclor, Pyralene, Clophen, Elaol, Kanechlor, Santotherm, Fenchlor, Apirolio and Sovol (WHO, 2003).

Although no longer manufactured (since 1977), PCBs are ubiquitous and persistent in the environment with food being the primary route of exposure for the general population (IPCS, 1993; ATSDR, 2000). Studies have demonstrated the carcinogenic potential of PCBs and furthermore the potential for PCBs to promoted the carcinogenicity of other chemicals (IPCS, 1993). Commercial PCBs may contain polychlorinated dibenzofurans (PCDFs) as impurities but do not contain polychlorinated dibenzo-p-dioxins (PCDDs) (IPCS, 1993).

There are potentially 209 PCB congeners however only 130 have been identified in commercial products (IPCS, 1993; WHO, 2000). Congeners with the same number of chlorines are referred to as isomers. The number and position of chlorine atoms predicts the environmental fate and toxicity of individual congeners. In general, PCBs with a higher degree of chlorination are more lipophilic, less volatile, less readily absorbed and less water-soluble (WHO, 2000).

28.1 Assessment of Carcinogenicity

Human studies provide inconclusive, yet suggestive, evidence of an association between exposure to PCBs and liver cancer; however, the studies are inconclusive due to confounding exposures and lack of exposure quantification (US EPA, 1997; ATSDR, 2000). Oral exposure studies in animals show an increase in liver tumors in rats and mice, as well as thyroid tumours in male rats (US EPA, 1997; ATSDR, 2000). No animal inhalation studies are available on the health effects of PCBs; however, PCBs are absorbed through inhalation indicating that there may be a concern for this exposure route (ATSDR, 2000).

The US EPA (1997) has classified PCBs as a group B2 substance; probable human carcinogen. The International Agency for Research on Cancer (IARC, 1987) has classified PCBs as a Group 2A substance; probably carcinogenic to humans.

Health Canada does not classify PCBs as carcinogens; therefore, similar to the evaluation of 2,3,7,8-TCDD in this assessment, PCBs are evaluated as non-carcinogens.

28.2 Susceptible Populations

Two susceptible populations were identified by the Agency for Toxic Substances and Disease Registry (ATSDR, 2000). The first was populations with incompletely developed conjugation mechanisms such as those with Gilbert's syndrome, a congenital liver disorder which occurs in approximately 3 to 7% of the adult population. These individuals are considered susceptible because of their diminished

capacity to detoxify and excrete PCBs. Others with decreased hepatic activity, including individuals with hepatitis B or liver cirrhosis, may also be susceptible to PCB toxicity (ATSDR, 2000).

The second susceptible population identified by ATSDR was children, as there is strong evidence that PCBs may be transferred across the placenta of pregnant women. This together with transfer in breast milk, and the more common routes of exposure such as consumption of contaminated foods, may potentially contribute to altered development, specifically neurobehavioral alterations (ATSDR, 2000).

28.3 Selection of Toxicity Reference Values

Since PCBs usually occur as mixtures of congeners with varying degrees of chlorination, toxicity data must be based on PCB mixtures to predict potential health effects. Information on PCB exposure, however, is primarily from occupational studies and accidental exposures that may be associated with exposure to other chemicals.

The most documented cases of human exposure to PCDFs are the Yusho (Japan, 1968) and Yucheng (Taiwan, 1979) incidents where people were accidentally exposed to PCDF and PCB contaminated food supply (IARC, 1978; IARC, 1987). These two incidences produced conflicting human health effects. At Yoshu, Japan, an increase in liver cancer was observed in Japanese men while no excess liver mortality was observed in the affected Yucheng, Taiwan population (IARC, 1978; IARC, 1987).

28.3.1 Non-Cancer Oral Toxicity Reference Values

The US EPA provides toxicity reference values for PCB mixtures such as Aroclor 1254 and 1016. The US EPA (1996a) established an oral reference dose (RfD) for Aroclor 1254 of 2.0E-05 mg/kg-day based on immunological effects in monkeys. The RfD was calculated from a lowest observable adverse effect level (LOAEL) of 0.005 mg/kg-day. The US EPA (1996b) has also developed an RfD for Aroclor 1016 of 7.0E-05 mg/kg-day based on a no observable adverse effect level (NOAEL) of 0.007 mg/kg-day and LOAEL of 0.028 mg/kg-day. Aroclor 1016 is a commercial PCB mixture that is devoid of chlorinated dibenzofurans (US EPA, 1996b). The oral RfDs and effects are summarized below.

Table 52 Oral Reference Dose for PCB Mixtures

Congener	TRV	TRV Type	Agency	Effects
Aroclor 1254	2.0E-05 mg/kg-day	RfD	IRIS, US EPA	Ocular exudate, inflamed and prominent Meibomian glands, distorted growth of finger and toe nails; decreased IgG and IgM response to sheep erythrocytes.
Aroclor 1016	7×10^{-5} mg/kg-day	RfD	IRIS, US EPA	Reduced birth weights

The ATSDR (2000) provides oral minimal risk levels (MRLs) for intermediate and chronic exposures to PCBs. These MRLs were derived to reflect exposure to PCB mixtures and are based on studies that involved Aroclor 1254 (Table 17).

Table 53 Minimal Risk Levels for Oral Exposure to PCBs

Exposure	TRV	Basis	Effects
Intermediate (15-364 days)	0.03 µg/kg-day	LOAEL (0.0075 mg/kg-day)	Neurobehavioral alterations in infant monkeys that were exposed to a PCB congener mixture representing 80% of the congeners typically found in human breast milk
Chronic (365 days or more)	0.02 µg/kg-day	LOAEL (0.005 mg/kg-day)	Immunological effects in adult monkeys that were evaluated after 23 and 55 months of exposure to Aroclor 1254

The chronic MRL calculated by the ATSDR is similar to the US EPA RfD for Aroclor 1254.

Health Canada (2004) provides a TDI of 0.001 mg/kg-day; however no supporting documentation on the derivation of this TDI is available. For this assessment, the Health Canada (2004) TDI was selected to represent the non-cancer oral TRV for PCBs.

28.3.2 Cancer Oral Toxicity Reference Value

The lack of suitable positive carcinogenic data precludes the derivation of an oral slope factor and unit risk for PCBs.

28.3.3 Non-Cancer Inhalation Toxicity Reference Value

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

28.3.4 Cancer Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data precludes the derivation of an inhalation slope factor and unit risk for PCBs.

28.4 Bioavailability

PCBs are well absorbed following oral, inhalation or dermal exposure, and transported similarly to the systemic circulation (US EPA, 1997; ATSDR, 2000). Initially, absorbed PCBs are transported to the liver and muscle, however, soon after they are stored in fat and skin (US EPA, 1996c).

28.4.1 Oral Bioavailability

Studies with animals have shown that PCBs are readily absorbed from the gastrointestinal tract with the degree of absorption ranging from 66 to 96% (ATSDR, 2000; WHO, 2000).

Specific information concerning absorption of Aroclor 1254 is limited. Pregnant ferrets administered a single oral dose of 0.06 mg/kg Aroclor 1254 absorbed 85% of the administered dose

(Bleavins *et al*., 1984). Rats, mice and monkeys absorb between 75 to >90% of orally administered doses of PCBs (US EPA, 1996a). Oral exposure through consumption of contaminated food (including breast milk) is the major route of exposure to PCBs for the general population.

The oral relative bioavailability factor for PCBs used in this assessment was 1.0.

28.4.2 Inhalation Bioavailability

Inhalation is considered a major occupational route of exposure to PCBs; however, quantitative data concerning inhalation exposure is scarce (ATSDR, 2000). In rats, absorption and distribution of PCBs is similar following inhalation or oral administration (WHO, 2000; US EPA, 1997). Furthermore, PCB mixtures are readily absorbed after administration via aerosol with 50% of the maximum applied concentration measured in the liver 2 h later (IPCS, 1993).

The ATSDR summarized a study by Wolff (1985) wherein it was suggested that approximately 80% of PCB levels in adipose tissue of exposed capacitor workers may have been absorbed by the inhalation route. A maximum of 20% would have been derived from dermal and/or oral exposures (ATSDR, 2000).

The relative inhalation bioavailability factor used in this assessment was 1.0.

28.4.3 Dermal Bioavailability

In experimental animals, dermal absorption has been observed ranging from 20 to 60% (WHO, 2000). This is consistent with Wolff (1985), where approximately 20% of PCB levels in adipose tissue were attributed to oral and/or dermal exposures. The US EPA Region III (1995) recommends a dermal bioavailability factor of 0.06 based on the dermal absorption of 3,3',4,4'-tetrachlorobiphenyl.

For this assessment, the relative dermal bioavailability has been assumed to be 1.0.

28.5 Conclusion

The following tables summarize the selected TRVs and relative bioavailabilities for PCBs.

Table 54 Selected Toxicity Reference Values for PCBs

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.001 mg/kg-day	TDI	Health Canada, 2004
Inhalation	0.001 mg/kg-day	TDI	Health Canada, 2004
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

Notes: NA - Not Available

Table 55 Selected Bioavailabilities for PCBs

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	1.0	Assumed

28.6 References

ATSDR (Agency for Toxic Substances and Disease Registry), 2000. Toxicological Profile for Polychlorinated Biphenyls (PCBs). November, 2000.

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

IARC (International Agency for Research on Cancer), 1978. Environmental Monographs Volume 18: Polychlorinated Biphenyls. Available: http://193.51.164.11/htdocs/monographs/vol18/polychlorinatedbiphenyls.html.

IARC (International Agency for Research on Cancer), 1987. Environmental Monographs Supplement 7: Polychlorinated Biphenyls. Available: http://193.51.164.11/htdocs/monographs/suppl17/polychlorinatedbiphenyls.html.

IPCS (International Programme on Chemical Safety), 1993. Environmental Health Criteria 140: Polychlorinated Biphenyls and Terphenyls, 2nd ed. Available at http://www.inchem.org/documents/ehc/ehc /ehc140.htm#p5.0

US EPA (United States Environmental Protection Agency). 1996a. Integrated Risk Information System (IRIS) Database – Aroclor 1254. Confirmed current as of November, 2005. Available on-line at: http://www.epa.gov/iris

US EPA (United States Environmental Protection Agency). 1996b. Integrated Risk Information System (IRIS) Database – Aroclor 1016. Confirmed current as of November, 2005. Available on-line at: http://www.epa.gov/iris

US EPA (United States Environmental Protection Agency). 1996c. PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures. September 1996. Available at: http://www.epa.gov/opptintr/pcb/pcb.pdf

US EPA (United States Environmental Protection Agency). 1997. Integrated Risk Information System (IRIS) Database - Polychlorinated Biphenyls (PCBs). Available on-line at: http://www.epa.gov/iris

US EPA (United States Environmental Protection Agency) Region III. 1995. Risk Assessment: Technical Guidance Manual. Assessing Dermal Contact with Soil. http://www.epa.gov/reg3hwmd/risk/solabsg2.htm.

Wolff MS. 1985. Occupational exposure to polychlorinated biphenyls (PCBs). *Environ Health Perspect* 60:133-138.

WHO (World Health Organization). 2000. Air Quality Guidelines for Europe: Second Edition. WHO Regional Publications, European Series, No. 91.

WHO (World Health Organization). 2003. Concise International Chemical Assessment Document 55, Polychlorinated Biphenyls: Human Health Aspects.

Last reviewed: May 2007 (RJ)

29.0 1,2,4,5-TETRACHLOROBENZENE

According to the US EPA, 1,2,4,5-Tetrachlorobenzene is an odorless man-made substance that can range in appearance from a colorless crystal to a white flaky or chunky solid. It is used as an intermediate to make herbicides, insecticides and defoliants (US EPA, 2006).

29.1 Assessment of Carcinogenicity

1,2,4,5-Tetrachlorobenzene has not been classified as a carcinogen by any of the major regulatory review agencies including the IARC, US EPA or Health Canada.

29.2 Susceptible Populations

No susceptible populations were identified.

29.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to 1,2,4,5-Tetrachlorobenzene.

29.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004) provides a tolerable daily intake (TDI) of 0.00021 mg/kg-day, which was used as the oral TRV in this assessment. Health Canada based their TDI value on the results of a study conducted by the National Toxicological Program in 1991 in which subchronic doses of 1,2,4,5-tetrachlorobenzene (0, 30, 100, 300, 1,000 or 2,000 ppm [mg/kg]) were administered to rats for 13 weeks. Effects including compound-related clinical symptoms, haematological changes and histopathological effects in the liver were observed in animals in the highest dose groups. A NOAEL value of 2.1 mg/kg bw/day was derived from this study. Health Canada applied an uncertainty factor of 10,000 to account for intraspecies variation (10), interspecies variation (10), a less than chronic study (10) and for a lack of adequate data on carcinogenicity and reproductive toxicity (10). The resulting TDI is 0.00021 mg/kg-day.

The US EPA non-cancer oral TRV provided is 0.0003 mg/kg-day. The referenced study (Chu et al., 1984) involved groups of 15/sex weanling rats who were fed diets containing 0, 0.5, 5.0, 50, and 500 ppm of 1,2,4,5-tetrachlorobenzene (TCB) for 13 weeks. The corresponding dose range in mg/kg bw/day was given as 0.034-34. An uncertainty factor of 1000 was applied to reflect both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and for extrapolation of a subchronic effect level to its chronic equivalent.

The Health Canada (2004) value was used for this assessment because is based on more recent data and is more conservative than the US EPA value.

29.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2,4,5-Tetrachlorobenzene as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

29.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

29.3.4 Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2,4,5-Tetrachlorobenzene as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

29.4 Bioavailability

29.4.1 Oral Bioavailability

The relative oral absorption factor for 1,2,4,5-Tetrachlorobenzene has been conservatively assumed to be 1.0.

29.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for 1,2,4,5-Tetrachlorobenzene has been conservatively assumed to be 1.0.

29.4.3 Dermal Bioavailability

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, RAIS values were used. RAIS (2007) recommends a relative dermal absorption factor of 0.01 for 1,2,4,5-Tetrachlorobenzene

29.5 Conclusion

Table 56: Selected Toxicity Values for 1,2,4,5-Tetrachlorobenzene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.00021 mg/kg-day	TDI	Health Canada, 2004
Inhalation	0.00021 mg/kg-day	TDI	Health Canada, 2004
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 57: Selected Relative Bioavailabilities for 1,2,4,5-Tetrachlorobenzene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.01	RAIS, 2007

29.6 References

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.

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

RAIS (Risk Assessment Information System). 2007. Oak Ridge National Laboratory. U.S. Department of Energy. Available online at: http://rais.ornl.gov/cgi-bin/tox/TOX_select?select=nrad

US EPA , 2006. Priority Chemicals Fact Sheets, EPA's National Partnership for Environmental Priorities (NPEP) Waste Minimization Program. Available online at: http://www.epa.gov/epaoswer/hazwaste/minimize/chemlist.htm

Last reviewed: May 2007 (RJ)

30.0 1,2,4-TRICHLOROBENZENE

1,2,4 -Trichlorobenzene is a man-made chemical that looks like a colorless liquid (US EPA, 2006). 1,2,4-Trichlorobenzene has several uses; it is used as an intermediate or building block to make herbicides, substances that destroy or prevent the growth of weeds. It is also used as a solvent and dielectric fluid (a liquid that conducts little or no electricity), a degreaser (a substance that removes grease), and as a lubricant (US EPA, 2006).

30.1 Assessment of Carcinogenicity

1,2,4-Trichlorobenzene has not been classified as a carcinogen by any of the major regulatory review agencies including the IARC, US EPA or Health Canada.

30.2 Susceptible Populations

No particular susceptible populations are identified y the US EPA.

30.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to 1,2,4-Trichlorobenzene.

30.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.0016 mg/kg-day, which was used as the oral TRV in this assessment. The Health Canada TDI is based on a 13-week study undertaken by Cote et al in 1988. Rats were exposed to 1,2,4-trichlorobenzene at 0.07 to 146 mg/kg bw/day in the diet (Cote et al., 1988).

Significant increases in the relative liver weight and absolute and relative kidney weight were seen in males at the highest doses. Histopathological changes in the liver and thyroid were significant only at the highest dose and were more severe in males than females (Cote et al., 1988). Health Canada derived the TDI of 0.0016 mg/kg bw/day based on a NOEL of 7.8 mg/kg bw/day in the Cote et al., 1988 study. An uncertainty factor of 5000 was applied (10 for intraspecies variation, 10 for interspecies variation, 10 for use of a subchronic study, and 5 for the lack of adequate data on carcinogenicity).

The US EPA provides a non-cancer oral TRV of 0.01 mg/kg-day. The derivation of the oral RfD is based on a multigeneration reproductive study on rats by Robinson et al. (1981).

The Health Canada (2004b) value was used in this assessment because it is based on more recent data and is more conservative than the US EPA value.

30.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2,4-Trichlorobenzene as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

30.3.3 Non-Cancer Inhalation Toxicity Reference Values

Health Canada (2004b) provides a tolerable concentration (TC) of 0.007 mg/m^3, which was used as the inhalation TRV in this assessment. A tolerable concentration (TC) of 0.007 mg/m^{3}was derived based on the lowest NOAEL (223 mg/m^3) in subchronic studies (Kociba et al., 1981). Following the subchronic inhalation exposure of rats, rabbits and beagle dogs to 1,2,4-trichlorobenzene (up to 742 mg/m^3) for 44 days, there was an increase in liver (rats and dogs) and kidney (rats) weights at 742 mg/m^3, and an increase in the excretion of porphyrins (rats) at 223 mg/m^3 [NOEL in rabbits = 742 mg/m^3; no-observed-adverse-effect level (NOAEL) in rats and NOEL in dogs = 223 mg/m^3] (Kociba et al., 1981).

Factors of 7/24 and 5/7 were used to convert from intermittent to continuous exposure. The NOAEL was further modified for the ratio of inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg]. An uncertainty factor of 5,000 was applied (10 for intraspecies variation; 10 for interspecies variation; 10 for use of a less than chronic study; and 5 for lack of adequate carcinogenicity and chronic toxicity data).

There was no value available from the US EPA for the non-cancer inhalation TRV therefore the Health Canada (2004b) value was used in this assessment.

30.3.4 Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2,4-Trichlorobenzene as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

30.4 Bioavailability

30.4.1 Oral Bioavailability

The relative oral absorption factor for 1,2,4-Trichlorobenzene has been conservatively assumed to be 1.0.

30.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for 1,2,4-Trichlorobenzene has been conservatively assumed to be 1.0.

30.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.08 for 1,2,4-Trichlorobenzene.

30.5 Conclusion

Table 58: Selected Toxicity Values for 1,2,4-Trichlorobenzene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.0016 mg/kg-day	TDI	Health Canada, 2004b
Inhalation	0.007 mg/m^3	TC	Health Canada, 2004b
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 59: Selected Relative Bioavailabilities for 1,2,4-Trichlorobenzene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.08	Health Canada, 2004a

30.6 References

Cote, M., I. Chu, D.C. Villeneuve, V.E. Secours and V.E. Valli. 1988. Drug Chem. Toxicol. 11: 11-28.

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA). September, 2004.

Health Canada. 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values. Environmental Health Assessment Services, Safe Environments Programme.

Kociba, R.J., B.K.J. 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: 229-249.

Robinson, K.S., R.J. Kavlock, N. Chernoff and E. Gray. 1981. Multi- generation study of 1,2,4-trichlorobenzene in rats. J. Toxicol. Environ. Health. 8: 489-500.

US EPA , 2006. Priority Chemicals Fact Sheets, 1,2,4-Trichlorobenzene. EPA's National Partnership for Environmental Priorities (NPEP) Waste Minimization Program. Available online at: http://www.epa.gov/epaoswer/hazwaste/minimize/chemlist.htm

31.0 1,2-DICHLOROBENZENE

Dichlorobenzenes do not occur naturally. Dichlorobenzenes are chemical intermediates used widely in the manufacture of dyes, pesticides and various industrial products. Ortho-Dichlorobenzene (1,2-dichlorobenzene) is a colorless to pale yellow liquid used as a solvent and an insecticide (IARC, 1999).

Exposure to high levels of 1,2- dichlorobenzene may be very irritating to your eyes and nose and cause difficult breathing, and an upset stomach (ATSDR, 2006). 1,2-Dichlorobenzene has been identified in at least 281 of the 1,662 National Priorities List sites identified by the Environmental Protection Agency (EPA).

31.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC) has found that 1,2-Dichlorobenzene is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1999). It states there is inadequate evidence in humans for the carcinogenicity of dichlorobenzenes and that is evidence suggesting lack of carcinogenicity in experimental animals of ortho-dichlorobenzene (IARC, 1999).

31.2 Susceptible Populations

According to the ATSDR (2006), exposure to dichlorobenzenes mostly occurs from breathing indoor air or workplace air.

31.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to 1,2-dichlorobenzene.

31.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.43 mg/kg-day, which was used as the oral TRV in this assessment. Health Canada TDI has been derived on the basis of the NOEL of 60 mg/kg bw/day (tubular regeneration in the kidney at the next highest dose) derived in a long-term NTP bioassay conducted by the oral route (NTP, 1983).

In the NTP study, groups of F344 rats and B6C3F1 mice (both sexes) were administered 0, 60, or 120 mg/kg bw/day 1,2-dichlorobenzene by gavage for 5 days/week for 103 weeks (NTP, 1983). In mice exposed, there was a dose-related increase in the incidence of tubular regeneration of the kidney of males at 120 mg/kg bw/day. Based on the occurrence of these effects at higher doses, the NOEL of 60 mg/kg bw/day was derived (NTP, 1983). Health Canada adjusted the dose to account for the dosing schedule of 5 days/week, and a 100-fold uncertainty factor (10 for intraspecies variation and 10 for interspecies variation) was applied.

US EPA provides a non-cancer oral TRV of 0.09 mg/kg-day, where 1,2-Dichlorobenzene in corn oil was given by gavage to F344/N rats and B6C3F1 mice (50 males and 50 females/group) at doses of 0, 60, or 120 mg/kg-day, 5 days/week for 103 weeks (NTP, 1985).

The Health Canada (2004b) value was used in this assessment and it corresponds with the proposed MOE (2007) standards for 1,2-Dichlorobenzene.

31.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2-dichlorobenzene as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

31.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

31.3.4 Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2-dichlorobenzene as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

31.4 Bioavailability

31.4.1 Oral Bioavailability

The relative oral absorption factor for 1,2-Dichlorobenzene has been conservatively assumed to be 1.0.

31.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for 1,2-Dichlorobenzene has been conservatively assumed to be 1.0.

31.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.1 for 1,2-Dichlorobenzene.

31.5 Conclusion

Table 60: Selected Toxicity Values for 1,2-Dichlorobenzene

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.43 mg/kg-day	TDI	Health Canada, 2004b
Inhalation	0.43 mg/kg-day	TDI	Health Canada, 2004b
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 61: Selected Relative Bioavailabilities for 1,2-Dichlorobenzene

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2004

31.6 References

ATSDR, 2006. ToxFAQs Summary for Dichlorobenzenes. Agency for Toxic Substances and Diseases Registry. August, 2006. Available at : http://www.atsdr.cdc.gov/tfacts10.html

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA).

Health Canada, 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs).

IARC, 1999. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer . Volume 73, p.223. 1999.

MOE (Ontario Ministry of the Environment). 2007. Rationale for the Development of Generic Soil and Groundwater Standards for Use at Contaminated Sites in Ontario. Standards Development Branch. March 7, 2007. Draft.

NTP (National Toxicology Program). 1983. Carcinogenesis studies of 1,2-dichlorobenzene (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC, United States Department of Health and Human Services, Public Health Service, National Institutes of Health, NTP TR 255.

NTP (National Toxicology Program). 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 255. NIH Publ. No. 86-2511.

Last reviewed: May 2007 (RJ))

32.0 2,3,4,6-TETRACHLOROPHENOL

Chlorophenols (CPs) are organic chemicals formed from phenol (1-hydroxybenzene) by substitution in the phenol ring with one or more atoms of chlorine. Nineteen congeners are possible, ranging from monochlorophenols to the fully chlorinated pentachlorophenol (PCB). Chlorophenols, particularly trichlorophenols (T3CP), tetrachlorophenols (T4CP), and PCP, are also available as sodium or potassium salts (INCHEM, 1989).

Chlorophenols are solids at room temperature. The aqueous solubility of chlorophenols is low, but the sodium or potassium salts of chlorophenols are up to four orders of magnitude more soluble in water than the parent compounds (INCHEM, 1989). The acidity of chlorophenols increases as the number of chlorine substitutions increases. The n-octanol/water partition coefficients of chlorophenols increase with chlorination, indicating a propensity for the higher chlorophenols to bioaccumulate (INCHEM, 1989). The taste and odour thresholds of chlorophenols are quite low.

According to the ATSDR (1999), some chlorophenols are used as pesticides, while others are used in antiseptics. Small amounts are produced when water is disinfected with chlorine. They are also produced while bleaching wood pulp with chlorine to make paper (ATSDR,1999).

32.1 Assessment of Carcinogenicity

According to IARC (1999), there is limited evidence in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts. There is limited evidence in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts. Combined exposures to polychlorophenols or to their sodium salts are possibly carcinogenic to humans (Group 2B) (IARC, 1999).

32.2 Susceptible Populations

No particularly susceptible populations were identified.

32.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to 2,3,4,6-Tetrachlorophenol.

32.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004) provides a tolerable daily intake (TDI) of 0.01 mg/kg-day, which was used as the oral TRV in this assessment. No backup information on the basis for development of this TRV is available.

The US EPA provides a non-cancer oral TRV of 0.03 mg/kg-day. The study was completed by the US EPA (1986). Sprague-Dawley rats (30/sex/dose) were gavaged daily with 0, 25, 100 or 200 mg/kg-day 2,3,4,6-tetrachlorophenol in olive oil. Body weight gain, food consumption, clinical signs of toxicity and mortality were recorded throughout the study. The sub-chronic NOAEL found was 25 mg/kg-day and by applying an uncertainty factor of 1000 to this NOAEL, an RfD of 0.025 mg/kg-day or 0.03 mg/kg-day was derived.

The Health Canada (2004b) value of 0.01 mg/kg-day was used in this assessment because it is more conservative than the US EPA value.

32.3.2 Cancer Oral Toxicity Reference Values

Due to the lack of sufficient data a cancer oral TRV has not been selected for this assessment.

32.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

32.3.4 Cancer Inhalation Toxicity Reference Values

Due to the lack of sufficient data a cancer inhalation TRV has not been selected for this assessment.

32.4 Bioavailability

32.4.1 Oral Bioavailability

The relative oral absorption factor for 2,3,4,6-Tetrachlorophenol has been conservatively assumed to be 1.0.

32.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for 2,3,4,6-Tetrachlorophenol has been conservatively assumed to be 1.0.

32.4.3 Dermal Bioavailability

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, RAIS values were used. RAIS (2007) recommends a relative dermal absorption factor of 0.01 for 2,3,4,6-Tetrachlorophenol.

32.5 Conclusion

Table 62: Selected Toxicity Values for 2,3,4,6-Tetrachlorophenol

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.01 mg/kg-day	RfD	Health Canada, 2004
Inhalation	0.01 mg/kg-day	RfD	Health Canada, 2004
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 63: Selected Relative Bioavailabilities for 2,3,4,6-Tetrachlorophenol

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.01	RAIS, 2007

32.6 References

ATSDR (Agency for Toxic Substances and Diseases Registry), 1999. ToxFAQs for Chlorophenols. June, 1999. Available at: http://www.atsdr.cdc.gov/tfacts107.html

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA). September, 2004.

IARC (International Agency for Research on Cancer), 1999. Monograph on the Evaluation of Carcinogenic Risk to Humans: Polychlorophenols and their Sodium Salts. Volume 71, p.769. 1999.

INCHEM (International Programme on Chemical Safety). 1989. Environmental Health Criteria 93: Chlorophenols other than Pentachlorophenol. Available online at: http://www.inchem.org/documents/ehc/ehc/ehc093.htm.

RAIS (The Risk Assessment Information System), 2007. Toxicity & Chemical-Specific Factors Data Base Search Results: Absorption Factor, Dermal. Data current as of May 2007. Available at: http://rais.ornl.gov/cgi-bin/tox/TOX_select?select=nrad

U.S. EPA. 1986. 2,3,4,6-Tetrachlorophenol. 90-Day subchronic oral toxicity study in rats. Office of Solid Waste, Washington, DC.

Last reviewed: May 2007 (RJ))

33.0 2,4,6-TRICHLOROPHENOL

Chlorophenols (CPs) are organic chemicals formed from phenol (1-hydroxybenzene) by substitution in the phenol ring with one or more atoms of chlorine. Nineteen congeners are possible, ranging from monochlorophenols to the fully chlorinated pentachlorophenol (PCB). Chlorophenols, particularly trichlorophenols (T3CP), tetrachlorophenols (T4CP), and PCP, are also available as sodium or potassium salts (INCHEM, 1989).

Chlorophenols are solids at room temperature. The aqueous solubility of chlorophenols is low, but the sodium or potassium salts of chlorophenols are up to four orders of magnitude more soluble in water than the parent compounds (INCHEM, 1989). The acidity of chlorophenols increases as the number of chlorine substitutions increases. The n-octanol/water partition coefficients of chlorophenols increase with chlorination, indicating a propensity for the higher chlorophenols to bioaccumulate (INCHEM, 1989). The taste and odour thresholds of chlorophenols are quite low.

According to the ATSDR (1999), some chlorophenols are used as pesticides, while others are used in antiseptics. Small amounts are produced when water is disinfected with chlorine. They are also produced while bleaching wood pulp with chlorine to make paper (ATSDR,1999).

33.1 Assessment of Carcinogenicity

According to IARC (1999), there is limited evidence in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts. There is limited evidence in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts. Combined exposures to polychlorophenols or to their sodium salts are possibly carcinogenic to humans (Group 2B) (IARC, 1999).

The Department of Health and Human Services (DHHS) has determined that 2,4,6-trichlorophenol may reasonably be anticipated to be a carcinogen (ATSDR, 1999).

33.2 Susceptible Populations

No particularly susceptible populations have been identified.

33.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to 2,4,6-Trichlorophenol.

33.3.1 Non-Cancer Oral Toxicity Reference Values

Due to lack of data, non-cancer inhalation TRVs were unavailable from the major regulatory agencies (e.g., Health Canada, US EPA), therefore, RIVM values were used. RIVM (2000) provides a tolerable daily intake (TDI) of 0.003 mg/kg-day, which was used as the oral TRV in this assessment. No back-up information on the derivation of this TRV is available.

33.3.2 Cancer Oral Toxicity Reference Values

US EPA (1994) provides an oral slope factor of 0.011 $(mg/kg\text{-}d)^{-1}$ based on a study by NCI (1979) where 2,4,6-Trichlorophenol (96-97% pure) was added to the diet of 50 each male and female F344 rats and B6C3F1 mice . In both male and female mice there was a statistically significant trend in the incidence of combined hepatocellular adenomas and carcinomas.

No Health Canada cancer oral TRV was available, therefore, the US EPA value was used in this assessment.

33.3.3 Non-Cancer Inhalation Toxicity Reference Values

A non-cancer inhalation TRV has not been selected for this assessment because 2,4,6-trichlorophenol is carcinogenic by inhalation.

33.3.4 Cancer Inhalation Toxicity Reference Values

US EPA (1994) provides an inhalation unit risk of 3.1E-06 $(\mu g/m^3)^{-1}$ for 2,4,6-trichlorophenol based on a linearized multistage extrapolation from data collected by NCI (1979), as described in Section 33.3.2.

No Health Canada cancer inhalation TRV was available, therefore, the US EPA value was used in this assessment.

33.4 Bioavailability

The following sections outline the oral, inhalation, and dermal bioavailabilities of 2,4,6-Trichlorophenol.

33.4.1 Oral Bioavailability

33.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for 2,4,6-Trichlorophenol has been conservatively assumed to be 1.0.

33.4.3 Dermal Bioavailability

Health Canada (2004) recommends a relative dermal absorption factor of 0.26 for 2,4,6-Trichlorophenol.

33.5 Conclusion

Table 64: Selected Toxicity Values for 2,4,6-Trichlorophenol

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.003 mg/kg-day	TDI	RIVM (2000)
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	0.011 $(mg/kg\text{-}d)^{-1}$	SF	US EPA (1994)
Inhalation	3.1E-06 $(\mu g/m^3)^{-1}$	UR	US EPA (1994)

NA – Not Applicable

Table 65: Selected Relative Bioavailabilities for 2,4,6-Trichlorophenol

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.26	Health Canada, 2004

33.6 References

ATSDR (Agency for Toxic Substances and Diseases Registry), 1999. ToxFAQs for Chlorophenols. June, 1999. Available at: http://www.atsdr.cdc.gov/tfacts107.html

Health Canada. 2004. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA). September, 2004.

IARC (International Agency for Research on Cancer), 1999. Monograph on the Evaluation of Carcinogenic Risk to Humans: Polychlorophenols and their Sodium Salts. Volume 71, p.769. 1999.

INCHEM (International Programme on Chemical Safety). 1989. Environmental Health Criteria 93: Chlorophenols other than Pentachlorophenol. Available online at: http://www.inchem.org/documents/ehc/ehc/ehc093.htm.

NCI (National Cancer Institute). 1979. Bioassay of 2,4,6-Trichlorophenol for Possible Carcinogenicity. U.S. DHEW Publ. No. NCI-CG-TR-155.

RIVM (The National Institute of Public Health & Environmental Protection, the Netherlands) 2000. Baars AJ et al. 2001. Re-evaluation of human-toxicological maximum permissible risk levels. RIVM report no. 711701025, National Institute of Public Health and the Environment, Bilthoven, The Netherlands, March 2001, p 143-152.

US EPA (United States Environmental Protection Agency. 1994. Integrated Risk Information System (IRIS) Database, 2,4,6-Trichlorophenol. . Available on-line at: http://www.epa.gov/iris/.

34.0 2,4-DICHLOROPHENOL

Chlorophenols with at least two chlorines either have been used directly as pesticides or converted into pesticides (ATSDR, 1999). In addition to being produced commercially, small amounts of some chlorophenols, especially the mono- and dichlorophenols, may be produced when waste water or drinking water is disinfected with chlorine, if certain contaminants are present in the raw water (ATSDR, 1999). They are also produced during the bleaching of wood pulp with chlorine when paper is being produced.

34.1 Assessment of Carcinogenicity

According to the IARC (1999), there is evidence suggesting lack of carcinogenicity of 2,4-dichlorophenol in experimental animals. However the IARC evaluated the combined exposures to polychlorophenols or to their sodium salts, and determined that, combined, they are possibly carcinogenic to humans (Group 2B).

34.2 Susceptible Populations

No particularly susceptible subpopulation was identified by the ATSDR (1999).

34.3 Selection of Toxicity Values

The following sections present the toxicity reference values (TRVs) selected for the assessment of risks due to 2,4-Dichlorophenol.

34.3.1 Non-Cancer Oral Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.1 mg/kg-day; no further information on the derivation of this TRV is available.

The US EPA provides a non-cancer oral TRV of 0.003 mg/kg-day, where Exon and Koller (1985) exposed female rats to 3, 30, or 300 ppm 2,4-dichlorophenol in drinking water from weaning age through breeding at 90 days, parturition, and weaning of pups.

The Health Canada (2004b) TDI of 0.1 mg/kg-day was selected for this assessment.

34.3.2 Cancer Oral Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2-dichlorobenzene as carcinogenic to humans; therefore no cancer oral TRVs have been selected for use in this risk assessment.

34.3.3 Non-Cancer Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, the inhalation TRV was set equal to the oral TRV.

34.3.4 Cancer Inhalation Toxicity Reference Values

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify 1,2-dichlorobenzene as carcinogenic to humans; therefore no cancer inhalation TRVs have been selected for use in this risk assessment.

34.4 Bioavailability

34.4.1 Oral Bioavailability

The relative oral absorption factor for 2,4-Dichlorophenol has been conservatively assumed to be 1.0.

34.4.2 Inhalation Bioavailability

The relative inhalation absorption factor for 2,4-Dichlorophenol has been conservatively assumed to be 1.0.

34.4.3 Dermal Bioavailability

Health Canada (2004a) recommends a relative dermal absorption factor of 0.4 for 2,4-Dichlorophenol.

34.5 Conclusion

Table 66: Selected Toxicity Values for 2,4-Dichlorophenol

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	0.1 mg/kg-day	RfD	Health Canada, 2004b
Inhalation	0.1 mg/kg-day	RfD	Health Canada, 2004b
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 67: Selected Relative Bioavailabilities for 2,4-Dichlorophenol

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.4	Health Canada, 2004

34.6 References

ATSDR, 1999. Toxicological Profile for Chlorophenols. Agency for Toxic Substances and Diseases Registry. July 1999. Available at: http://www.atsdr.cdc.gov/toxprofiles/phs107.html

Exon, J.H. and L.D. Koller. 1985. Toxicity of 2-chlorophenol, 2,4- dichlorophenol and 2,4,6-trichlorophenol. In: Water Chlorination: Chemistry, Environmental Impact and Health Effects, Jolley et al., Ed. Vol. 5.

Health Canada. 2004a. Federal Contaminated Site Risk Assessment in Canada, Part I: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA).

Health Canada, 2004b. Federal Contaminated Site Risk Assessment in Canada, Part II: Health Canada Toxicological Reference Values (TRVs).

IARC, 1999. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer . Volume 71, p.769. 1999.