APPENDIX H

HHRA Toxicity Profiles

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Glossary

Benchmark Concentration	Statistically calculated lower 95% confidence limit on the concentration that produces a defined response (called the benchmark response or BMR, usually 5 % or 10 %) for an adverse effect compared to background, often defined as 0 % or 5%.
Human equivalent concentration	Human concentration of an agent that is believed to induce the same magnitude of a toxic effect that the known animal dose has induced.
Lowest-observed-adverse-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.
Lowest-observed-effects-level	A term that describes the benchmark on a threshold dose-response curve at which the lowest dose results in any observed health effects. May be used in place of a NOEL where a NOEL cannot be determined.
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 non carcinogenic health effects over a specified route and duration of exposure.
No-observed-adverse-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.
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 any effects.
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.
Reference Dose	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.
Reference Exposure Level	A term used by California EPA to describe an airborne level of a chemical that is not anticipated to present a significant risk of an adverse non-carcinogenic health effect
Relative bioavailability	A comparative fraction which predicts bioavailability in one medium or form in relation to the medium for which the TRV was derived.

Glossary

Slope Factor	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.
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.
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.
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.
Uncertainty Factor	A factor that is applied to NOAELs or LOAELs to yield an RfC or RfD. For example, the UF can be used to account for intra-species and inter-species extrapolations.
Unit Risk (UR)	Unit 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.

Acronyms

AAQC	Ambient Air Quality Criteria
AAQO	Ambient Air Quality Objective
AENV	Alberta Environment
Ah	Aryl hydrocarbon
ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMC	Benchmark Concentration

Acronyms

BMDL	Benchmark Dose (lower confidence limit)
CalEPA	California Environmental Protection Agency
CCME	Canadian Council of Ministers of the Environment
CEPA	Canadian Environmental Protection Act
COPC	Contaminants of Potential Concern
ESL	Effects Screening Level
ESOD	Erythrocyte Superoxide Dismutase
FAO	Food and Agriculture Organization. An organization of the United Nations
HC	Health Canada
HCN	Health Council of the Netherlands
HEC	Human equivalent concentration
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-adverse-effects-level
LOEL	Lowest-observed-effects-level
MAC	Maximum Allowable Concentration
MADEP	Massachusetts Department of Environmental Protection
MOE	Ontario Ministry of the Environment
MRL	Minimal Risk Level

Acronyms

NATO	North Atlantic Treaty Organization
NCEA	National Center for Environmental Assessment
NE	Not Evaluated
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-adverse-effects-level
NOAL	No-observed-effects-level
NRC	National Research Council
NV	No Value
OEHHA	Office of Environmental Health Hazard Assessment
ORD	Office of Research and Development
PBPK Model	Physiologically-Based Pharmacokinetic Model
PCB	Polychlorinated biphenyls
PCDD	Polychlorinated dibenzo-p-dioxins
PCDF	Polychlorinated dibenzofurans
PEL	Permissible Exposure Level
PQRA	Preliminary Quantitative Risk Assessment
PTWI	Provisional Tolerable Weekly Intake
RAIS	Risk Assessment Information System
RAF	Relative absorption factor
RDA	Recommended Dietary Allowance
REL	Reference Exposure Level
RfC	Reference Concentration

Acronyms

RfD	Reference Dose
SF	Slope factor
SLRA	Screening Level Risk Assessment
STSC	Superfund Health Risk Technical Support Center
TC	Tolerable Concentration.
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
TCE	Trichloroethylene
TCEQ	Texas Commission on Environmental Quality
TD	Tumorigenic Dose
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
TLV	Threshold Limit Value
TLV-C	Threshold Limit Value-Ceiling
TRV	Toxicity Reference Value
TWA	Time Weighted Average
UF	Uncertainty Factor
UL	Tolerable upper intake level
UR	Unit Risk
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

1.0 INTRODUCTION

The methods and approaches used by Jacques Whitford to determine Toxicity Reference Values (TRVs) for use in the HHRA are outlined in this document. Toxicity Reference Values were obtained for each of the identified chemicals of potential concern (COPC). For the purpose of this assessment, TRVs are defined as values used to describe acceptable doses of chemicals that will not result in the development of unacceptable adverse health effects (e.g., RfD, RfC) or are benchmarks that are policy derived and health based (e.g., AAQC).

Numerous sources were consulted in order to obtain toxicological and benchmark values (e.g., Health Canada; US EPA Integrated Risk Information System (IRIS); Ontario Ministry of the Environment (MOE); Agency for Toxic Substances and Disease Registry (ATSDR); Canadian Council of the Ministers of the Environment (CCME); World Health Organization (WHO); California Environmental Protection Agency (CalEPA); Texas Commission on Environmental Quality (TCEQ)). When TRVs for a particular COPC were available from multiple regulatory agencies, all of the TRVs were reviewed and professional judgment of an experienced toxicologist was used to select the most appropriate TRV for use in this assessment.

1.1 Dose-Response Patterns

Chemicals generally follow either a threshold (non-carcinogens) or non-threshold (carcinogens) dose-response relationship. For threshold dose-responses, a specific dose (e.g., lowest observed adverse effect level (LOAEL) or a no-observable adverse effect level (NOAEL)) can be identified. These values, adjusted by appropriate uncertainty factors (when required) are known as the reference dose (RfD) or reference concentration (RfC) for the oral and inhalation routes of exposure, respectively. Some regulatory agencies have substituted the term RfD to be reflective of objectives and toxicological endpoints; for example, Health Canada replaces the term with tolerable daily intake (TDI) and the ATSDR uses a minimal risk level (MRL). Health Canada also uses a tolerable concentration (TC) to express concentrations in air that a person can be continuously exposed to over their lifetime without adverse effects rather than an RfC. In some cases, a TC or RfC may not be available for a COPC and an inhalation value may be calculated using a route-to-route extrapolation based on the oral TDI. For the purposes of this risk assessment, this route-to-route extrapolation involves an assumed Health Canada body weight of 70.7 kg and an inhalation rate of 15.8 m^3/day for an adult, where applicable.

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 (SF) and unit risk (UR). 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. Health Canada uses tumorigenic doses and concentrations to develop slope factors 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}).

1.2 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). 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).

CRITERIA AIR CONTAMINANTS

2.0 AMMONIA

Ammonia is a colorless gas with a very distinct odor. Many household and industrial cleaners contain ammonia, and it is also used to make fertilizers for farm crops, lawns, and other plants (ATSDR, 2004).

There are no documented health effects from exposure to low levels of ammonia (ATSDR, 2004). Exposure to high levels of ammonia in the air can cause irritation of the skin, eyes, throat and lungs, potentially causing coughing and burns (ATSDR, 2004). Inhalation of very high concentrations of ammonia can cause lung damage and possible death (ATSDR, 2004). Ingestion of concentrated ammonia can burn the mouth, throat and stomach. Contact of ammonia with eyes can cause burns and blindness (ATSDR, 2004).

2.1 Assessment of Carcinogenicity

The IARC and the US EPA have not classified ammonia for carcinogenicity and is not considered as a carcinogen in the HHRA.

2.2 Susceptible Populations

People who suffer from severe liver or kidney disease may be susceptible to ammonia intoxication (ATSDR, 2004). Since ammonia is a respiratory tract irritant, persons who are hyper-reactive to other respiratory irritants, or who are asthmatic, would be expected to be more susceptible to ammonia inhalation effects (ATSDR, 2004).

2.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

2.3.1 Oral Exposure

2.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, ammonia is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

2.3.1.2 Cancer Toxicity Reference Values

Ammonia is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

2.3.2 Inhalation Exposure

2.3.2.1 Non-Carcinogenic Toxicity Reference Values

2.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

The California Environmental Protection Agency (CalEPA, 2008a) derived a 1-hour exposure limit of 3200 µg/m^3 based on four human studies from which eye and respiratory irritation was observed (Industrial Biotest Laboratories, 1973; MacEwen et al., 1970; Silverman et al., 1949; Verberk, 1977). Each study used volunteer human subjects exposed to ammonia at varying durations (5 minutes to 2 hours) and at varying concentrations of ammonia (2100 to 3.55 x 10^5 µg/m^3). A benchmark concentration (BC) approach was used to obtain the exposure limit using a log-normal probit analysis. The 95% lower confidence limit (LCL) of the concentration expected to produce a response rate of 5% is defined as the BC_{05}; therefore, the BC_{05} for ammonia from this analysis was 9520 µg/m^3. An inter-individual uncertainty factor of 3 was applied to account for variation in the human population. The resulting value 3200 µg/m^3 was selected for the risk assessment.

The 24-hour exposure limit used in this risk assessment was selected from the Ontario Ministry of the Environment (MOE). A 24-hour AAQC benchmark of 100 µg/m^3 was derived (MOE, 2008) based on respiratory irritation with no additional information regarding benchmark derivation provided.

2.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The US EPA (1991) derived an RfC of 100 µg/m^3 based on an occupational study conducted by Holness et al (1989). Holness et al. (1989) investigated 52 production workers exposed to ammonia in a soda ash facility. The control group used in the study consisted of 31 other plant workers from stores and office areas of the plant without previous exposure to ammonia. The mean age of the workers was 38.9 years and duration of exposure was 12.2 years. The mean time-weighted average (TWA) ammonia exposures based on personal sampling over one work shift (average sample collection 8.4 hours) of the exposed and control groups were 6,400 µg/m^3 and 210 µg/m^3 respectively. A questionnaire was administered at the beginning and end of each work shift on the first workday of the week and the last workday of the week to obtain information on exposure and work histories and to determine eye, skin and respiratory symptomatology. No statistical difference in the prevalence of the reporting symptoms was evident between the exposed and control groups, although workers reported that exposure at the plant had aggravated specific symptoms including coughing, wheezing, nasal complaints, eye irritation, throat discomfort and skin problems. Baseline lung functions were similar in the exposed and control groups. No changes in lung function were demonstrated over either work shift (days 1 or 2) or over the workweek in the exposed group compared with controls.

Based on the lack of subjective symptomatology and changes in spirometry, the US EPA (1991) established a NOAEL 6,400 µg/m^3. An adjustment was made to convert the occupational scenario NOAEL into a continuous exposure NOAEL of 2,300 µg/m^3 (breathing volume for an 8-hour occupational exposure = 10 m^3/day, breathing volume for a 24-hour continuous exposure = 20 m^3/day; therefore, NOAEL(ADJ) = 6400 µg/m^3 x ((10/20) x 5 days/7 days = 2300 µg/m^3). The adjusted NOAEL of 2,300 µg/m^3 was modified by a cumulative uncertainty factor of 30 (10 to account for the protection of sensitive humans and 3 to account for database deficiencies) to arrive at a RfC of 100 µg/m^3.

ATSDR (2004) derived a chronic MRL of 70 µg/m^3 based on the same study as US EPA (1991) (Holness et al., 1989). The MRL was calculated by adjusting the NOAEL of 6,440 µg/m^3 (the mean TWA exposure concentration) to a continuous exposure (6,440 x 8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 for the protection of sensitive individuals. A modifying factor of 3 was used for the lack of reproductive and developmental studies to arrive at a chronic MRL of 70 µg/m^3 (ATSDR, 2004).

CalEPA (2008b) also derived a chronic REL of 200 µg/m^3 based on the same occupational study (Holness et al., 1989) from which the US EPA derived their chronic inhalation RfC. The CalEPA (2008b) chronic REL value differs from the US EPA (1991) RfC because CalEPA did not apply an uncertainty factor of 3 to account for database deficiencies, resulting in a less stringent REL.

The US EPA RfC value of 100 µg/m^3 was selected for the risk assessment because, while ATSDR MRLs are appropriate as screening levels for hazardous substances, the US EPA provided a more comprehensive review of epidemiologic literature and as such, a higher level of confidence was placed in the RfC.

2.3.2.2 Cancer Inhalation Toxicity Reference Values

Ammonia is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

2.4 Bioavailability

In this risk assessment, ammonia is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that ammonia is completely absorbed (i.e. absorption factor is 1).

2.9 Conclusion

The following tables present Ammonia TRVs selected for use in this risk assessment.

Table 2-1 Ammonia Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Ammonia	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 2-2 Ammonia Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Ammonia	1-Hour	3200	Eye and Respiratory Irritation	Benchmark	CalEPA, 1999
	24-Hour	100	Eye and Respiratory	Benchmark	MOE AAQC,

			Irritation		2005
	Annual Average	100	Lack of evidence of decreased pulmonary function changes in subjective symptomology	RfC	US EPA, 1991

[a] Units: Non-carcinogenic COPC (µg/m^3)

2.10 References

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Verberk, M.M. 1977. Effects of ammonia in volunteers. *International Archives of Occupational and Environmental Health*. 39: 73-81.

3.0 CARBON MONOXIDE

Carbon monoxide (CO) is a colorless, tasteless, odorless, and non-irritating gas. It is a primary product of incomplete combustion of fuels such as natural gas, oil, wood, propane and kerosene.

Exposure to low concentrations of CO can lead to fatigue; at higher concentrations, health effects of CO inhalation include impaired vision, impaired coordination, headaches, dizziness, confusion, nausea, and flu-like symptoms and can escalate to angina, reduced brain function and ultimately death (US EPA, 2009).

The mechanism of toxicity principally associated with health effects of greatest concern from CO exposure is it entering the bloodstream and reducing oxygen delivery to the body's organs and tissues, known as hypoxia induced by elevated carboxyhemoglobin (COHb) blood levels (US EPA, 2000).

3.1 Assessment of Carcinogenicity

The US EPA and Health Canada have not classified carbon monoxide (CO) with respect to carcinogenicity. For the purpose of this risk assessment carbon monoxide was evaluated as a non-carcinogenic substance.

3.2 Susceptible Populations

Evidence suggests that individuals with heart disease, including stable exercise-induced angina, coronary artery disease, and ischemic heart disease, represent that population at greatest risk from exposure to ambient CO levels (Health Canada, 1994). In addition, pregnant women, fetuses and young infants, individuals with anemia or respiratory disease, the elderly, children, and persons with peripheral vascular disease and chronic obstructive lung disease may be more susceptible to the effect of CO exposure (Health Canada, 1994).

3.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

3.3.1 Oral Exposure

3.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, CO is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

3.3.1.2 Cancer Toxicity Reference Values

Carbon monoxide is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

3.3.2 Inhalation Exposure

3.3.2.1 Non-Carcinogenic Toxicity Reference Values

3.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Based on uncertainties in the available data, along with conservative assumptions, Health Canada (1994) recommended that the National Ambient Air Quality Objective (NAAQO) maximum desirable level (MDL) be based upon a carboxyhaemoglobin (COHb) blood level of less than 1%. This level is the upper end of the range of baseline COHb levels experienced in normal, non-smoking individuals from endogenous population. The Physiologically Based Pharmacokinetic (PBPK) model of Coburn, Forster and Kane (1965) was used to produce ambient CO concentrations based on the allowable COHb level. Based on this modeling exercise, a 1-hour exposure of 15,000 µg/m^3 would result in less than 1% COHb in exposed people. This value was adopted as the 1-hour NAAQO MDL for CO by Health Canada (1994).

The U.S. EPA National Ambient Air Quality Standards provide a maximum acceptable 1-hour level of CO of 40,000 µg/m^3 (US EPA, 2009). No further information regarding the derivation of this value was available.

As it is most conservative, the 1-hour TRV of 15,000 µg/m^3 was selected as the acute exposure limit for CO for the current assessment. A 24-hour TRV for CO was not identified for use in the risk assessment.

3.3.2.1.2 Chronic Inhalation Toxicity Reference Values

No chronic non-carcinogenic TRV for CO was identified for use in the risk assessment.

3.3.2.2 Cancer Inhalation Toxicity Reference Values

Carbon monoxide is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation TRV has not been selected.

3.4 Bioavailability

In this risk assessment, CO is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that CO is completely absorbed (i.e. absorption factor is 1.

3.5 Conclusion

The following tables present CO TRVs selected for use in this risk assessment.

Table 3-1 Carbon Monoxide Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Carbon Monoxide	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 3-2 Carbon Monoxide Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Carbon Monoxide	1-Hour	15,000	carboxyhaemoglobin (COHb) blood level of less than 1%.	Benchmark	Health Canada, 1994
	24-Hour	NV			
	Annual Average	NV			

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , NV – No Value

3.6 References

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4.0 HYDROGEN CHLORIDE

At room temperature, hydrogen chloride is a colorless to slightly yellow, corrosive, nonflammable gas that is heavier than air and has a strong irritating odor (ATSDR, 2002). On exposure to air, hydrogen chloride forms dense white corrosive vapors. Upon contact with water, it forms hydrochloric acid. Both hydrogen chloride and hydrochloric acid are corrosive (ATSDR, 2002). Hydrogen chloride has many uses, including cleaning, pickling, electroplating metals, tanning leather, and refining and producing a wide variety of products (ATSDR, 2002). Hydrogen chloride can be formed during the burning of many plastics (ATSDR, 2002).

Hydrogen chloride is irritating and corrosive to any tissue it contacts. Brief exposure to low levels causes throat irritation (ATSDR, 2002). Exposure to higher levels can result in rapid breathing, narrowing of the bronchioles, blue coloring of the skin, accumulation of fluid in the lungs, and even death. Exposure to even higher levels can cause swelling and spasm of the throat and suffocation. Some people may develop an inflammatory reaction to hydrogen chloride. This condition is called reactive airways dysfunction syndrome (RADS), a type of asthma caused by some irritating or corrosive substances (ATSDR, 2002).

Depending on the concentration, hydrogen chloride can produce mild irritation to severe burns of the eyes and skin (ATSDR, 2002). Long-term exposure to low levels can cause respiratory problems, eye and skin irritation, and discoloration of the teeth (ATSDR, 2002).

4.1 Assessment of Carcinogenicity

No information from is available from Health Canada or the US EPA on the carcinogenic effects of hydrogen chloride in.

The US EPA has not classified HCl with respect to potential carcinogenicity (US EPA, 1995).

Hydrogen Chloride is not carcinogenic; therefore it is only being evaluated as a non- carcinogenic substance in this assessment.

4.2 Susceptible Populations

People working in occupations in which hydrogen chloride is used have the highest risk of being exposed to this compound (ATSDR, 2002). Exposure of the general population is minimal (ATSDR, 2002).

4.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

4.3.1 Oral Exposure

4.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, hydrogen chloride is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral toxicological reference value has not been selected.

4.3.1.2 Cancer Toxicity Reference Values

Hydrogen chloride is not classified as a carcinogenic substance; therefore, a carcinogenic oral toxicological reference value has not been selected.

4.3.2 Inhalation Exposure

4.3.2.1 Non-Carcinogenic Toxicity Reference Values

4.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

The 1-hour exposure limit used in this risk assessment was selected from Alberta Environment (AENV). AENV (2007) derived an AAQO benchmark (1-hour) of 75 µg/m^3 for hydrogen chloride, This value is based on health effects with no additional information regarding benchmark derivation provided.

A 24-hour exposure benchmark of 690 µg/m^3 for hydrogen chloride was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

4.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The US EPA (1995) has developed an RfC of 20 µg/m^3 for hydrogen chloride based on a study conducted by Albert et al. (1982), and discussed by Sellakumar et al. (1985). 100 male Sprague-Dawley rats were exposed to 15,000 µg/m^3 hydrogen chloride (HCl) for 6 hours/day, 5 days/week for their lifetimes. All animals were observed daily, weighed monthly, and allowed to die naturally or were sacrificed when moribund. Complete necropsy was performed on all animals, with particular attention given to the respiratory tract. Histologic sections were prepared from the nasal cavity, lung, trachea, larynx, liver, kidneys, testes and other organs where gross pathological signs were present; however, Sellakumar et al. (1985) did not discuss histopathological events in organs other than the respiratory tract. HCl-exposed animals showed no differences in body weights or survival when compared with air controls. The researchers indicated 62/99 exposed animals with epithelial or squamous hyperplasia in the nasal mucosa vs. 51/99 in the concurrent control group. Incidence of squamous metaplasia was 9 and 5 in the exposed and control rats, respectively. There was a 24% incidence of hyperplasia of laryngeal-tracheal segments in exposed rats vs. 6% in the controls. Based on the results, the 15,000 µg/m^3 concentration was considered a LOAEL. This LOAEL was adjusted for human equivalency and resulted in a LOAEL(HEC) of 6100 µg/m^3 (US EPA, 1995). The US EPA (1995) applied a cumulative uncertainty factor of 300 (a factor of 3 for interspecies differences, 10 for intraspecies extrapolations, and 10 to extrapolate from a LOAEL to a NOAEL) to arrive at a final RfC of 20 µg/m^3 for hydrogen chloride.

4.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Hydrogen chloride is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

4.4 Bioavailability

In this risk assessment, hydrogen chloride is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that hydrogen chloride is completely absorbed (i.e. absorption factor is 1).

4.5 Conclusion

The following tables present Hydrogen Chloride TRVs selected for use in this risk assessment.

Table 4-1 Hydrogen Chloride Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Hydrogen Chloride	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 4-2 Hydrogen Chloride Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Hydrogen Chloride	1-Hour	75	Health Based	Benchmark	AENV AAQO, 2007
	24-Hour	20	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	20	Hyperpasia of the nasal mucosa larynx and trachea	RfC	US EPA, 1995

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$

4.6 References

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ATSDR (Agency for Toxic Substances and Disease Registry). 2002. ToxFAQs for Hydrogen Chloride. April 2002.

MOE (Ontario Ministry of the Environment). 2008. Summary of O.REG. 419/05 Standards and Point of Impingement Guidelines & Ambient Air Quality Criteria (AAQCs). Standards Development Branch. Ontario Ministry of the Environment.

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US EPA (United States Environmental Protection Agency). 1995. Integrated Risk Information System (IRIS) Database, Hydrogen Chloride (CASRN 7647-01-0). Available on-line at: http://www.epa.gov/ncea/iris/subst/0396.htm

5.0 HYDROGEN FLUORIDE

Hydrogen fluoride is a naturally-occurring gas that is very irritating to the skin, eyes, and respiratory tract (ATSDR, 2003). At very high levels it can also damage the heart (ATSDR, 2003). It dissolves in water to form hydrofluoric acid.

5.1 Assessment of Carcinogenicity

Epidemiological studies have not demonstrated an association between fluoride in drinking water and an increased risk of cancer (US EPA, 1989). Increased rates of cancer have been observed in workers involving possible fluoride exposure; however, these situations involved mixed exposures to several chemicals and hydrogen fluoride could not be specifically implicated as the cause of the cancers (ATSDR, 2003). US EPA has not classified hydrogen fluoride with respect to potential carcinogenicity.

For the purpose of this risk assessment hydrogen fluoride will be evaluated as a non-carcinogenic substance.

5.2 Susceptible Populations

Existing data indicate that the elderly, people with deficiencies of calcium, magnesium, and/or vitamin C, and people with cardiovascular and kidney problems may be unusually susceptible to the toxic effects of fluoride and its compounds; however, these effects would not be expected at typical ambient exposure levels (i.e., 1 ppm) (ATSDR, 2003).

5.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

5.3.1 Oral Exposure

5.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, hydrogen fluoride is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

5.3.1.2 Carcinogenic Toxicity Reference Values

Hydrogen fluoride is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

5.3.2 Inhalation Exposure

5.3.2.1 Non-Carcinogenic Toxicity Reference Values

5.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

The Texas Commission on Environmental Quality (TCEQ, 2008) has recently updated its 1-hour value for hydrogen fluoride to 25 µg/m^3 (Lee, 2009). The updated value from the TCEQ is based on an American Conference of Industrial Hygienists (ACGIH) TLV-Ceiling of 2455 µg/m^3. The TLV-ceiling value is based on repeated experimental human exposures to hydrogen fluoride 6 hours per day for 10 to 50 days. Redness of the skin and some burning and irritation of the nose and eyes were noted at approximately 2455 µg/m^3 noted as the LOAEL (Largent, 1961). The short-term ESL was derived by adding a safety factor of 100 to the LOAEL of 2455 µg/m^3 without any exposure duration adjustments (Lee, 2009). Furthermore, this current 1-hour health-based value from TCEQ is consistent with the ATSDR Acute (1-hr) Minimal Risk Level of 16 µg/m^3 (ATSDR, 2003). TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

CalEPA (2008) has established an acute 1-hour inhalation REL of 240 µg/m^3 based on a study conducted by Lund et al. (1997). 20 healthy male volunteers were exposed in a chamber to constant hydrogen fluoride concentrations that ranged from 200 to 5200 µg/m³. The volunteers were asked to report itching or soreness of the eyes and upper airways and to grade these subjective responses on a scale from 1 to 5 with a standardized questionnaire. Lower airway symptoms of chest tightness and soreness, coughing, expectoration, and wheezing were similarly reported and graded by the volunteers. For the purposes of analysis the authors grouped the subjects into exposure groups of 200-600 µg/m³ (low), 700-2400 µg/m³ (medium), and 2500-5200 µg/m³ (high). Lower airway scores were not significantly different for any concentration range. The upper airway and total symptom score was significantly increased at the end of exposure for the highest exposure range and for all exposures when considered as a single group. The total symptom score was also significantly increased at the end of exposure for the lowest concentration range although individual scores for eye irritation, upper respiratory irritation, and lower respiratory irritation were not significantly different comparing before and after exposure. 2400 µg/m³ was considered to be a NOAEL and the range of 2500-5200 µg/m³ was deemed to be a LOAEL for upper airway irritation. CalEPA (2008) applied an uncertainty factor of 10 (for the protection of sensitive populations) to the NOAEL to arrive at an REL of 240 µg/m^3.

The TCEQ (2008) 1-hour value of 25 µg/m^3 was selected for use in this risk assessment because it is the most conservative value.

5.3.2.1.2 Chronic Inhalation Toxicity Reference Values

No 24-hour TRV for hydrogen fluoride was identified for use in the risk assessment

5.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Hydrogen fluoride is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

5.4 Bioavailability

In this risk assessment, hydrogen fluoride is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that hydrogen fluoride is completely absorbed (i.e. absorption factor is 1).

5.5 Conclusion

The following tables present hydrogen fluoride TRVs selected for use in this risk assessment.

Table 5-1 Hydrogen Fluoride Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Hydrogen Fluoride	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 5-2 Hydrogen Fluoride Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Hydrogen Fluoride	1-Hour	25	Redness of the skin and some burning and irritation of the nose and eyes	Benchmark	TCEQ, 2008
	24-Hour	NV			
	Annual Average	NV			

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$), NV – No Value

5.6 References

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Largent, E.J. 1961. Fluorosis. The Health Aspects of Fluorine Compounds. Ohio State University Press, Columbus, Ohio, pp34-48.

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MOE (Ontario Ministry of the Environment), 2004. Basic Comprehensive Certificates of Approval(Air) – User Guide. Version 2.0. Environmental Assessment & Approvals Branch. April 2004.

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6.0 NITROGEN OXIDES (NO_X) AND NITROGEN DIOXIDE (NO_2)

Nitrogen oxides (NO_x) are mixtures of gases composed of nitrogen and oxygen. Different nitrogen oxides have different physical properties. Major sources of NO_x in the air are the exhaust of motor vehicles, the burning of coal, oil and natural gas, and processes such as arc welding, electroplating and dynamite blasting (ATSDR, 2002). Nitrogen oxides are also produced commercially. They can be used in the production of nitric acid, lacquers, dyes, rocket fuels, and explosives (ATSDR, 2002).

NOx causes a wide variety of health and environmental impacts because of various compounds and derivatives in the family of nitrogen oxides, including nitrogen dioxide (NO_2), nitric acid, nitrous oxide, nitrates, and nitric oxide. Low concentrations of NO_x in the air can irritate the eyes, nose, throat and lungs as well as causing shortness of breath, fluid build-up in the lungs (after 1 or 2 days of exposure), tiredness and nausea (ATSDR, 2002). Inhalation of high doses of NO_x can cause burning, spasms and swelling of the throat and upper respiratory tract, reduced oxygenation of body tissues, cause a build-up of fluid in the lungs and result in possible death (ATSDR, 2002).

Dermal contact with NO_x (gas or liquid) can cause severe burns (ATSDR, 2002).

Nitrogen dioxide can irritate the lungs and lower resistance to respiratory infections such as influenza. The effects of short-term exposure are still unclear, but continued or frequent exposure to concentrations that are typically much higher than those normally found in the ambient air may cause increased incidence of acute respiratory illness in children.

Ambient air quality guidelines/objectives are generally specific to nitrogen dioxide (NO_2).

6.1 Assessment of Carcinogenicity

Nitrogen oxides are not classified as carcinogenic.

6.2 Susceptible Populations

Two general groups in the population may be more susceptible to the effects of NO_2 exposure than other individuals: persons with pre-existing respiratory disease and children 5 to 12 years old (US EPA, 2008). Individuals in these groups appear to be affected by lower levels of NO_2 than individuals in the rest of the population. Asthmatics are considered to be one of the groups most responsive to NO_2 exposure (US EPA, 2008). Patients with chronic obstructive pulmonary disease (COPD) constitute another subpopulation that is potentially susceptible to NO_2 exposure, as are immunocompromised individuals (e.g., individuals suffering from the human immunodeficiency virus and cancer patients being treated with chemotherapy) (US EPA, 2008).

6.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

6.3.1 Oral Exposure

6.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, NO_2 is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

6.3.1.2 Cancer Toxicity Reference Values

Nitrogen dioxide is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

6.3.2 Inhalation Exposure

6.3.2.1 Non-Carcinogenic Toxicity Reference Values

6.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

1-hour and 24-hour exposure limits used in this risk assessment were selected from the Ontario Ministry of the Environment (MOE). The 1-hour AAQC benchmark of 400 µg/m^3 and 24-hour AAQC benchmark of 200 µg/m^3 were derived by the MOE (2008). These acute inhalation values were based on occupational health effects (respiratory irritation) with appropriate safety factors applied (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

Health Canada's National Ambient Air Quality Objectives also provide maximum acceptable 1-hour and 24-hour levels of NO_2 of 400 and 200 µg/m^3, respectively, which are equivalent to those criteria established by the Ontario Ministry of the Environment (Health Canada, 2006). These values are based on respiratory irritation with no additional information regarding benchmark derivation provided.

6.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada's National Ambient Air Quality Objectives provide a maximum desirable annual level of nitrogen dioxide of 60 µg/m^3. This value has been selected for this risk assessment. It is an effects-based level that is also reflective of technological, economic and societal considerations. Furthermore, it represents the air quality management goal for the protection of the general public and the environment of Canada (Health Canada, 2006). No further information regarding the derivation of this value is available.

The U.S. EPA National Ambient Air Quality Standards provide an equivalent maximum acceptable annual level of NO_2 of 100 µg/m^3 (US EPA, 2009). No further information regarding the derivation of this value is available.

6.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Nitrogen dioxide is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

6.4 Bioavailability

In this risk assessment, NO_2 is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that nitrogen dioxide is completely absorbed (i.e., absorption factor is 1).

6.5 Conclusion

The following tables present NO_x TRVs selected for use in this risk assessment.

Table 6-1 Nitrogen Oxides Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Nitrogen Oxides	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 6-2 Nitrogen Oxides Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Nitrogen Oxides	1-Hour	400	Respiratory Irritation	Benchmark	MOE AAQC, 2008
	24-Hour	200	Respiratory Irritation	Benchmark	MOE AAQC, 2008
	Annual Average	60	Health Based	Benchmark	Health Canada, 2006

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)

6.6 References

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. ToxFAQs for Nitrogen Oxides. April 2002.

Health Canada. 2006. Regulations Related To Health And Air Quality. Health Canada. Available at: http://www.hc-sc.gc.ca/ewh-semt/air/out-ext/reg_e.html.

MOE (Ontario Ministry of the Environment). 2008. Summary of O.REG. 419/05 Standards and Point of Impingement Guidelines & Ambient Air Quality Criteria (AAQCs). Standards Development Branch. Ontario Ministry of the Environment.

Szakolcai, A. 2009. Personal Communication, Akos Szakolcai. Coordinator, Air Standards Risk Management - Human Toxicology and Air Standards Section. Ontario Ministry of the Environment.

US EPA (United States Environmental Protection Agency). 2008. Risk and Exposure Assessment to Support the Review of the National Ambient Air Quality Standards for Nitrogen Dioxide:

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US EPA (United States Environmental Protection Agency). 2009. National Ambient Air Quality Standards (NAAQS). United States Environmental Protection Agency. Air and Radiation. February 2009. Available at: http://epa.gov/air/criteria.html

7.0 PARTICULATE MATTER (TSP, $PM_{2.5}$ AND PM_{10})

Total suspended particulate (TSP) or particulate matter (PM) consists of minute solid or liquid particles that remain suspended in air and can be inhaled into the respiratory system. Particles are not defined on the basis of their chemical composition, and may include a broad range of chemical species. Particles in the atmosphere have been characterized according to size mainly because of the different health effects from particles of different diameters. The smaller the particle size, the farther the particle can penetrate the lungs. Particulate matter in the atmosphere, as described in the current assessment, is composed of three groups: TSP, inhalable coarse particles (PM_{10} and $PM_{2.5-10}$) and fine or respirable particles ($PM_{2.5}$). It is important to recognize that TSP contains all particles smaller than 44 microns; PM_{10} contains all particles with a mean aerodynamic diameter of less than 10 microns; and $PM_{2.5}$ contains particles smaller than 2.5 microns as well as ultrafine PM of less than 0.1 micron (US EPA, 2004).

Particulate matter can cause serious health problems when fine particles get deep into the lungs. Health effects include increased respiratory symptoms (irritation of airways, coughing , difficulty breathing), decreased lung function, aggravated asthma, chronic bronchitis, irregular heartbeat, nonfatal heart attacks, and premature death in people with heart or lung disease (US EPA, 2008).

7.1 Assessment of Carcinogenicity

The US EPA and Health Canada have not classified particulate matter (PM) with respect to carcinogenicity. Relatively few studies are available that examine the effects of long term or chronic exposure on health end points. Available studies indicate that long term exposures (16 to 20 years) were associated with increases in mortality, respiratory disease symptoms, decrements in lung function and, possibly, with lung cancer (Health Canada, 1998). However, the effects on mortality cannot be ascribed with certainty to a true chronic effect, since they could equally be the result of cumulative effects of daily variations in PM. Moreover, the association with lung cancer was weak by comparison with other lifestyle factors such as smoking (Health Canada, 1998). Accordingly, particulate matter has been assessed as a non-carcinogen in this risk assessment.

7.2 Susceptible Populations

Epidemiological studies indicate that the elderly, children, and people with chronic lung disease, influenza, or asthma, are especially sensitive to the effects of particulate matter (Health Canada, 1998).

7.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

7.3.1 Oral Exposure

7.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, particulate matter is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

7.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, particulate matter is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

7.3.2 Inhalation Exposure

7.3.2.1 Non-Carcinogenic Toxicity Reference Values

7.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Epidemiological studies have indicated that there is little evidence that the dose-response curve for PM includes a threshold (Health Canada, 1998). The lack of a threshold at low concentrations suggests that it would be difficult to identify a level at which no adverse effects would be expected to occur as a result of exposure to particulate matter. Although 1-hour exposure limits have not been specified by government agencies, 24-hour exposure limits for all manner of particulate matter have been specified and selected for use in this risk assessment.

Total Suspended Particulates

Health Canada's National Ambient Air Quality Objectives provide a maximum acceptable annual level of total particulate matter of 120 $\mu g/m^3$. It is a level that is based on the critical effect of respiratory irritation and is also reflective of technological, economic and societal information. Furthermore, it represents the air quality management goal for the protection of the general public and the environment of Canada (Health Canada, 2006). No further information regarding the derivation of this value is available.

The Alberta Ambient Air Quality Objectives and Guidelines (2009) provide a 24-hour average for total particulate matter of 100 $\mu g/m^3$. This value is based on pulmonary effects but with no additional information regarding benchmark derivation provided.

As there is no information available regarding the derivation or basis of the Alberta (2007) 24-hour guideline, the Health Canada National Ambient Air Quality Objective of 120 $\mu g/m^3$ has been selected for this risk assessment even though it is slightly greater than the Alberta value.

$PM_{2.5}$

A number of government organizations have established health-based reference levels for fine particulate matter.

The CEPA/FRAC Working Group (Health Canada) recommended a 24-hour average reference level of 15 $\mu g/m^3$ for $PM_{2.5}$ on the basis of several key epidemiological studies (Health Canada, 1998). The reference level estimates the lowest ambient PM level at which statistically significant increases in health responses can be detected based upon available data and current technology. The reference level should not be interpreted as thresholds of effects, or level at which impacts do not occur (Health Canada, 1999).

The US EPA (2009) established a health-based 24-hour air quality standard of 35 μg/m^3 for $PM_{2.5}$. This is a primary standard, intended to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly.

The Canada Wide Standard (CCME, 2006) for 24-hour $PM_{2.5}$ is 30 μg/m^3. This Canada-Wide Standard is based on 98th percentile ambient measurements conducted annually and averaged over 3 years. The Ontario Ministry of the Environment (MOE, 2008) Ambient Air Quality Criteria is also 30 μg/m^3 for $PM_{2.5}$ and is based on the critical effect of respiratory irritation.

As the facility is to be built in Ontario, a reference exposure limit of 30 μg/m^3 has been selected for further use in this risk assessment, as per the Canada-Wide Standard and the Ontario Ministry of the Environment Ambient Air Quality Criteria.

PM_{10}

Much like fine particulate matter, many of the same government agencies have also established benchmarks for inhalable coarse particulate matter. The CEPA/FRAC Working Group (Health Canada) recommended a 24-hour average reference level of 25 μg/m^3 for PM_{10} on the basis of several key epidemiological studies (Health Canada, 1998). The reference level estimates the lowest ambient PM level at which statistically significant increases in health responses can be detected based upon available data and current technology. The reference level should not be interpreted as thresholds of effects, or level at which impacts do not occur (Health Canada, 1999).

The US EPA (2009) established a 24-hour health-based air quality standard for PM_{10} of 150 μg/m^3. Finally, the Ontario Ministry of the Environment (MOE, 2008) Ambient Air Quality Criteria is 50 μg/m^3 for PM_{10}, is based on based on cardiopulmonary effects and 24-hour averages.

As the facility is to be built in Ontario, a reference exposure limit of 50 μg/m^3 has been selected for further use in this risk assessment, as per the Ontario Ministry of the Environment Ambient Air Quality Criteria.

7.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Total Suspended Particulates

Health Canada's National Ambient Air Quality Objectives provide a maximum desirable annual level of total particulate matter of 60 μg/m^3. It is an effects-based level that is also reflective of technological, economic and societal information. Furthermore, it represents the air quality management goal for the protection of the general public and the environment of Canada (Health Canada, 2006). No further information regarding the derivation of this value is available. This value was selected for further use in the risk assessment.

$PM_{2.5}$

A chronic exposure limit was not identified for inhalable fine particulate matter.

PM_{10}

A chronic exposure limit was not identified for inhalable coarse particulate matter.

7.3.2.2 Cancer Inhalation Toxicity Reference Values

In this risk assessment, particulate matter is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

7.4 Bioavailability

In this risk assessment, particulate matter is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that particulate matter is completely absorbed (i.e. absorption factor is 1).

7.5 Conclusion

The following tables present Particulate Matter (TSP, $PM_{2.5}$, and PM_{10}) TRVs selected for use in this risk assessment.

Table 7-1 Particulate Matter Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Particulate Matter (TSP, $PM_{2.5}$, and PM_{10})	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 7-2 Particulate Matter Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
TSP	1-Hour	NV			
	24-Hour	120	Health-Based	Benchmark	Health Canada, 2006
	Annual Average	60	Health-Based	Benchmark	Health Canada, 2006
$PM_{2.5}$	1-Hour	NV			
	24-Hour	30	Health-Based	Benchmark	CCME, 2006
	Annual Average	NV			
PM_{10}	1-Hour	NV			
	24-Hour	50	Health-Based	Benchmark	MOE AAQC, 2005
	Annual Average	NV			

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , NV – No Value

7.6 References

Alberta Environment. 2009. Alberta Ambient Air Quality Objectives and Guidelines. Available at http://environment.gov.ab.ca/info/library/5726.pdf.

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US EPA (United States Environmental Protection Agency). 2008. Particulate Matter: Health and Environment. U.S. Environmental Protection Agency. Updated May 2007. Available at: http://www.epa.gov/particles/health.html

US EPA (United States Environmental Protection Agency). 2009. National Ambient Air Quality Standards (NAAQS). United States Environmental Protection Agency. Air and Radiation. February 2009. Available at: http://epa.gov/air/criteria.html

8.0 SULFUR DIOXIDE

Sulfur dioxide is a colorless gas with a pungent odor. It is a liquid when under pressure, and it dissolves in water very easily (ATSDR 1999). The burning of coal and oil at power plants or from copper smelting can result in the presence of sulfur dioxide in the air. In nature, sulfur dioxide can be released to the air from volcanic eruptions (ATSDR 1999).

Inhalation exposure to high levels of sulfur dioxide can be life threatening. Inhalation can lead to the burning of the nose and throat, breathing difficulties and severe airway obstruction (ATSDR 1999). Animal studies have shown that inhalation of high concentrations of sulfur dioxide can cause decreased respiration, inflammation of the airways, and destruction of lung tissue (ATSDR 1999). Chronic exposure to persistent levels of sulfur dioxide may also affect lung function (ATSDR 1999).

8.1 Assessment of Carcinogenicity

There are no studies that clearly show carcinogenic effects of sulfur dioxide in people (ATSDR, 1998). IARC (2006) has classified SO_2 as Group 3, not classifiable to human carcinogenicity.

Sulphur dioxide is not carcinogenic; therefore it is only being evaluated as a non- carcinogenic substance in this assessment.

8.2 Susceptible Populations

Asthmatics have been show to be sensitive to the respiratory effects of low concentrations of sulfur dioxide (ATSDR 1999) with exercising asthmatics recognized as the most susceptible group to SO_2 inhalation (ATSDR, 1998). Elderly adults with pre-existing respiratory or cardiovascular disease may be susceptible to the increased risk of mortality associated with acute-duration exposure to SO_2 (ATSDR, 1998). Children may be particularly susceptible to increased frequencies of respiratory illness following chronic-duration exposure to SO_2 (ATSDR, 1998).

8.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

8.3.1 Oral Exposure

8.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, SO_2 is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

8.3.1.2 Cancer Toxicity Reference Values

SO_2 is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

8.3.2 Inhalation Exposure

8.3.2.1 Non-Carcinogenic Toxicity Reference Values

8.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

1-hour and 24-hour exposure limits used in this risk assessment were selected from the Ontario Ministry of the Environment (MOE). The 1-hour AAQC benchmark of 690 µg/m^3 and 24-hour AAQC benchmark of 275 µg/m^3 were derived by the MOE (2008). These acute inhalation values were based on occupational health effects with appropriate safety factors applied (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

Health Canada's National Ambient Air Quality Objectives provide maximum desirable 1-hour and 24-hour levels for SO_2 of 875 and 300 µg/m^3, respectively, which are both less stringent than those criteria established by the Ontario Ministry of the Environment (Health Canada, 2006). These values are based on health effects with no additional information regarding benchmark derivation provided.

Although there is no 1-hour value, the US EPA National Ambient Air Quality Standards provide a maximum acceptable 24-hour level of sulfur dioxide of 370 µg/m^3 (US EPA, 2009). No further information regarding the derivation of this value is available.

MOE (2008) 1-hour and 24-hour values of 690 µg/m^3 and 275 µg/m^3, respectively, were selected for use in this risk assessment.

8.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada's National Ambient Air Quality Objectives provide a maximum desirable annual level of SO_2 of 29 µg/m^3. It is an effects-based level that is also reflective of technological, economic and societal information. Furthermore, it represents the air quality management goal for the protection of the general public and the environment of Canada (Health Canada, 2006). No further information regarding the derivation of this value is available.

The U.S. EPA National Ambient Air Quality Standards provide a maximum acceptable annual level of SO_2 of 79 µg/m^3 (US EPA, 2009). No further information regarding the derivation of this value is available.

The Health Canada (2006) value of 29 µg/m^3 was selected for use in this risk assessment.

8.3.2.2 Cancer Inhalation Toxicity Reference Values

SO_2 is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

8.4 Bioavailability

In this risk assessment, SO_2 is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that sulfur dioxide is completely absorbed (i.e. absorption factor is 1).

8.5 Conclusion

The following tables present SO_2 TRVs selected for use in this risk assessment.

Table 8-1 Sulfur Dioxide Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Sulfur Dioxide	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE- Not Evaluated

Table 8-2 Sulfur Dioxide Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Sulfur Dioxide	1-Hour	690	Health Based	Benchmark	MOE AAQC, 2008
	24-Hour	275	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	29	Health Based	Benchmark	Health Canada, 2006

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)

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NON-CRITERIA AIR CONTAMINANTS

9.0 1,1-DICHLOROETHENE

1,1-Dichloroethene (1,1-DCE) is a man-made chemical that does not occur naturally. The primary use of 1,1-DCE is in the production of polymers used in food packaging, as well as in the textile industry (ATSDR, 1994). 1,1-DCE is also a degradation product of 1,1,1-trichloroethane, tetrachloroethylene, 1,1,2-trichloroethene and 1,1-dichloroethane (US EPA, 2002).

Chronic inhalation of low levels of 1,1-DCE can damage the nervous system, liver and lungs. Animal studies have shown birth defects in the offspring of exposed individuals. Ingestion of 1,1-DCE has also resulted in damage to the liver, kidneys and lungs in animal studies. Dermal contact can cause irritation of the skin and eyes (ATSDR, 1995).

9.1 Assessment of Carcinogenicity

The US EPA (2002) lists 1,1-DCE as group C, a possible human carcinogen. This grouping is based on the induction of several tumor types in rats and mice treated by gavage and lung papillomas in mice after topical application

The IARC lists 1,1-DCE as a Group 3 chemical, describing it as not classifiable as to its carcinogenicity to humans (IARC, 1999).

For this risk assessment 1,1-DCE was evaluated as a non-carcinogen.

9.2 Susceptible Populations

Based on available literature, populations with unusual susceptibility to the health effects of 1,1-DCE were not identified; however, the following groups of people should be cautioned against exposure to 1,1-DCE: the very young, the elderly, the pregnant, those ingesting acetaminophen, those ingesting large amounts of alcohol, people using phenobarbital, those receiving thyroid replacement therapy or those who are hyperthyroid, people who are fasting as well as those with cardiac, hepatic, renal , and central nervous system dysfunctions (ATSDR, 1994).

9.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

9.3.1 Oral Exposure

9.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, 1,1-DCE is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

9.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, 1,1-DCE is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

9.3.2 Inhalation Exposure

9.3.2.1 Non-Carcinogenic Toxicity Reference Values

9.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 210 µg/m^3 for 1,1-DCE was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This is based on centrilobular swelling in liver in mice as the critical effect. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure limit was not identified for 1,1-DCE.

9.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The US EPA (2002) provides a reference concentration (RfC) of 200 µg/m^3. The basis is a rat chronic inhalation study conducted by Quast et al. (1986). This 2-year chronic study exposed 48 Sprague-Dawley rats (6-7 weeks old)/sex/group to 0, 50, 100 or 200 ppm 1,1-DCE in their drinking water. The time-weighted average exposures over the 2-years were 7, 10, or 20 mg/kg-day for males and 9, 14, or 30 mg/kg-day for females. The only treatment-related effect that was observed in rats at any treatment level was minimal hepatocellular midzonal fatty change and hepatocellular swelling. These changes were only statistically significant for male rats at 200ppm (20 mg/kg-day). For female rats, minimal hepatocellular midzonal fatty change was significant for the 100 and 200ppm treatment groups (14 and 30 mg/kg-day) and minimal hepatocellular swelling was significant for all treatment groups. The study established a human equivalent LOAEL of 53,200 µg/m^3 and a human equivalent NOAEL of 17,700 µg/m^3. From this NOAEL, a benchmark concentration was derived and the 10% lower bound confidence limit on the human equivalent of the benchmark concentration (BMCL10 HEC) was estimated at 6900 µg/m^3 for liver toxicity (fatty change). An uncertainty factor of 30, (3 for interspecies variability and 10 for intraspecies variability), was then applied to the BMCL10 HEC. This value was selected for use in the risk assessment.

9.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, 1,1-DCE is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

9.4 Bioavailability

In this risk assessment, 1,1-DCE is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that 1,1-DCE is completely absorbed (i.e. absorption factor is 1).

9.5 Conclusion

The following tables present 1,1-DCE TRVs selected for use in this risk assessment.

Table 9-1 1,1-Dichloroethene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
1,1-Dichloroethene	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] Units: NE – Not Evaluated

Table 9-2 1,1-Dichloroethene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
1,1-Dichloroethene	1-Hour	210	Centrilobular swelling in liver	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	200	Liver Effects	RfC	US EPA, 2002

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value,

9.6 References

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10.0 1,1,1 -TRICHLOROETHANE

1,1,1-Trichloroethane is a synthetic chemical that does not occur naturally in the environment (ATSDR, 2006). It also is known as methylchloroform, methyltrichloromethane, trichloromethylmethane, and α-trichloromethane. Its registered trade names are chloroethene NU® and Aerothene TT®.

1,1,1-Trichloroethane had many industrial and household uses, including use as a solvent to dissolve other substances, such as glues and paints; to remove oil or grease from manufactured metal parts; and as an ingredient of household products such as spot cleaners, glues, and aerosol sprays (ATSDR, 2006). However, no 1,1,1-trichloroethane has been manufactured for domestic use in the United States since January 1, 2002 because it affects the ozone layer.

The health effects of 1,1,1-trichloroethane are dependent on the dose, route of exposure and duration of exposure. Inhalation of high levels of 1,1,1-trichloroethane can cause dizziness, lightheadedness, and loss of coordination, however these symptoms will pass when exposure ceases. Inhalation of higher levels of 1,1,1-trichloroethane can lead to unconsciousness, low blood pressure, and can cause the heart to stop beating (ATSDR, 2006b). Animal studies show that inhalation of very high levels of 1,1,1-trichloroethane damage the breathing passages, cause mild effects on the liver, and affect the nervous system (ATSDR, 2006b). Chronic effects of low level inhalation exposure to 1,1,1-trichloroethane are not known (ATSDR, 2006b).

There are no human studies regarding ingestion of 1,1,1-trichloroethane, however animal studies, using very high doses, indicate nervous system effects, mild liver damage, unconsciousness, and possible death (ATSDR, 2006b). Dermal contact with 1,1,1-trichloroethane may lead to some irritation of the skin. Animal studies suggest that repeated exposure of 1,1,1-trichloroethane to the skin may affect the liver, and in very large amounts, cause death. These effects only occurred when evaporation was prevented (ATSDR, 2006b).

10.1 Assessment of Carcinogenicity

Available information does not indicate that 1,1,1-trichloroethane causes cancer (ATSDR, 2006). The US EPA (2007) lists 1,1,1-trichloroethane as group D, not classifiable as to its human carcinogenicity. This grouping is based on a lack of data concerning carcinogenicity in humans and animals. The IARC lists 1,1,1-trichloroethane as a Group 3 chemical: describing it as not classifiable as to its carcinogenicity to humans. (IARC, 1999). Accordingly, 1,1,1-trichloroethane was assessed as a non-carcinogen in this assessment.

10.2 Susceptible Populations

Because 1,1,1-trichloroethane is associated with some cardiovascular effects, persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure (ATSDR, 2006). Although there are no data available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given period than healthy people, since the majority of a single dose is expired from the lungs (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous

waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population (ATSDR, 2006).

10.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

10.3.1 Oral Exposure

10.3.1.1 Non-Carcinogenic Toxicity Reference Values

US EPA (2007) derived an oral chronic TRV of 2 mg/kg-day based on a subchronic rat and mouse dietary study (NTP, 2000). Groups of 10 male and 10 female F344/N rats and B6C3F1 mice were fed diets containing 0 (untreated feed), 0 (placebo microcapsules), 5000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (> 99% pure), 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 290, 600, 1200, 2400, and 4800 mg/kg in male rats; 310, 650, 1250, 2500, and 5000 mg/kg in female rats; 850, 1770, 3500, 7370, and 15,000 mg/kg in male mice; and 1340, 2820, 5600, 11,125, and 23,000 mg/kg in female mice. All rats survived to study termination and no clinical signs of toxicity were observed. The dose of 10,000 ppm was established as the NOAEL and 20,000 ppm (3500 mg/kg-day) was established as the LOAEL based on decreases in terminal body weight greater than 10% of the control values. The female body weight loss data was then used to establish a benchmark dose ($BMDL_{10}$) of 2,155 mg/kg-day. This benchmark dose was then modified by an uncertainty factor of 1,000 (10 each for inter and intraspecies variability, 3 for database deficiencies, and 3 for subchronic to chronic extrapolation). This value was selected for the current assessment.

10.3.1.2 Carcinogenic Toxicity Reference Values

1,1,1-Trichloroethane is not classified as a carcinogenic substance; therefore, a carcinogenic oral toxicological reference value has not been selected.

10.3.2 Inhalation Exposure

10.3.2.1 Non-Carcinogenic Toxicity Reference Values

10.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

US EPA (2007) derived 1-hour and 24-hour acute inhalation TRVs of 9000 µg/m^3 and 6000 µg/m^3, respectively. These TRVs were derived from a human study involving inhalation exposure of 12 adult male chamber-exposed volunteers to 0, 950, and 1900 mg/m^3 for 3.5 hours, followed by neurobehavioural tests. Measurements of 1,1,1-trichloroethane in blood, performed after 0, 20, 60, 120, and 180 minutes of exposure, showed that levels rose rapidly during the first 20 minutes and began leveling off after about 120 minutes. None of the subjects complained of headache, discomfort, or nausea. Changes in neurobehavioral performance were observed at both exposure levels, including increased simple reaction time, increased choice reaction time, impaired performance in the tracking test, and improved performance in the Stroop test. Based on impaired psychomotor performance,

particularly increased reaction time, a LOAEL of 950 mg/m^3 was established for acute CNS effects. With respecto the 1-hour RfC, the LOAEL was modified by an uncertainty factor of 100 to account for intraspecies differences and extrapolation from a LOAEL to a NOAEL. The 24-hour TRV was extrapolated using physiologically based pharmacokinetic modeling to determine what concentration of 1,1,1-trichloroethane would result in the same internal (blood) concentration after twenty four hours of inhalation exposure.

10.3.2.1.2 Chronic Inhalation Toxicity Reference Values

US EPA (2007) also derived a chronic RfC of 5,000 µg/m^3 based on studies conducted by Quast et al. (1984; 1988) and McNutt et al. (1975).

Quast et al. (1984, 1988) exposed groups of 80 male and 80 female F344 rats and B6C3F1 mice to 0, 150, 500, or 1500 ppm (0, 820, 2730, or 8190 mg/m^3) production-grade (94%) 1,1,1-trichloroethane vapor for 6 hours/day, 5 days/week for 2 years. The study identified a NOAEL at the highest dose (8190 mg/m^3); when adjusted for continuous exposure (6 hours/day, 5 days/week in rats and mice), the NOAEL is equivalent to 1460 mg/m^3.

McNutt et al. (1975) chamber-exposed male CF-1 mice to 0, 250, or 1000 ppm (0, 1370, or 5460 mg/m^3) technical grade 1,1,1-trichloroethane continuously for up to 14 weeks. The study identified a NOAEL of 1370 mg/m^3 and a LOAEL of 5460 mg/m^3 for liver effects including increases in relative liver weight, triglycerides, and lesions visible by light microscopy.

Combining the studies, the NOAEL established by Quast et al. (1984; 1988) and the LOAEL established by McNutt et al. (1975) were carried forward by US EPA. Physiologically based pharmacokinetic modeling was used to determine a NOAEL (Human Equivalent Concentration) of 1,553 mg/m^3 which was modified with a cumulative uncertainty of 100 (3 for interspecies variability, 10 for interspecies variability, and 3 for database deficiencies), resulting in an RfC of 16,000 µg/m^3 . This value is higher than the acute and subchronic RfC values derived by US EPA, and consequently, the chronic RfC was set equivalent to the subchronic RfC (5 µg/m^3) so as not to exceed the limiting reference value derived for short-term exposure.This value was selected for chronic inhalation in the current assessment.

10.3.2.1.3 Carcinogenic Inhalation Toxicity Reference Values

1,1,1-Trichloroethane is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

10.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.2 (Health Canada, 2004). With regards to the inhalation pathway, it has been conservatively assumed that 1,1,1-trichloroethane is completely absorbed (i.e. absorption factor is 1).

10.5 Conclusion

The following tables present 1,1,1-trichloroethane TRVs selected for use in this risk assessment.

Table 10-1 1,1,1-Trichloroethane Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
1,1,1-Trichloroethane	Non-carcinogenic TRV	2	Reduced Body Weight	RfD	US EPA, 2007
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 10-2 1,1,1-Trichloroethane Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
1,1,1-Trichloroethane	1-Hour	9000	Neurological Effects	RfC	US EPA, 2007
	24-Hour	6000	Neurological Effects	RfC	US EPA, 2007
	Annual Average	5000	Liver Effects	RfC	US EPA, 2007

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)

10.6 References

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11.0 1,1,2-TRICHLOROETHYLENE (TCE)

1,1,2-Trichloroethylene (TCE) is a non-flammable, colourless liquid at room temperature with a somewhat sweet odour and a sweet burning taste. TCE is mainly used as a solvent to remove grease from metal parts but is also used to make other chemicals (ATSDR, 1997). TCE can be found in various household products including typewriter correction fluid, paint remover, adhesives, and spot removers. TCE is a breakdown product of tetrachlorethylene.

The effects of TCE on human health are dependent on the dose, the route of contact, and the duration of contact. Acute (short term) inhalation of low doses of TCE can cause headache, lung irritation, dizziness, poor coordination and difficulty concentrating (ATSDR, 2003). Acute inhalation of higher doses of TCE can lead to impaired heart function, unconsciousness and death. Chronic inhalation of TCE can cause nerve, kidney and liver damage (ATSDR, 2003).

Ingestion of large amounts of 1,1,2-trichloroethylene can cause nausea, liver damage, unconsciousness, impaired heart function, and death. Chronic ingestion of smaller doses of TCE may lead to liver and kidney damage, impaired immune function, and impaired fetal development in pregnant women. The extent of these effects, however, is not yet known (ATSDR, 2003).

Acute dermal contact with 1,1,2-trichloroethylene can cause skin irritation and rashes (ATSDR, 2003).

11.1 Assessment of Carcinogenicity

US EPA (2001) reports that cancer epidemiology for 1,1,2-trichloroethylene has grown in recent years with several large well-designed studies being published. Consistency across epidemiological studies is strongest for an association between TCE exposure and kidney cancer (US EPA, 2001). The US EPA does not currently have a consensus classification for the carcinogenicity of TCE; however, it is reassessing the potential carcinogenicity of TCE and at this time, a strong characterization as “highly likely to be carcinogenic to humans” is most appropriate, given the still-open questions about TCE’s cancer potential (US EPA, 2001). Health Canada (1996) classified 1,1,2-trichloroethylene (TCE) as a Group II - probable human carcinogen, via oral and inhalation exposure.

For this assessment, 1,1,2-trichloroethylene is being assessed as an inhalation carcinogen.

11.2 Susceptible Populations

People who have worked with TCE for long periods of time may develop an allergy towards it or become sensitive to its effects on the skin. As well, smokers may increase their risk of toxic effects from TCE. People who consume alcohol or who are treated with disulfide can both inhibit the metabolism of TCE and can cause it to accumulate in the bloodstream, which may in turn affect the nervous system. When TCE was used as an anesthetic or inhaled at high concentrations intentionally or occupationally, it was known to cause cardiac arrhythmias in some people; therefore, those with a history of cardiac rhythm disturbances may be more susceptible to high- level TCE exposure (ATSDR, 1997).

11.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

11.3.1 Oral Exposure

11.3.1.1 Non-Carcinogenic Oral Toxicity Reference Values

In this risk assessment, 1,1,2-trichloroethylene is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

11.3.1.2 Carcinogenic Oral Toxicity Reference Values

In this risk assessment, 1,1,2-trichloroethylene is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

11.3.2 Inhalation Exposure

11.3.2.1 Non-Carcinogenic Toxicity Reference Values

11.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 540 µg/m^3 for 1,1,2-trichloroethylene was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 54 mg/m^3 based on the following critical effects: CNS impairment; cognitive decrements; and renal toxicity. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 12 µg/m^3 for 1,1,2-trichloroethylene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

11.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Chronic inhalation exposure to 1,1,2-trichloroethylene has been shown to affect the central nervous system (ASTDR, 1997), as well as the liver and kidneys (RIVM, 2001). A tolerable concentration in air of 200 µg/m^3 was developed by RIVM (2001) from a LOAEL of 200 mg/m^3 that was adjusted by an uncertainty factor of 1000 (10 each for interspecies variability, intraspecies variability and use of a LOAEL). The LOAEL was derived from a 30-day, 24-hour mice inhalation exposure study, in which hepatotoxicity was observed at all doses (200, 405, 810, and 1620 mg/m^3). Although RIVM has derived a chronic inhalation value, data available and information on toxicity via the inhalation route are still considered limited, therefore this value is considered provisional.

An annual exposure limit of 54 µg/m^3 for 1,1,2-trichloroethylene was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 11.3.2.1.1. To derive a long-term ESL for 1,1,2-trichloroethylene, TCEQ further divides the short-term ESL by an additional safety factor of 10

11.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Health Canada (2004) has derived a cancer inhalation unit risk (UR) value of 6.14 x 10^{-7} $(\mu g/m^3)^{-1}$. This value is calculated from a Health Canada (1996) TC05 value of 82 mg/m^3. The TC_{05} was modified to a unit risk by dividing it into 0.05 [UR_{inh}= 0.05/TC_{05}] (Health Canada, 2004). The carcinogenic potency (TC_{05}) value of 82 mg/m^3 is derived from a study by Maltoni et al. (1986, 1988) in which male Sprague-Dawley rats were exposed to 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m^3) TCE for 7 hours/day, 5 days/week for 104 weeks. The authors observed an exposure-related increase in the incidence of tumours of the Leydig cells in the testis (6/135, 16/130, 30/130 and 31/130, or when corrected for the number of animals alive at the time of appearance of the first Leydig cell tumour - 62 weeks, 6/120, 16/114, 30/114 and 31/120). Based on a multistage model, a TC_{05} of 556 mg/m^3 was derived. This was further modified to account for the ratio of inhalation volume/body weight of humans aged 5 to 11 [(12 m^3/day)/27 kg] to rats [(0.11 m^3/day)/0.35 kg] and by time factors (7/24, 5/7). The resulting Health Canada (2004) inhalation unit risk of 6.14 x 10^{-7} $(\mu g/m^3)^{-1}$ was selected for this assessment.

11.4 Bioavailability

In this risk assessment, 1,1,2-trichloroethylene is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that 1,1,2-trichloroethylene is completely absorbed (i.e. absorption factor is 1).

11.5 Conclusion

The following tables present 1,1,2-trichloroethylene TRVs selected for use in this risk assessment.

Table 11-1 1,1,2-Trichloroethylene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
1,1,2-Trichloroethylene	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] NE – Not Evaluated

Table 11-2 1,1,2-Trichloroethylene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
1,1,2-Trichloroethylene	1-Hour	540	CNS impairment; cognitive decrements; and renal toxicity	Benchmark	TCEQ ESL, 2008
	24-Hour	12	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	54	CNS impairment; cognitive decrements; and renal toxicity	Benchmark	TCEQ ESL, 2008
	Carcinogenic Annual Average	6.14×10^{-7}	Cancer	UR	Health Canada, 2004

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$

NE – Not Evaluated

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12.0 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).

Health effects of 1,2,4-trichlorobenzene include eye, skin, and respiratory tract irritation with short-term exposure, and potential liver effects with chronic exposure (ILO, 2003).

12.1 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. Accordingly, 1,2,4-trichlorobenzene was assessed as a non-carcinogen in this assessment.

12.2 Susceptible Populations

No particular susceptible populations are identified by the US EPA.

12.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

12.3.1 Oral Exposure

12.3.1.1 Non-Carcinogenic 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. This TDI is based on a 13-week study undertaken by Cote et al. (1988). Rats were exposed to 1,2,4-trichlorobenzene at 0.07 to 146 mg/kg bw-day in the diet. 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. 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 chronic toxicity and carcinogenicity).

The US EPA (1996) provides a non-carcinogenic oral reference dose (RfD) of 0.01 mg/kg-day. The derivation of the oral RfD is based on a multigeneration reproductive study on rats carried out by Robinson et al. (1981). Male and female progeny were administered 0, 25, 100 or 400 ppm of 1,2,4-trichlorobenzene in their drinking water. A LOAEL was derived from a significant increase (11% in males, 13% in females) in adrenal gland weights observed in the 400-ppm (53.6 mg/kg-day) groups of

males and females. A NOAEL of 100 ppm (14.8 mg/kg-day) was derived based on the absence of effects. This NOAEL was modified by 1000 to account for sensitive subpopulations (10), lack of chronic studies (10) and extrapolation from laboratory studies to humans (10).

RIVM (2001) provides a tolerable daily intake (TDI) of 0.008 mg/kg-day, based on the same Cote et al. (1988) study used by Health Canada (2004b). An identical NOEL of 7.8 mg/kg-day was established and modified by an uncertainty factor of 1000 (rather than 5000 as used by Health Canada).

The Health Canada (2004b) value was used in this assessment because it is based on more recent data than the US EPA study and is more conservative than the US EPA and RIVM values.

12.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, 1,2,4-trichlorobenzene is not being evaluated as a carcinogen; therefore, a carcinogenic oral toxicological reference value has not been selected.

12.3.2 Inhalation Exposure

12.3.2.1 Non-Carcinogenic Toxicity Reference Values

12.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 400 µg/m^3 for 1,2,4-trichlorobenzene was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 40 mg/m^3 based on eye and upper respiratory tract irritation. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 400 µg/m^3 for 1,2,4-trichlorobenzene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

12.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada (2004b) provides a tolerable concentration (TC) of 7 µg/m^3, which was used as the chronic inhalation TRV in this assessment. This value was derived based on subchronic inhalation exposure of rats, rabbits and beagle dogs to 1,2,4-trichlorobenzene (up to 742,000 µg/m^3) for 44 days. There was an increase in liver weight (rats and dogs) and kidney weight (rats) at 742,000 µg/m^3, and an increase in the excretion of porphyrins (rats) at 223,000 µg/m^3. A NOEL in rabbits was established at 742,000 µg/m^3, while a NOAEL in rats and a NOEL in dogs were established at 223,000 µg/m^3 (Kociba et al., 1981). The lowest NOAEL (223,000 µg/m^3) was adjusted based on an exposure time of 7 hours/day and 5 days/week. 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]. Finally, an uncertainty factor of 5,000 was applied (10 for intraspecies variation; 10 for interspecies variation; 10 for use of a subchronic study; and 5 for lack of adequate carcinogenicity and chronic toxicity data).

RIVM (2001) provides a provisional total concentration in air (pTCA) of 50 µg/m^3, derived based on a subchronic study of 1,2,4-trichlorobenzene in rats (Watanabe et al., 1977). Rats were exposed to 1,2,4-trichlorobenzene for 6 hours/day, 5 days/week for 3 months. A NOAEL of 22,300 µg/m^3 was established based on a slight, reversible increase in urinary porphyrins. An uncertainty factor of 500 was subsequently applied to obtain the pTCA.

The Health Canada (2004b) value was used for this assessment because it is based on more recent data and is more conservative than the RIVM value.

12.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, 1,2,4-trichlorobenzene is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

12.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.08 (Health Canada, 2004a). With regards to the inhalation pathway, it has been conservatively assumed that 1,2,4-trichlorobenzene is completely absorbed (i.e. absorption factor is 1).

12.5 Conclusion

The following tables present 1,2,4-trichlorobenzene TRVs selected for use in this risk assessment.

Table 12-1 1,2,4-Trichlorobenzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
1,2,4-Trichlorobenzene	Non-carcinogenic TRV	0.0016	Increases in the relative liver weight and absolute and relative kidney weight.	RfD	Health Canada, 2004b
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 12-2 1,2,4-Trichlorobenzene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
1,2,4-Trichlorobenzene	1-Hour	400	Eye and Upper Respiratory Tract Irritation	Benchmark	TCEQ ESL, 2008
	24-Hour	400	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	7	Increase in the excretion of porphyrins	RfC	Health Canada, 2004b

[a] Units: Non-carcinogenic COPC (µg/m^3)

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13.0 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).

1,2,4,5-Tetrachlorobenzene can affect human health through both inhalation exposure and ingestion. Short-term inhalation exposure can lead to coughing. Long-term exposure can result in liver impairment (ILO, 2003).

13.1 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. Accordingly, 1,2,4,5-tetrachlorobenzene was assessed as a non-carcinogen in this assessment.

13.2 Susceptible Populations

No susceptible populations were identified.

13.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

13.3.1 Oral Exposure

13.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.00021 mg/kg-day. This value was derived based on the results of a study conducted by the National Toxicological Program (NTP, 2001) in which subchronic doses (0, 30, 100, 300, 1,000 or 2,000 mg 1,2,4,5-tetrachlorobenzene/kg diet) 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. In lower dose groups, increased kidney and liver weights, histopathological effects in the kidney and thyroid and reduced levels of free thyroxin and total thyroxin in serum were observed. Based on histopathological effects in the thyroid, a NOAEL value of 2.1 mg 1,2,4,5-tetrachlorobenzene/kg-day was derived from this study, corresponding to an oral dose of 30 mg 1,2,4,5-tetrachlorobenzene/kg diet. Health Canada applied an uncertainty factor of 10,000 to account for intraspecies variation (10), interspecies variation (10), the subchronic duration of the 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 (1991) provides a non-carcinogenic oral TRV of 0.0003 mg/kg-day. This value was derived based on a study by Chu et al. (1984) which involved groups of weanling Sprague-Dawley rats (15 per sex) who were fed diets containing 0, 0.5, 5.0, 50, and 500 mg 1,2,4,5-tetrachlorobenzene/kg

diet for 13 weeks. Dose-related increases in the frequency and severity of kidney lesions for male rats were observed at levels of 5.0 mg 1,2,4,5-tetrachlorobenzene/kg diet and greater. The severity of effects was considered significant only at the 50 and 500 mg 1,2,4,5-tetrachlorobenzene/kg diet levels because of a high incidence of mild kidney lesions in the controls. Consequently, a LOAEL of 3.4 mg 1,2,4,5-tetrachlorobenzene/kg-day (50 mg 1,2,4,5-tetrachlorobenzene/kg diet) and a NOAEL of 0.34 mg 1,2,4,5-tetrachlorobenzene/kg-day (5.0 mg 1,2,4,5-tetrachlorobenzene/kg diet) were established. An uncertainty factor of 1000 was applied to the NOAEL to reflect both interspecies (10) and interspecies (10) variability to the toxicity of this chemical in lieu of specific data, and for extrapolation of a subchronic effect level to its chronic equivalent (10).

The Health Canada (2004b) value was used for this assessment because it is based on more recent data and is more conservative than the US EPA value.

13.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, 1,2,4,5-tetrachlorobenzene is not being evaluated as a carcinogen; therefore, a carcinogenic oral toxicological reference value has not been selected.

13.3.2 Inhalation Exposure

13.3.2.1 Non-Carcinogenic Toxicity Reference Values

13.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

No acute inhalation TRVs for 1,2,4,5-tetrachlorobenzene were identified for use in the risk assessment.

13.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The study team used the previously described Health Canada (2004b) TDI of 0.00021 mg/kg-day to calculate a chronic inhalation exposure limit based on route-to-route extrapolation. A body weight of 70.7 kg and an inhalation rate of 15.8 m^3/day were assumed for the purposes of the calculation. This resulted in a calculated chronic inhalation exposure limit of 0.94 µg/m^3.

13.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, 1,2,4,5-tetrachlorobenzene is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

13.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.1 (RAIS, 2006). With regards to the inhalation pathway, it has been conservatively assumed that 1,2,4,5-tetrachlorobenzene is completely absorbed (i.e. absorption factor is 1).

13.5 Conclusion

The following tables present 1,2,4,5-tetrachlorobenzene TRVs selected for use in this risk assessment.

Table 13-1 1,2,4,5-Tetrachlorobenzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
1,2,4,5-Tetrachlorobenzene	Non-carcinogenic TRV	0.00021	Histopathological changes in the thyroid.	RfD	Health Canada, 2004b
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 13-2 1,2,4,5-Tetrachlorobenzene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
1,2,4,5-Tetrachlorobenzene	1-Hour	NV			
	24-Hour	NV			
	Annual Average	0.94	Calculated route-to-route extrapolation from oral TDI.	RfD	Health Canada, 2004b

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value

13.6 References

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14.0 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). Animal studies have found that 1,2-dichlorobenzene can cause effects in the kidneys and blood. 1,2-Dichlorobenzene has been identified in at least 281 of the 1,662 National Priorities List sites identified by the U.S. Environmental Protection Agency (US EPA).

14.1 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). Two well-conducted animal studies have been conducted in which 1,2-dichlorobenzene was administered orally to rats and mice. No increased incidence of tumours was observed in these studies leading IARC to conclude that evidence in experimental animal studies suggest a lack of carcinogenicity. Inadequate evidence in humans was available (IARC, 1999). Accordingly, 1,2-dichlorobenzene was assessed as a non-carcinogen in this assessment.

14.2 Susceptible Populations

According to the ATSDR (2006), exposure to dichlorobenzenes mostly occurs from breathing indoors or workplace air.

14.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

14.3.1 Oral Exposure

14.3.1.1 Non-Carcinogenic 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. This Health Canada TDI has been derived on the basis of a NOEL of 60 mg/kg-day (tubular regeneration in the kidney at the next highest dose) derived in a long-term National Toxicology Program (NTP) bioassay conducted via oral exposure (NTP, 1983). In the study, groups of F344 rats and B6C3F1 mice (both sexes) were administered 0, 60, or 120 mg 1,2-dichlorobenzene/kg-day by gavage, 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-day. Based on the occurrence of these effects at higher doses, the NOEL of 60 mg/kg-day was derived. 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.

The US EPA (1991) provides a non-carcinogenic oral reference dose (RfD) of 0.09 mg/kg-day, based on a study 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 survival of high-dose (120 mg/kg-day) male rats was decreased compared with controls (19/50 vs. 42/50), but the difference appeared largely because of deaths from gavage error (4 controls vs. 20 high-dose). A statistically significant increase in renal tubular regeneration in high-dose male mice was observed (17/49) compared with the low-dose group (12/50) or the controls (8/48). There was no other evidence of treatment-related renal lesions in either species. The US EPA questioned the significance of the abovementioned effects, and consequently, established a NOAEL of 120 mg/kg-day. This NOAEL was then adjusted to 85.7 mg/kg-day to account for a gavage schedule of 5 days/week. To this value, an uncertainty factor of 1000 was applied for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10), uncertainty in the threshold for sensitive humans (10), and uncertainty because of the lack of studies assessing reproductive effects and adequate chronic toxicity in a second species (10).

The Agency for Toxic Substances and Disease Registry (ATSDR, 2006) provides a non-carcinogenic oral minimal risk level (MRL) of 0.3 mg/kg-day, based on the same previously described study that formed the basis of the US EPA RfD. However, ATSDR placed a higher degree of confidence in the observed effects and assigned a LOAEL of 120 mg/kg-day and a NOAEL of 60 mg/kg-day from the study. From this data, a $BMDL_{10}$ of 30.74 mg/kg-day was derived, to which an uncertainty factor of 100 was applied (factor of 10 for each of intraspecies and interspecies extrapolation).

Additionally, RIVM (2001) derived a TDI identical to that derived by Health Canada (2004b)

The Health Canada (2004b) value of 0.43 mg/kg-day was selected for use in this assessment because it is based on a TDI rather than a minimal risk level.

14.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, 1,2-dichlorobenzene is not being evaluated as a carcinogen; therefore, a carcinogenic oral TRV has not been selected.

14.3.2 Inhalation Exposure

14.3.2.1 Non-Carcinogenic Toxicity Reference Values

14.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure benchmark of 30,500 µg/m^3 for 1,2-dichlorobenzene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

A 24-hour exposure limit was not identified for 1,2-dichlorobenzene.

14.3.2.1.2 Chronic Inhalation Toxicity Reference Values

RIVM (2001) developed a provisional total concentration in air (pTCA) of 600 µg/m^3 based on five to seven month subchronic inhalation studies of various species (Hollingworth et al.,1958). A LOAEL of 560,000 µg/m^3 was established based on decreased spleen weights observed in male guinea pigs. Subsequently, a NOAEL of 290,000 µg/m^3, based on the absence of adverse effects, was adjusted to 60,000 µg/m^3 for duration (7 hours/day for 5 days/week) and an uncertainty factor of 100 was applied to establish this pTCA which was selected for use in this risk assessment.

14.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, 1,2-dichlorobenzene is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation TRV has not been selected.

14.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004a). With regards to the inhalation pathway, it has been conservatively assumed that 1,2-dichlorobenzene is completely absorbed (i.e. absorption factor is 1).

14.5 Conclusion

The following tables present 1,2-dichlorobenzene TRVs selected for use in this risk assessment.

Table 14-1 1,2-Dichlorobenzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
1,2-Dichlorobenzene	Non-carcinogenic TRV	0.43	Tubular regeneration in the kidney.	RfD	Health Canada, 2004b
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 14-2 1,2-Dichlorobenzene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
1,2-Dichlorobenzene	1-Hour	30,500	Health Based	Benchmark	MOE AAQC, 2008
	24-Hour	NV			
	Annual Average	600	NOAEL from various semichronic animal studies	RfC	RIVM, 2001

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value

14.6 References

ATSDR (Agency for Toxic Substances and Diseases Registry). 2006. ToxFAQs Summary for Dichlorobenzenes. Available at : http://www.atsdr.cdc.gov/tfacts10.html

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US EPA (United States Environmental Protection Agency). 1991. Integrated Risk Information System (IRIS): 1,2-dichlorobenzene. Available at: http://www.epa.gov/ncea/iris/subst/ 0408.htm

15.0 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 (PCP). 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 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).

Chlorophenols can have a number of toxic effects on human health. Humans exposed to chlorophenols as well as other chemicals through inhalation and dermal contact developed acne and mil liver injuries. Animal studies have concluded that ingestion of high levels of chlorophenols can affect the liver and immune system. Putting chlorophenols on the skin and eyes of animals can also cause injusry such as swelling, redness, and scabbling. This is more common with mono and dichlorophenols however (ATSDR, 1999).

15.1 Assessment of Carcinogenicity

According to IARC (1999), combined exposures to polychlorophenols or to their sodium salts, are possibly carcinogenic to humans (Group 2B); however given the lack of evidence for the purpose of this risk assessment 2,3,4,6-tetrachlorophenol was evaluated as a non-carcinogen.

15.2 Susceptible Populations

No particularly susceptible populations were identified.

15.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

15.3.1 Oral Exposure

15.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, 2,3,4,6-tetrachlorophenol is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

15.3.1.2 Cancer Toxicity Reference Values

2,3,4,6-Tetrachlorophenol is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

15.3.2 Inhalation Exposure

15.3.2.1 Non-Carcinogenic Toxicity Reference Values

15.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

No acute inhalation TRV for 2,3,4,6-tetrachlorophenol was identified for use in the risk assessment.

15.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada (2004) provides an oral TDI of 0.01 mg/kg-day for 2,3,4,6-tetrachlorophenol. This value is based on a study in which pregnant Sprague-Dawley rats received doses 3, 10, 30, 100 or 300 mg commercial grade tetrachlorophenol/kg-day for 10 consecutive days (Schwetz et al., 1974). At 100 and 300 mg/kg-day, signs of toxicity and death were observed. At 30 mg/kg-day, a statistically significant increase in delayed ossification of the skull bones of fetus' was observed. No statistically significant adverse effects were observed at 10 mg/kg-day, and as a result, a NOAEL was established at this level. Health Canada subsequently modified this NOAEL by an uncertainty factor of 1000 to account for interspecies variation (10), intraspecies variation (10) and subchronic study duration (10).

The US EPA (1992) provides an oral TDI of 0.03 mg/kg-day for 2,3,4,6-tetrachlorophenol. This value is based on a study in which Sprague-Dawley rats (30/sex/dose) were gavaged daily with 0, 25, 100 or 200 mg 2,3,4,6-tetrachlorophenol/kg-day in olive oil, over the course of 90 days (US EPA, 1986). Statistically significant effects were observed in rats exposed to 100 and 200 mg/kg-day doses, including depression of body weight, increase in liver and kidney weights, and reduced platelet count. Based on this information, a LOAEL of 100 mg/kg-day and a NOAEL of 25 mg/kg-day were established. This NOAEL was modified by an uncertainty factor of 1000, representing interspecies (10) and interspecies (10) variability, as well as the use of a subchronic study (10).

The Health Canada oral TDI of 0.01 mg/kg-day was then used by the risk assessment study team to calculate a chronic inhalation exposure limit based on route-to-route extrapolation. The Health Canada value was chosen as it is most conservative. A body weight of 70.7 kg and an inhalation rate of 15.8 m^3/day were assumed for the purposes of the calculation. This resulted in a calculated chronic inhalation exposure limit of 44.7 µg/m^3.

15.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

2,3,4,6-Tetrachlorophenol is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation unit risk has not been selected.

15.4 Bioavailability

In this risk assessment, 2,3,4,6-tetrachlorophenol is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that 2,3,4,6-tetrachlorophenol is completely absorbed (i.e. absorption factor is 1).

15.5 Conclusion

The following tables present 2,3,4,6-tetrachlorophenol TRVs selected for use in this risk assessment.

Table 15-1 2,3,4,6-Tetrachlorophenol Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
2,3,4,6-Tetrachlorophenol	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 15-2 2,3,4,6-Tetrachlorophenol Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
2,3,4,6-Tetrachlorophenol	1-Hour	NV			
	24-Hour	NV			
	Annual Average	44.7	Route-to-route extrapolation from oral reference dose	RfD	Health Canada, 2004

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value

15.6 References

ATSDR (Agency for Toxic Substances and Diseases Registry). 1999. ToxFAQs for Chlorophenols. June 1999. Available at: http://www.atsdr.cdc.gov/tfacts107.html

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16.0 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 (PCP). 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 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).

Chlorophenols can have a number of toxic effects on human health. Humans exposed to chlorophenols as well as other chemicals through inhalation and dermal contact developed acne and mil liver injuries. Animal studies have concluded that ingestion of high levels of chlorophenols can affect the liver and immune system. Putting chlorophenols on the skin and eyes of animals can also cause injusry such as swelling, redness, and scabbling. This is more common with mono and dichlorophenols however (ATSDR, 1999).

16.1 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. Combined exposures to polychlorophenols or to their sodium salts are possibly carcinogenic to humans (Group 2B) (IARC, 1999).

ATSDR determined that 2,4,6-trichlorophenol has the potential to be a carcinogenic substance (ATSDR, 1999); therefore, for this risk assessment, it is conservatively assumed that 2,4,6-trichlorophenol is a carcinogen.

16.2 Susceptible Populations

No particularly susceptible populations were identified.

16.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

16.3.1 Oral Exposure

16.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, 2,4,6-trichlorophenol is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

16.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, 2,4,6-trichlorophenol is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

16.3.2 Inhalation Exposure

16.3.2.1 Non-Carcinogenic Toxicity Reference Values

16.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

No acute inhalation TRVs for 2,4,6-trichlorophenol were identified for use in the risk assessment.

16.3.2.1.2 Chronic Inhalation Toxicity Reference Values

No chronic non-carcinogenic inhalation TRV for 2,4,6-trichlorophenol was identified for use in the risk assessment.

16.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

The US EPA (1994) provides an inhalation unit risk of 3.1×10^{-6} $(\mu g/m^3)^{-1}$ for 2,4,6-trichlorophenol based on a linearized multistage extrapolation from data collected from an oral study. The oral study involved ingestion of 2,4,6-trichlorophenol by male and female F344 rats and B6C3F1 mice (NCI, 1979). In rats 2,4,6- trichlorophenol was administered at 5000 or 10,000 ppm in feed for 106 or 107 weeks. Male mice also received 5000 or 10,000 ppm of 2,4,6-trichlorophenol for 105 weeks. Female mice were initially administered 10,000 or 20,000 ppm of 2,4,6-trichlorophenol in feed. As the animals were observed to have decreased body weights, these concentrations were lowered to 2500 and 5000 ppm at week 38 (TWA dose = 5214 or 10,428 ppm). While both rodent species showed dose-related decreases in mean body weight, no increased mortality nor other toxic signs were observed. Observations included statistically significant increases in the incidence of lymphomas or leukemias in male rats and hepatocellular adenomas or carcinomas in male and female mice.

The US EPA carcinogenic inhalation unit risk value of 3.1×10^{-6} $(\mu g/m^3)^{-1}$ was used in this risk assessment.

16.4 Bioavailability

In this risk assessment, 2,4,6-trichlorophenol is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that 2,4,6-trichlorophenol is completely absorbed (i.e. absorption factor is 1).

16.5 Conclusion

The following tables present 2,4,6-trichlorophenol TRVs selected for use in this risk assessment.

Table 16-1 2,4,6-Trichlorophenol Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
2,4,6-Trichlorophenol	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] NE – Not Evaluated

Table 16-2 2,4,6-Trichlorophenol Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
2,4,6-Trichlorophenol	1-Hour	NV			
	24-Hour	NV			
	Annual Average	NV			
	Carcinogenic Annual Average	3.1×10^{-6}	Lymphomas or leukemias in male rats and hepatocellular adenomas or carcinomas in male and female mice.	UR	US EPA, 1994

[a] Units: Carcinogenic COPC $(\mu g/m^3)^{-1}$, NV – No Value

16.6 References

ATSDR (Agency for Toxic Substances and Diseases Registry). 1999. ToxFAQs for Chlorophenols. June 1999. Available at: http://www.atsdr.cdc.gov/tfacts107.html

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.

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17.0 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). Chlorophenols are also produced during the bleaching of wood pulp with chlorine when paper is being produced.

Chlorophenols can have a number of toxic effects on human health. Humans exposed to chlorophenols through inhalation and dermal contact developed acne and mild liver injuries. Animal studies have concluded that ingestion of high levels of chlorophenols can affect the liver and immune system. Application of chlorophenols on the skin and eyes of animals can also lead to swelling, redness and scabbling. This is more common with mono- than dichlorophenols (ATSDR 1999).

17.1 Assessment of Carcinogenicity

According to IARC (1999), combined exposures to polychlorophenols or to their sodium salts, are possibly carcinogenic to humans (Group 2B); however given the lack of evidence, for the purpose of this risk assessment, 2,4-dichlorophenol was evaluated as a non-carcinogen.

17.2 Susceptible Populations

No particularly susceptible populations were identified by ATSDR (1999).

17.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

17.3.1 Oral Exposure

17.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, 2,4-dichlorophenol is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

17.3.1.2 Carcinogenic Toxicity Reference Values

2,4-Dichlorophenol is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

17.3.2 Inhalation Exposure

17.3.2.1 Non-Carcinogenic Toxicity Reference Values

17.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 530 µg/m^3 for 2,4-dichlorophenol was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009). TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

A 24-hour inhalation TRV was unavailable for 2,4-dichlorophenol at the time of this assessment.

17.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Non-carcinogenic chronic inhalation TRVs from Health Canada and the US EPA were not available at the time of this assessment.

An annual exposure limit of 53 µg/m^3 for selenium was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 17.3.2.1.1. To derive a long-term ESL for selenium, TCEQ further divides the short-term ESL by an additional safety factor of 10.

17.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

2,4-Dichlorophenol is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation unit risk has not been selected.

17.4 Bioavailability

In this risk assessment, 2,4-dichlorophenol is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that 2,4-dichlorophenol is completely absorbed (i.e. absorption factor is 1).

17.5 Conclusion

The following tables present 2,4-dichlorophenol TRVs selected for use in this risk assessment.

Table 17-1 2,4-Dichlorophenol Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
2,4-Dichlorophenol	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 17-2 2,4-Dichlorophenol Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
2,4-Dichlorophenol	1-Hour	530	Health Based	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	53	Health Based	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$), NV – No Value

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18.0 ACETALDEHYDE

Acetaldehyde is ubiquitous in the environment and may be formed in the body from the breakdown of ethanol; however, it is mainly used as an intermediate in the synthesis of other chemicals (US EPA, 2000). Acetaldehyde is also used in the production of perfumes, polyester resins, and basic dyes (US EPA, 2000).

Acetaldehyde is used as a chemical intermediate in the production of acetic acid and a number of other chemicals (US EPA 1994). To a lesser extent, it is used as a fragrance, deodorizer, and flavouring agent in food (Environment Canada, 2000). Anthropogenic sources include combustion from motor vehicles, furnaces, power plants, waste incinerators, cigarettes, and cooking of certain types of food. Emissions also result from industrial manufacturing of products with residual acetaldehyde. These sources include chemical manufacturing plants, pulp and paper mills, tire rubber plants, and petroleum refining and coal processing plants (Environment Canada 2000). The secondary formation of acetaldehyde from photochemical reactions with organic compounds and pollutants in the atmosphere is a major source that often exceeds primary emissions (Environment Canada, 2000). Acetaldehyde is also a degradation product of sewage and biological wastes. Biomass combustion is a major natural source of acetaldehyde. Acetaldehyde is a metabolic intermediate in human metabolism, plant respiration, and alcohol fermentation. Humans are exposed to acetaldehyde primarily through the inhalation of ambient and indoor sources (Environment Canada 2000), but also via ingestion since acetaldehyde occurs naturally in certain foods (e.g., coffee, fruit, breads).

Since acetaldehyde is a major metabolite of ethanol many adverse health effects from ethanol are attributed to acetaldehyde. Acute (short-term exposure) health effects of acetaldehyde include irritation of the eyes and respiratory tract, and altered respiratory function. Prolonged or chronic dermal exposure can cause burns and dermatitis. Chronic inhalation exposure has been shown to cause adverse effects on the respiratory tracts of animals (US EPA, 2000).

18.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC, 2006), classifies acetaldehyde as Group 2B, “possibly carcinogenic to humans.” The US EPA (1991) classifies acetaldehyde as Group B2, a probable human carcinogen via inhalation, based on limited evidence in humans, and sufficient evidence in animals, as shown via increased incidence of nasal tumours in rats and laryngeal tumours in hamsters.

For this assessment, acetaldehyde is being evaluated as a carcinogen.

18.2 Susceptible Populations

Populations with increased susceptibility to exposure to acetaldehyde were not identified.

18.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

18.3.1 Oral Exposure

18.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, acetaldehyde is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

18.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, acetaldehyde is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

18.3.2 Inhalation Exposure

18.3.2.1 Non-Carcinogenic Toxicity Reference Values

18.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit was not identified for acetaldehyde.

The 24-hour exposure limit used in this risk assessment was selected from the Ontario Ministry of the Environment (MOE). A 24-hour AAQC benchmark of 500 µg/m^3 was derived (MOE, 2008). This value is based upon tissue damage observed during a rat inhalation study (Appleman et al. 1986). This 4 week inhalation study exposed groups of 10 male rats to different levels of acetaldehyde (0, 150 or 500ppm) 6 h/day, 5 d/week, with or without interruption. No toxic effect was observed in rats interruptedly or uninterruptedly exposed to 150 ppm acetaldehyde during the 4 weeks. This was translated to a NOAEL of 270,000 µg/m^3. An adjusted NOAEL of 49,000 µg/m^3 was calculated after adjusting the study NOAEL of 270,000 µg/m^3 for continuous exposure (6/24 hours, 5/7 days). A safety factor of 100 was applied for human variability (10) and interspecies variability (10).

18.3.2.1.2 Chronic Inhalation Toxicity Reference Values

A chronic RfC of 9.0 µg/m^3 was derived by the US EPA (1991) using a NOAEL (HEC) of 8,700 µg/m^3 derived from two short-term rat inhalation studies (Appleman et al. 1982; 1986). Although the two reference studies were only four weeks in duration, they establish a concentration-response for lesions that is pathologically consistent with the effects seen in longer-term studies. The studies exposed Wistar rats (10/sex/group) to different levels of acetaldehyde (ranging from 0-5000ppm, or 0 to 9100 mg/m^3). No compound related effects (i.e., degenration of olfactory epithelium) were observed at 150ppm (273,000 µg/m^3) and this was set as the study NOAEL. This value was adjusted for continuous exposure (6/24 hour, 5/7 days) and subsequently converted to a NOAEL (HEC) of 8,700 µg/m^3. An uncertainty factor of 1,000 was applied to determine the RfC (10 for sensitive human populations 10 for subchronic to chronic extrapolation, and 10 for interspecies extrapolation using dosimetric adjustments and to account for the incompleteness of the database).

The California Environmental Protection Agency (2008) established a reference exposure level of 140 µg/m^3 based on the same previously described studies used by the US EPA (Appleman et al. 1982; 1986). The previously described NOAEL of 273,000 µg/m^3 was used to obtain a benchmark

concentration of 178,000 µg/m^3 using continuous polynomial models of analysis. A dosimetric adjustment factor of 1.36 was then applied to account for interspecies variation, and further adjustment for continuous exposure was applied to obtain an adjusted NOAEL of 43,200 µg/m^3. A subsequent uncertainty factor of 300 was applied to account for subchronic to chronic, interspecies and intraspecies extrapolations.

Health Canada (2004) established a tolerable inhalation concentration (TC) of 390 µg/m^3 based on the same studies as identified above, but used the 95% lower confidence limit of a benchmark concentration associated with a 5% increase in non-neoplastic lesions in nasal olfactory epithelium.

For the purposes of this assessment, the US EPA RfC of 9.0 µg/m^3 will be used.

18.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

The US EPA (1991) provides an inhalation unit risk of 2.2 x 10^{-6} (µg/m^3)$^{-1}$, extrapolated from a linear multistage-variable input model. This value is derived from a study (Woutersen and Appleman, 1984) of the effects of inhalation exposure to acetaldehyde in male rats that showed nasal squamous cell carcinomas or adenocarcinoma. Woutersen and Appleman (1984) and Woutersen et al., (1986) assessed the carcinogenicity of acetaldehyde using four groups of 105 male and 105 female albino Wistar rats by exposing animals to atmospheres containing 0, 750, 1500, or 3000 ppm acetaldehyde for 6 hours/day, 5 days/week, for 27 months. Exposure to acetaldehyde increased the incidence of tumors in an exposure-related manner in both male and female rats. Adenocarcinomas were increased significantly in both male and female rats at all exposure levels, whereas squamous cell carcinomas were increased significantly in male rats at middle and high doses and in female rats only at the high dose. The squamous cell carcinoma incidences showed a clear dose-response relationship. The incidence of adenocarcinoma was highest in the mid-exposure group (1500 ppm) in both male and female rats, but this was probably due to the high mortality and competing squamous cell carcinomas at the highest exposure level. In the low-exposure group (750 ppm or 130 ppm human equivalent), the adenocarcinoma incidence was higher in males than in females.

US EPA warns that this unit risk may not be appropriate if the air concentration exceeds 5000 ug/m^3.

Health Canada (2004) estimated the carcinogenic potency of acetaldehyde with a tumorigenic concentration (TC05) of 86,000 µg/m^3. This concentration was derived from a Woutersen et al. (1986) study that also showed increased incidence of the aforementioned carcinomas in male rats exposed to acetaldehyde for up to 28 months. The study exposed male and female Wistar rats to 750, 1500 or 3000 ppm (1350, 2700 or 5400 mg/m^3) acetaldehyde for 6 hours per day, 5 days/week for up to 28 weeks. The LOAEL (for non-neoplastic histopathological effects in the upper respiratory tract, was 750 ppm. The TC_{05} was calculated using a multistage model, with adjustment for intermittent to continuous exposure (6/24 hours, 5/7 days). However, the highest exposure concentration group was not included in the derivation because of high mortality. The inhalation unit risk value, calculated by dividing the TC05 into 0.05, is 5.8 x 10^{-7} (µg/m^3)$^{-1}$.

For this assessment, the Health Canada (2004) inhalation toxicity reference value of 5.8 x 10^{-7} (µg/m^3)$^{-1}$ was selected.

18.4 Bioavailability

In this risk assessment, acetaldehyde is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that acetaldehyde is completely absorbed (i.e. absorption factor is 1).

18.5 Conclusion

The following tables present acetaldehyde TRVs selected for use in this risk assessment.

Table 18-1 Acetaldehyde Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Acetaldehyde	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 18-2 Acetaldehyde Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Acetaldehyde	1-Hour	NV			
	24-Hour	500	Tissue Damage	Benchmark	MOE AAQC, 2008
	Annual Average	9	Degeneration of olfactory epithelium	RfC	US EPA, 1991
	Carcinogenic Annual Average	5.8×10^{-7}	Increased incidence of nasal adenocarcinomas (combined)	UR	Health Canada, 2004

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$, UR (unit risk), NV (no value)

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19.0 ANTIMONY

Antimony is a silvery-white metal that is found in the earth's crust (ATSDR 1995).

The effects of antimony on human health are dependent on the dose, the route of contact, and the duration of contact. Inhalation of high levels of antimony over a long period can cause eye and lung irritation; heart and lung problem; and stomach pain, stomach ulcers, diarrhea and vomiting (ATSDR, 1995). Acute inhalation of very high doses of antimony in animal studies has been shown to cause heart, lung, liver and kidney damage; reproductive problems; and death (ATSDR, 1995). Animal studies of chronic inhalation of low doses of antimony have resulted in eye irritation, hair loss, lung damage, heart problems, and fertility problems (ATSDR, 1995).

Ingesting large doses of antimony can cause vomiting in humans. Long term animal studies have also reported liver damage and changes in the blood (ATSDR, 1995). Dermal contact with antimony can lead to skin irritation (ATSDR, 1995).

In controlled doses, when used for medical reasons, antimony can have positive effects. It has been used as a treatment for people infected with parasites (ATSDR,1995).

19.1 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) states 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. As such, antimony is only being evaluated as a non- carcinogenic substance in this assessment.

19.2 Susceptible Populations

Individuals with existing chronic respiratory or cardiovascular disease or problems are likely to 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).

19.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

19.3.1 Oral Exposure

19.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004) does not provide a non-carcinogenic TRV for oral exposures to antimony.

An oral RfD of 0.0004 mg/kg-day was derived for antimony by the U.S. EPA (1991) based on a chronic study by Schroeder et al. (1970) examining ingestion of 5 ppm potassium antimony tartrate in water by rats (50 male and 50 female). Among the most significant effects were reduced median lifespans in exposed male and female rats (106 and 107 fewer days respectively). In addition, non-fasting blood glucose levels were decreased in treated males, and cholesterol levels were altered, relative to controls, in both sexes. A NOAEL could not be established as only one dose level was tested in this study. 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 derive the RfD. The US EPA (1991) notes that confidence in the principal study is rated low as only one test species was used, only one dose level was tested, and gross pathology and histopathology were poorly described. The US EPA also rates confidence in the database low due to lack of adequate oral exposure studies on antimony compounds. Thus, there is a low degree of confidence in the oral RfD. It should also be recognized that potassium antimony tartrate is a highly water soluble form that is unlikely to occur in ambient soil, water, or air, although it may occur in foods.

The US EPA RfD of 0.0004 mg/kg-day was adopted as the chronic oral exposure limit for non-carcinogenic effects for the current assessment.

19.3.1.2 Carcinogenic Toxicity Reference Values

Antimony is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected..

19.3.2 Inhalation Exposure

19.3.2.1 Non-Carcinogenic Toxicity Reference Values

19.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 5 µg/m^3 for antimony was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 500 µg/m^3 based on the following critical effects: skin and upper respiratory tract irritation. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 25 µg/m^3 for antimony was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

19.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada (2004) does not provide a non-carcinogenic TRV for inhalation exposures to antimony.

An inhalation RfC of 0.2 µg/m^3 was provided for antimony trioxide by the U.S. EPA (1995). This was based on a one-year study in which groups of 65 Fischer 344 rats/sex/group were exposed to varying concentrations (0, 50, 500, or 5000 µg/m^3) of antimony trioxide by inhalation for six hours a day, five days per week. The RfC was calculated using a benchmark concentration for pulmonary toxicity, and chronic interstitial inflammation in rats exposed to antimony trioxide in air, in the chronic rat study reported in Newton et al. (1994) and Bio/dynamics (1990). No significant differences in survival, body weight change or hematological parameters were observed between control and exposed groups. While an increase in mean corpuscular hemoglobin concentration was observed in both sexes exposed to the highest concentration only, for one year, this effect was not observed at other exposure intervals, or at lower test concentrations. The U.S. EPA (1995) reported a BMC10(HC) of 74 µg/m^3, and applied an uncertainty factor of 300 (10 to protect sensitive individuals, 3 for interspecies extrapolation, 3 for database inadequacies, and 3 because it was less-than-lifetime exposure duration). There is medium confidence in this RfC.

The US EPA RfC of 0.2 µg/m^3 was adopted as the chronic inhalation exposure limit for non-carcinogenic effects for the current assessment

19.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Antimony is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

19.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004).

19.5 Conclusion

The following tables present antimony TRVs selected for use in this risk assessment.

Table 19-1 Antimony Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Antimony	Non-carcinogenic TRV	0.0004	Longevity, clinical chemistry	RfD	US EPA, 1991
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 19-2 Antimony Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Antimony	1-Hour	5	Skin and Upper Respiratory Tract Irritation	Benchmark	TCEQ ESL, 2008
	24-Hour	25	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	0.2	Pulmonary Toxicity, Chronic Interstitial Inflammation	RfC	US EPA, 1995

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)

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20.0 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 than 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, unlike inorganic arsenic, no conclusive evidence has been found on the carcinogenicity of organic arsenic (ATSDR, 2000; WHO, 1981; WHO, 2001). Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic; therefore for the purposes of this assessment total concentrations of arsenic were modeled as the inorganic form.

Inhalation of high doses of inorganic arsenic can irritate the throat and lungs (ATSDR, 2007). Ingestion of inorganic arsenic can result in nausea, vomiting, decreased production of red and white blood cells, abnormal heart rhythm, damage to blood vessels, a sensation of pins and needles in the extremities, and at very high levels, death (ATSDR, 2007). Chronic ingestion or inhalation of low levels of arsenic can cause a darkening of the skin, and small “corns” or “warts” on the palms, soles, and torso (ATSDR, 2007). Dermal contact with inorganic arsenic can cause redness or swelling of the skin (ATSDR, 2007).

20.1 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).

20.2 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). Also, a number of studies have indicated potentially greater toxicity of arsenic exposure during childhood (Cal EPA, 2008).

20.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

20.3.1 Oral Exposure

20.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004) does not provide a non-carcinogenic TRV for oral exposures to arsenic since carcinogenicity is considered the critical endpoint.

The United States Environmental Protection Agency (US EPA, 1993) provides an oral RfD for non-carcinogenic effects from inorganic arsenic of 0.0003 mg/kg-day. This value is based on the extensive data set of both non-carcinogenic and carcinogenic health effects experienced by Taiwan residents exposed to inorganic arsenic (predominately as arsenate (As V) in their drinking water. Tseng (1977) studied the prevalence of 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 US EPA RfD was developed based on the NOAEL of 0.0008 mg/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. This RfD is appropriate for comparison to exposures averaged over an entire lifetime (US EPA, 1993). The US EPA (1993) weights the selected study as medium given the poor characterization of doses and the possibility that the presence of other contaminants may have influenced study outcomes despite the large sample population. Based on the same study, ATSDR (2007) has also derived chronic oral exposure limits of 0.0003 mg/kg-day.

The US EPA RfD of 0.0003 mg/kg-day was selected as the chronic oral toxicity reference value for non-carcinogenic effects for the current assessment.

20.3.1.2 Carcinogenic Toxicity Reference Values

The US EPA (1998) provides an oral cancer SF of 1.5 per mg/kg-day. 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. Dose-response data were developed over three dose intervals and four exposure durations, for males and females separately. It was assumed that a

constant exposure was experienced from birth, and that the drinking water consumption rate for males and females was 3.5 and 2.0 L/day, respectively. The doses were converted to equivalent doses for US males and females and it was assumed that the skin cancer risk in the US population would be similar to that in the Taiwanese population. Dose-specific and age-specific skin cancer prevalence rates were calculated using the multistage model with time.

Based on the same data set, however, incorporating background skin cancer rates for Canadians, Health Canada (2004) recommended an oral SF of 2.8 per mg/kg-day based on a TD_{05}.

The US EPA (1998) SF of 1.5 per mg/kg-day was selected as the oral slope factor to evaluate long-term human health effects of exposure to arsenic for the current assessment.

20.3.2 Inhalation Exposure

20.3.2.1 Non-Carcinogenic Toxicity Reference Values

20.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

An acute REL of 0.2 µg/m^3 was derived for arsenic by Cal EPA (2008) for decreased fetal weight in mice during a developmental study (Nagymajtényi et al. 1985). Pregnant mice were exposed to 3 dose levels (plus a control) of arsenious acid via inhalation for 4 hours on gestation days 9 through 12. An uncertainty factor of 1,000 was applied to the study LOAEL of 190 µg As/m^3 for interspecies variation (10), the use of a LOAEL (10), and intraspecies variation (10). This value was selected as the 1-hour acute exposure limit for arsenic for the current assessment.

In 1981, the MOE (2008) derived an AAQC (24-hour averaging time) for arsenic of 0.3 µg/m^3. This value was based on human health effects including irritation, sensitization, immunosuppression, teratogenesis, genotoxicity and carcinogenicity in exposed individuals. No further information regarding the derivation of this exposure limit was available; however, it was selected as the 24-hour exposure limit for arsenic for the current assessment.

20.3.2.1.2 Chronic Inhalation Toxicity Reference Values

A number of studies have indicated potentially greater toxicity of arsenic exposure during childhood (Cal EPA, 2008). Chronic arsenic exposure appears to have adverse effects on intellectual development and visual perception in children. It is uncertain whether neurological effects are the most sensitive caused by chronic arsenic exposure in children. Additional studies in exposed children are needed to adequately quantify adverse effects; however, the child-based values from various studies to date range from 0.015 to 1.6 µg/m^3. The neurodevelopmental endpoint was selected by Cal EPA (2008) as the critical effect for deriving the chronic REL for inorganic arsenic, based on studies by Wasserman et al. (2004) and Tsai et al. (2003) where 210 ten year olds were exposed to arsenic in drinking water for 9.5-10.5 years. Based on this study, a value of 0.015 µg/m^3, based on an LOAEL of 0.23 µg/m^3 (50% inhalation absorption assumed - 0.46 µg/m^3) with an uncertainty factor of 30 applied

for the use of a LOAEL (3) and inter-individual variation (10), was selected as the chronic inhalation exposure limit for arsenic for the current assessment.

20.3.2.2 Carcinogenic 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 $\mu g/m^3$, respectively. These equate to unit risks of 0.0064 $(\mu g/m^3)^{-1}$, of 0.0049 $(\mu g/m^3)^{-1}$, and of 0.0099 $(\mu g/m^3)^{-1}$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. More recently, Health Canada (2004) has recommended an inhalation SF of 0. $(\mu g/m^3)^{-1}$ based on a TC_{05} of 7.8 $\mu g/m^3$ for arsenic and its inorganic compounds.

The US EPA has developed a unit risk of .0043 $(\mu g/m^3)^{-1}$ 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 (three studies yielding average unit risk of 0.0026 $(\mu g/m^3)^{-1}$ and the ASARCO (Tacoma, Washington) smelter cohort (average of two estimates of 0.0072 $(\mu g/m^3)^{-1}$ (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 4.3×10^{-3} $(\mu g/m^3)^{-1}$ was select for the current assessment.

20.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.03 (Health Canada, 2004).

20.5 Conclusion

The following tables present arsenic TRVs selected for use in this risk assessment.

Table 20-1 Arsenic Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value[a]	Critical Effect	Reference Type	Source
Arsenic	Non-carcinogenic TRV	0.0003	Hyperpigmentation,, keratosis and possible vascular complications	RfD	US EPA, 1993
	Carcinogenic Slope Factor	1.50	Skin Cancer Prevalence	SF	US EPA, 1998

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC $(mg/kg/day)^{-1}$

Table 20-2 Arsenic Inhalation TRVs used in the risk assessment

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Arsenic	1-Hour	0.2	Decreased fetal weight in mice	Benchmark	CalEPA REL, 2008
	24-Hour	0.3	Irritation, sensitization, immune suppression,	Benchmark	MOE AAQC, 2008

			teratogenesis, genotoxicity and carcinogenicity in exposed individuals		
	Annual Average	0.015	Decreased intellectual function in 10 year old children	Benchmark	CalEPA REL, 2008
	Carcinogenic Annual Average	0.0043	Lung Cancer	UR	US EPA, 1998

[a] Units: Non-carcinogenic COPC (µg/m^3) , Carcinogenic COPC (µg/m^3) $^{-1}$, UR (unit risk)

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21.0 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 (e.g., barium sulfate and barium carbonate). Barium is sometimes found naturally in drinking water and food. Because certain barium compounds 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).

The effects of barium compounds on human health are largely dependant on the solubility of the compound in the stomach and the compounds water solubility. Barium compounds that do not dissolve easily are generally not harmful (ATSDR, 2007). The health effects of ingesting water-soluble barium compounds are dependent on the dose and the duration of exposure. Short term ingestion of all levels of barium above EPA drinking water standards have been found to cause vomiting, abdominal cramps, diarrhea, difficulty breathing, changes in blood pressure, numbness around the face, and muscle weakness (ATSDR, 2007). Ingestion of high amounts of barium can lead to changes in heart rhythm, paralysis and death (ATSDR, 2007). Chronic ingestion of barium in animal studies has resulted in damage to the kidneys, decreases in body weight, and possible death (ATSDR, 2007).

21.1 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 limited animal studies (US EPA, 2005).

21.2 Susceptible Populations

The limited data available suggests 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).

21.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

21.3.1 Oral Exposure

21.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004b) provides a tolerable daily intake (TDI) of 0.016 mg/kg-day. This TDI was derived from the barium drinking water quality maximum acceptable concentration guideline of 0.73 mg/L, which is based on the results of an epidemiological study by Brenniman and Levy (1985). This study showed no adverse effects on blood pressure or increases in the prevalence of cardiovascular disease in a population of 1175 adults ingesting water containing a mean concentration of 7.3 mg/L barium (compared to a population of 1203 adults ingesting water containing a mean of 0.1 mg/L). 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.

US EPA IRIS, (2005) changed their reference dose (RfD) value to 0.2 mg/kg-day as compared to their 1998 value which was 0.07 mg/kg-day. The change in value was attributed to the "selection of a new principle study and critical effect, the use of benchmark dose modeling to determine the point of departure, and a new evaluation of both the literature and application of uncertainty factors." (US EPA, 2005). The principle study used to derive the RfD was the NTP (1994) study in which male and female mice were exposed to barium chloride (0-2500 ppm) in their drinking water for a period of either 13 weeks or two years. The chronic study assessed 60 animals/sex/group and the subchronic (13 week) study assessed 10 animals/sex/group. Results showed that rodents in both the subchronic and chronic studies had lesions, and particular chemical induced nephropathy was observed. Renal damage was used as the critical effect for deriving the RfD since it showed the best dose-response relationship. Additionally, survival rates were considerably decreased among treated animals as compared to the controls. For the uncertainty factor a value of 300 was used (10 for extrapolation for interspecies differences 10 for intraspecies variation and 3 for lack of toxicity data).

The US EPA (2005) TRV of 0.2 mg/kg-day was used in this assessment as it is based on more current data.

21.3.1.2 Carcinogenic Toxicity Reference Values

In this assessment barium is not being evaluated as a carcinogenic substance; therefore a carcinogenic oral TRV was not selected.

21.3.2 Inhalation Exposure

21.3.2.1 Non-Carcinogenic Toxicity Reference Values

21.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 5 µg/m^3 for barium was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 500 µg/m^3 based on the following critical effects: eye, skin and gastrointestinal tract irritation; and muscular stimulation. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 10 µg/m^3 for barium was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

21.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Non-cancer inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, values developed by the Netherlands Institute of Public Health and the Environment (RIVM) were considered.

RIVM (2001) derived a tolerable concentration in air (TCA) value of 1.0 µg/m^3 based on Baars et al. (2001). This TCA was based on a study evaluating continuous inhalation of insoluble barium compounds by rats, resulting in a no observed adverse effects concentration (NOAEC) of 0.16 mg/m^3. An uncertainty factor of 100 was applied for intra and inter-species extrapolation resulting in a TCA of 1.0 µg/m$^{3.}$ This value was chosen as the chronic inhalation exposure limit for the current assessment. No toxicity data was available resulting from inhalation of soluble barium compounds in animals or humans, however, kinetic studies showed that after inhalation of either soluble or insoluble barium salts there were no differences in absorption.

21.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this assessment barium is not being evaluated as a carcinogenic substance; therefore a carcinogenic inhalation TRV was not selected.

21.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004a).

21.5 Conclusion

The barium TRVs used in this HHRA are tabulated below.

Table 21-1 Barium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Barium	Non-carcinogenic TRV	0.2	Nephropathy	RfD	US EPA, 2005
	Carcinogenic Slope Factor	NV			

NV-no value

Table 21-2 Barium Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Barium	1-Hour	5	Eye, Skin and Gastrointestinal Tract irritation; muscular stimulation	Benchmark	TCEQ ESL, 2008
	24-Hour	10	Health Based	Benchmark	MOE AAQC, 2005
	Annual Average	1	Cardiovascular Effects	RfC	RIVM, 2001

[a] Units: Non-carcinogenic COPC (µg/m^3)

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22.0 BENZENE

Benzene is a colourless liquid with a sweet odour. It is highly flammable, 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, 2007). Natural emissions are discharged from volcanic gases, forest fires and present in crude oil and gasoline (ATSDR, 2007).

The health effects of benzene depend on the route, dose, and duration of exposure. Acute inhalation of high levels of benzene can lead to drowsiness, dizziness, rapid heart rate, headache, tremors, confusion, unconsciousness, and at very high levels, death (ATSDR, 2007). Ingestion of high levels of benzene can lead to vomiting, stomach irritation, dizziness, sleepiness, convulsions, rapid heart rate, and possible death (ATSDR, 2007).

Chronic effects of benzene exposure can harm the bone marrow and cause a decrease in red blood cells, leading to anemia. It can also cause excessive bleeding, and disturb immune function, increasing susceptibility to infection (ATSDR, 2007). In some women, chronic exposure to benzene has lead to irregular menstrual periods and a decrease in ovary size, however this evidence is inconclusive (ATSDR, 2007). Benzene's effects on fertility in men are unknown (ATSDR, 2007).

22.1 Assessment of Carcinogenicity

Benzene is a known human carcinogen (Category A, US EPA, 2003) and is listed as a Group 1 carcinogen by IARC (2006). Health Canada (1996; CEPA, 1993) has also classified benzene as carcinogenic to humans (Group I).

For this assessment, benzene is being assessed for both non-carcinogenic and carcinogenic endpoints.

22.2 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, 2007). 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, 2007). 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, 2007).

22.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

22.3.1 Oral Exposure

22.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, benzene is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

22.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, benzene is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

22.3.2 Inhalation Exposure

22.3.2.1 Non-Carcinogenic Toxicity Reference Values

22.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 170 µg/m^3 for benzene was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008) based on studies that showed depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in mice. TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

The 24-hour exposure limit used in this risk assessment was selected from the ATSDR. ATSDR (2008) derived an acute MRL for benzene of 29 µg/m^3 based on an acute toxicity study in mice (Rozen et al. 1984). Rozen et al. (1984) exposed male C57BL/6J mice (7–8/group) for 6 hours/day for 6 consecutive days to concentrations of 3.26 x 10^4, 9.9 x 10^4, 3.2 x 20^5, 9.6 x 10^5 µg/m^3. Erythrocyte counts were depressed in C57BL/6 mice only at 100 and 301 ppm. The 10.2 ppm exposure level resulted in significant depression of femoral lipopolysaccharide-induced B-colony-forming ability in the absence of a significant depression of total numbers of B cells. At 31 ppm, splenic phytohemagglutinin-induced blastogenesis was significantly depressed without a concomitant significant depression in numbers of T-lymphocytes. Peripheral lymphocyte counts were depressed at all exposure levels. Based on these results ATSDR (2008) derived an LOAEL of 3.26 x 10^4. The LOAEL was adjusted to a continuous exposure (LOAEL x 6/24) and a cumulative uncertainty factor of 300 (10 for use of a LOAEL, 3 for the extrapolation from animals to humans, and 10 to protect sensitive individuals) was applied. Based on the adjustments, ATSDR (2008) derived an acute inhalation MRL of 29 µg/m^3.

22.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada (2004) does not provide a non-carcinogenic TRV for inhalation exposures to benzene.

The US EPA (2003) IRIS database derived a chronic inhalation RfC of 30 µg/m^3 for benzene based on a decreased lymphocyte count observed during a human occupational inhalation study (Rothman et al., 1996). Rothman et al. (1996) conducted a cross-sectional study of 44 workers exposed to a range of benzene concentrations and 44 age and gender-matched unexposed controls, all from Shanghai,

China. Benzene exposure 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. The percentage of erythrocytes in whole blood was chosen as the critical effect. The continuous linear model and the US EPA's Benchmark Dose Modeling Software were used to calculate the unadjusted BMCL of 23,000 µg/m^3. An adjusted BMCL was calculated by correcting for continuous exposure (5/7 days) and the occupational inhalation rate (10/20 m^3/day). A safety factor of 300 (3 for effect level extrapolation 10 for intraspecies variability, 3 for sub-chronic to chronic extrapolation, and 3 for database deficiencies) was applied to the adjusted BMCL of 8,200 µg/m^3.

The ATSDR (2007) has derived a chronic inhalation MRL of 98 µg/m^3 based on a worker study by Lan et al. (2004). A cross-sectional study was performed on 250 workers (approximately two-thirds female) exposed to benzene at two shoe manufacturing facilities in Tianjin, China. 140 age- and gender-matched workers in clothing manufacturing facilities that did not use benzene were used as controls. The benzene-exposed workers had been employed for an average of 6.1 years. Benzene exposure was monitored by individual organic vapor monitors 5 or more times during the 16 months prior to blood testing. The researchers observed decreased counts of B-lymphocytes in the shoe factory works in Tianjin, China. The derived MRL was calculated from an adjusted BMCL of 96 µg/m^3.

The more conservative US EPA RfC of 30 µg/m^3 was adopted as the chronic inhalation exposure limit for non-carcinogenic effects for the current assessment

22.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

A TC_{05} of 15,000 µg/m^3 was developed by Health Canada (CEPA 1993; Health Canada 1996) and corresponds to the inhalation UR of 3.3×10^{-3} (µg/m^3)$^{-1}$ (Health Canada, 2004). This value was derived from three epidemiological studies of humans following occupational exposure (Bond et al., 1986; Wong, 1987a,b; Rinsky et al., 1987). In each study workers with occupational exposure to sources of benzene were followed and evaluated by researchers for varying time periods. The results of each study indicated a statistically significant increase in the incidence of leukemia following occupational exposure to benzene. From these results Health Canada (2004) derived a UR of 3.3×10^{-3} (µg/m^3)$^{-1}$.

The US EPA (2000) 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 five human occupational studies (Rinsky et al., 1981; 1987; Paustenbach et al., 1993; Crump and Allen, 1984; Crump, 1994; US EPA, 1998). In each study workers were exposed occupationally to various concentrations of benzene in the air. In each case researchers noted a statistically significant increase in the incidence of leukemia following occupational exposure to benzene. The extrapolation method employed was low-dose linearity utilizing maximum likelihood estimates (Crump, 1994) to arrive at a unit risk range of 2.2×10^{-6} (µg/m^3)$^{-1}$ to 7.8×10^{-6} (µg/m^3)$^{-1}$.

The Health Canada (2004) unit risk falls within the US EPA range; however the high end of the US EPA range (7.8×10^{-6} (µg/m^3)$^{-1}$) was selected for evaluation of carcinogenic inhalation exposures in this assessment.

22.4 Bioavailability

In this risk assessment, benzene is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that benzene is completely absorbed (i.e. absorption factor is 1).

22.5 Conclusion

The following tables present benzene TRVs selected for use in this risk assessment.

Table 22-1 Benzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Benzene	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 22-2 Benzene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Benzene	1-Hour	170	depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes (mice)	Benchmark	TCEQ ESL, 2008
	24-Hour	29	Reduces lymphocyte proliferation following mitogen stimulation	RfC	ATSDR, 2008
	Annual Average	30	Decreased lymphocyte count	RfC	US EPA, 2003
	Carcinogenic Annual Average	7.8×10^{-6}	Leukemia	UR	US EPA, 2000

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$

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23.0 BERYLLIUM

According to the ATSDR (2002b), 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.

The effects of beryllium on human health are dependent on the dose, the route of contact, and the duration of contact. Short term inhalation of high levels of beryllium can lead to acute beryllium disease, a condition that resembles pneumonia (ATSDR, 2002a). Chronic inhalation exposure to beryllium (over many years) can lead to beryllium sensitivity in some people (1-15%). These individuals may develop chronic beryllium disease, an inflammatory reaction in the respiratory system, which can cause feelings of weakness and tiredness, difficulty breathing, anorexia, weight loss, and right side heart enlargement and heart disease in advanced cases (ATSDR, 2002a).

Ingestion of beryllium is not reported to cause effects in humans because very little beryllium is absorbed through the stomach or intestines; however, ingestion of beryllium has been shown to cause ulcers in dogs (ATSDR, 2002a). Dermal contact with beryllium can cause rashes or ulcers if the skin is already broken (ATSDR, 2002).

23.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC, 2007) has determined that beryllium is a human carcinogen. The U.S. EPA (1998) has determined that beryllium is a probable human carcinogen. For this assessment, beryllium was assessed as a carcinogen.

23.2 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. It is unknown whether or not children differ from adults in their susceptibility to beryllium (ATSDR, 2002b).

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.

23.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

23.3.1 Oral Exposure

23.3.1.1 Non-Carcinogenic Toxicity Reference Values

Non-carcinogenic oral TRVs were not available from Health Canada at the time of this assessment

The US EPA (1998), ATSDR (2002b) and WHO (2001) derived a chronic oral exposure limit of 0.002 mg/kg-day based on small intestinal lesions observed during a dietary dog study with a duration of 172 weeks (Morgareidge et al., 1976). In this study 5 male and 5 female dogs were fed food with 0, 5, 50 or 500 ppm beryllium (as beryllium sulfate tetrahydrate) for 172 weeks, and another 5 male and 5 female dogs were fed food with 1 ppm beryllium for 143 weeks. These beryllium concentrations correspond to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg-day for male dogs and 0.029, 0.15, 1.3, and 17.4 mg/kg-day for females. The high dose treatment was terminated after 33 weeks after signs of overt toxicity (lassitude, weight loss, anorexia, and visibly bloody feces) and mortality. The chronic exposure limit was based on a benchmark dose analysis (10% relative increase in incidence of inflammatory lesions in small intestine was selected as the benchmark response). An uncertainty factor of 300 was applied to the $BMDL_{10}$ of 0.46 mg /kg-day for database deficiencies (UF=3), and intraspecies (UF=10) and interspecies variation (UF=10).

The Cal EPA (2001) derived a similar value; however, a BMD_{05} of 0.244 mg /kg-day and an uncertainty factor of 100 (intraspecies (10) and interspecies (10) variation) were used to derive this guideline value (0.0024 mg/kg-day).

The chronic exposure limit of 0.002 mg /kg-day established by US EPA IRIS (1998), ATSDR (2002), Cal EPA (2001) and WHO (2001) was adopted as the chronic oral exposure limit for the current assessment.

23.3.1.2 Carcinogenic Toxicity Reference Values

Though beryllium is classified as a carcinogen through inhalation exposure, the human carcinogenic potential of ingested beryllium cannot be determined. The lack of suitable positive carcinogenic oral data precludes the derivation of an oral slope factor or unit risk for beryllium.

23.3.2 Inhalation Exposure

23.3.2.1 Non-Carcinogenic Toxicity Reference Values

23.3.2.2 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.02 $\mu g/m^3$ for beryllium was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 2 $\mu g/m^3$ based on the following critical effects: lung cancer and berylliosis. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

The 24-hour exposure benchmark of 0.01 µg/m^3 used in this risk assessment was selected from the Ontario Ministry of the Environment (MOE, 2008). The MOE (2008) AAQC 24-hour benchmark value is based on respiratory irritation as the critical effect. There is no additional information regarding benchmark derivation provided.

23.3.2.3 Chronic Inhalation Toxicity Reference Values

A non-carcinogenic inhalation TRV was not available from Health Canada at the time of this assessment.

US EPA IRIS (1998) and the WHO (2001) derived a chronic inhalation exposure limit of 0.02 µg/m^3 for beryllium using a cross sectional study based on beryllium sensitization and chronic beryllium disease in occupationally exposed humans (136/139) working in a beryllium ceramics plant (Kreiss et al. 1996). Measurements from 1981 and later were reviewed for the study. The study LOAEL of 0.55 µg/m^3 was adjusted for continuous exposure (10/20 hrs, 5/7 days) and converted to a LOAEL (HEC) of 0.2 µg/m^3. The US EPA (1998) and WHO (2001) applied a safety factor of 10 to account for database uncertainties (3) (poor quality of exposure monitoring) and for the sensitive nature of the endpoint (beryllium sensitization) (3).

The CalEPA (2001) derived a chronic REL of 0.007 µg/m^3 for beryllium based on the same study (Kreiss et al. 1996). An uncertainty factor of 30 was applied for the use of a LOAEL (10) and for intraspecies variation (3) as the beryllium sensitized may not be the only sensitive subpopulation.

In the US EPA (1998) and WHO (2001) derivation of the TRV no adjustment was made for the use of a LOAEL to derive the chronic exposure limit; therefore, the chronic REL of 0.007 µg/m^3 derived by the CalEPA (2001) was selected as the chronic inhalation exposure limit for beryllium as it was the most conservative value

23.3.2.4 Cancer Inhalation Toxicity Reference Values

A carcinogenic inhalation TRV was not available from Health Canada at the time of this assessment.

The US EPA IRIS (1998) derived an inhalation unit risk of 0.0024 (µg/m^3)$^{-1}$ based on an increased incidence of lung cancer observed in a human occupational study (Wagoner et al. 1980). Wagoner et al. (1980) conducted a cohort mortality study of white males (3,055) employed at a beryllium extraction, processing, and fabrication facility in Reading, Pennsylvania between 1942 and 1967. The study cohort was followed until 1975. Significant ($p < 0.05$) increases in the number of deaths due to malignant neoplasm of trachea, bronchus, and lung were observed even when possible confounding variables were removed from analysis (e.g., smoking, latency time, mortality associated with non-neoplastic respiratory disease). From this study US EPA derived a inhalation unit risk but the selected unit risk should not be used if the air concentration exceeds 4.0 µg/m^3, since the unit risk may not be appropriate above this concentration.

23.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.03 (Health Canada, 2004).

23.5 Conclusion

The following tables present beryllium TRVs selected for use in this risk assessment.

Table 23-1 Beryllium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value[a]	Critical Effect	Reference Type	Source
Beryllium	Non-carcinogenic TRV	0.002	Small intestinal lesions	RfD	US EPA, 1998
	Carcinogenic Slope Factor	NV			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NV – No Value

Table 23-2 Beryllium Inhalation TRVs used in the HHRA

COPC	Duration	Value[a]	Critical Effect	Reference Type	Agency
Beryllium	1-Hour	0.02	Lung Cancer, Berylliosis	Benchmark	TCEQ ESL, 2008
	24-Hour	0.01	Respiratory Irritation	Benchmark	MOE AAQC, 2008
	Annual Average	0.007	Beryllium sensitization and progression to chronic beryllium disease	Benchmark	CalEPA REL, 2001
	Carcinogenic Annual Average	0.0024	Lung Cancer	UR	US EPA, 1998

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$, UR – Unit Risk

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WHO. 2001. Concise International Chemical Assessment Document 32: Beryllium and Beryllium Compounds. World Health Organization, 2001.

24.0 BIPHENYL

Biphenyl, also commonly referred to as diphenyl, is a combustible white crystalline or flaky substance, which possesses a characteristic odour (ILO, 2006). Biphenyl is commonly used in the production of heat-transfer fluids (e.g., as an intermediate for polychlorinated biphenyls) and dye carriers for textile dyeing. Lesser uses are as a mould retardant in citrus fruit wrappers, optical brighteners, hydraulic fluids and in the plastic formation process (NPI, 2005).

Biphenyl can affect human health through inhalation, ingestion or contact with skin and eyes. Symptoms of acute exposure include eye, skin and respiratory tract irritation, while chronic exposure targets the liver and nervous system (ILO, 2006).

24.1 Assessment of Carcinogenicity

According to US EPA (1991), the data available on the carcinogenicity of biphenyl has been deemed inadequate. A classification of D, not classfiable as to human carcinogenicity was assigned. Given this lack of evidence, for the purpose of this risk assessment, biphenyl was evaluated as a non-carcinogen.

24.2 Susceptible Populations

No susceptible populations were identified.

24.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

24.3.1 Oral Exposure

24.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, biphenyl is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

24.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, biphenyl is only being evaluated through the inhalation pathway, and as biphenyl is not considered to be a carcinogenic substance, a carcinogenic oral TRV has not been selected.

24.3.2 Inhalation Exposure

24.3.2.1 Non-Carcinogenic Toxicity Reference Values

24.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

No acute inhalation TRV for biphenyl was identified for use in the risk assessment.

24.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Chronic inhalation TRVs from Health Canada or the US EPA were not available at the time of writing of this risk assessment.

The US EPA (1989) provides an oral reference dose (RfD) of 0.05 mg/kg-day for biphenyl. This value is based on a study (Ambrose et al., 1960) in which fifteen weanling albino rats of each sex were placed in each of eight experimental groups: 0.0, 0.001, 0.005, 0.01, 0.05, 0.10, 0.50, and 1.0% biphenyl in the diet. Dietary levels of 0.5% biphenyl and greater were associated with kidney damage, reduced hemoglobin levels, decreased food intake, and decreased longevity. A LOAEL of 0.5% and a NOAEL of 0.1% of diet (corresponding to 50 mg/kg-day) were established based on these results. The NOAEL was modified by an uncertainty factor of 1000 (10 for interspecies variability and 100 for intraspecies variability) to obtain the RfD of 0.05 mg/kg-day.

The US EPA oral RfD of 0.05 mg/kg-day was then used by the risk assessment study team to calculate a chronic inhalation exposure limit based on route-to-route extrapolation. A body weight of 70.7 kg and an inhalation rate of 15.8 m^3/day were assumed for the purposes of the calculation. This resulted in a calculated chronic inhalation exposure limit of 224 µg/m^3.

24.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, biphenyl is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

24.4 Bioavailability

In this risk assessment, biphenyl is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that biphenyl is completely absorbed (i.e. absorption factor is 1).

24.5 Conclusion

The following tables present biphenyl TRVs selected for use in this risk assessment.

Table 24-1 Biphenyl Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Biphenyl	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] NE – Not Evaluated

Table 24-2 Biphenyl Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Biphenyl	1-Hour	NV			
	24-Hour	NV			
	Annual Average	224	Calculated route-to-route extrapolation from oral TDI.	RfD	US EPA, 1989

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value

24.6 References

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25.0 BORON

Boron is a solid substance that occurs widely in nature. It usually does not occur alone, and 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 and for high-energy fuel. Insecticides and wood preservatives also contain borates (ATSDR, 1992).

Exposure to boron dust can lead to the irritation of the nose throat and eyes (ATSDR, 2007). More serious effects are seen when exposed to higher doses of boron. Acute exposure to high doses of boron can affect the stomach, intestines, liver, kidney, and brain, and can eventually result in death (ATSDR, 2007). Animal studies indicate that exposure to high levels of boron, over short or long periods, can affect the male reproductive organs, especially the testes (ATSDR, 2007).

25.1 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. Accordingly, boron was not assessed as a carcinogen in this assessment.

25.2 Susceptible Populations

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

25.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

25.3.1 Oral Exposure

25.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004) derived a non-carcinogenic oral TRV of 0.0175 mg/kg-day based on an oral dosing study (boron in water) with dogs where the lowest reported NOAEL for adverse testicular effects was 8.75 mg/kg bw per day (Weir and Fisher 1972). Health Canada applied a 500 fold uncertain factor (10 for interspecies variation; 10 for intraspecies variation; and 5 for limitations of the critical study) to derive the TDI.

US EPA (2004) derived an oral non-carcinogenic RfD of 0.2 mg/kg-day. According to US EPA (2004) this dose was derived from a $BMDL_{05}$ (i.e., the 95 percent lower confidence limit) calculated by Allen et al. 1996 based on the data provided in two studies relating to developmental toxicity; Price et al. (1996) and Heindel et al. (1992). These studies evaluated groups of rats (groups of 14 or 29) fed a diet

containing different concentrations of boric acid (0-0.8%) from gestational day 0 to 20. These concentrations translated to 0, 78, 163, 330 and 539 mg boric acid/kg-day. The measurement endpoint chosen was a benchmark response of a 5% decrease in fetal weight relative to control samples although a number of endpoints were evaluated (e.g., changes in food and water intake and body weights; clinical signs of toxicity during pregnancy; mass changes in dam livers, kidneys, and intact uteri). 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. Using several benchmark dose analyses (BMD), Allen et al. (1996) calculated a $BMDL_{05}$ of 10.3 mg/kg-day (the Price et al. 1996 NOAEL was 9.6 mg/kg-day).US EPA (2004) applied an uncertainty factor of 66 to this $BMDL_{05}$ (to account for animal-to-human and sensitive-human uncertainty) to derive a RfD of 0.2 mg/kg-day.

Though the Health Canada TDI is lower than the IRIS RfD, the IRIS RfD of 0.2 mg/kg-day was used for this assessment because the data used to derive it were reviewed and assessed more recently than the Health Canada boron evaluation (HC 1990).

25.3.1.2 Cancer 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.

25.3.2 Inhalation Exposure

25.3.2.1 Non-Carcinogenic Toxicity Reference Values

25.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 50 $\mu g/m^3$ for boron was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008) based on the critical effects of eye and upper respiratory tract irritation. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour TRV was not available from any regulatory agencies at the time of this assessment.

25.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 5 $\mu g/m^3$ for boron was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 25.3.2.1.1. To derive a long-term ESL for boron, TCEQ further divides the short-term ESL by an additional safety factor of 10.

25.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Boron is not being evaluated as a carcinogenic substance; therefore no carcinogenic inhalation TRV was selected.

25.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was assumed to be 0.1.

25.5 Conclusion

The following tables present boron TRVs selected for use in this risk assessment.

Table 25-1 Boron Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Boron	Non-carcinogenic TRV	0.2	Decreased fetal weight	RfD	US EPA, 2004
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 25-2 Boron Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Boron	1-Hour	50	Eye and respiratory tract irritation	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	5	Eye and respiratory tract irritation	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3), NV-no value

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26.0 BROMODICHLOROMETHANE

Bromodichloromethane is a colorless, nonflammable liquid that readily evaporates in air and can be dissolved in water (ATSDR, 1999).

There are no studies on the effects of bromodichloromethane on human health, however, animal studies have shown a number of effects, depending on the duration of exposure (ATSDR, 1999). Acute (short term) exposure to bromodichloromethane can affect the central nervous system, inducing symptoms such as sleepiness and incoordination. Chronic exposure to lower doses of bromodichloromethane can cause liver and kidney damage (ATSDR, 1999). High levels of bromodichloromethane have also been shown to cause birth defects in animal studies (ATSDR, 1999).

26.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC, 2006), classifies bromodichloromethane as Group 2B, “possibly carcinogenic to humans.” The US EPA (1993) classifies bromodichloromethane as Group B2, a probable human carcinogen via ingestion, based on inadequate human data and sufficient evidence of carcinogenicity in two animal species (mice and rats) as shown by increased incidence of kidney tumors and tumors of the large intestine in male and female rats, kidney tumors in male mice, and liver tumors in female mice.. There is evidence that eating or drinking bromodichloromethane causes liver, kidney, and intestinal cancer in rats and mice (ATSDR 1999).

There is no evidence of bromodichloromethane carcinogenicity after being inhaled, and because bromodichloromethane is being assessed from the inhalation pathway, it is considered as a non-carcinogen.

26.2 Susceptible Populations

Populations with increased susceptibility to exposure to bromodichloromethane were not identified.

26.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

26.3.1 Oral Exposure

26.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, bromodichloromethane is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

26.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, bromodichloromethane is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

26.3.2 Inhalation Exposure

26.3.2.1 Non-Carcinogenic Toxicity Reference Values

26.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 20 µg/m^3 for bromodichloromethane was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure limit was not identified for bromodichloromethane.

26.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 2 µg/m^3 for bromodichloromethane was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 26.3.2.1.1. To derive a long-term ESL for bromodichloromethane, TCEQ further divides the short-term ESL by an additional safety factor of 10.

26.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Bromodichloromethane is not considered carcinogenic by inhalation; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

26.4 Bioavailability

In this risk assessment, bromodichloromethane is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that bromodichloromethane is completely absorbed (i.e. absorption factor is 1).

26.5 Conclusion

The following tables present Bromodichloromethane TRVs selected for use in this risk assessment.

Table 26-1 Bromodichloromethane Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Bromodichloromethane	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] NE – Not Evaluated

Table 26-2 Bromodichloromethane Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Bromodichloromethane	1-Hour	20	Health Based	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	2	Health Based	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)
NV – No Value

26.6 References

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OSHA (Occupational Safety and Health Administration). 1988. Permissible Exposure Limits http://www.cdc.gov/niosh/pel88/npelname.html

TCEQ (Texas Commission on Environmental Quality). 2008. Effects Screening Levels. http://www.tceq.state.tx.us/implementation/tox/index.html.

US EPA. 1993. Integrated Risk Information System (IRIS) Database, Bromodichloromethane Available at: http://www.epa.gov/iris/. United States Environmental Protection Agency. http://www.epa.gov/ncea/iris/subst/0213.htm

27.0 BROMOFORM

Bromoform is a colorless to yellow, heavy, nonflammable, liquid with a sweet odor. It is mainly used as a laboratory reagent (ATSDR, 2005a). Most of the bromoform and dibromochloromethane that enters the environment is formed as byproducts when chlorine is added to drinking water to kill bacteria (ATSDR, 2005a).

Ingestion of large amounts of bromoform can cause sleepiness through slowing down normal brain activity, however these effects generally pass within the day. Exposure to very high levels of bromoform may cause unconsciousness and possible death (ATSDR 2005b). Animal studies have demonstrated toxic effects to the liver and kidneys, as well as reproductive effects, from exposure to high levels of bromoform, however this hasn't been demonstrated in people (ATSDR 2005b)

27.1 Assessment of Carcinogenicity

The IARC (2006) identifies bromoform as not classifiable with respect to carcinogenicity. The US EPA's IRIS program classifies bromoform as B2, probable human carcinogen (US EPA 1991). The Agency for Toxic Substances and Disease Registry (ATSDR, 2005a) states that while it has been shown that exposure to bromoform may cause liver and kidney cancer in animals, there is no conclusive information available on the carcinogenic potential of bromoform in humans.

For this assessment, bromoform is being assessed as a carcinogen.

27.2 Susceptible Populations

The elderly, and people with existing renal or hepatic disease may be more susceptible to exposure to bromoform, and differences in susceptibility could exist between humans as a function of sex, age, or other metabolism influencing factors (ATSDR, 2005a).

27.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

27.3.1 Oral Exposure

27.3.1.1 Non-Carcinogenic Toxicity Reference Values

Both the US EPA (1991) and ATSDR (2005a) have derived an oral reference dose (RfD) of 0.02 mg/kg/day for bromoform based on a study by NTP (1989); however, derivation is based on different exposure doses and uncertainty factors. The NTP (1989) study was a sub-chronic gavage bioassay involving rats showing hepatic lesions. During the 13-week study, 20 F344/N rats (male and female) were given 0, 12, 25, 50, 100 or 200 mg/kg bromoform/day by gavage and 20 B6C3F1 mice (male and female) were given 0, 25, 50, 100, 200, or 400 mg/kg bromoform/day by gavage, 5 days/week. In the rats, there were elevated instances of clear cell foci at doses of 50 mg/kg/day (the LOAEL) but not in the next lowest dose (25 mg/kg/day) which was, therefore set as the study NOAEL.

The US EPA (1991) oral reference dose (RfD) of 0.02 mg/kg/day is derived from a NOAEL of 25 mg/kg-day, converted for exposure, with an uncertainty factor of 1000 applied to account for use of a subchronic study, extrapolation from animal data and protection of sensitive human subpopulation. Whereas, the ATSDR (2005a) derived their minimal risk level (MRL) of 0.02 mg/kg/day based on histopathological changes (vacuolization) in the liver of rats identified at a LOAEL of 50 mg/kg/day. The LOAEL was further modified by a factor of 3000 to account for use of a LOAEL, extrapolation from animals to humans, human variability, and to account for a lower LOEAL in a shorter study.

For this assessment, an oral reference dose of 0.02 mg/kg/day has been selected.

27.3.1.2 Carcinogenic Toxicity Reference Values

An oral slope factor of 0.0079 $(mg/kg/d)^{-1}$ was derived by the US EPA (1991) from a gavage study conducted by NTP (1988). F344/N rats and B6C3F1 mice (50/sex/group) were administered bromoform in corn oil by gavage 5 days/week for 2 years at 0, 100, or 200 mg/kg (rats and female mice) or 0, 50, or 100 mg/kg (male mice). Neoplastic lesions (adenomatous polyps or adenocarcinomas) were observed in the large intestine of both male and female rats.

This US EPA (1991) oral slope factor was selected for this assessment.

27.3.2 Inhalation Exposure

27.3.2.1 Non-Carcinogenic Toxicity Reference Values

27.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 50 $\mu g/m^3$ for bromoform was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 500 $\mu g/m^3$ based on the following critical effects: upper respiratory tract irritation and liver damage. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 55 $\mu g/m^3$ for bromoform was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

27.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 5 $\mu g/m^3$ for bromoform was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 27.3.2.1.1. To derive a long-term ESL for bromoform, TCEQ further divides the short-term ESL by an additional safety factor of 10.

27.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

The lack of suitable positive carcinogenic data from inhalation exposure precludes the selection of a unit risk for bromoform.

27.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.11 (Health Canada, 2004).

27.5 Conclusion

The following tables present bromoform TRVs selected for use in this risk assessment.

Table 27-1 Bromoform Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Bromoform	Non-carcinogenic TRV	0.02	Hepatic Lesions	RfD	US EPA, 1991
	Carcinogenic Slope Factor	0.0079	Neoplastic lesions (adenomatous polyps or adenocarcinomas)	SF	US EPA, 1991

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC $(mg/kg/day)^{-1}$

Table 27-2 Bromoform Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Bromoform	1-Hour	50	Upper respiratory tract irritation; liver damage	Benchmark	TCEQ ESL, 2008
	24-Hour	55	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	5	Upper respiratory tract irritation; liver damage	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC $(\mu g/m^3)$

27.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

ATSDR (Agency for Toxic Substances and Disease Registry), 2005a. Toxicological Profile for Bromoform and Dibromochloromethane. August 2005.

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TCEQ (Texas Commission on Environmental Quality). 2008. Effects Screening Level Lists. Available at: http://www.tceq.state.tx.us/implementation/tox/esl/list_main.html

US EPA (United States Environmental Protection Agency). 1991. Bromoform: Full IRIS Summary. US Environmental Protection Agency Integrated Risk Information System. Available at: www.epa.gov/iris.

28.0 BROMOMETHANE

Bromomethane is a manufactured chemical. It also occurs naturally in small amounts in the ocean where it is formed, probably by algae and kelp. It is a colorless, nonflammable gas with no distinct smell (ATSDR, 1992). Bromomethane is used to kill a variety of pests including rats, insects, and fungi. It is also used to make other chemicals or as a solvent to get oil out of nuts, seeds, and wool (ATSDR, 1992). Bromomethane is also known as methyl bromide, mono-bromomethane, and methyl fume. Trade names include Embafume and Terabol.

The effects of bromomethane on human health are dependent on the dose, the route of contact, and the duration of contact. Inhalation of bromomethane can lead to headache and feelings of weakness and nausea. Inhalation of high doses can lead to fluid buildup in lungs (leading to difficulty breathing) muscle tremors, seizures, kidney damage, nerve damage and possible death (ATSDR, 1995). Chronic inhalation exposure to low doses of bromomethane have resulted in moderate to severe nervous system effects in rabbits and monkeys, but this has not been demonstrated in humans (ATSDR, 1995). Effects on the reproductive system have only been seen in animal studies, and only at very high exposure levels (ATSDR, 1995).

Ingestion of bromomethane can cause stomach irritation, and dermal contact with bromomethane can cause itching, redness and blisters (ATSDR, 1995).

28.1 Assessment of Carcinogenicity

US EPA (2005) lists bromomethane as group D, not classifiable as to its human carcinogenicity. This grouping is based on a lack of data concerning carcinogenicity in humans and animals.

The IARC (1999) lists bromomethane as a Group 3 chemical: describing it as not classifiable as to its carcinogenicity to humans.

For this risk assessment bromomethane was evaluated as a non-carcinogen.

28.2 Susceptible Populations

No studies were located to suggest that any specific human subpopulation may be more susceptible to bromomethane than average, although it may be expected that the young, the elderly, and people with lung, kidney, or neurological disease might be more readily affected than healthy adults (ATSDR, 1992).

Studies in animals reveal that there are differences in sensitivity between species (e.g., Irish et al. 1940), and some studies have noted small differences in sensitivity between males and females (Eustis et al. 1988). It is not known if these differences apply to humans

28.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

28.3.1 Oral Exposure

28.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, bromomethane is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

28.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, bromomethane is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

28.3.2 Inhalation Exposure

28.3.2.1 Non-Carcinogenic Toxicity Reference Values

28.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 120 µg/m^3 for bromomethane was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure limit was not identified for bromomethane.

28.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The US EPA (1992) has published an inhalation RfC of 5 µg/m^3 for bromomethane. This TRV is based on a LOAEL for the appearance of degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity from a chronic inhalation study conducted by Reuzel et al. (1987, 1991). Fifty male and sixty female Wistar rats were exposed to 0, 3, 30, or 90 ppm (0, 11.7, 117, or 350 mg/m^3) 98.8 % pure bromomethane for 6 hours/day, 5 days/week for up to 29 months. Based on the study results, a LOAEL of 3 ppm (11.7 mg/m^3 or 2.08 mg/m^3 adjusted for non-continuous exposure) was determined. This LOAEL was further adjusted to derive a human equivalent concentration (LOAEL (HEC)) of 0.48 mg/m^3 and divided by an uncertainty factor of 100 to reflect intraspecies uncertainty (10), the use of a LOAEL for a mild effect (3) and interspecies extrapolation because dosimetric adjustments have been applied (3) (US EPA, 1992).

ATSDR (1992) has established a chronic minimal risk level for bromomethane of 20 µg/m^3. The value is based on an epidemiological study of workers who had an increased prevalence of muscle ache, fatigue, and ataxia following chronic exposure to average levels of approximately 9000 µg/m^3 (Anger et al. 1986). The MRL was derived by adjusting this LOAEL to account for non-continuous exposure (8

hr/day, 5 days/week), and by dividing by an uncertainty factor of 100 (10 for use of a LOAEL, and 10 for human variability).

As it is more conservative, the US EPA value of 5 µg/m^3 was selected for this risk assessment.

28.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, bromomethane is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation TRV has not been selected.

28.4 Bioavailability

In this risk assessment, bromomethane is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that bromomethane is completely absorbed (i.e. absorption factor is 1).

28.5 Conclusion

The following tables present bromomethane TRVs selected for use in this risk assessment.

Table 28-1 Bromomethane Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Bromomethane	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] NE – Not Evaluated

Table 28-2 Bromomethane Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Bromomethane	1-Hour	120	Health Based	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	5	Degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity	RfC	US EPA, 1992

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value

28.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

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TCEQ (Texas Commission on Environmental Quality) 2008. Effects Screening Levels. http://www.tceq.state.tx.us/implementation/tox/index.html.

US EPA (United States Environmental Protection Agency). 2005. Integrated Risk Information System (IRIS). Bromomethane (CASRN 74-83-9). http://www.epa.gov/ncea/iris/subst/0015.htm

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29.0 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).

Acute inhalation exposure to high levels of cadmium can severely damage lungs. Ingestion of high levels of cadmium can lead to stomach irritation including vomiting and diarrhea. Chronic effects of long-term exposure to lower doses of cadmium in air, food, or water, can lead to build-up of cadmium in the kidneys and possible kidney disease. Other long-term effects include lung damage and fragile bones (ATSDR, 2008). Although cadmium accumulates in bone, the bone disease that results from excessive cadmium exposure is believed to be secondary to changes in calcium metabolism due to cadmium-induced renal damage (ATSDR 1999). Itai-itai disease (ouch-ouch disease), characterized by weak and deformed bones was identified in people from Japan exposed to excessive levels of cadmium in their diets over their lifetime.

29.1 Assessment of Carcinogenicity

Several occupational studies have reported an increased 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).

For this assessment, cadmium is being assessed as an inhalation carcinogen.

29.2 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).

29.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

29.3.1 Oral Exposure

29.3.1.1 Non-Carcinogenic 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, 1972; 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 (1972) 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 IRIS (1994) derived a chronic oral RfD for water consumption of 0.0005 mg/kg-day. This value was based upon a NOAEL of 0.005 mg/kg-day for significant proteinuria in human studies involving chronic exposures (US EPA 1985). This value, in turn, was derived from a toxicokinetic model that determined the chronic human oral exposure which results in 0.2 mg Cd/gm wet human renal cortex (the highest renal level not associated with renal proteinuria (the critical effect) based on numerous studies). The toxicokinetic model assumes that 0.01% day of the Cd body burden is eliminated per day, and that absorption rates are 2.5% from food and 5% from water. An uncertainty factor of 10 was applied to account for inter-human variability. The choice of NOAEL used to develop the chronic RfD does not reflect the information from a single study, but rather data from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism and elimination therefore; high confidence is given for the oral RfD and database.

The US EPA (1994) TRV of 0.0005 mg/kg-day was used in this assessment.

29.3.1.2 Carcinogenic Toxicity Reference Values

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

29.3.2 Inhalation Exposure

29.3.2.1 Non-Carcinogenic Toxicity Reference Values

29.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.1 $\mu g/m^3$ for cadmium was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 10 $\mu g/m^3$ based on the following critical effects: eye and upper respiratory tract irritation; CNS impairment; and cardiac system impairment. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 0.025 µg/m^3 for cadmium was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational respiratory irritation with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

29.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The MOE (2007) derived a chronic AAQC (annual averaging time) of 0.005 µg/m^3 which was based on the scientific approach used by European Commission (EC) (2000). The value was derived by applying an uncertainty factor of 50 (5 for use of a LOAEL and 10 for inter-individual variability) to an adjusted LOAEL of 0.270 µg/m^3 for proteinuria associated with proximal tubular dysfunction and lung cancer as a result of workplace exposure (Thun et al. 1991). The Thun et al. (1991) study pooled data from 7 epidemiological studies. The study showed a sharp increase in the prevalence of tubular dysfunction with exposures greater than 500 µg/m^3-years (i.e. 8.8% at 400 µg/m^3-years, 50% at 1000 µg/m^3-years and >80% at more than 4500 µg/m^3-years). Other studies reviewed also showed increases in the prevalence of tubular dysfunction between 100-400 µg/m^3-years. The starting point of an air limit value was therefore set to be a LOAEL of 100 µg/m^3-years worktime exposure, extrapolated to derive the lifetime exposure LOAEL of 0.270 µg/m^3. The uncertainty adjusted value of 0.005 µg/m^3, which is consistent with the chronic inhalation RfC for cadmium utilized by the EC (2000) and WHO (2000), was selected as the chronic inhalation exposure limit in the current assessment.

29.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Health Canada (2004b) has calculated an inhalation unit risk of 0.0098 (µg/m^3)$^{-1}$ which is equivalent to an inhalation slope factor of 42.9 (mg/kg-day)$^{-1}$ for adults which was based on a TC_{05} of 5.1 µg/m^3 (Health Canada, 1996). The estimated TD_{05} for cadmium chloride was based on multistage model of lung tumour incidences observed in rats by Takenaka et al. (1983). Male Wistar rats were exposed to 13.4 to 50.8 µg Cd/m3 cadmium chloride aerosols (23 hours/day for 18 months) and significant dose related increases in lung tumours were seen. The study came up with a TD_{05} of 2.9 µg of cadmium/m^3 which 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 µg/m^3 (Environment Canada and Health Canada, 1994).

The US EPA (1994) has developed an inhalation unit risk of 0.0018 (µg/m^3)$^{-1}$ to be used only if the air concentration does not exceed 6 µg/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.

The Health Canada TC_{05} provides a more conservative unit risk estimate of the potency of inhaled cadmium; therefore, an inhalation unit risk of 0.0098 (µg/m^3)$^{-1}$ was used in this assessment.

29.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.14 (Health Canada, 2004a).

29.5 Conclusion

The following tables present cadmium TRVs selected for use in this risk assessment.

Table 29-1 Cadmium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Cadmium	Non-carcinogenic TRV	0.0005	Significant proteinuria	RfD	US EPA, 1994
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 29-2 Cadmium Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Cadmium	1-Hour	0.1	Kidney Damage	Benchmark	TCEQ ESL, 2008
	24-Hour	0.025	Respiratory Irritation	Benchmark	MOE AAQC, 2008
	Annual Average	0.005	Kidney Effects	Benchmark	MOE AAQC, 2007
	Carcinogenic Annual Average	0.0098	Detection of Lung Tumours	UR	Health Canada, 2004b

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$, UR (unit risk)

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30.0 CARBON TETRACHLORIDE

Carbon tetrachloride is a manufactured clear liquid with a sweet smell that can be detected at low levels. It is most often found in the air as a colorless gas. It is not flammable and does not dissolve in water very easily. It was used in the production of refrigeration fluid and propellants for aerosol cans, as a pesticide, as a cleaning fluid and degreasing agent, in fire extinguishers, and in spot removers (ATSDR, 2005b). Because of its harmful effects, these uses are now banned and it is only used in some industrial applications (ATSDR, 2005b).

Ingestion, inhalation, and potentially dermal contact with high levels of carbon tetra chloride can cause liver, kidney (and the consequent building up of waste in the blood) and central nervous system damage, with the liver being especially sensitive (ATSDR 2005b). If exposure is low and short in duration then the liver and kidneys can repair themselves and resume normal function (ATSDR 2005b).

Very high exposure can result in nervous system (including the brain) damage. People can feel intoxicated, have headaches, dizziness, sleepiness, nausea and vomiting. In some cases, these effects may subside if exposure stops, but in severe cases, coma and death can occur (ATSDR 2005b).

There are not studies on the effects of carbon tetrachloride on human reproduction, but chronic inhalation of carbon tetrachloride in rats has been shown to decrease fertility (ATSDR 2005b).

30.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC) classifies carbon tetrachloride as possibly carcinogenic to humans (2B). The US EPA's classifies carbon tetrachloride as probably carcinogenic to humans based on carcinogenicity in rats, mice and hamsters (US EPA, 1992). The Agency for Toxic Substances and Disease Registry indicates that carbon tetrachloride may reasonably be anticipated to be a carcinogen based on adrenal gland and liver tumors in animals. Studies in humans have not been able to determine whether or not carbon tetrachloride can cause cancer because usually there has been exposure to other chemicals at the same time (ATSDR, 2005b). Health Canada has identified carbon tetrachloride as a carcinogen in drinking water (HC, 2004).

For this assessment carbon tetrachloride is being assessed for both non-carcinogenic and carcinogenic endpoints.

30.2 Susceptible Populations

Some populations may be unusually susceptible to toxicity from carbon tetrachloride. There are a number of chemicals that can exacerbate the toxic effects of carbon tetrachloride, so individuals exposed to these chemicals may be more susceptible. This includes people who take certain drugs (such as phenobarbital, pentobarbital, and phenylbutazone), or in contact with certain insecticides (such as DDT) (ATSDR 2005a). Moderate to heavy drinkers also have significantly increased risk of liver and/or kidney injury resulting from carbon tetrachloride exposure (ATSDR 2005a). There is also some evidence that diabetics may be particularly susceptible to carbon tetrachloride poisoning (ATSDR 2005a).

30.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

30.3.1 Oral Exposure

30.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004) does not provide a non-carcinogenic TRV for oral exposures to carbon tetrachloride.

The US EPA (1991) provides an oral non-cancer TRV for carbon tetrachloride of 0.0007 mg/kg body weight/day. A recent reanalysis of the same data by the US EPA (2008) for IRIS has proposed the oral RfD for carbon tetrachloride should increase by a factor of approximately 6 to 0.004 mg/kg-day. The proposed draft RfD relies on the same principal study as the previous RfD, but applies benchmark dose analysis to derive the point of departure (POD) of 3.9 mg/kg-day, whereas the previous RfD used the NOAEL of 0.7 mg/kg-day as the POD. Both RfDs were derived using a total uncertainty factor of 1,000.

As discussed above, it should be noted that carbon tetrachloride is under external review by the US EPA at this time (see US EPA, 2008), and new values have been proposed for the oral RfD, inhalation RfC, inhalation unit risk, and oral slope factor toxicological benchmarks; however, these values do not yet represent official US EPA policy and may change pending external review. As such, it is not appropriate to use these draft benchmarks in a HHRA at this time.

The current US EPA (1991) oral RfD is based on the study by Bruckner et al. (1986) in which male Sprague-Dawley rats were administered 1, 10, or 33 mg carbon tetrachloride/kg/day by corn oil gavage, 5 days/week for 12 weeks. Liver lesions (mild centrilobular vacuolization as well as statistically significant increases in serum sorbitol dehydrogenase activity, occurred at the 10 and 33 mg/kg/day dose levels, with more severe effects at 33 mg/kg/day. The LOAEL and NOAEL were established at 10 and 1 mg/kg/day, respectively. Both values were adjusted by a factor of 5/7 (to account for the 5 day per week dosing regimen used in the study) to yield a LOAEL and NOAEL of 7.1 mg/kg/day and 0.71 mg/kg/day, respectively. A cumulative uncertainty factor of 1,000 (for interspecies and intrahuman variability and extrapolation from a subchronic to a chronic exposure duration) was applied to the adjusted NOAEL to yield the oral RfD. The US EPA (1991) has an overall medium level of confidence in this RfD. This confidence rating reflects that the principal study (Bruckner et al., 1986) was well conducted and a good dose-response relationship was observed in the liver, which is the target organ for carbon tetrachloride. The principal study is supported by other subchronic studies; however, reproductive and developmental effects are not well investigated in these or other studies

The US EPA RfD of 0.0007 mg/kg-day was adopted as the chronic oral exposure limit for non-carcinogenic effects for the current assessment.

30.3.1.2 Carcinogenic Toxicity Reference Values

Health Canada (2004) provides a carcinogenic slope factor for oral exposures to carbon tetrachloride of 0.049 $(mg/kg\text{-}d)^{-1}$, derived from the Guideline for Canadian Drinking Water Quality (GCDWQ) for carbon tetrachloride (Health Canada, 1989). The GCDWQ provides a unit lifetime risk associated with

the ingestion carbon tetrachloride in drinking water of 3.30 x 10^{-7} (based on hepatocellular carcinomas in male mice) to 1.04 x 10^{-6} (based on hepatic neoplastic nodules and hepatocellular carcinomas in male rats).

The US EPA (1991) provides an oral slope factor of 0.13 $(mg/kg\text{-}day)^{-1}$. This slope factor was derived using the linearized multistage procedure with extra risk. It is based on the tumour incidence data from five oral (gavage) animal studies with carbon tetrachloride (Della Porta et al., 1961; Edwards et al., 1942; NCI, 1976a,b, 1977). These studies showed significant dose-related increases in the incidence of hepatocellular carcinomas and hepatomas in hamsters, mice and rats. The confidence in the oral slope factor is relatively low as all studies were deficient in some respects, which precluded the choice of any one study as the principal study. For all studies, data from males and females were combined because of the small sample sizes used. Some studies only tested single doses and some failed to report tumour incidence in control groups. In the NCI (1976a, b) studies, tumour incidence in the mice was near 100%, and goodness-of-fit criteria were not satisfied for the linearized multistage model. In addition, tumour incidence in rats in these studies was higher at low doses, presumably because early mortality at higher doses prevented tumour formation. All studies also lacked pharmacokinetic data. Despite these many shortcomings, a common biological mechanism, cell death and regeneration, leading to development of the same tumour type in all species tested, was observed in all studies. Also, since the risk estimates from these studies varied by two orders of magnitude, a geometric mean was derived as the final risk estimate to accommodate for the various study deficiencies.

The US EPA slope factor of 0.13 $(mg/kg\text{-}day)^{-1}$was adopted as the chronic oral exposure limit for carcinogenic effects for the current assessment.

30.3.2 Inhalation Exposure

30.3.2.1 Non-Carcinogenic Toxicity Reference Values

30.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 130 $\mu g/m^3$ for carbon tetrachloride was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008) based on the critical effects of skin and eye irritation; CNS depression; liver and kidney injury. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009). TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

The 24-hour exposure limit TRV of 2.4 $\mu g/m^3$ has been chosen for carbon tetrachloride based on central nervous system effects for the current assessment. This value is the current MOE (2008) 24-hour ambient air quality criterion for carbon tetrachloride

30.3.2.1.2 Chronic Inhalation Toxicity Reference Values

CalEPA (2000) provides a chronic inhalation non-cancer REL of 0.006 ppm (40 µg/m^3) derived principally on a study by Adams et al. (1952). In this study, 9 male and 9 female guinea pigs were exposed to carbon tetrachloride *via* discontinuous whole body inhalation, for 7 hours/day, 5 days/week, for 203 days. A LOAEL of 5 ppm was identified, based on increased liver weights and increased liver lipid content in females. A NOAEL was not observed in this study. Cal EPA (2000) converted this LOAEL to a human-equivalent air concentration of 1.7 ppm. A cumulative uncertainty factor of 300 (3 for interspecies differences, 3 for use of a LOAEL instead of a NOAEL 10 for intraspecies variability, and 3 to extrapolate from a subchronic to a chronic exposure duration) was then applied to the human equivalent concentration to yield the chronic REL (0.006 ppm which equals 40 µg/m^3).

The ATSDR provides a minimum risk level (MRL) of 0.03 ppm (190 µg/m^3) (ATSDR, 2005a). The ATSDR MRL is based on a 2-year bioassay study of F344/DuCrj rats and BDF_1 mice (50/sex/group) exposed to 0, 5, 25 or 125 ppm carbon tetrachloride for 6 hours/day, 5 days/week for 104 weeks (Japan Bioassay Research Center 1998; Nagano et al. 1998). Increased liver weight, serum enzymes and liver histopathology in rats and mice was the critical endpoint. A NOAEL of 5 ppm was converted to 0.9 ppm to account for the human equivalent concentration, and modified by an uncertainty factor of 30 to account for extrapolation from animals to humans and human variability. ATSDR reviewed a number of chronic inhalation studies, including Adams et al. (1952) and selected the Japan Bioassay Research Center (1998) and Nagano et al. (1998) studies as the basis of the MRL because they were chronic-duration inhalation bioassay where hepatic effects (increased serum enzyme levels, liver weight, and liver histopathology) were assessed without increased mortality. ATSDR used the Adams et al srusy as the basis of the intermediate-duration inhalation MRL,

The ATSDR MRL of 190 µg/m^3 was adopted as the chronic inhalation exposure limit for non-carcinogenic effects for the current assessment.

30.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

The US EPA (1991) provides an inhalation UR of 1.5×10^{-5} per µg/m^3. This UR was derived using the linearized multistage procedure with extra risk. Inhalation risk estimates were calculated from the oral exposure data using oral to inhalation route extrapolation. Specifically, inhalation risk was calculated assuming an air intake of 20 m^3/day and a 40% lung absorption rate by humans (U.S EPA, 1984). A range of UR estimates was determined, with 1.5×10^{-5} per µg/m^3 calculated as the geometric mean UR. Confidence in this UR is low for the same reasons that are discussed above in the description of the oral slope factor, and the fact that oral to inhalation route extrapolation was conducted.

Cal EPA (2005) used the US EPA quantitative carcinogenic risk estimate for carbon tetrachloride as the basis for their reported UR. This value (4.2×10^{-5} per µg/m^3) is slightly more conservative than the original US EPA UR, as California Department of Health Services (DHS was the agency that originally derived the UR reported in Cal EPA, 2005) modified some of the assumptions. Cal EPA's DHS used a similar database of studies to that reviewed by the US EPA, but their review differed by the four following points: 1) applied an absorption fraction of 50% instead of 40%; 2) omitted one rat bioassay used by the US EPA; 3) assumed an average inhalation intake of 18 µg/day instead of 20 µg/day; and 4) presented the range of resulting unit risks instead of the geometric mean.

The US EPA unit risk of 1.5 x 10^{-5} per µg/m^3 was selected for evaluation of carcinogenic inhalation exposures in this assessment.

30.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.2 (Health Canada, 2004).

30.5 Conclusion

The following tables present carbon tetrachloride TRVs selected for use in this risk assessment.

Table 30-1 Carbon Tetrachloride Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Carbon Tetrachloride	Non-carcinogenic TRV	0.0007	Liver lesions	RfD	US EPA, 1991
	Carcinogenic Slope Factor	0.13	Hepatocellular carcinomas and hepatomas	UR	US EPA, 1991

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC (mg/kg/day)$^{-1}$

Table 30-2 Carbon Tetrachloride Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Carbon Tetrachloride	1-Hour	130	Skin and Eye Irritation; CNS depression; liver, kidney injury; potential occupational carcinogen	Benchmark	TCEQ ESL, 2008
	24-Hour	2.4	Central Nervous System Effects	Benchmark	MOE AAQC, 2008
	Annual Average	190	increased liver weight, serum enzymes and liver histopathology in rats and mice	RfC	ATSDR MRL, 2005a
	Carcinogenic Annual Average	1.5 x 10^{-5}	Hepatocellular carcinomas/hepatomas	UR	US EPA, 1991

[a] Units: Non-carcinogenic COPC (µg/m^3) , Carcinogenic COPC (µg/m^3) $^{-1}$

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31.0 CHLOROFORM

Chloroform is a colorless liquid with a pleasant, nonirritating odor and a slightly sweet taste (ATSDR, 1997a). It will burn only when it reaches very high temperatures. In the past, chloroform was used as an inhaled anesthetic during surgery, however this is no longer the case. Today, chloroform is used to make other chemicals, as well as being formed in small amounts when chlorine is added to water (ATSDR, 1997a). Chloroform is also known as trichloromethane and methyl trichloride.

Inhalation of high levels of chloroform for a short period of time can cause dizziness, fatigue and headache (ATSDR, 1997b). Chronic inhalation or ingestion of chloroform can lead to liver and kidney damage (ATSDR, 1997b). Dermal contact with high doses of chloroform can cause skin irritation and sores (ATSDR, 1997b).

Animal studies have shown that inhalation and ingestion of chloroform during pregnancy can cause miscarriages and birth defects, and that inhalation of chloroform can cause abnormal sperm. It is not known whether chloroform causes reproductive effects or birth defects in humans (ATSDR, 1997b).

31.1 Assessment of Carcinogenicity

ATSDR (1997a) 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.

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).

For this assessment chloroform is being assessed for both non-carcinogenic and carcinogenic endpoints.

31.2 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).

31.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

31.3.1 Oral Exposure

31.3.1.1 Non-Carcinogenic Toxicity Reference Values

An oral RfD of 0.01 mg/kg-day was derived for chloroform by the U.S. EPA (2001), based on a study by Heywood et al. (1979). The study exposed groups (8 dogs each) of male and female beagle dogs, plus an untreated group of 16 dogs (half female, half male) to a dose of 15 or 30 mg chloroform/kg-day in gelatin capsules, 6 days/week, for a total duration of 7.5 years. Termination of dosing was followed by a 20 to 24 week recovery period. The control group received non-chloroform placebos (Heywood et al., 1979). In the exposed groups, hepatic fatty cysts were increased in both size and severity compared to the control group. The exposed groups also showed an increase in serum glutamate-pyruvate transaminase levels (SGPT, also known as alanine aminotransferase), which indicates low-level liver damage (Heywood et al., 1979). The LOAEL identified by Heywood et al. (1979) was 15 mg/kg-day. To yield the oral RfD of 0.01 mg/kg-day, the LOAEL was divided by a cumulative uncertainty factor of 1,000 (10 to extrapolate from LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for human variability) and adjusted for continuous exposure by applying a factor of 6/7 (accounting for 6 days of exposure per week instead of 7 days).

The US EPA (2001) also evaluated chloroform using the benchmark dose approach using data from the Heywood et al. 1979 study as well as three other dosing studies (Hard et al., 2000; Larson et al., 1994b; Larson et al., 1995). The $BMDL_{10}$ was 1.2 mg/kg-day which was converted to 1.0 mg/kg-day, the same as the RfD calculated from the dosing study. However, only an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitivity) was applied.

A chronic MRL of 0.01 mg/kg-day was derived by ATSDR (1997a) using the same principle study (*i.e.,* Heywood et al., 1979), and the same or similar adjustments and uncertainty factors as used by the US EPA (2001) to derive the oral RfD.

The US EPA RfD of 0.01 mg/kg-day was selected as the chronic oral exposure limit for non-carcinogenic effects for the current assessment.

31.3.1.2 Carcinogenic Toxicity Reference Values

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

31.3.2 Inhalation Exposure

31.3.2.1 Non-Carcinogenic Toxicity Reference Values

31.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

CalEPA (1999) has an acute (1-hour) REL of 150 $\mu g/m^3$ based on fetoxicity in a pregnant rat study (Schwetz et al. 1974), and histological changes in nasal epithelium in humans. The Schwetz et al. (1974) study exposed pregnant rats to 30, 100 or 300 ppm chloroform for 7hours/day during days 6-15 of gestation. The LOAEL for the study was 30 ppm, and this was adjust by an uncertainty factor of

1000 (LOAEL uncertainty (10), interspecies uncertainty (10) and intraspecies uncertainty (10)) resulting in an REL of 0.03ppm (150 µg/m^3).

A 1-hour exposure limit of 100 µg/m^3 for chloroform was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008) based on an increase in the incidence of renal tumours. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure benchmark of 1 µg/m^3 for chloroform was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects (central nervous system effects) with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

31.3.2.1.2 Chronic Inhalation Toxicity Reference Values

RIVM (2001) selected a chronic tolerable concentration in air of 100 µg/m^3 based on a human epidemiology study by Bomski et al. (1967) in which workers were exposed to chloroform over a period of one to four years; and a six month rat inhalation study with a NOAEL of 110 mg/m^3 (presumed adjusted from the LOAEL of 25 ppm). Critical affects in the rat study included liver, kidney and developmental toxicity. Uncertainty factors of 100 were applied (10 for the NOAEL and 10 for sensitive groups in the human population).

Bomski et al. (1967) was the study selected by ATSDR (1997a) to derive the chronic inhalation MRL of 0.02 ppmv (100 µg/m^3) for chloroform. This study examined a group of 68 workers exposed to chloroform air concentrations ranging from 2 to 205 ppm for a 1 to 4 year period, in a pharmaceutical plant. Hepatomegaly was found in 25% of exposed workers. Toxic hepatitis was found in 5.6% of the exposed workers and hepatosteatosis (fatty liver) was found to occur in 20.6% of the exposed group. Jaundice was also of a higher frequency in the exposed workers than in the control group. A systemic LOAEL of 2 ppm was identified from the Bomski et al. (1967) study. To yield the inhalation MRL of 0.02 ppm (100 µg/m^3), the LOAEL was divided by a cumulative uncertainty factor of 100 (10 to extrapolate from a LOAEL to a NOAEL and 10 for human variability).

The ATSDR MRL of 100 µg/m^3 was adopted as the chronic inhalation exposure limit for non-carcinogenic effects for the current assessment

31.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

US EPA (2001) has derived an inhalation unit risk of 2.3 x 10^{-5} per µg/m^3 based on a mouse oral gavage study (NCI, 1976) where the critical effect was hepatocellular carcinoma. B6C3F1 mice (50/sex/dose group) were treated with 100 or 200 mg/kg/day, raised to 150 or 300 mg/kg/day at 18 weeks (male), and 200 or 400 mg/kg/day raised to 250 or 500 mg/kg/day at 18 weeks (female) chloroform in corn oil 5 times/week for 78 weeks. Highly significant increases in hepatocellular carcinomas, compared to controls, were observed in both sexes at both dose levels. Extrapolation of

metabolism-dependent carcinogenic responses from mice to humans on the basis of body surface area is supported by experimental data. The incidence data for both male and female mice were used to derive slope factors of 3.3×10^{-2} and 2.0×10^{-1} per (mg/kg)/day, respectively. The unit risk was prepared by taking a geometric mean of the slope factor and assuming 100% for low doses of chloroform in air.

The US EPA unit risk of 2.3×10^{-5} per $\mu g/m^3$ was selected for evaluation of carcinogenic inhalation exposures in this assessment.

31.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004).

31.5 Conclusion

The following tables present chloroform TRVs selected for use in this risk assessment.

Table 31-1 Chloroform Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Chloroform	Non-carcinogenic TRV	0.01	Moderate Marked fatty cyst formation in the liver and elevated SGPT	RfD	US EPA, 2001
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day)
NE – Not Evaluated

Table 31-2 Chloroform Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Chloroform	1-Hour	100	Increase in the incidence of renal tumours	Benchmark	TCEQ ESL, 2008
	24-Hour	1	Central nervous system effects	Benchmark	MOE AAQC, 2008
	Annual Average	100	Liver Effects	RfC	ATSDR, 1997a
	Carcinogenic Annual Average	2.3×10^{-5}	Hepatocellular carcinomas	UR	US EPA, 2001

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$)$^{-1}$

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32.0 CHROMIUM (TOTAL AND HEXAVALENT CHROMIUM)

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. Both total chromium and hexavalent chromium will be addressed in this toxicity profile.

The health effects of chromium compounds are greatly dependent on their speciation. Chromium (III) is an essential nutrient; helping the body effectively use sugar, protein and fat. Although it can be toxic, this generally occurs at doses far higher than toxic doses of chromium (VI) (ATSDR, 2008).

Inhalation of chromium (VI) (or very high doses of chromium (III)) can cause irritation of the lining of the nose, resulting in nose ulcers and runny nose, as well as causing breathing problems such as asthma, cough, shortness of breath and wheezing (ATSDR, 2008). Ingestion of chromium (VI) has lead to irritation and ulcers in the stomach and small intestine, as well as anemia, in animal studies. Sperm damage and damage to the male reproductive system has also been observed in animal studies following exposure to chromium (VI) (ATSDR, 2008).

Dermal contact with chromium (VI) can cause skin ulcers. Allergic reactions, consisting of severe redness and swelling of the skin, have been seen in people sensitive to either chromium (III) or chromium (VI) (ATSDR, 2008).

32.1 Assessment of Carcinogenicity

Health Canada (2004b) has evaluated total chromium as an inhalation carcinogen but not an oral carcinogen. Inhalation carcinogenicity of total chromium is a result of chromium (VI), a known carcinogen, being a component of total chromium, not chromium (III).

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, 2008).

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 (ATSDR, 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, 2008, Health Canada, 2004a).

32.2 Susceptible Populations

It is suggested that female animals are more sensitive to the lethal effects of hexavalent chromium compounds (ATSDR, 2008). The risk of lung cancer due to inhalation of carcinogenic chromium compounds may be exacerbated in individuals who smoke cigarettes or are excessively exposed to

passive smoke (ATSDR, 2008).

32.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

32.3.1 Oral Exposure

32.3.1.1 Non-Carcinogenic Toxicity Reference Values

Chromium (VI)

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.

Chromium (III and Total)

US EPA (1998) derived a reference dose (RfD) of 1.5 mg/kg-day. The study was conducted through feeding chromic oxide baked in bread (dietary levels of 0, 1, 2 or 5%) to groups of 60 male and female rats 5 days/week for 600 feedings (840 total days). The average total amounts of chromic oxide ingested were 360, 720, and 1,800 g/kg bw for the 1, 2 and 5% treatment groups respectively. No effects were observed at any dose level. The NOAEL from this study (1,800 g/kg) was converted to a NOAEL for chromium (III) of 1,468 mg/kg-day by adjusting by a factor of 0.6849 g Cr/g Cr2O3 and then adjusting for continuous exposure. An uncertainty factor of 100 was used to account for interspecies and interhuman variability; a modifying factor of 10 was used to reflect database deficiencies (total = 1000).

32.3.1.2 Carcinogenic Toxicity Reference Values

Chromium (VI)

A carcinogenic oral TRV was not available for chromium (VI) from regulatory agencies; therefore, a carcinogenic oral TRV was not selected

Chromium (Total and III)

A carcinogenic oral TRV was not available for total chromium of chromium III from regulatory agencies; therefore, a carcinogenic oral TRV was not selected

32.3.2 Inhalation Exposure

32.3.2.1 Non-Carcinogenic Toxicity Reference Values

32.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Chromium (VI)

A 1-hour exposure limit of 0.1 µg/m^3 for chromium (VI) was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 10 µg/m^3 based on the following critical effects: lung cancer. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark for chromium (VI) was not available from any regulatory agency at the time of this assessment.

Chromium (Total)

A 1-hour exposure limit of 1 µg/m^3 for chromium (total) was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure benchmark for chromium (total) was not available from any regulatory agency at the time of this assessment.

32.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Chromium (VI)

The US EPA (1998) has developed an RfC for chromium (VI) of 0.1 µg/m^3. This value is based on a two subchronic rat study using lactate dehydrogenase in bronchioalveolar lavage fluid as the endpoint (Glaser et al., 1985, 1990). Glaser et al. (1990) exposed 8 week old male Wistar rats to sodium dichromate (in levels of 0.05-0.4 mg Cr(VI)/m^3) for 30-90 days (7 days/wk, 22hr/day). Glaser et al. (1985) exposed 5-week old make Wistar rats to aerosols of sodium dichromate (in levels of 0.05-0.4 mg Cr(VI)/m^3) for 28 or 90 days (22hr/day). In both studies, chromium induced effects occurred in a dose dependant manner. A BMC of 0.016mg/m^3 was determined (the lower 95% confidence limit on the dose corresponding to a 10% relative change in the endpoint compared to the control) from the studies. This was then converted to an RfC using an approach offered by Malsch et al. (1994). To arrive at an RfC, the BMC was multiplied by a Regional Deposited Dose Ratio (RDDR) to account for pharmacokinetic differences between species, a 3x uncertainty factor (to account for additional pharmacokinetic differences between species), another 3x uncertainty factor (to account for extrapolating from subchronic to chronic exposures, and a 10x uncertainty factor (to account for human to human variations in sensitivity). The resulting RfC for chromium (VI) of 0.1 µg/m^3 is the RfC used in this assessment

Chromium (Total and III)

The US EPA (1998) has not developed an RfC for chromium III (or total) citing that available data are considered to be inadequate for development of an RfC due to the lack of a relevant toxicity study addressing respiratory effects of Cr(III).

A chronic inhalation RfC of 60 µg/m^3 was derived by RIVM (2001) based on a study by Triebig et al., (1987) where a NOAEC of 0.6 mg/m^3 for kidney effects in humans was the study endpoint. An uncertainty factor of 10 for intraspecies variability was applied to the study NOAEC. This value was selected for use in the risk assessment.

32.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Chromium (VI)

Health Canada (2004a) derived an inhalation unit risk for chromium VI of 0.076 (µg/m^3)$^{-1}$ based on an increased incidence of lung cancer in occupationally exposed workers at a chromate production plant (Mancuso 1975). The concentration of Cr (VI) was estimated to be one seventh (1/7) of the reported total chromium concentration presented by Mancuso (1975), as an earlier study in the same chromate production plant reported that the proportion of trivalent to hexavalent chromium was about 6:1, or less (Bourne and Yee 1950). A $TD_{0.05}$ for Cr (VI) was estimated to be 0.66 µg/m^3. This was converted to an inhalation unit risk of 0.076 (µg/m^3)$^{-1}$ (unit risk = 0.05/$TD_{0.05}$). This value was selected as the inhalation unit risk factor of Cr (VI) for the current assessment.

Chromium (Total)

Health Canada (2004a) derived an inhalation unit risk for total chromium of 0.0109 (µg/m^3)$^{-1}$ based on an increased incidence of lung cancer in occupationally exposed workers at a chromate production plant (Mancuso 1975). The age-specific death rate was assumed to be a time-weighted quadratic function of exposure to chromium. A $TD_{0.05}$ for total chromium was estimated to be 4,600 µg/m^3. This was converted to an inhalation unit risk of 0.0109 (µg/m^3)$^{-1}$ (unit risk = 0.05/$TD_{0.05}$). This value was selected as the inhalation unit risk factor of total chromium for the current assessment

32.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 for both chromium (VI) and Chromium (total) (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set at 0.09 for chromium (VI) and 0.4 for chromium (total) (Health Canada, 2004).

32.5 Conclusion

The following tables present chromium (VI) and chromium (total) TRVs selected for use in this risk assessment.

Table 32-1 Chromium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Chromium (VI)	Non-carcinogenic TRV	0.001	Based on NOAEL from drinking water maximum	RfD	Health Canada,

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
			acceptable concentration		2004
	Carcinogenic Slope Factor	NE			
Chromium (total)	Non-carcinogenic TRV	1.5	Kidney effects	RfD	US EPA, 1998
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) , NE – Not Evaluated

Table 32-2 Chromium Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Chromium (VI)	1-Hour	0.1	Lung Cancer	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	0.1	Respiratory effects	RfC	US EPA, 1998
	Carcinogenic Annual Average	0.076	Increased incidence of lung cancer	UR	Health Canada, 2004b
Chromium (total)	1-Hour	1	Health Based	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	60	Kidney effects in humans	RfC	RIVM, 2001
	Carcinogenic Annual Average	0.019	Increased incidence of lung cancer	UR	Health Canada, 2004b

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$)$^{-1}$, NV – No Value, UR-Unit risk

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33.0 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. 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 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). No essential biological function of inorganic cobalt in the human body has been identified (ATSDR, 2001).

In high doses cobalt can cause toxic effects in humans. High level exposure can result in heart and lung effects and dermatitis. Effects on the liver and kidney have also been observed in animals exposed to high levels of cobalt (ATSDR, 2004).

33.1 Assessment of Carcinogenicity

The ATSDR (2001) discusses carcinogenicity data in its toxicological profile for cobalt; however, it does not currently assess cancer potency. 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.

For this assessment, cobalt is being assessed as a non-carcinogen.

33.2 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).

33.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

33.3.1 Oral Exposure

33.3.1.1 Non-Carcinogenic Toxicity Reference Values

No non-carcinogenic oral TRVs were available from Health Canada or the US EPA at the time of the assessment.

ATSDR (2001) has developed an intermediate exposure duration MRL of 0.01 mg/kg-day. This is based on a LOAEL of 150 mg/day cobalt as cobalt chloride (1 mg Co/kg-day) exposure for polycythemia 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).

RIVM (2001) selected a TDI of .0014 mg/kg-day based on a migration limit for packaging materials derived in a study by Vermiere et al. (1991). For the onset of cardiomyopathy in humans after intermediate oral exposure, the LOAEL was found to be 0.04 mg/kg-day (RIVM, 2001). After applying an uncertainty factor of 3 for intra-human variation and a factor of 10 to extrapolate to a NOAEL, a TDI of 1.4 µg/kg-day was derived (RIVM 2001).

The more conservative RIVM (2001) TDI of 0.0014 mg/kg-day was selected for the chronic oral exposure limit in the current assessment.

33.3.1.2 Cancer Toxicity Reference Values

Cobalt is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

33.3.2 Inhalation Exposure

33.3.2.1 Non-Carcinogenic Toxicity Reference Values

33.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.2 µg/m^3 for cobalt was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 20 µg/m^3 based on the following critical effects: Asthma, pulmonary function effects and myocardial effects. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

The 24-hour exposure limit used in this risk assessment was selected from the Ontario MOE. The MOE (2008) derived a 24-hour AAQC benchmark of 0.1 µg/m^3 for cobalt. The MOE 24-hour benchmark selected for this risk assessment is based on respiratory irritation. There is no additional information regarding benchmark derivation provided.

33.3.2.1.2 Chronic Inhalation Toxicity Reference Values

No chronic non-carcinogenic inhalation TRVs were available from Health Canada or US EPA at the time of this assessment.

ATSDR (2004) has established an intermediate inhalation MRL of 0.1 µg/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 WHO (2006) determined that the study by Nemery et al. (1992) provided an adequate basis for setting a tolerable concentration for inhaled cobalt. The NOAEC in the study was 5.3 µg/m^3. Assuming an 8 hour workday and a 5 days/week exposure, the NOAEC in the study is adjusted to derive a NOAEC for the general population of 1.3 ug/m^3 (5.3 µg/m^3 x 8hr/24hr/d x 5d/7d/wk). This NOAEC was divided by an uncertainty factor of 10 for human variability to give a tolerable concentration of 0.13 µg/m^3, which was rounded to 0.1 µg/m^3, for the general population (WHO 2006).

For this assessment, a TRV of 0.1 µg/m^3 was selected.

33.3.2.2 Cancer Inhalation Toxicity Reference Values

Cobalt is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation TRV has not been selected.

33.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004).

33.5 Conclusion

The following tables present cobalt TRVs selected for use in this risk assessment.

Table 33-1 Cobalt Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Cobalt	Non-carcinogenic TRV	0.0014	Cardiomyopathy	RfD	RIVM, 2001
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 33-2 Cobalt Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Cobalt	1-Hour	0.2	Asthma; Pulmonary Function; Myocardial effect	Benchmark	TCEQ ESL, 2008
	24-Hour	0.1	Respiratory Irritation	Benchmark	MOE AAQC, 2005
	Annual Average	0.1	Respiratory Irritation	RfC	WHO, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3)

33.6 References

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34.0 DICHLORODIFLUOROMETHANE

Dichlorodifluoromethane is a colorless gas with a characteristic ether-like odor; it can be pressurized and used in liquid form (OSHA, 1996), typically as a refrigerant.

High concentrations of dichlorodifluoromethane can cause severe human health effects. Inhalation exposure can cause narcosis (including dizziness, drowsiness, trembling, amnesia), cardiac arrhythmias, unconsciousness, cardiac arrest and death. The abovementioned effects can be a result of either the narcotic effects of dichlorodifluoromethane or its displacement of oxygen (OSHA, 1999). Dermal exposure to dichlorodifluoromethane can cause frostbite, and associated pain, redness, and then whiteness of the skin (OSHA, 1999). There is no evidence of adverse health effects from chronic exposure to low levels of dichlorodifluoromethane (OSHA, 1999).

34.1 Assessment of Carcinogenicity

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify dichlorodifluoromethane as a carcinogen.

34.2 Susceptible Populations

Individuals with cardiac or respiratory disorders may prove especially susceptible to dichlorodifluoromethane (OSHA, 1996).

34.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

34.3.1 Oral Exposure

34.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, dichlorodifluoromethane is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

34.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, dichlorodifluoromethane is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

34.3.2 Inhalation Exposure

34.3.2.1 Non-Carcinogenic Toxicity Reference Values

34.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 50,000 µg/m^3 for dichlorodifluoromethane was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is

derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 5,000,000 µg/m^3 based on the following critical effect of cardiac sensitization. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure limit was not identified for dichlorodifluoromethane.

34.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 5,000 µg/m^3 for dichlorodifluoromethane was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 34.3.2.1.1. To derive a long-term ESL for dichlorodifluoromethane, TCEQ further divides the short-term ESL by an additional safety factor of 10.

34.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, dichlorodifluoromethane is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation TRV has not been selected.

34.4 Bioavailability

In this risk assessment, dichlorodifluoromethane is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that dichlorodifluoromethane is completely absorbed (i.e. absorption factor is 1).

34.5 Conclusion

The following tables present dichlorodifluoromethane TRVs selected for use in this risk assessment.

Table 34-1 Dichlorodifluoromethane Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Dichlorodifluoromethane	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 34-2 Dichlorodifluoromethane Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Dichlorodifluoromethane	1-Hour	50,000	Cardiac sensitization	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	5000	Cardiac sensitization	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3),
NV – No Value

34.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

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MOE (Ontario Ministry of the Environment). 2004. Basic Comprehensive Certificates of Approval(Air) – User Guide. Version 2.0. Environmental Assessment & Approvals Branch. April 2004.

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OSHA (United States Occupational Safety and Health Administration). 1999. Occupational Health and Safety Guideline for Dichlorodifluoromethane. United States Occupational Safety and Health Administration.

TCEQ (Texas Commission on Environmental Quality). 2008. Effects Screening Levels. http://www.tceq.state.tx.us/implementation/tox/index.html.

US EPA (United States Environmental Protection Agency). 1995. Integrated Risk Information System (IRIS) Database, Dichlorodifluoromethane. United States Environmental Protection Agency. http://www.epa.gov/ncea/iris/subst/0040.htm

35.0 DICHLOROMETHANE (METHYLENE CHLORIDE)

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).

Inhalation of high doses of dichloromethane can cause unsteadiness, dizziness, nausea, and tingling or numbness in the extremities. Inhalation of lower levels of dichloromethane can make a person less attentive and have reduced hand-eye coordination. Dermal contact with dichloromethane can cause burning and redness of the skin (ATSDR, 2001).

35.1 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.

For this assessment, dichloromethane is being assessed for carcinogenic and non-carcinogenic endpoints.

35.2 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).

35.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

35.3.1 Oral Exposure

35.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004b) derived a tolerable daily intake (TDI) of 0.05 mg/kg-day based on a study by Serota et al. (1986). Serota et al. (1986) conducted a 2-year study in which F344 rats were administered concentrations of dichloromethane in their drinking water equivalent to doses of 0, 5, 50, 125, and 250 mg/kg bw/day. The researchers observed small but significant decreases in body-weight gain and water consumption in both sexes at 125 and 250 mg/kg bw/day. At an interim sacrifice after 78 weeks of exposure, it was observed that both sexes had increased incidences of hepatic changes, consisting of areas of cellular alteration and fatty change; these changes occurred at all doses except 0 and 5 mg/kg bw/day. Serota et al. (1986) suggested a NOAEL of 5 mg/kg bw/day and a LOAEL of 50 mg/kg bw/day for both sexes based upon toxicological and non-neoplastic histopathological effects on the liver. The Health Canada (2004b) TDI of 0.05 mg/kg-day was derived by applying an uncertainty factor of 100 for interspecies and intraspecies variability to the NOAEL.

The US EPA (1995) derived a RfD of 0.06 mg/kg-day. The RfD value is based on a study (National Coffee Association (NCA), 1983) 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 the study NOAEL. Supporting studies are limited.

The Health Canada and US EPA TRVs are essentially the same (0.05 vs. 0.06 mg/kg-day, respectively) but for this assessment, the Health Canada TRV was chosen because, it is the more conservative of the two agencies' value.

35.3.1.2 Carcinogenic Toxicity Reference Values

An oral slope factor of 0.0075 $(mg/kg\text{-}day)^{-1}$ was derived by US EPA (1995) for critical effects of hepatocellular adenomas or carcinomas in mice. This slope factor is an arithmetic mean of slope factors, 0.0026 $(mg/kg\text{-}day)^{-1}$ and 0.012 $(mg/kg\text{-}day)^{-1}$, derived from two studies, NTP (1986) and the NCA (1983).

The NCA study (1983) consisted of a 2-year study where groups of 85 F344 rats/sex/dose received 5, 50, 125, or 250 mg dichloromethane/kg/day in drinking water. Control groups consisted of 135 rats per sex. In female rats, the incidence of combined hepatocellular carcinoma and neoplastic nodules was statistically significantly increased in the 50 and 250 mg/kg dose groups when compared with matched controls. The incidence of hepatocellular carcinoma alone was not significantly increased. The combined incidence of hepatocellular carinoma and neoplastic nodules in controls and the 4 dose groups (472 rats: 4 with carcinoma and 8 with neoplastic nodules) was similar to that for historical controls (419 rats; 5 with carcinoma, 19 with neoplastic nodules). Male rats showed no increase in liver tumors. A slope factor of 0.012 $(mg/kg\text{-}day)^{-1}$ was derived from this study.

In the NTP (1986) study, groups of 50 male and 50 female F344/N rats and B6C3F1 mice were exposed to dichloromethane by inhalation, for 6 hours/day, 5 days/week for 2 years (NTP, 1986). Exposure concentrations were 0, 1000, 2000, or 4000 ppm for rats and 0, 2000, or 4000 ppm for mice. The researchers observed significant increases in mammary adenomas and fibroadenomas in male and female rats after survival adjustment, as well as mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were

significant dose-related increases in the number of lung tumors per animal multiplicity in both sexes of mice. A slope factor of 0.0026 $(mg/kg\text{-}day)^{-1}$ was derived from this study.

The US EPA (1995) oral slope factor of 0.0075 $(mg/kg\text{-}day)^{-1}$ was used in the risk assessment.

35.3.2 Inhalation Exposure

35.3.2.1 Non-Carcinogenic Toxicity Reference Values

35.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Cal EPA (1999) selected an acute inhalation REL of 14,000 $\mu g/m^3$ for subtle impairment of the central nervous system. This value was based on the Putz et al. (1976) study where twelve healthy adult volunteers were exposed to 68,000 $\mu g/m^3$ of dichloromethane for 4 hours. Statistically significant decrements in performance were first noted after 90 minutes of exposure; with increasing decrements observed with prolonged exposure. Blood COHb levels rose from 1.35% pre-exposure to 5.1% post-exposure. The study did not address subjective symptoms such as headache, nausea, or irritation of the nose and throat. A NOAEL was not observed. A LOAEL of 68,000 $\mu g/m^3$ was derived from the study based on 90 minutes of exposure to dichloromethane. This LOAEL was then extrapolated to a 1-hour concentration of 833,669 $\mu g/m^3$. Finally, an uncertainty factor of 60 (6 for LOAEL 1 for interspecies, and 10 for intraspecies) was applied to derive the REL of 14,000 $\mu g/m^3$.

A 24-hour exposure benchmark of 220 $\mu g/m^3$ for Dichloromethane was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

35.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Cal EPA (1999) selected a chronic reference level of 400 $\mu g/m^3$ for COHb formation above 2% in human workers. This value was based on the Divenzo and Kaplan (1981) occupational inhalation exposure study. A group of 19 workers were exposed to 40 ppm of dichloromethane during the workday (8 hour/day, 5 days/week), the length of exposure was not specified. Personal monitors on 3 of the subjects indicated an 8-hour time-weighted average of 33 ppm over a 2-week period. The average COHb levels were 3.9% at the end of the work-shift. Elevated COHb concentrations of above 2% are considered high enough to aggravate angina in some individuals. The researchers derived an occupational exposure LOAEL of 34,736 $\mu g/m^3$ (rounded to 40,000 $\mu g/m^3$) and applied an uncertainty factor of 100 (10 for LOAEL 1 for interspecies, and 10 for intraspecies) to arrive at a REL of 400 $\mu g/m^3$.

35.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

For dichloromethane, Health Canada has determined two tumourigenic concentrations (TC_{05}) 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 TC_{05}s" 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 (1986) bioassay, versus amortized delivered dose by the GST pathway. The resulting values of the "PBPK modified TC_{05}s" range from 2.2 x 10^6 µg/m^3 for adenomas and carcinomas (combined) of the lung in females to 1.42 x 10^7 µg/m^3 for adenomas and carcinomas (combined) of the liver in males (ITER, 2007). As per Health Canada (1996) guidance, the TC_{05} was modified to a unit risk by dividing it into 0.05 [UR_{inh}= 0.05/TC_{05}] (Health Canada, 2004a) to derive a value of 2.3 x 10^{-8} (µg/m^3)$^{-1}$.

The US EPA (1995) derived an inhalation unit risk is 4.70 x 10^{-7} (µg/m^3)$^{-1}$, based on the NTP (1986) study discussed above. The researchers observed significant increases in mammary adenomas and fibroadenomas in male and female rats after survival adjustment, as well as mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were significant dose-related increases in the number of lung tumors per animal variety in both sexes of mice.

For this assessment, the US EPA (1995) inhalation unit risk value of 4.7 x 10^{-7} (µg/m^3)$^{-1}$ was selected as it corresponds with current MOE standards for dichloromethane.

35.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004a).

35.5 Conclusion

The following tables present dichloromethane TRVs selected for use in this risk assessment.

Table 35-1 Dichloromethane Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Dichloromethane	Non-carcinogenic TRV	0.05	Non-neoplastic effects	RfD	Health Canada, 2004b
	Carcinogenic Slope Factor	0.0075	Hepatocellular adenomas or carcinomas in mice	SF	US EPA, 1995

[a] Units: Non-carcinogenic COPC (mg/kg/day), Carcinogenic COPC (mg/kg/day)$^{-1}$

Table 35-2 Dichloromethane Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Dichloromethane	1-Hour	14,000	Subtle impairment of the central nervous system.	Benchmark	CalEPA REL, 1999
	24-Hour	220	Health Based	Benchmark	MOE AAQC, 2008

	Annual Average	400	Carboxyhemoglobin formation above 2% in human workers	Benchmark	CalEPA REL, 1999
	Carcinogenic Annual Average	4.7×10^{-7}	increased incidence of both hepatocellular adenomas and carcinomas in mice	UR	US EPA, 1995

[a] Units: Non-carcinogenic COPC (µg/m^3) , Carcinogenic COPC (µg/m^3) $^{-1}$

35.6 References

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36.0 DIOXINS AND FURANS (PCDD/FS)

Polychlorinated dibenzo-para-dioxins (PCDD) refers to a group of chemicals that are differentiated by their number of chlorine atoms (ATSDR, 1998). PCDDs are not intentionally manufactured through industrial processes; instead PCDDs are considered impurities that are created as a result of municipal, hospital and hazardous waste incineration, fossil fuel combustion, as well as several other sources (IPCS, 1989; ATSDR, 1998).

In general, PCDDs are lipophilic and tend not to dissolve in water. Consequently, the presence of PCDD in water is very limited, as well as the amount evaporated into the air (ATSDR, 1998). PCDDs do tend to sorb to soil but the affected particles are filtered out during water treatment processes (ATSDR, 1998). Occupational exposure to CDDs most likely occurs mainly through inhalation of CDD-contaminated particles or dust and through dermal contact with solutions containing CDDs (ATSDR, 1998).

Like PCDDs, polychlorinated dibenzofurans (PCDF) are not intentionally manufactured through industrial processes and are considered impurities as a result of municipal, hospital and hazardous waste incineration, fossil fuel combustion, as well as several other sources (IPCS, 1989; ATSDR, 1998; IARC, 1997). Like PCDDs, PCDFs with chlorine atoms in positions 2, 3, 7, and 8 are the more toxic (ATSDR, 1998). The main source of PCDF intake by humans is food while intake via drinking water is negligible (WHO, 2000).

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).

As 2,3,7,8-TCDD is the most toxic member of the family, is used as reference compound. All other dioxins and furans are assigned a toxic potency relative to TCDD, based on experimental studies, known as a toxic equivalency factor (TEF).

The risk of health effects from dioxins and furans is dependent on the dose, route and duration of exposure. These health effects include skin disorders (chloracne), liver problems, impairment of the immune system, impairment of the endocrine system, reproductive effects and developmental effects including effects on the developing nervous system (Health Canada, 2005).

36.1 Assessment of Carcinogenicity

The IARC (1997) has classified PCDDs as Group III, not classifiable as a human carcinogen; however, 2,3,7,8-TCDD has been designated by IARC as Group I, carcinogenic to humans. Furthermore, the US EPA has determined that a mixture of PCDDs with six chlorine atoms (where 4 of the atoms are in the 2,3,7 and 8 position) may be a probable human carcinogen (ATSDR, 1998)

The most documented cases of human exposure to PCDFs are the Yusho (Japan, 1968) and Yucheng (Taiwan, 1979) incidents where people were exposed to PCDF and PCB contaminated food supply (IPCS, 1989; IARC, 1997). From these incidences contradicting results were observed, an increase in liver cancer in Japanese men was observed while no excess of liver mortality in the affected Taiwanese population was observed (IARC, 1997). The IARC (1997) has designated PCDFs as Group III, not classifiable as a human carcinogen.

The International Agency for Research on Cancer has classified 2,3,7,8-TCDD as carcinogenic to humans (Group 1).

Health Canada does not assess 2,3,7,8-TCDD as a carcinogen and 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.

36.2 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. Of 187 individuals with chloracne, 88% percent of them were children aged 0 to 14 (Bisanti et al., 1980) indicating that children may be unusually susceptible to the dermal toxicity of 2,3,7,8-TCDD. Experimental data also suggests that the prenatal and postnatal population may be sensitive to the compound effects. Furthermore, persons who have an 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).

No data regarding populations susceptible to general PCDD exposure were found. Studies have been conducted regarding 2,3,7,8-TCDD and these populations should also be, to a lesser extent, susceptible to other PCDDs with chlorine atoms in the 2, 3, 7 and 8 positions. Therefore, children and individuals with an Ah receptor that has a high affinity for 2,3,7,8-TCDD may be more susceptible than other subpopulations.

No information regarding susceptible populations to PCDFs was found. There may be, however, similarities between 2,3,7,8-TCDD and structurally related PCDFs potentially making individuals with a high Ah receptor affinity for 2,3,7,8-TCDD susceptible to PCDFs (ATSDR, 1998).

36.3 Selection of Toxicity Reference Values

Toxic Equivalency Factors

People generally are exposed to a mixture of PCDDs and PCDFs in the environment. The World Health Organization (Van den Berg et al., 2006) and Health Canada use the concept of toxic equivalency factors (TEFs) to facilitate risk assessment of exposure to these mixtures. TEFs allow large groups of

compounds with a common mechanism of action such as dioxins and furans to be assessed when limited data are available for all but one of the compounds (i.e. 2,3,7,8-TCDD). TEFs for individual dioxins and furans, in combination with their chemical concentration, can be used to calculate the total 2,3,7,8-TCDD toxic equivalents (TEQs).

For the current assessment, health risks related to PCDD/F exposures were evaluated through the grouping of the 17 PCDD/F congeners using WHO/Health Canada accepted (Van den Berg et al. 2006) TEFs (Table 36-1).

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

36.3.1 Oral Exposure

36.3.1.1 Non-Carcinogenic Toxicity Reference Values

Based on the WHO/FAO Joint Expert Committee on Food Additives and Contaminants (JECFA, 2001), Health Canada (2004b; 2005) has adopted a tolerable level of 70 pg TEQ/kg bw/month or approximately 2.3 pg TEQ/kg bw/day. JECFA (2001) re-evaluated dioxins using newly published data reporting reproductive effects on the male reproductive system in the offspring of dams exposed during pregnancy (Ohsako et al. 2001; Faqi et al. 1998). JECFA (2001) proposed a provisional tolerable monthly intake of 70 pg TEQ/kg body weight, based upon the lowest LOAEL (Faqi et al. 1998; sperm counts); and, a NOAEL (Ohsako et al. 2001; decreased ventral prostate weight) for developmental effects in male rat offspring (equivalent to 2.3 pg TEQ/kg bw/day) calculated from a maternal body burden with a 7.6 years half-life. For the NOAEL, an uncertainty factor of 3.2-fold was applied rather than 9.6-fold. The provisional tolerable monthly intake of 70 pg TEQ/kg bw/day represents the mid-range of TDI estimates based on the LOAEL *versus* the NOAEL (JECFA 2001).

The JECFA (2001) and Health Canada (2004b; 2005) TRV is a systemic exposure limit including both inhalation and oral exposure; therefore, this oral TDI was used to extrapolate a chronic inhalation TRV (further described in Section 36.3.2.1.2**Error! Reference source not found.**).

The California Environmental Protection Agency (CalEPA, 2008) has adopted a chronic oral reference exposure level of 1×10^{-8} mg/kg body weight/day for TCDD/TCDF. This value was derived from a chronic rat study by Kociba et al. (1978) in which Sprague-Dawley rats were given a continuous dietary exposure to dioxins starting at 7 weeks of age for 2 years. At doses of 100 ng/kg bw/day, observations included increased mortality, decreased weight gain, depressed erythroid values, increased urinary excretion of porphyrins and delta-aminolevulinic acid, and increased serum activities of alkaline phosphatase, gamma-glutamyl transferase, and glutamic-pyruvic transaminase. A LOAEL of 10 ng/kg bw/day was determined based on the reduction of symptoms at this dosage, and furthermore, a NOAEL of 1 ng/kg bw/day was established based on the absence of significant toxic effects. An uncertainty factor of 100 (10 each for intraspecies and interspecies extrapolation) was subsequently applied to the NOAEL to obtain the oral reference exposure level of 1×10^{-8} mg/kg bw/day.

The Agency for Toxic Substances and Disease Registry (ATSDR) (1998) evaluated the non-carcinogenic oral toxicity data for 2,3,7,8- TCDD and derived a chronic MRL of 1.0 x 10^{-9} mg/kg/day based on a LOAEL of 1.2 x 10^{-7} mg/kg-day for developmental toxicity in rhesus monkeys (Schantz *et al*., 1992).

The Health Canada TDI of 2.3 pg TEQ/kg body weight/day (or 2.3 x 10^{-9} mg TEQ/kg body weight/day) has been adopted for the current study as the exposure limit for 2,3,7,8-TCDD TEQ Toxic Equivalent because it is the presently accepted value for use in Canada for the assessment of dioxin exposure.

36.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, dioxins and furans are not being evaluated as a carcinogen; therefore, a carcinogenic oral toxicological reference value has not been selected.

36.3.2 Inhalation Exposure

36.3.2.1 Non-Carcinogenic Toxicity Reference Values

36.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Acute inhalation TRVs from Health Canada or the US EPA were not available at the time of writing of this risk assessment.

A 1-hour exposure limit was not identified for dioxins and furans.

A 24-hour exposure limit was selected from the Ontario Ministry of the Environment (MOE, 2008). A value of 5 pgTEQ/m^3 for dioxins and furans TEQ toxic equivalent was derived based on health effects; no additional information regarding derivation is provided.

36.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The previously described Health Canada (2004b; 2005) TDI of 2.3 pg TEQ/kg body weight/day (or 2.3 x 10^{-9} mg TEQ/kg body weight/day) was used to calculate a chronic inhalation exposure limit based on route-to-route extrapolation. A body weight of 70.7 kg and an inhalation rate of 15.8 m^3/day were assumed for the purposes of the calculation. This resulted in a calculated chronic inhalation exposure limit of 1.03 x 10^{-5} µg TEQ/m^3.

The California Environmental Protection Agency (CalEPA, 2008) has adopted a chronic inhalation reference exposure level of 4 x 10^{-5} µg/m^3 for TCDD/TCDF. This value was derived from the previously described chronic rat study by Kociba et al. (1978). A NOAEL of 1 ng/kg bw/day was established based on the absence of significant toxic effects. An uncertainty factor of 100 (10 each for intraspecies and interspecies extrapolation) was subsequently applied to the NOAEL to obtain the previously described oral reference exposure level of 1 x 10^{-8} mg/kg bw/day. Route-to-route

extrapolation, assuming 3500 µg/m^3 per mg/kg bw/day, was performed to obtain the inhalation reference exposure level.

The chronic inhalation exposure limit (1.03 pgTEQ/m^3) calculated from the selected Health Canada oral TDI has been adopted for the current study as the exposure limit for 2,3,7,8-TCDD TEQ Toxic Equivalent.

36.3.2.2 Cancer Inhalation Toxicity Reference Values

In this risk assessment, dioxins and furans are not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

36.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.03 (RAIS, 2006). With regards to the inhalation pathway, it has been conservatively assumed that dioxins and furans are completely absorbed (i.e. absorption factor is 1).

36.5 Conclusion

The following tables present the dioxin and furan TEF scheme and the TRVs selected for use in this risk assessment.

Table 36-1 Toxic Equivalency Factors (TEFs) for PCDD/F Congeners (WHO, 2005; Van den Berg, 2006)

Chemical	TEF	Source Agency
1,2,3,4,6,7,8-HpCDD	0.01	WHO, 2005
1,2,3,4,6,7,8-HpCDF	0.01	WHO, 2005
1,2,3,4,7,8,9-HpCDF	0.01	WHO, 2005
1,2,3,4,7,8-HpCDD	0.1	WHO, 2005
1,2,3,4,7,8-HxCDD	0.1	WHO, 2005
1,2,3,4,7,8-HxCDF	0.1	WHO, 2005
1,2,3,6,7,8-HxCDF	0.1	WHO, 2005
1,2,3,7,8,9- HxCDD	0.1	WHO, 2005
1,2,3,7,8,9- HxCDF	0.1	WHO, 2005
1,2,3,7,8-PeCDD	1	WHO, 2005
1,2,3,7,8-PeCDF	0.03	WHO, 2005
2,3,4,6,7,8-HxCDF	0.1	WHO, 2005
2,3,4,7,8-PeCDF	0.3	WHO, 2005
2,3,7,8-TCDD	1	WHO, 2005
2,3,7,8-TCDF	0.1	WHO, 2005

Chemical	TEF	Source Agency
OCDD	0.0003	WHO, 2005
OCDF	0.0003	WHO, 2005

Table 36-2 Dioxins as Toxic Equivalents (TEQ)Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Dioxins as Toxic Equivalents (TEQ)	TDI	2.3×10^{-9}	Reproductive Effects	RfD	Health Canada, 2004b
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg TEQ/kg/day) ' NE – Not Evaluated

Table 36-3 Dioxins as Toxic Equivalents (TEQ)Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Dioxins as Toxic Equivalents (TEQ)	1-Hour	NV			
	24-Hour	5	Health-based	Benchmark	MOE, 2008
	Annual Average	1.03	Route-to-route extrapolation from oral dose	TC	Health Canada, 2004b

[a] Units: Non-carcinogenic COPC (pg TEQ/m^3) , NV – No Value

36.6 References

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37.0 ETHYLBENZENE

Ethylbenzene is a clear, colourless flammable liquid that smells like gasoline. It evaporates quickly at room temperature and burns easily; it occurs naturally in coal tar and petroleum and can be found in many products, including paints, inks and insecticides (ATSDR, 1999). Ethylbenzene is commonly used as a solvent, chemical intermediate in the manufacture of styrene and synthetic rubber and as an additive in fuels (ATSDR, 1999).

The effects of ethylbenzene on human health are dependent on the dose and the duration of contact. Acute (short term) inhalation of high doses of ethylbenzene can cause eye and throat irritation. Acute exposure to higher doses can result in dizziness (ATSDR, 2007). Inhalation of low doses of ethylbenzene over several days to weeks has been shown to cause irreversible damage to the inner ear and the auditory system in animal studies. Inhalation exposure to low doses of ethylbenzene over several months to years has been shown to cause kidney damage in animals (ATSDR 2007).

37.1 Assessment of Carcinogenicity

The US EPA (1991) identifies ethylbenzene as classification D, “Not Classifiable as a Human Carcinogen.” The International Agency for Research on Cancer (IARC) (2006) classifies ethylbenzene as 2B, “Possibly Carcinogenic to Humans. As such, in this risk assessment, ethylbenzene is not being evaluated as a carcinogen.

37.2 Susceptible Populations

Individuals with impaired pulmonary function or liver or kidney disease may be susceptible to the toxic effects of ethylbenzene (ATSDR, 1999). In addition, young children, fetuses, pregnant women, and individuals taking hepatotoxic medications or drugs may also be more susceptible to ethylbenzene toxicity than other members of the population (ATSDR, 1999).

37.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

37.3.1 Oral Exposure

37.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, ethylbenzene is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

37.3.1.2 Carcinogenic Toxicity Reference Values

Ethylbenzene is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected

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37.3.2 Inhalation Exposure

37.3.2.1 Chronic Inhalation Toxicity Reference Values

37.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour inhalation TRV was unavailable for ethylbenzene at the time of this assessment.

A 24-hour exposure benchmark of 1000 µg/m^3 for ethylbenzene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects (dizziness, throat and eye irritation) with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

37.3.2.2 Chronic Inhalation Toxicity Reference Values

A chronic RfC of 1,000 µg/m^3 was derived by the US EPA IRIS (1991) for ethylbenzene for developmental toxicity observed during rat and rabbit developmental inhalation studies (Andrew et al., 1981; Hardin et al., 1981). Inhalation experiments were conducted with Wistar rats (78-107 per ethylbenzene concentration) and New Zealand white rabbits (29-30 per ethylbenzene concentration). The animals were exposed 6 to 7 hours per day, 7 days a week during gestation days 1-19 for rats and 1-24 for rabbits. Concentrations of ethylbenzene used in the study were 0, 4.34 x 10^5 µg/m^3, or 4.342 x 10^6 µg/m^3. All pregnant animals were sacrificed 1 day prior to term (21 days for rats; 30 days for rabbits). Maternal organs (liver, lungs, kidney, heart, spleen, adrenals, ovaries, and brain) were examined histopathologically. Uteri were examined and fetuses were weighed, sexed, and measured for crown-to-rump length, and examined for external, internal and skeletal abnormalities. For statistical analyses, the litter was chosen as the experimental unit.

Exposure to ethylbenzene did not cause embryotoxicity, fetotoxicity, or teratogenicity in rabbits at either exposure level. There were no significant incidences of major malformations, minor anomalies, or common variants in fetal rabbits from exposed groups. Maternal toxicity in the rabbits was not evident. There was no evidence of histologic damage in any of the dams' organs.

There were no effects on fertility or on any of the other measures of reproductive status in rats. No fetal toxicity was noted at either exposure level. Body weights, placental weights, and sex ratios were within normal limits.

The results of the rabbit and rat studies suggested that a NOAEL of 4.34 x 10^5 µg/m^3 could be derived based on the lack of developmental effects. A LOAEL of 4.34 x 10^6 µg/m^3 was based on the clustering of mild effects (some increased liver, spleen and kidney weights) at this concentration.

The US EPA (1991) derived a chronic RfC of 1,000 µg/m^3 from the NOAEL after applying a cumulative uncertainty factor of 300 (factor of 10 to protect unusually sensitive individuals, 3 to adjust for

interspecies conversion and 10 to adjust for the absence of multigenerational reproductive and chronic studies).

An MRL of 1,302 µg/m^3 was derived by ATSDR based on a study by NTP (1999). Groups of F344/N rats and B6C3Fl mice (50 animals/sex/dose group) were exposed to 0, 3.25 x 10^5, 1.08 x 10^6, or 1.59 x 10^6 µg/m^3 ethylbenzene by inhalation for 5 days/week, 6 hours/day, for 104 (rats) or 103 (mice) weeks. The severity of kidney disease observed in exposed rats was significantly increased in females at ≥3.25 x 10^5 µg/m^3 and in males at 1.59 x 10^6 µg/m^3. Kidney disease was characterized by dilation of renal tubules with hyaline or cellular casts, interstitial fibrosis, infiltration of inflammatory cells, tubular regeneration, and transitional hyperplasia of the renal papilla. A LOAEL of 325,644 µg/m^3 was established based on significant increases in the severity of nephropathy in female rats after 2 years of exposure. A NOAEL was not established in the study. A cumulative uncertainty factor of 300 (factor of 10 for use of a LOAEL, factor of 3 to account for interspecies variation, and a factor of 10 to account for human variability) was applied by ATSDR to derive a MRL of 1,302 µg/m^3.

The more conservative US EPA IRIS (1991) RfC value of 1,000 µg/m^3 was selected for use in this risk assessment because it was based on a NOAEL.

37.3.2.3 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, ethylbenzene is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

37.4 Bioavailability

In this risk assessment, ethylbenzene is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that ethylbenzene is completely absorbed (i.e. absorption factor is 1).

37.5 Conclusion

The following tables present ethylbenzene TRVs selected for use in this risk assessment.

Table 37-1 Ethylbenzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Ethylbenzene	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NA			

NE – Not Evaluated, NA – Not Applicable

Table 37-2 Ethylbenzene Inhalation TRVs used in the risk assessment

COPC	Duration	Value[a]	Critical Effect	Reference Type	Agency
Ethylbenzene	1-Hour	NV			
	24-Hour	1,000	Dizziness, throat and eye irritation	Benchmark	MOE AAQC, 2008
	Annual Average	1,000	Developmental Toxicity	RfC	US EPA, 1991

[a]Units: Non-carcinogenic COPC (µg/m^3)

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38.0 ETHYLENE DIBROMIDE (1,2-DIBROMOETHANE)

Ethylene dibromide is a manufactured, colorless liquid at ambient temperature, with a sweetish odor. While used in the past as a scavenger for lead in gasoline and as a pesticide and ingredient of soil and grain fumigant formulations, it currently has more minor uses as a chemical intermediate and as a nonflammable solvent for resins, gums, and waxes (ATSDR, 1995).

Relatively little is known about the non-carcinogenic effects of ethylene dibromide on human health. Acute (short term) inhalation of high levels of ethylene dibromide has been shown to cause depression and collapse in animals which is indicative of effects on the brain. Mortality has occurred in rat studies where inhalation was the route of exposure (ATSDR, 1995). Inhalation of lower levels of 1,2-dibromoethane has been shown to cause liver and kidney damage in rats, as well as birth defects (ATSDR, 1995). Inhalation of ethylene dibromide over a long period of time by male humans has been associated with reproductive effects, including damage to sperm. It is not known to cause birth defects in humans, however (ATSDR, 1995). Ingestion of ethylene dibromide has resulted in testicular atrophy, adrenal cortical degeneration, and liver engorgement in rats (US EPA 2004)

Ingestion of large amounts of ethylene dibromide in humans can cause redness and inflammation, skin blisters, and mouth and stomach ulcers (ATSDR 1995).

38.1 Assessment of Carcinogenicity

The IARC classifies ethylene dibromide as probably carcinogenic to humans (2A) (IARC 1999). The US EPA has classified ethylene dibromide as “likely to be carcinogenic to humans” based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population (US EPA, 2004). ATSDR indicates that ethylene dibromide can reasonably be anticipated to be a carcinogen based on ethylene dibromide-induced tumors in multiple sites and by various routes of exposure in animals (ATSDR, 1995). Health Canada has not classified ethylene dibromide with respect to carcinogenicity.

For the purpose of this risk assessment ethylene dibromide was evaluated as a carcinogenic substance.

38.2 Susceptible Populations

Individuals with asthma or other chronic respiratory diseases may have increased susceptibility to the toxic effects of ethylene dibromide (ATSDR, 1995).

38.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

38.3.1 Oral Exposure

38.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, ethylene dibromide is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

38.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, ethylene dibromide is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

38.3.2 Inhalation Exposure

38.3.2.1 Non-Carcinogenic Toxicity Reference Values

38.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 4 µg/m^3 for ethylene dibromide was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). The ESL was based on the following critical effects: skin, eye, upper respiratory irritation, dermatitis with vesiculation; liver, heart, spleen, kidney damage, and reproductive effects. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure benchmark of 3 µg/m^3 for ethylene dibromide was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

38.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The inhalation reference concentration (RfC) for ethylene dibromide of 9 µg/m^3 used in this assessment was obtained from the US EPA (2004). The RfC was developed from a chronic inhalation exposure study of ethylene dibromide to mice (NTP, 1982). Male and female Fischer 344 rats and B6C3F$_1$ mice (50 per sex, species, and exposure group) were exposed to 0, 77,000 µg/m^3 or 307,000 µg/m^3 of ethylene dibromide for 6 hr/day, 5 days/week. The study was designed to assess potential adverse effects of ethylene dibromide following 103 weeks of exposure. In the high-exposure groups, rats of both sexes and female mice exhibited high mortality (84-90%) resulting in the early termination of these exposure groups (between 78 and 91 weeks). The low exposure groups were not terminated until the end of the study (104-106 weeks). US EPA (2004) did not consider the male mouse study from NTP (1982) relevant for derivation of an RfC because of high mortality in control and exposed groups due to complications from urinary tract infections that were not exposure-related. The noncarcinogenic effects observed in the NTP (1982) study were hepatic necrosis (in both male and female rats), testicular degeneration (in male rats), retinal atrophy (in female rats), adrenal cortical degeneration (in female rats), splenic hematopoiesis (in female mice), and inflammation of the nasal cavity (in female mice).

A human equivalent concentration (HEC) Benchmark Concentration Limit ($BMCL_{10}$) of 2,800 µg/m^3 for nasal inflammation noted in female mice was modified by an uncertainty factor of 300 for interspecies variability, intraspecies variability to sensitivity and database uncertainty in order to establish the US EPA RfC.

The US EPA (2004) TRV of 9 µg/m^3 was used in the risk assessment.

38.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

The US EPA (2004) unit risk concentration for ethylene dibromide of 0.0006 (µg/m^3)$^{-1}$ used in this assessment was derived from a study conducted by the NTP (1982) noted above and was based on ethylene dibromide-induced nasal cavity tumors in male and female Fischer 344 rats. Hemangiosarcoma was also demonstrated in high-dose (307,000 µg/m^3) animals of both sexes. Mesothelioma of the tunica vaginalis, mammary fibroadenoma, and adenocarcinoma were observed in both males and females, respectively. In female $B6C3F_1$ mice, a similar tumor pattern was observed when compared to female rats; however, female mice displayed treatment-related alveolar/bronchiolar adenoma and carcinoma, lung/bronchiolar adenoma and carcinoma, and fibrosarcoma. Benign squamous papilloma was also observed in male and female $B6C3F_1$ mice exposed to the high dose of ethylene dibromide. Mortality was not reported in this study and only the nasal cavities were examined.

The 95% upper bound unit risk was extrapolated to derive an inhalation unit risk of 0.0006 (µg/m^3)$^{-1}$ (US EPA, 2004). This value was chosen for use in the current risk assessment.

38.4 Bioavailability

In this risk assessment, ethylene dibromide is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that ethylene dibromide is completely absorbed (i.e. absorption factor is 1).

38.5 Conclusion

Ethylene dibromide TRVs selected for use in this risk assessment are presented in the following tables.

Table 38-1 Ethylene dibromide Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Ethylene dibromide	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] Units: NE – Not Evaluated

Table 38-2 Ethylene dibromide Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Ethylene dibromide	1-Hour	4	Skin, Eye, Upper Respiratory Irritation;	Benchmark	TCEQ ESL, 2008

			dermatitis with vesiculation; liver, heart, spleen, kidney damage; reproductive effects; potential occupational carcinogen		
	24-Hour	3	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	9	Inflammation of the nasal cavity	RfC	US EPA, 2004
	Carcinogenic Annual Average	0.0006	nasal cavity tumours, hemangiosarcomas and mesotheliomas	UR	US EPA, 2004

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$

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39.0 FORMALDEHYDE

At room temperature, formaldehyde is a colourless, highly reactive, highly flammable gas with a pungent, irritating odour (Environment Canada/Health Canada, 2001). It polymerizes easily in air and water to form a variety of other compounds (Environment Canada/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).

The effects of formaldehyde on human health vary by dose. At low doses, formaldehyde acts as an irritant, affecting the eyes, nose, throat and skin. People with asthma may be more susceptible to irritation from inhalation (ATSDR, 1999). Ingestion of large doses of formaldehyde can lead to vomiting, severe pain, coma, and possible death (ATSDR, 1999).

39.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC, 2006), 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. Environment Canada/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 initiate carcinogenicity. For this risk assessment, formaldehyde was evaluated as a carcinogenic substance.

39.2 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.

39.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

39.3.1 Oral Exposure

39.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, formaldehyde is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

39.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, formaldehyde is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

39.3.2 Inhalation Exposure

39.3.2.1 Non-Carcinogenic Toxicity Reference Values

39.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 15 µg/m^3 for formaldehyde was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This value was based on the following critical effects: eye and nose irritation and symptoms of rhinitis. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

The 24-hour exposure limit used in this risk assessment was selected from the Ontario Ministry of the Environment (MOE). The MOE (2008) derived a 24-hour AAQC benchmark of 65 µg/m^3 based on chronic human health effects and short-term odor irritation. No additional information regarding benchmark derivation was available from the MOE.

39.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Non-carcinogenic TRVs were not available from Health Canada or the US EPA at the time of this risk assessment.

The CalEPA (2008a,b) derived a chronic REL of 9 µg/m^3 for formaldehyde based on an occupational inhalation exposure study conducted by Wilhelmsson and Holmstrom (1992). Sixty-six adult workers at a formaldehyde production plant were exposed to an average concentration of 260 µg/m^3 of formaldehyde. The exposure duration was assumed to be 8 hours/day and 5 days/week over a range of 1-36 years of employment (average 10 years of employment). A control group was used and consisted of 36 office workers in a government office with exposure to a mean concentration of 90 µg/m^3 of formaldehyde, and no industrial solvent or dust exposure. Symptom data was collected by questionnaire and was separated into general and work-related, and allowed identification of individuals with allergies and mucosal hyperreactivity. The critical effects from chronic exposure to formaldehyde in this study included nasal obstruction, lower airway discomfort, and eczema or itching. Wilhelmsson and Holmstrom (1992) observed that the frequency of reported lower airway discomfort (intermittent cough, wheezing, or symptoms of chronic bronchitis) was significantly higher among formaldehyde-exposed versus non-exposed workers. Work-related nasal discomfort also was significantly higher in the formaldehyde group compared with the referent group. Similarly, work-related eye discomfort was 20% in the formaldehyde group but nonexistent among referents. The investigators also concluded that formaldehyde can induce nonspecific nasal hypersensitivity (Wilhelmsson and Holmstrom, 1992). A LOAEL and a NOAEL of 260 µg/m^3 and 90 µg/m^3 respectively, were concluded from the study results. CalEPA (2008a,b) derived a REL of 9 µg/m^3 after applying an uncertainty factor of 10 to account for exceptionally sensitive populations to the NOAEL.

ATSDR (1999) has derived a chronic inhalation MRL of 10 µg/m^3 based on a study by Holmstrom et al. (1989). The study examined histological changes in nasal tissue specimens from occupationally exposed individuals. A group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper and a non-exposed control group of 36 office workers in the same village as the factory were evaluated in the study (Holmstrom et al., 1989). The exposure duration was assumed to be 8 hours/day and 5 days/week over a range of 1-36 years of employment (average 10.4 years of employment). Estimates of personal breathing zone air concentrations averaged 294.8 µg/m^3 for the chemical plant workers and from 85.97 µg/m^3 for the office workers. Clinical symptoms of mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium were observed in chemical plant workers exposed for 10.4 years to an average time weighted concentration of 284.8 µg/m^3. The LOAEL of 284.8 µg/m^3 was considered to be a minimal LOAEL by ATSDR (1999). ATSDR (1999) applied a cumulative uncertainty factor of 30 (3 for use of a LOAEL and 10 for human variability) to derive an MRL of 10 µg/m^3.

For this risk assessment, the CalEPA (2008a,b) REL value of 9 µg/m^3 was selected because it is based on a NOAEL and is a more conservative value than the ATSDR MRL.

39.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Environment Canada/Health Canada (2001) derived a unit risk of 5.3 x 10^{-6} (µg/m^3)$^{-1}$ based on the incidence of nasal squamous tumours and the exposure-response observed during a rat inhalation study (Monticello et al., 1996; Environment Canada, 2001). A multistage model was used for the exposure-response data to calculate the TC_{05} of 9,500 µg/m^3. The TC_{05} was modified to a unit risk by dividing it into 0.05 [UR_{inh}= 0.05/TC_{05}] (Health Canada, 2004).

Based upon the two-stage clonal growth model, the predicted additional risks of upper respiratory tract cancer for non-smokers, associated with an 80-year continuous exposure to levels of formaldehyde between 0.001 and 0.1 ppm (1.2 and 120 µg/m^3), range from 2.3 x 10^{-10} to 2.7 x 10^{-8}, respectively (Environment Canada, 2001; Conolly et al., 2000). The majority of the general population is exposed to airborne concentrations of formaldehyde less than those typically associated with sensory irritation (*i.e.,* 100 µg/m^3) (Liteplo and Meek, 2003). Based primarily upon data derived from laboratory studies, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation within the respiratory tract is considered to present a carcinogenic hazard to humans. Conolly et al. (2004) have analyzed the production of nasal squamous cell carcinoma in rats by formaldehyde inhalation at 6 ppm and above, and prepared quantitative implications for human cancer risk. An essential feature of this analysis was the investigation of the rat tumour dose-response assuming that both DNA-reactive and cytotoxic effects of formaldehyde contributed to nasal squamous cell carcinoma development. Regional dosimetry predictions for the entire respiratory tract were obtained by merging a three-dimensional computational fluid dynamics model for the human nose with a one-dimensional typical path model for the lower respiratory tract. The predicted human dose-response for DNA-protein cross-links produced by formaldehyde in cells of the respiratory tract was based on rat and rhesus monkey data (Conolly et al., 2004). The maximum likelihood estimates produced by this computational model were lower by as much as 1,000-fold when compared to estimates from previous cancer dose-response assessments for formaldehyde (Conolly *et al*., 2004). The analysis of the human implications of the rat nasal squamous cell carcinoma data indicated that (1) cancer risks associated with inhaled formaldehyde are *de minimis* (10^{-6} or less) at relevant human exposure levels (Liteplo and Meek, 2003), and (2) protection from the noncancer effects of

formaldehyde should be sufficient to protect from its potential carcinogenic effects (Conolly et al., 2004).

US EPA (1991) derived an inhalation unit risk of 1.3×10^{-5} $(\mu g/m^3)^{-1}$ based on a principal study by Kerns et al. (1983). In this study, the effects of inhalation exposure to formaldehyde in Fischer 344 rats and B6C3F1 mice were evaluated. Approximately 120 animals/sex/species were exposed to 0, 2456, 6878 or 17563 $\mu g/m^3$. Exposure duration was 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 sacrificed at 18 months. At 24 and 27 months the number sacrificed was unclear. The studies were terminated at 30 months. Kearns et al. (1983) observed a positive association between exposure to formaldehyde and the formation of squamous cell carcinomas for both sexes.

For this assessment, the more conservative Environment Canada/Health Canada (2001) inhalation TRV of 5.3×10^{-6} $(\mu g/m^3)^{-1}$ was selected.

39.4 Bioavailability

In this risk assessment, formaldehyde is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that formaldehyde is completely absorbed (i.e. absorption factor is 1).

39.5 Conclusion

The following tables present formaldehyde TRVs selected for use in this risk assessment.

Table 39-1 Formaldehyde Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Formaldehyde	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 39-2 Formaldehyde Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Formaldehyde	1-Hour	15	Eye and nose irritation and symptoms of rhinitis	Benchmark	TCEQ ESL, 2008
	24-Hour	65	Chronic human health effects and short-term odor irritation	Benchmark	MOE AAQC, 2008
	Annual Average	9	Respiratory Irritation	Benchmark	CalEPA REL, 2008a,b
	Carcinogenic Annual Average	5.3×10^{-6}	Nasal squamous tumours	UR	Environment Canada, 2001

[a] Units: Non-carcinogenic COPC $(\mu g/m^3)$, Carcinogenic COPC $(\mu g/m^3)^{-1}$, UR (unit risk)

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40.0 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, 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).

Ingestion of hexachlorobenzene can negatively affect human health. In a study of people in Turkey who accidentally ate bread contaminated with hexachlorobenzene, some people suffered from porphyria cutanea tarda, a disease which causes red-coloured urine, skin sores, changes in skin colour, arthritis, and problems with the liver, nervous system and stomach (ATSDR, 2002). It was determined that hexachlorobenzene could be transmitted from mother to child, both to unborn infants and through breastfeeding. Children of mothers who were exposed to hexachlorobenzene or young children who ate it themselves had lower survival rates (ATSDR, 2002).

Animal studies have shown that ingestion of hexachlorobenzene over a long period can damage the liver, thyroid, nervous system, bones, kidney, blood, immune and endocrine systems. Inhalation of hexachlorobenzene has been shown to harm the immune system of rats (ATSDR, 2002).

40.1 Assessment of Carcinogenicity

The International Agency for Research on Cancer (IARC) 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); accordingly, hexachlorobenzene was assessed as a carcinogen in this assessment.

40.2 Susceptible Populations

According to ATSDR (2002), a study has shown that the young children of mothers who 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 mothers have been exposed (ATSDR, 2002).

40.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

40.3.1 Oral Exposure

40.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004b) 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 a number of studies conducted on pigs and rats (den Tonkelaar et al., 1978; Arnold et al., 1985; Mollenhauer et al., 1975, 1976). In den Tonkelaar et al. (1978), pigs exposed for 90 days to doses of 0.5 mg/kg-day and up in diet were porphyric, and had altered liver histology and microsomal enzyme activities, while no effects were observed at 0.05 mg/kg-day. This was the lowest NOEL reported among the studies, and a tolerable daily intake (TDI) of 0.0005 mg/kg-day was derived by modifying the NOEL by an uncertainty factor of 100 (10 for intraspecies variation and 10 for interspecies variation).

The US EPA (1991) provides an oral reference dose (RfD) of 0.0008 mg/kg-day. The derivation of the oral RfD is based on a two generation feeding study conducted by Arnold et al. (1985), in which male and female weanling Sprague-Dawley rats were fed 0, 0.32, 1.6, 8.0, or 40 ppm of hexachlorobenzene for 3 months prior to mating and through weaning of F1 offspring, when they were sacrificed. The F1 offspring were continued on their parents' diet from weaning throughout the remainder of their lives (130 weeks). Statistically significant increases were observed in the incidences of periportal glycogen depletion at 1.6 ppm, peribiliary lymphocytosis at 0.32, 1.6 and 40 ppm, and peribiliary fibrosis at 0.32 and 40 ppm in the F1 male rat groups; however, the US EPA did not consider these effects to be induced by hexachlorobenzene because they were observed in a large number of F1 control males as well. A LOAEL was established at 8.0 ppm based on a statistically significant increase in hepatic centrilobular basophilic chromogenesis in F1 groups and, consequently, a NOAEL was established at 1.6 ppm [0.08 mg/kg-day based on actual food consumption and body weights provided by Arnold et al. (1985) at 30 weeks of exposure]. This NOAEL was subsequently modified by an uncertainty factor of 100 (10 for intraspecies variation and 10 for interspecies variation).

ATSDR (2002) derived a minimal risk level (MRL) of 0.00005 mg/kg-day based on the previously discussed study conducted by Arnold et al. (1985). While the US EPA did not consider a number of statistically significant effects to be induced by hexachlorobenzene because they were observed in a large number of F1 control males as well as in test subjects, ATSDR determined otherwise and established a LOAEL at the lowest dose of 0.32 ppm (0.016 mg/kg-day). It is acknowledged by ATSDR that effects at this level were minimal and common in aging rats. This LOAEL was subsequently modified by an uncertainty factor of 300 (10 for intraspecies variation, 10 for interspecies variation, and 3 for LOAEL to NOAEL extrapolation) to obtain the specified MRL.

The Health Canada (2004b) value of 0.005 mg/kg-day was selected for use in this assessment because it is based on a TDI rather than a minimal risk level.

40.3.1.2 Carcinogenic Toxicity Reference Values

Health Canada (2004b) provides an oral slope factor of 0.83 $(mg/kg\text{-}d)^{-1}$, derived from the results of the previously described study by Arnold et al. (1985). In exposed F1 females at the highest dose, there were increased incidences of neoplastic liver nodules (0/49, 0/49, 2/50, 2/49, 10/49 with increasing dose) and adrenal phaeochromocytomas (2/49, 4/49, 4/50, 5/49, 17/49). A significantly increased incidence of parathyroid adenomas was noted in males receiving 40 ppm in their diet (2/48, 4/48, 2/48, 1/49, 12/49). Owing 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 Tumorigenic Dose 05 (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-day for hepatic neoplastic nodules in females to 0.17 mg/kg-day for parathyroid adenomas in males. The oral slope factor was then calculated by dividing the lowest TD_{05} into 0.05.

The US EPA (1996) cancer oral slope factor is 1.6 $(mg/kg\text{-}day)^{-1}$ based on a linearized multistage extrapolation from data collected by Ertuk et al. (1986). Groups of 94 Sprague-Dawley rats per sex per dose were fed 0, 75, or 150 ppm hexachlorobenzene (purity >99.5%) in the diet for up to 2 years. Treated animals of both sexes surviving past 12 months showed significant increases in liver and renal tumors. Hemangiohepatomas, hepatocellular carcinomas and bile duct tumors were significantly increased in treated females; males and females in both dose groups had increased incidences of renal cell adenomas and hemangiohepatomas. Females were far more susceptible to hepatocarcinogenicity while males were generally more sensitive to renal carcinogenicity. The time- to-tumor onset in each dose group was generally longer than 1 year.

The Health Canada value of 0.83 $(mg/kg\text{-}day)^{-1}$ was used because it is more conservative than the US EPA value.

40.3.2 Inhalation Exposure

40.3.2.1 Non-Carcinogenic Toxicity Reference Values

40.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.25 $\mu g/m^3$ for hexachlorobenzene was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009). TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

A 24-hour inhalation TRV was unavailable for hexachlorobenzene at the time of this assessment.

40.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 0.025 µg/m^3 for hexachlorobenzene was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 40.3.2.1.1. To derive a long-term ESL for hexachlorobenzene, TCEQ further divides the short-term ESL by an additional safety factor of 10 (Lee, 2009).

40.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

US EPA (1996) provides an inhalation unit risk of 0.00046 (µg/m^3)$^{-1}$ for hexachlorobenzene. A linearized multistage extrapolation was conducted based on the results of the previously discussed oral study by Ertuk et al. (1986) to attain this unit risk. This value was selected for further use in the risk assessment.

40.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.13 (Health Canada, 2004a). With regards to the inhalation pathway, it has been conservatively assumed that hexachlorobenzene is completely absorbed (i.e. absorption factor is 1).

40.5 Conclusion

The following tables present hexachlorobenzene TRVs selected for use in this risk assessment.

Table 40-1 Hexachlorobenzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Hexachlorobenzene	Non-carcinogenic TRV	0.0005	Liver Effects	RfD	Health Canada, 2004b
	Carcinogenic Slope Factor	0.83	Liver and Thyroid Cancer	SF	Health Canada, 2004b

[a] Units: Non-carcinogenic COPC (mg/kg/day), Carcinogenic COPC (mg/kg/day)$^{-1}$

Table 40-2 Hexachlorobenzene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Hexachlorobenzene	1-Hour	0.25	Health Based	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	0.025	Health Based	Benchmark	TCEQ ESL, 2008
	Carcinogenic Annual Average	0.00046	Liver and Renal Tumours	UR	US EPA, 1996

[a] Units: Non-carcinogenic COPC (µg/m^3), Carcinogenic COPC (µg/m^3)$^{-1}$, NV – No Value

40.6 References

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41.0 LEAD

Lead is a naturally occurring element found in the earth's crust. While most of the lead found in the environment is the result of anthropogenic activities, there are significant natural sources as well, including volcanoes, forest fires, sea spray, and weathering of lead-containing minerals (Environment Canada, 1996). The different forms of lead found in the environment are governed by factors such as temperature, pH, and the presence of humic materials. Elemental lead occurs rarely in the ambient environment; the most common form of lead in the environment is Pb2+. Particulate-bound lead emitted from mining operations, smelters, and combustion sources occurs primarily in the form of lead-sulphur compounds such as PbSO4, PbO·PbSO4, and PbS (US EPA, 1986). In the ambient atmosphere, lead exists primarily in the form of particulate-bound PbSO4 and PbCO3, and is deposited onto soil and water surfaces in this form (ATSDR, 2007).

The toxic effects of lead in humans are widely believed to be the same regardless of the route of entry, and are correlated to blood lead (PbB) in the vast majority of studies (ATSDR, 2007). The effects from chronic exposure to lead in humans and experimental animals are primarily neurological, renal, hematological, reproductive, and developmental (ATSDR, 2007). Well characterized human health effects include neurotoxicity and renal toxicity, which can be severe at blood lead levels greater than 120 µg/dL (US EPA, 1986). Severe lead exposure in children (PbB above 380 µg/dL) can cause coma, convulsions, and even death.

The most commonly reported and well-studied effects of environmental lead exposure are (1) adverse effects on neurological function and neurobehavioural development in children, and (2) reduced growth rate. However, it remains unclear if lead causes such effects in adults (US EPA 2004). The effects in children often manifest as decreased IQ and memory, decreased gestation period, and retarded growth rate.

41.1 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.

Health Canada (1992) classified lead as Group IIIB – possibly carcinogenic to humans (inadequate data in humans, limited evidence in animals) according to the classification scheme of the Environmental Health Directorate of Health and Welfare Canada (CCME, 1999). 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.

For this assessment, lead was not assessed as a carcinogen.

41.2 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 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.

41.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

41.3.1 Oral Exposure

41.3.1.1 Non-Carcinogenic Toxicity Reference Values

The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) (1987) derived a provisional tolerable daily intake (pTDI) of lead of 0.0036 mg/kg-day based on the provisional tolerable weekly intake (pTWI) of 25 µg/kg-week for adults and children. This value assumes that lead accumulates in the body and that increases in the body burden of lead (above 5 µg/dL blood lead) should be avoided from any sources (e.g., oral or inhalation) to avoid any potential negative effects (Ryu et al. 1983; Ziegler et al. 1978). The value was derived from studies by Ryu et al. (1983) and Ziegler et al. (1978). Ryu et al. (1983) examined infants who were between 8 to 195 days old that were fed formula or breast milk containing lead. Mean dose for those between 8 and 111 days old was 0.017 mg/kg-day and those who were 112 to 195 days old the dosage was 0.016 or 0.061 mg/kg-day. The overall duration was 103 or 187 days. Again, significant increases in blood lead concentrations were measured. Ziegler et al. (1978) conducted a metabolic balance study whereby infants who were between 14 and 746 days old were administered a lead dose of 0.00172 to 0.02261 µg/kg-day through their milk, formula or strained foods for a period of 72 hours. Results showed increased blood lead in the infants. Overall from these studies, a NOAEL of 0.003 to 0.004 mg/kg-day was determined on the basis that increases in blood lead levels or body burden of lead would not occur at this level. This value has been adopted by both RIVM (2001) and Health Canada (2004a).

The US EPA has not selected an oral RfD due to the apparent lack of a threshold for lead and the high level of uncertainty in lead pharmacokinetics (US EPA, 2004). They argue that oral RfDs are not representative of the potential risk from lead since it is difficult to account for pre-existing body burdens (i.e., primarily in the skeleton since lead accumulates primarily in bone). Lead body burdens vary significantly with age, health status, nutritional state, maternal body burden during gestation and lactation; thus the US EPA believes it is inappropriate to develop a reference concentration for lead.

The Ontario MOE (1994) derived an Intake of Concern (IOC) of 0.00185 mg/kg/day based on behavioural effects and learning disabilities in children. A blood lead level of 0.01 mg/dL was chosen by the Ministry to be the LOAEL for children. A NOAEL was not established by the MOE (1994). The intake level of concern for Ontario children was derived by estimating the lead intake that would result in a blood lead level of 0.01 mg/dL. This intake level was estimated to be 0.0037 mg/kg/day. This value

was then divided by a safety factor of two which resulted in an IOC of 0.00185 mg/kg/day. The safety factor of two was used to account for potential variations within the population.

The MOE (1994) IOC of 0.00185 mg/kg-day was used as the exposure limit in this assessment as it is the most conservative value and is protective of all individuals.

41.3.1.2 Cancer Oral Toxicity Reference Values

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

41.3.2 Inhalation Exposure

41.3.2.1 Non-Carcinogenic Toxicity Reference Values

41.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

The 1-hour exposure limit used in this risk assessment was selected from Alberta Environment (AENV). AENV (2007) derived an AAQO benchmark (1-hour) of 1.5 µg/m^3 for lead using a California Environmental Protection Agency (CalEPA) state ambient air quality standard (AAQS). This AAQS was first established in 1970 and is based on data that showed airborne lead levels above 1.5 µg/m^3 could result in an increased quantities of lead in the body that were sufficient to impair the hemopoietic system.

The 24-hour exposure limit used in this risk assessment was selected from the Ontario Ministry of the Environment (MOE). The MOE (2008) 24-hour AAQC benchmark of 0.5 µg/m^3 was derived based on considerable review of air quality criteria from various agencies worldwide (e.g., CalEPA, US EPA, WHO, etc), current toxicology and epidemiological research (MOE, 2007). From this review, health effects associated with increased blood lead levels were regularly used to derive lead benchmarks. Similarly, the MOE in deriving an AAQC benchmark considered neurological effects in children as an appropriate and sensitive endpoint for assessing toxicity at low blood lead levels.

41.3.2.2 Chronic Inhalation Toxicity Reference Values

The chronic exposure limit used in this risk assessment was selected from the World Health Organization (WHO). WHO (2000) derived a guideline value (annual averaging time) of 0.5 µg/m^3 for lead based on blood lead levels in children (Mahaffey et al., 1982; Rosen et al., 1980). As discussed in the section above, regulatory guidelines for lead in air are based on a critical level of lead in the blood. WHO (2000) has set this critical level to 100 µg/L, as the earliest adverse effects observed in children start at blood lead levels between 100-150 µg/L.

41.3.2.3 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.

41.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0; while the relative dermal absorption fraction (RAF) was set as 0.006 (Health Canada, 2004b).

41.5 Conclusion

The following tables present lead TRVs selected for use in this risk assessment.

Table 41-1 Lead Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Lead	Non-carcinogenic TRV	0.00185	Behavioural effects and learning disabilities in children	RfD	MOE, 1994
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) ' NE – Not Evaluated

Table 41-2 Lead Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Lead	1-Hour	1.5	Impairment of hematopoietic system	Benchmark	ANEV AAQO, 2007
	24-Hour	0.5	Neurological effects in children	Benchmark	MOE AAQC, 2008
	Annual Average	0.5	Blood lead levels	RfC	WHO, 2000

[a] Units: Non-carcinogenic COPC (µg/m^3)

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42.0 MERCURY

Mercury occurs naturally in the environment and exists in several forms. These forms can be organized under two headings: 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, 1999a).

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, 1999a).

Mercury toxicity has a large effect on the nervous system. While all forms of mercury can be toxic, methylmercury and metallic mercury vapours are especially harmful because mercury in these forms can reach the brain, permanently damaging it. This can lead to irritability, shyness, tremours, changes in vision or hearing, and memory problems (ATSDR, 1999b). Exposure to high levels of metallic, inorganic, or organic mercury can also result in damage to the kidneys as well as developing fetuses (in the case of maternal exposure) (ATSDR, 1999b).

Acute (short term) exposure to metallic mercury vapour can cause lung damage, nausea, vomiting, diarrhea, increased blood pressure and heart rate, skin rashes and eye irritation (ATSDR 1999b).

42.1 Assessment of Carcinogenicity

The US EPA (1995, 2001) has classified inorganic mercury and methylmercury as Group C chemicals, indicating that they are possible human carcinogens. (US EPA, 2001) 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. For the purpose of this assessment, mercury (inorganic and methylmercury) will not be assessed as a carcinogen.

42.2 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 very young because of their immature and developing organs (ATSDR, 1999a).

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, 1999a).

42.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

42.3.1 Oral Exposure

42.3.1.1 Non-Carcinogenic Toxicity Reference Values

Inorganic Mercury

Health Canada (2004b) provides an oral TRV for non-carcinogenic effects from inorganic mercury (i.e., mercuric chloride) of 0.0003 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 (1995) 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 an intensive review and workshop discussion of the entire inorganic mercury database, however the weight of evidence is from three studies using Brown Norway rats as well as 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.

MethylMercury

The Bureau of Chemical Safety Food Directorate of Health Canada (HC, 2007) has adopted a provisional tolerable daily intake of 0.0002 mg/kg-d of methylmercury for pregnant women (or women of child bearing age) and toddlers, and a general population value of 0.00047 mg/kg-d of methylmercury exposure from fish in diet. This is consistent with the WHO/FAO Expert Committee on Food Additives (JECFA) which recommendeds a provisional tolerable weekly intake (pTWI) for methylmercury of 0.00016 mg/kg bw/week (equivalent to 0.00023 mg methylmercury/kg bw/day) in order to sufficiently protect the developing fetus (WHO, 2003).This was based on observed effects between exposure of pregnant mothers to methylmercury and developmental effects in their children. In these observations, appreciable adverse effects were not observed, however long-term neuropsychological effects, particularly regarding cognition and learning, are not known.

The US EPA (2001) derived oral TRV for methyl mercury of 0.0001 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.

For this assessment, Health Canada (2004b, 2007) oral TRVs of 0.0003 mg/kg-day and 0.0002 mg/kg-day were adopted as oral TRVs for inorganic mercury and methylmercury, respectively.

42.3.1.2 Cancer Toxicity Reference Values

Mercury (inorganic and methylmercury) is not classified as a carcinogenic substance; therefore, a carcinogenic oral toxicological reference value has not been selected.

42.3.2 Inhalation Exposure

42.3.2.1 Non-Carcinogenic Toxicity Reference Values

42.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Inorganic Mercury

CalEPA (2008) derived an acute inhalation REL of 0.6 µg/m^3 for a 1-hour exposure time based on behavioural deficits in rats exposed to metallic mercury vapour *in utero* (Danielsson et al*. 1*993). The study exposed groups of 12 pregnant rats to 1,800 µg/m^3 of inorganic mercury vapour for 1 hour/day (0.07 mg/kg/day) or 3 hours/day (0.2 mg/kg/d) during gestational days 11-14 and 17-20. Tests of motor activity of the offspring at 3 months of age saw significant dose dependant hypoactivity. This was no longer seen at 14 months, replaced with significant hyperactivity in the 0.2 mg/kg/d group. Significant learning disabilities were also seen in the 0.2 mg/kg/day group, but not the 0.07 mg/kg/day group. A cumulative uncertainty factor of 3,000 was applied: 10 for the use of a LOAEL, 10 for intraspecies uncertainty, and 30 for interspecies extrapolation. This REL is considered to be an overestimate for inorganic mercury (CalEPA, 2008). This value was adopted as the 1-hour acute exposure limit for the current assessment.

A 24-hour exposure benchmark of 2.0 µg/m^3 for inorganic mercury was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

Methylmercury

Acute inhalation TRVs were not identified for methylmercury.

42.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Inorganic Mercury

An annual average guideline of 1.0 µg/m^3 was established by WHO (2000) for objective tremors, renal tubular effects (changes is plasma enzymes) and non-specific symptoms in workers subjected to long

term mercury vapour exposure (WHO 1991; Cardenas et al. *1*993). The reported LOAELs, which were assumed to be approximately equivalent to ambient air concentrations, ranged from 10,000 to 30,000 µg/m^3. As human studies were used, an uncertainty factor of 10 was suggested; however, an uncertainty factor of 20 was applied. The LOAELs utilized were only rough estimates of air concentrations at which the observed effects occurred at a low frequency. In addition, it seems unlikely that these adverse effects would occur in occupationally exposure workers at concentrations measuring only one half of the LOAELs; therefore, an uncertainty factor of 20 was selected.

CalEPA (2008) derived a chronic REL of 0.3 µg/m^3 based on several occupational exposure studies (Piikivi and Hanninen, 1989; Fawer et al.,1983; Piikivi and Tolonen, 1989; Piikivi, 1989; Ngim et al. 1992). In each study workers were exposed to mercury vapor for 8-hours per day 5 days a week, for durations of 13.7 to 15.6 years at various concentrations. Neurotoxicity as measured by: intention tremor; memory and sleep disturbances; decreased performance on neurobehavioral tests (finger tapping, visual scan, visuomotor coordination, visual memory); decreased EEG activity was found as the critical effect in each study. CalEPA (2008) derived a LOAEL of 25 µg/m$^{3,\ a}$ NOAEL was not observed. The LOAEL was time adjusted to 9 µg/m$^{3.}$ and a cumulative uncertainty factor of 300 was applied (10 use of a LOAEL and 30 for intraspecies variability) to arrive at an REL of 0.3 µg/m^3.

For this risk assessment the CalEPA (2008) REL of 0.3 µg/m^3 was chosen because it was a more conservative value.

Methylmercury

Chronic inhalation TRVs were not identified for methylmercury.

42.3.2.2 Cancer Inhalation Toxicity Reference Values

Mercury (inorganic and methylmercury) is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

42.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.05 for inorganic mercury and 0.2 for methylmercury (Health Canada, 2004a).

42.5 Conclusion

The following tables present inorganic mercury and methylmercury TRVs selected for use in this risk assessment.

Table 42-1 Mercury Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Mercury (Inorganic)	Non-carcinogenic TRV	0.0003	Autoimmune effects	RfD	Health Canada, 2004b

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
	Carcinogenic Slope Factor	NE			
Methylmercury	Non-carcinogenic TRV	0.0002	Neuropsychological dysfunctions	RfD	Health Canada, 2007
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC (mg/kg/day)$^{-1}$
NE – Not Evaluated

Table 42-2 Mercury Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Mercury (Inorganic)	1-Hour	0.6	CNS disturbances in rat offspring	Benchmark	CalEPA REL, 2008
	24-Hour	2	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	0.3	Neurotoxicity	Benchmark	CalEPA REL, 2008
Methylmercury	1-Hour	NV			
	24-Hour	NV			
	Annual Average	NV			

[a] Units: Non-carcinogenic COPC (µg/m^3) , Carcinogenic COPC (µg/m^3) $^{-1}$
NV – No Value

42.6 References

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43.0 NICKEL

Nickel (Ni) is a naturally occurring metal existing in various mineral forms. It 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 with most metals, the toxicity of nickel is dependent on the route of exposure and the solubility of the nickel compound (Coogan et al., 1989).

Nickel is a transition metal and exists in several oxidation states (most often +2) (Budavari et al. 1989). The toxicokinetics and toxicity of nickel are strongly influenced by its form (*e.g.*, metallic, salt, oxide) and solubility. The more soluble nickel compounds include the nickel salts (nickel chloride and nickel sulphate) and nickel nitrate, while less soluble nickel compounds include nickel oxide (*i.e.,* black crystalline form and more stable green form) and nickel sub-sulphide (ATSDR 2005a). In general, the more soluble nickel compounds have a greater toxicity than less soluble forms; however, at the site of tissue deposition, the less-soluble compounds are more likely to be carcinogenic (ATSDR, 2005a).

The most common form of nickel toxicity in humans is allergic reactions, generally resulting in skin rashes at the site of contact, but less frequently resulting in other skin rashes or asthma attacks. People generally become sensitive to nickel after prolonged contact with the skin (such as in the case of jewelry). Once sensitized, people can react to low levels of nickel in the air, food or water. Approximately 10-20% of people are sensitive to nickel (ATSDR, 2005b).

Chronic inhalation exposure to higher levels of nickel can lead to chronic bronchitis and reduced lung function (ATSDR, 2005b). Ingesting large amounts of nickel can lead to stomach ache and negative effects on the blood and kidneys (ATSDR, 2005b). Animal studies have shown lung and nasal cavity damage as a result of nickel inhalation. Ingestion of large amounts of nickel has caused lung disease in dogs and rats. In rats and mice, effects on the stomach, blood, liver, kidneys immune system, reproductive system, as well as developmental affects, have been documented following the ingestion of large amounts of nickel (ATSDR, 2005b).

43.1 Assessment of Carcinogenicity

Certain forms of nickel (essentially sulphate and sulphide) are considered to be carcinogenic to humans and are listed as Group 1 carcinogens by IARC. The US EPA (1996) 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, 1996). 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. Therefore, nickel is not being assessed as a carcinogen in this risk assessment.

43.2 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).

43.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

Note that the selection of TRVs is specific to the form of nickel most relevant to this study – soluble salts of nickel.

43.3.1 Oral Exposure

43.3.1.1 Non-Carcinogenic Toxicity Reference Values

The oral RfD developed by the US EPA (1996) for nickel (soluble salts) is 0.02 mg/kg-day. The RfD was based on a two-year study (Ambrose, 1976) where rats were fed 0, 100, 1000 or 2500 ppm nickel (estimated as 0, 5, 50 and 125 mg Ni/kg bw). The form of nickel administered was nickel sulphate hexahydrate. Body weights were significantly less than controls for the high-dose male and female rats, and were also significantly reduced for rats at the 1000ppm nickel level. Changes in organ weights were also documented. 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 were used to derive the RfD. An uncertainty factor of 10 was used for interspecies extrapolation and 10 to protect sensitive populations. An additional uncertainty factor of 3 was used to account for inadequacies in the reproductive studies culminating in a cumulative uncertainty factor of 300, which was applied to the NOAEL to general the RfD.

Health Canada (2004b) established a TDI for nickel sulfate of 0.05 mg/kg-day. The derivation of this value is identical to the previously discussed derivation of the US EPA value, however, Health Canada did not include an uncertainty factor of 3 for inadequacies in the study, resulting in a cumulative uncertainty factor of 100.

The California Environmental Protection Agency (CalEPA, 2008b) has also derived a reference exposure limit of 0.05 mg/kg-day based on the same derivation procedure as previously described by Health Canada (2004b).

TERA (2004) calculated an oral reference dose of 0.008 mg/kg-day nickel for ingested nickel-soluble salts. Several studies were considered as the basis for the RfD for soluble nickel salts, however Vyskocil et al. (1994) was the principal study. The most sensitive endpoint was determined to be

increased albuminuria (indicating renal glomerular dysfunction) in male and female rats exposed to nickel in drinking water for 6 months (Vyskocil et al. 1994). Increased albuminuria was observed at 6 months but not after three months of exposure. In this study, only a single dose was tested (*i.e.*, 6.9 mg/kg-day in males and 7.6 mg/kg-day in females). These doses were the LOAEL values for this study, as albuminuria was considered a biologically significant effect. Despite this limitation of single doses, the LOAELs are supported by several other oral studies (TERA 2004). Other limitations of Vyskocil et al. (1994) and the other available oral studies with soluble nickel compounds noted by TERA (2004), included subchronic durations, lack of comparison to baseline values, small numbers of test animals, considerable variability in responses in both control and exposed groups, uncertainty surrounding biological significance of renal effects, inadequate reporting, and high mortality rates in both treated and control groups. An overall uncertainty factor of 1,000 was applied (10 for intraspecies extrapolation, 10 for interspecies extrapolation, and 10 for subchronic-to-chronic extrapolation, an insufficient toxicological database, and use of a minimal LOAEL) to the LOAEL of 7.6 mg/kg-day to yield the oral RfD of 0.008 mg/kg body weight/day.

Health Canada (2004b) also derived a TDI of 0.0013 mg/kg-day for nickel chloride, which 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.

43.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, nickel is not being evaluated as a carcinogen; therefore, a carcinogenic oral toxicological reference value has not been selected.

43.3.2 Inhalation Exposure

43.3.2.1 Non-Carcinogenic Toxicity Reference Values

43.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

CalEPA (2008a) derived an acute, 1-hour reference exposure level (REL) for nickel compounds (excluding nickel oxide) of 6.0 µg/m^3. This value was derived using the LOAEL of 67 µg/m^3 for decreased forced expiratory volume (>15%) from the study by Cirla et al. (1985) involving seven volunteer metal plating workers with occupational asthma. The nickel species in this study was nickel sulphate hexahydrate, and the exposure duration was 30 minutes. CalEPA extrapolated the LOAEL to a 1 hour concentration, which was 33 µg/m^3. A cumulative uncertainty factor of 6 was applied to this value (based on use of a LOAEL) to yield the acute REL.

For this assessment the CalEPA RfC of 6.0 µg/m^3 was used. A 24-hour exposure limit was not

identified for nickel.

43.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Health Canada (2004b) has identified a chronic RfC of 0.0035 µg/m^3 for nickel sulfate. No rationale has been provided for the derivation of this value.

CalEPA (2008a) derived a chronic reference exposure level (REL) for nickel compounds (excluding nickel oxide) of 0.05 µg/m^3. This value was derived using a LOAEL of 60 µg/m^3 and a NOAEL of 30 µg/m^3 for pathological changes in lung, lymph nodes, and nasal epithelium from the study by NTP (1994) involving male and female F344/N rats. The nickel species in this study was nickel sulphate hexahydrate and the rats were exposed 6 hrs/day, 5 days/week for 104 weeks. A human equivalency NOAEL of 1.6 µg/m^3 was extrapolated and a cumulative uncertainty factor of 30 was applied to this value (factor of 3 for interspecies extrapolation and 10 for intraspecies extrapolation) to yield the acute REL.

ATSDR (2005a) provides a chronic inhalation MRL of 0.09 µg/m^3 based on exposure of male and female rats to nickel sulfate hexahydrate. From a NOAEL of 30 µg/m^3, a human equivalent NOAEL of 2.7 µg/m^3 was developed for chronic active inflammation and lung fibrosis. An uncertainty factor of 30 was applied to the NOEAL to account for extrapolation from animals to humans and human variability. ATSDR evaluated the non-carcinogenic toxicity of various forms of nickel, and derived a chronic minimal risk level (MRL) based on nickel sulfate. This MRL most precisely pertains to the soluble nickel compounds (i.e., nickel chloride, nickel sulfate, and nickel nitrite), but ATSDR stated that this value would also be protective against the toxicity of other nickel compounds (i.e., the less-soluble compounds, including nickel oxide, nickel subsulfide, and metallic nickel).

TERA (2004) and Haber et al. (2000) suggest a reference concentration of 0.2 µg/m^3 for inhaled nickel soluble salts, based on lung fibrosis in male rats, as reported in NTP (1996). TERA reviewed the data from the NTP (1996) study on the incidence of respiratory tract lesions and then fit these data to a polynomial mean response regression model and a Weibull power mean response regression model, using the maximum likelihood method. This was followed by benchmark dose modelling. Based on the modelling results, the most sensitive endpoint was lung fibrosis in male rats. The BMCL10 (HEC) for lung fibrosis in male rats was 1.7 µg/m^3. An uncertainty factor of 10 was applied to this value to account for intrahuman variability, and yielded the RfC.

For this assessment the CalEPA chronic RfC of 0.05 µg/m^3 was used.

43.3.2.2 Cancer Inhalation Toxicity Reference Values

In this risk assessment, nickel is not being evaluated as a carcinogen; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

43.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.35 (RAIS, 2006). With regards to the inhalation pathway, it has been conservatively assumed that nickel is completely absorbed (i.e. absorption factor is 1).

43.5 Conclusion

The following tables present nickel TRVs selected for use in this risk assessment.

Table 43-1 Nickel Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Nickel	Non-carcinogenic TRV	0.02	Decreased body and organ weight	RfD	US EPA, 1996
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day)
NE – Not Evaluated

Table 43-2 Nickel Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Nickel	1-Hour	6	Small decrements in airway function tests, especially in asthmatics	Benchmark	CalEPA, 2008a
	24-Hour	NV			
	Annual Average	0.05	Respiratory system; hematopoietic system	Benchmark	CalEPA, 2008b

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)
NV – No Value

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44.0 POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)

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. Non-carcinogenic PAHs are evaluated individually.

Animal studies have shown that PAHs can cause reproductive effects (difficulties reproducing, high rate of birth defects, lower bodyweights – occurring in both adult rats and later in their offspring), and harmful effects on the skin, body fluids, and immune system. This can occur after both short and long-term exposure; however, these effects have not been seen in humans (ATSDR 1996).

44.1 Assessment of Carcinogenicity

Although there is strong evidence of carcinogenicity for several PAH compounds, only benzo(a)pyrene has reliable carcinogenic toxicity studies. 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. Different agencies (US EPA, Health Canada, WHO, etc.) provide different TEFs depending on the PAH being considered. Table 1-1 provides the list of TEFs used in this assessment for the various PAH compounds. Anthracene, benzo(a)fluorene, benzo(b)fluorene, fluorene, 1- and 2-methylnaphthylene, and naphthalene are not considered carcinogenic for this assessment, although the US EPA (1998) classifies naphthalene as Group C, a possible human carcinogen and it is classified as Group 2B by the International Agency for Research on Cancer (IARC, 2002) possibly carcinogenic to humans.

44.2 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).

44.3 Selection of Toxicity Reference Values

Toxic Equivalency Factors

As indicated in Health Canada (2007) and other regulatory guidance, the assessment of risks related to exposures to carcinogenic PAHs is primarily conducted through the use of potency or toxicity equivalence factors (PEF or TEF). TEFs allow large groups of compounds with a common mechanism of action such as PAHs to be assessed when limited data is available for all but one of the compounds (*i.e.*, benzo(a)pyrene). Through this approach, exposures to each of the carcinogenic PAHs are adjusted by their carcinogenic potency relative to benzo(a)pyrene. These potency-adjusted exposures can then be summed to provide an overall exposure to the group of carcinogenic PAHs, based on benzo(a)pyrene as the primary surrogate

This approach was utilized in the current assessment. Table 44-1 shows each of the carcinogenic PAHs evaluated in the current assessment and the respective TEFs selected for use with this approach.

Non-carcinogenic PAHs can be assessed individually without the use of PEFs or TEFs.

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

44.3.1 Carcinogenic PAHs

44.3.1.1 Oral Exposure

Many agencies base their carcinogenicity assessment of benzo(a)pyrene on an oral exposure study by Neal and Rigdon (1967) study including Health Canada (2004b), US EPA (1994), and Cal EPA (2005). In this feeding study benzo(a)pyrene was given to mice at concentrations ranging from 0.001 to 0.25 mg/g in feed (duration of oral exposure: 98 to 197 days). No tumours were noted in controls or in several low dose groups. The incidence of stomach tumours (squamous cell papillomas and carcinomas) increased in groups treated with 40 to 250 ppm doses. From this study, Health Canada derived an oral slope factor of 2.3 $(mg/kg\text{-}day)^{-1}$. The US EPA (1994) derived an oral slope factor of 7.3 $(mg/kg\text{-}day)^{-1}$ based on the geometric mean of four slope factors (ranging from 4.5 to 11.7 $(mg/kg\text{-}day)^{-1}$ obtained from animal studies, including the study by Neal and Rigdon (1967). The California Environmental Protection Agency (CalEPA, 2005) calculated an oral slope factor of 12 $(mg/kg\text{-}day)^{-1}$ using on a linearized multistage procedure which incorporates a linear upper bound on extra risk for exposures below the experimental range when estimating carcinogenic risk. Given that the Neal and Rigdon (1967) study is the foundation for interpreting toxicity from oral exposure to benzo(a)pyrene and used by all agencies as a principal study, the more conservative Health Canada (2004b) value of 2.3 $(mg/kg\text{-}day)^{-1}$ was selected for use in this risk assessment.

44.3.1.2 Inhalation Exposure

Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

Acute, 1-hour exposure limits were selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for all carcinogenic PAHs except benzo(a)pyrene and dibenzo(a,c)anthracene. A value of 1 µg/m^3 was derived for acenaphthalene and acenaphthene, while a value of 0.5 µg/m^3 was derived for all other carcinogenic PAHs except the previously mentioned benzo(a)pyrene and dibenzo(a,c)anthracene. TCEQ derives these 1-hour ESL values after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OEL, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive 1-hour exposure limits (Lee, 2009).

A 24-hour exposure benchmark of 0.001 µg/m^3 for benzo(a)pyrene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

Chronic Inhalation Toxicity Reference Values

TEF values were used to derive inhalation toxicity reference values for the carcinogenic PAHs based upon an inhalation unit risk of 0.087 (µg/m^3)$^{-1}$ provided for benzo(a)pyrene by the World Health Organization (2000). The carcinogenic potential for each of the individual PAHs is summed to provide a cumulative incremental lifetime cancer risk for carcinogenic PAHs. This inhalation unit risk value was based on epidemiological studies on oven-coke workers who showed increased incidence of lung cancer. The WHO identified an upper-bound individual lifetime unit risk estimate associated with continuous exposure to 1 g/m^3 of benzene-soluble compounds of coke-oven emissions in ambient air of 0.00062 based on a linearized multistage model. Benzo(a)pyrene was selected as an indicator of general PAH mixtures from emissions of coke ovens and similar combustion processes in urban air. In the benzene-soluble fraction of coke oven emissions, 0.71% is benzo(a)pyrene.

44.3.2 Non - Carcinogenic PAHs

44.3.2.1 Acenaphthene

44.3.2.1.1 Oral Exposure

The US EPA (1989) derived a chronic oral RfD of 6x10^{-2} mg/kg/day based on no observed effects during a subchronic gavage study in mice with a duration of 90 days. Four groups of CD-1 mice (20/sex/group) were gavaged daily with 0, 175, 350, or 700 mg/kg/day acenaphthene for 90 days. The toxicological evaluations of this study included body weight changes, food consumption, mortality, clinical pathological evaluations, organ weights and histopathological evaluations of target organs. The results of the study indicated no treatment-related effects on survival, clinical signs, body weight

changes, total food intake, and ophthalmological alterations. Liver weight changes accompanied by microscopic alterations (cellular hypertrophy) were noted in both mid- and high-dose animals and seemed to be dose-dependent. Additionally, high-dose males and mid- and high-dose females showed significant increases in cholesterol levels. Although increased liver weights, without accompanying microscopic alterations or increased cholesterol levels, were also observed at the low dose, this change was considered to be adaptive and was not considered adverse. The LOAEL derived from the study was 350 mg/kg/day based on hepatotoxicity, and the NOAEL derived from the study was 175 mg/kg/day. An uncertainty factor of 3,000 for interspecies (10) and intraspecies (10) variation, and for the use of a subchronic study, lack of reproductive/developmental data, and adequate toxicity data in a second species (30) was applied to the study NOAEL to derive an oral chronic RfD of $6x10^{-2}$ mg/kg/day.

44.3.2.2 Anthracene

44.3.2.2.1 Oral Exposure

The US EPA (1993) derived a chronic oral RfD of 0.3 mg/kg-day based on no observed effects during a subchronic gavage study in mice with a minimum duration of 90 days (US EPA, 1989). No significant changes in mortality, clinical signs, body weights, food consumption, opthalmology findings, hematology and clinical chemistry results, organ weights, organ-to-body weight ratios, gross pathology, and histopathology were found in anthracene exposed mice. An uncertainty factor of 3,000 for interspecies (10) and intraspecies (10) variation, and for the use of a subchronic study, lack of reproductive/developmental data, and adequate toxicity data in a second species (30) was applied to the study NOAEL of 1,000 mg/kg/day.

44.3.2.2.2 Inhalation Exposure

Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.5 µg/m^3 was selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for anthracene. As described above, the majority of TCEQ ESLs are derived from OELs which are then divided further by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure limit was not identified for anthracene.

Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 0.05 µg/m^3 was selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for anthracene. The TCEQ ESL selected is based on OELs used to derive the short-term (1-hour) ESL, long-term exposures are further divided by a safety factor of 10.

44.3.2.3 Fluorene

44.3.2.3.1 Oral Exposure

An oral TRV of 0.04 mg/kg/day was provided for fluorene by the U.S. EPA (1990) based on a subchronic toxicity study, where oral exposure to mice for 13 weeks via gavage established a NOAEL of 125 mg/kg-day and a LOAEL of 250 mg/kg-day for decreased red blood cells, packed cell volume and hemoglobin. A total uncertainty factor of 3000 was applied to the NOAEL (10 each for inter- and intraspecies variability, 10 for use of a subchronic study and 3 for data inadequacies).

44.3.2.3.2 Inhalation Exposure

Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 10 µg/m^3 was selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for fluorene. . As described above, the majority of TCEQ ESLs are derived from OELs which are then divided further by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour exposure limit was not identified for fluorene.

Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 1 µg/m^3 was selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for fluorene.

44.3.2.4 Benzo(a)fluorene and Benzo(b)fluorene

44.3.2.4.1 Oral Exposure

Oral exposure limits were not identified for benzo(a)fluorene and benzo(b)fluorene.

44.3.2.4.2 Inhalation Exposure

Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

An annual exposure limit of 0.5 µg/m^3 was selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for benzo(a)fluorene and benzo(b)fluorene. The TCEQ ESL selected is based on OELs used to derive the short-term (1-hour) ESL, long-term exposures are further divided by a safety factor of 10.

24-hour exposure limits were not identified for benzo(a)fluorene and benzo(b)fluorene.

Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 0.05 µg/m^3 was selected from the Texas Commission on Environmental Quality (TCEQ, 2008) for benzo(a)fluorene and benzo(b)fluorene.

44.3.2.5 Naphthalene and Alkylated Naphthalenes (1-methylnaphthalene and 2-methylnaphthalene)

It is relevant to note that CalEPA (2004) considers Naphthalene to have carcinogenic or mutagenic properties. This conclusion is based in a study conducted by the National Toxicology Program (2000) in which groups of 49 male and female Fischer 344N rats were exposed to naphthalene by inhalation to concentrations of 0, 10, 30 or 60 ppm for 6.2 hours per day, 5 days/week for 105 weeks. These studies found evidence of carcinogenic activity in the exposed male and female rats based on increased incidences of rare tumours, respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose. While CalEPA derived a unit risk and oral slope factor based on this study, it is relevant to note that there is considerable debate in the scientific community regarding the potential carcinogenic nature of naphthalene. Currently, IARC, Health Canada and US EPA only consider naphthalene as a possible carcinogen to humans and US EPA considers the current data to be inadequate to derive carcinogenic inhalation or oral TRVs; therefore, naphthalene has been evaluated as a non-carcinogenic substance in this risk assessment.

44.3.2.5.1 Oral Exposure

In this risk assessment, naphthalene and alkylated naphthalenes are only being evaluated through the inhalation pathway; therefore, non-carcinogenic oral toxicological reference values have not been selected.

44.3.2.5.2 Inhalation Exposure

Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 24-hour exposure benchmark of 22.5 µg/m^3 for naphthalene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

A 1-hour exposure limit was not identified for naphthalene. 1-hour and 24-hour exposure limits were not identified for 1-methylnaphthalene and 2-methylnaphthalene.

Chronic Inhalation Toxicity Reference Values

An inhalation reference concentration (RfC) of 3 µg/m^3 is derived by the US EPA (1998) for naphthalene. This value is derived from a human equivalent LOAEL of 9.3 mg/m^3 in a chronic mouse inhalation study (NTP, 1992). 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). The ATSDR (2005) derived the same exposure limit (3.0 µg/m^3) using more recent scientific studies (NTP 2000; Abdo *et al.* 2001).

A chronic inhalation RfC of 9 µg/m^3 was derived for naphthalene by the California Environmental Protection Agency (CalEPA, 2005). The basis of this value is the same NTP (1992) study that was used as a basis for the derivation of the previously described US EPA RfC value. However, the US EPA

used a total uncertainty factor of 3000, whereas CalEPA derived their value using a total uncertainty factor of 1000 – the factor of 3 for database deficiencies was not applied by CalEPA.

The more conservative US EPA RfC of 3 µg/m^3 for naphthalene was selected for further use in this risk assessment. There are no inhalation values derived from US EPA, WHO RIVM, CalEPA, ATSDR or Health Canada for 1-methylnaphthalene and 2-methylnaphthalene. ATSDR (2005) however lists both 1-methylnaphthalene and 2-methylnaphthalene as naphthalene-related compounds; therefore, for this risk assessment, the US EPA RfC of 3 µg/m^3 for naphthalene was selected as a surrogate to evaluate chronic 1-methylnaphthalene and 2-methylnaphthalene inhalation exposure.

44.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.2 for benzo(a)pyrene, fluorene and other carcinogenic PAHs (Health Canada, 2004a). Additionally, a dermal absorption factor of 0.29 was specified for anthrancene (Health Canada, 2004a). With regards to the inhalation pathway, it has been conservatively assumed that PAHs are completely absorbed (i.e. absorption factor is 1).

44.5 Conclusion

The following tables present polycyclic aromatic hydrocarbon TRVs selected for use in this risk assessment.

Table 44-1 Toxic Equivalency Factors (TEFs) for PAHs

Chemical	TEF	Source Agency
Acenaphthylene	0.01	RIVM, 2001
Acenaphthene	0.001	RIVM, 2001; ATSDR, 1995
Anthracene	NA	Non-carcinogenic
Benzo(a)anthracene	0.1	Health Canada, 2007
Benzo(b)fluoranthene	0.1	Health Canada, 2007
Benzo(k)fluoranthene	0.1	Health Canada, 2007
Benzo(a)fluorene	NA	Non-carcinogenic
Benzo(b)fluorene	NA	Non-carcinogenic
Benzo(ghi)perylene	0.01	Health Canada, 2007
Benzo(a)pyrene	1	NA
Benzo(e)pyrene	0.01	IPCS, 1998
Chrysene	0.01	Health Canada, 2007
Dibenzo(a,c)anthracene	0.1	IPCS, 1998
Dibenzo(a,h)anthracene	1	Health Canada, 2007
Fluoranthene	0.001	Health Canada, 2007
Fluorene	NA	Non-carcinogenic
Indeno(1,2,3 – cd)pyrene	0.1	Health Canada, 2007

Chemical	TEF	Source Agency
1 – methylnaphthalene	NA	Non-carcinogenic
2 – methylnaphthalene	NA	Non-carcinogenic
Naphthalene	NA	Non-carcinogenic
Perylene	0.001	IPCS, 1998
Phenanthrene	0.001	Health Canada, 2007
Pyrene	0.001	RIVM, 2001

Notes:
NA – Not Applicable

Table 44-2 Oral TRVs for PAHs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Benzo(a)pyrene	Carcinogenic Slope Factor	2.3	Stomach Tumours	SF	Health Canada, 2004b
Acenaphthene	Non-Carcinogenic TRV	$6x10^{-2}$	Hepatotoxicity	RfD	US EPA, 1994b
Anthracene	Non-Carcinogenic TRV	0.3	No Observed Effects	RfD	US EPA, 1993
Fluorene	Non-Carcinogenic TRV	0.04	Decreased red blood cells, packed cell volume and hemoglobin	RfD	US EPA, 1990
Benzo(a)fluorene	Non-Carcinogenic TRV	NV			
Benzo(b)fluorene	Non-Carcinogenic TRV	NV			
Naphthalene	NE				
1-Methylnaphthalene	NE				
2-Methylnaphthalene	NE				

Notes:
SF for all other carcinogenic PAHs were derived based on the appropriate TEF, as presented in Table 1-1
[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC $(mg/kg/day)^{-1}$
NE – Not Evaluated
NV – No Value

Table 44-3 Acute Inhalation TRVs for PAHs used in the HHRA

Chemical	1-Hour TRV ($\mu g/m^3$)	Source Agency	24-Hour TRV ($\mu g/m^3$)	Source Agency
Acenaphthylene	1	TCEQ, 2008	NV	NA
Acenaphthene	1	TCEQ, 2008	NV	NA
Anthracene	0.5	TCEQ, 2008	NV	NA

Benzo(a)anthracene	0.5	TCEQ, 2008	NV	NA
Benzo(b)fluoranthene	0.5	TCEQ, 2008	NV	NA
Benzo(k)fluoranthene	0.5	TCEQ, 2008	NV	NA
Benzo(a)fluorene	0.5	TCEQ, 2008	NV	NA
Benzo(b)fluorene	0.5	TCEQ, 2008	NV	NA
Benzo(ghi)perylene	0.5	TCEQ, 2008	NV	NA
Benzo(a)pyrene	NV	NA	0.001	MOE, 2008
Benzo(e)pyrene	0.5	TCEQ, 2008	NV	NA
Chrysene	0.5	TCEQ, 2008	NV	NA
Dibenzo(a,c)anthracene	NV	NA	NV	NA
Dibenzo(a,h)anthracene	0.5	TCEQ, 2008	NV	NA
Fluoranthene	0.5	TCEQ, 2008	NV	NA
Fluorene	10	TCEQ, 2008	NV	NA
Indeno(1,2,3 – cd)pyrene	0.5	TCEQ, 2008	NV	NA
1 – methylnaphthalene	NV	NA	NV	NA
2 – methylnaphthalene	NV	NA	NV	NA
Naphthalene	NV	NA	22.5	MOE, 2008
Perylene	0.5	TCEQ, 2008	NV	NA
Phenanthrene	0.5	TCEQ, 2008	NV	NA
Pyrene	0.5	TCEQ, 2008	NV	NA

Notes:
All values (TCEQ, 2008; MOE, 2008) are benchmarks based on health effects.
NV – No Value
NA – Not Applicable

Table 44-4 Chronic Inhalation TRVs for PAHs used in the HHRA

COPC	Value [a]	Critical Effect	Reference Type	Agency
Benzo(a)pyrene	0.087	Lung and Skin Cancer	UR	WHO, 2000
Anthracene	0.05	Health Based	Benchmark	TCEQ, 2008
Fluorene	1	Health Based	Benchmark	TCEQ, 2008
Benzo(a)fluorene	0.05	Health Based	Benchmark	TCEQ, 2008
Benzo(b)fluorene	0.05	Health Based	Benchmark	TCEQ, 2008
Naphthalene	3	Nasal effects, hyperplasia, and metaplasia in respiratory and olfactory epithelium, respectively	RfC	US EPA, 1998
1-Methylnaphthalene	3	Nasal effects, hyperplasia, and metaplasia in respiratory and olfactory epithelium, respectively	RfC	US EPA, 1998
2-Methylnaphthalene	3	Nasal effects, hyperplasia, and metaplasia in respiratory and olfactory epithelium, respectively	RfC	US EPA, 1998

Notes:

SF for all other carcinogenic PAHs were derived based on the appropriate TEF, as presented in Table 1-1
[a] Units: Non-carcinogenic COPC ($\mu g/m^3$) , Carcinogenic COPC ($\mu g/m^3$) $^{-1}$

44.6 References

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45.0 O-TERPHENYL

Terphenyls can be found as three isomers, i.e., o-terphenyl, m-terphenyl, and p-terphenyl. Pure terphenyl is a white crystalline solid; commercial grades are light yellow with a faint, pleasant odour (HCN, 2002). The mixtures are used industrially as heat storage and transfer agents, as textile dye carriers, and as intermediates in the production of non-spreading lubricants, while the individual isomers are used as solvents (HCN, 2002).

45.1 Assessment of Carcinogenicity

Health Canada, the US EPA's IRIS program and the IARC have not evaluated the carcinogenicity of o-terphenyl.

45.2 Susceptible Populations

There are no specific populations that have been identified that are unusually susceptible to o-terphenyl.

45.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

45.3.1 Oral Exposure

45.3.1.1 Non-Carcinogenic Toxicity Reference Values

A non-carcinogenic oral toxicological reference value was not identified for o-terphenyl.

45.3.1.2 Carcinogenic Toxicity Reference Values

As mentioned, Health Canada, the US EPA's IRIS program and the IARC have not evaluated the carcinogenicity of o-terphenyl, therefore a carcinogenic oral toxicological reference value has not been identified.

45.3.2 Inhalation Exposure

45.3.2.1 Non-Carcinogenic Toxicity Reference Values

45.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 50 µg/m^3 for o-terphenyl was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 5000 µg/m^3 based on the following critical effects: eye and upper respiratory tract irritation. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e.,

10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure limit was not identified for o-terphenyl.

45.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 5 µg/m^3 for o-terphenyl was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 1.3.2.1.1. To derive a long-term ESL for o-terphenyl, TCEQ further divides the short-term ESL by an additional safety factor of 10

45.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

O-terphenyl is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

45.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.2 (assumed value for organic chemicals). With regards to the inhalation pathway, it has been conservatively assumed that ammonia is completely absorbed (i.e. absorption factor is 1).

45.5 Conclusion

The following tables present o-terphenyl TRVs selected for use in this risk assessment.

Table 45-1 O-terphenyl Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
O-terphenyl	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC (mg/kg/day)$^{-1}$
NE – Not Evaluated

Table 45-2 O-terphenyl Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
O-terphenyl	1-Hour	50	Eye and respiratory tract irritation	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	5	Eye and respiratory tract irritation	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3).
NV – No Value

45.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

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

TCEQ (Texas Commission on Environmental Quality). 2008. Effects Screening Levels. http://www.tceq.state.tx.us/implementation/tox/index.html.

46.0 PENTACHLOROBENZENE

Chlorobenzenes are cyclic aromatic compounds formed by the addition of 1-6 atoms of chlorine to the benzene ring; this addition 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).

The health effects of pentachlorobenzene specifically are not well addressed; however, exposure to high levels of chlorobenzenes has caused health effects in humans including central nervous system effects, irritation of the eyes and upper respiratory tract, and effects on the blood, including anemia (INCHEM, 1991).

46.1 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. Accordingly, pentachlorobenzene has not been assessed as a carcinogen in this HHRA.

46.2 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).

46.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

46.3.1 Oral Exposure

46.3.1.1 Non-Carcinogenic Toxicity Reference Values

An oral TRV of 0.001 mg/kg-day was provided for pentachlorobenzene by Health Canada (1996; 2004b) based on a subchronic toxicity study (NTP, 1991) in which F344 rats and B6C3F1 mice were administered pentachlorobenzene in the diet (0, 33, 100, 330, 1000 or 2000 ppm) for 13 weeks (i.e., 2.2 to 164 mg pentachlorobenzene/kg bw/day in rats; 5.2 to 410 mg pentachlorobenzene/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. The lowest LOAEL observed in the study, based on the occurrence of histopathological lesions in male mice, was 5.2 mg/kg-day (NTP, 1991). To derive the tolerable daily intake (TDI) for pentachlorobenzene of 0.001 mg/kg-day, this LOAEL was divided by an uncertainty factor of 5000 (*i.e.*,

10 for intraspecies variation; 10 for interspecies variation; 10 for use of a subchronic study; and 5 for lack of data on carcinogenicity).

The US EPA (1988) derived a non-carcinogenic oral toxicity reference value of 0.0008 mg/kg-day for pentachlorobenzene. This US EPA value is based on a study (Linder et al., 1980) that used eight experimental groups (3 female, 5 male) of 10 rats each exposed to doses of pentachlorophenol between 8.3 and 72 mg/kg-day. A statistically significant increase in kidney weights, decreased heart weight, and an increase in hyaline droplets in proximal kidney tubules was noted in rats receiving 8.3 mg/kg-day. Female rats receiving the next highest dose, 18 mg/kg/day, and their offspring, showed increased liver/body weight ratios. The lowest dose of 8.3 mg/kg-day was considered a LOAEL. This value was modified by an uncertainty factor of 10,000 to account for interspecies (10) and interspecies (10) extrapolation, use of a subchronic study (10), and use of a LOAEL (10).

The Health Canada (1996; 2004b) value of 0.001 mg/kg-day was selected for use in this assessment over the US EPA value as it incorporates an assessment of more recent toxicity data including the Linder et al. 1980 study.

46.3.1.2 Carcinogenic Toxicity Reference Values

Pentaclorobenzene is not classified as a carcinogenic substance; therefore, a carcinogenic oral slope factor has not been selected.

46.3.2 Inhalation Exposure

46.3.2.1 Non-Carcinogenic Toxicity Reference Values

46.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 1000 µg/m^3 for pentachlorobenzene was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009). TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

A 24-hour exposure limit value was not available.

46.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 100 µg/m^3 for pentachlorobenzene was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 46.3.2.1.1. To derive a long-term ESL for pentalchlorobenzene, TCEQ further divides the short-term ESL by an additional safety factor of 10.

46.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Pentachlorobenzene is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation unit risk has not been selected.

46.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.01 (RAIS, 2007). With regards to the inhalation pathway, it has been conservatively assumed that pentachlorobenzene is completely absorbed (i.e. absorption factor is 1).

46.5 Conclusion

The following tables present pentachlorobenzene TRVs selected for use in this risk assessment.

Table 46-1 Pentachlorobenzene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Pentachlorobenzene	Non-carcinogenic TRV	0.001	Liver and Kidney effects	RfD	Health Canada, 1996; 2004b
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 46-2 Pentachlorobenzene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Pentachlorobenzene	1-Hour	1000	Health Based	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	100	Health Based	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$), NV – No Value

46.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

Health Canada. 1996. Canadian Environmental Protection Act. Priority Substances List. Supporting Documentation: Health-Based Tolerable Daily Intakes/Concentrations and Tumorigenic Doses/Concentrations for Priority Substances. Report no.96-EHD-194. Ottawa, Ontario.

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Health Canada. 2004b. Federal Contaminated Risk Assessment in Canada. Part II: Health Canada Toxicological Reference Values (TRVs). Environmental Health Assessment Services - Safe Environments Programme. September 2004.

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.

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MOE (Ontario Ministry of the Environment). 2004. Basic Comprehensive Certificates of Approval (Air) – User Guide. Version 2.0. Environmental Assessment & Approvals Branch. April 2004.

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. NIOSH Publication 2005-149.

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.

OSHA (Occupational Safety and Health Administration). 1988. Permissible Exposure Limits http://www.cdc.gov/niosh/pel88/npelname.html

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.

TCEQ (Texas Commission on Environmental Quality). 2008. Effects Screening Level Lists. Available at: http://www.tceq.state.tx.us/implementation/tox/esl/list_main.html

US EPA (United States Environmental Protection Agency). 1988. Integrated Risk Information System (IRIS) Database - Pentachlorobenzene. Available on-line at: http://www.epa.gov/ncea/iris/subst/0085.htm

47.0 PENTACHLOROPHENOL (PCP)

Pentachlorophenol (PCP) is a manufactured chemical that does not occur naturally. Pure pentachlorophenol exists as colorless crystals while 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).

Exposure to high levels of pentachlorophenol can cause cells in the body to produce excess heat, leading to high fever, sweating, difficulty breathing, potential injury to organs and tissues, and possible death. Chronic exposure to high levels of pentachlorophenol can damage the liver and the immune system. In animal studies, damage to the thyroid and reproductive system has also been observed (ATSDR 2001). Some harmful effects of pentachlorophenol are caused by other chemicals found in technical grade pentachlorophenol (ATSDR, 2001).

47.1 Assessment of Carcinogenicity

ATSDR (2001) suggests a possible association between inhalation of pentachlorophenol 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); accordingly, PCP was assessed as a carcinogen in this assessment.

47.2 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 the notion that young children are at an elevated risk, compared to older children and adults (ATSDR, 2001).

47.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

47.3.1 Oral Exposure

47.3.1.1 Non-Carcinogenic 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. This value is based on a study (Schwetz et al., 1978) in which twenty-five rats per sex were administered 1 of 3 doses in the diet (3, 10 and 30 mg PCP/kg-day). 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. Health Canada applied a total uncertainty factor of

500 to this value (10 for intraspecies variation; 10 for interspecies variation; and 5 for use of a subchronic and limited chronic study) to arrive at a final TDI of 0.006 mg/kg-day.

The US EPA provides a reference dose (RfD) of 0.03 mg/kg-day. This value is based on the same study used by Health Canada (Schwetz et al., 1978). However, the US EPA applied an uncertainty factor of 100 to the NOAEL, omitting the factor of 5 for use of a subchronic and limited chronic study as applied by Health Canada (2004).

ATSDR (2001) provides an MRL (minimal risk level) of 0.001 mg/kg-day. This MRL was based on a LOAEL of 1 mg/kg-day (only dose tested) for significantly decreased serum thyroxine concentrations in first generation males and both males and females of the second generation, and decreased relative thyroid weight in second generation females when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study (Beard and Rawlings, 1998). An uncertainty factor of 1000 was applied: 10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for interspecies extrapolation.

RIVM (2001) provides a TDI of 0.003 mg/kg-day based on the same study used in the derivation of the ATSDR MRL (Beard and Rawlings, 1998). However, RIVM applied an uncertainty factor of 300, rather than 1000, opting to use a factor of 3 for the use of a LOAEL, rather than 10.

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, and holds more validity than the ATSDR and RIVM values since they are based on studies that only assessed single exposure dosage.

47.3.1.2 Carcinogenic Toxicity Reference Values

The US EPA (1993) calculated an oral slope factor of 0.12 $(mg/kg\text{-}day)^{-1}$ based on a two year study in which two different 90% pure preparations of PCP were tested on B6C3Fl mice (NTP, 1989). PCP was administered daily in the feed at dose levels of 0, 100, 200 and 600 (for one preparation only) ppm to groups of 50 male and 50 female mice. Two groups of control mice (35 per sex) were fed basal diets. Survival of the mice did not appear to be affected by exposure to PCP at any dose level tested; however, dose-related increases in the incidence of liver tumors in mice was observed. A linearized multistage extrapolation was performed by the US EPA to determine the oral slope factor of 0.12 $(mg/kg\text{-}day)^{-1}$, which was used in this assessment.

47.3.2 Inhalation Exposure

47.3.2.1 Non-Carcinogenic Toxicity Reference Values

47.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 5 $\mu g/m^3$ for pentachlorophenol was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 0.5 mg/m^3 based on the following critical effects: eye and upper respiratory tract irritation; CNS impairment; and cardiac system impairment. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 20 µg/m^3 for pentachlorophenol was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

47.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 0.5 µg/m^3 for pentachlorophenol was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 47.3.2.1.1. To derive a long-term ESL for pentachlorophenol, TCEQ further divides the short-term ESL by an additional safety factor of 10.

47.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

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

47.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004a). With regards to the inhalation pathway, it has been conservatively assumed that 1,2,4,5-tetrachlorobenzene is completely absorbed (i.e. absorption factor is 1).

47.5 Conclusion

The following tables present pentachlorophenol TRVs selected for use in this risk assessment.

Table 47-1 Pentachlorophenol Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Pentachlorophenol	Non-carcinogenic TRV	0.006	Pigmentation of the liver and kidneys.	TDI	Health Canada, 2004b
	Carcinogenic Slope Factor	0.12	Hepatocellular adenoma/carcinoma, phenochromocytoma/malignant phenochromocytoma, hemangioscarcoma/hemangioma	SF	US EPA, 1993

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC (mg/kg/day)$^{-1}$

Table 47-2 Pentachlorophenol Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Pentalchlorophenol	1-Hour	5	Eye and upper respiratory tract irritation; CNS impairment; and cardiac system impairment	Benchmark	TCEQ ESL, 2008
	24-Hour	20	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	0.5	Cardiac system impairment	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3)

47.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

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MOE (Ontario Ministry of the Environment). 2008. Summary of O. Reg. 419/05 - Standards and Point of Impingement Guidelines & Ambient Air Quality Criteria (AAQCs). Standards Development Branch. Ontario Ministry of the Environment. PIBS # 6570e. February, 2008.

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48.0 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. 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).

There are no specific health risks from phosphorus.

48.1 Assessment of Carcinogenicity

The major regulatory agencies (i.e., US EPA, Health Canada, and IARC) do not classify phosphorus as carcinogenic to humans.

48.2 Susceptible Populations

No information on potentially susceptible populations to phosphorus was found.

48.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

48.3.1 Oral Exposure

48.3.1.1 Non-Carcinogenic Toxicity Reference Values

The non-carcinogenic TRV selected for this assessment is from a Health Canada (1990) a tolerable daily intake (TDI) of 14,300 mg/kg-day, based on a recommended daily nutrient intake rate. No further information on the derivation of this TRV is available.

48.3.1.2 Carcinogenic Toxicity Reference Values

Phosphorus is not classified as a carcinogenic substance; therefore, a carcinogenic oral toxicological reference value has not been selected.

48.3.2 Inhalation Exposure

48.3.2.1 Non-Carcinogenic Toxicity Reference Values

48.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

1-hr and 24-hour TRVs for phosphorus were not available from any regulatory agency.

48.3.2.1.2 Chronic Inhalation Toxicity Reference Values

Due to a lack of sufficient data, non-carcinogenic inhalation TRVs are unavailable from the major regulatory agencies (e.g., Health Canada, US EPA); therefore, for this assessment, a route-to-route extrapolation was conducted in order to derive an inhalation TRV. The Health Canada (1990) TDI (14,300 mg/kg-day) was modified by multiplying by the typical adult body weight (70.7 kg) and dividing by the inhalation rate (15.8 m^3/day) as per Health Canada (2004). The chronic inhalation TRV is 6.4 x 10^7 µg/m^3.

48.3.2.2 Cancer Inhalation Toxicity Reference Values

Phosphorus is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

48.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was assumed to be 0.1.

48.5 Conclusion

The following tables present phosphorus TRVs selected for use in this risk assessment.

Table 48-1 Phosphorus Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Phosphorus	Non-carcinogenic TRV	14,300	Recommended daily nutrient intake rate	RfD	Health Canada, 1990
	Carcinogenic Slope Factor	NV			

[a] Units: Non-carcinogenic COPC (mg/kg/day)
NV: No Value

Table 48-2 Phosphorus Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Phosphorus	1-Hour	NV			
	24-Hour	NV			
	Annual Average	6.4 x 10^7	Calculated route to route extrapolation from oral RfD	RfD	Health Canada, 1990

[a] Units: Non-carcinogenic COPC (µg/m^3)
NV – No Value

48.6 References

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

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

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

49.0 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). 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). 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).

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).

The most common health effects in people exposed to high levels of PCBs are skin irritation such as acne and rashes, however, blood and urine changes have also been observed that may indicate liver damage (ATSDR, 2001). In animal studies, acute (short term) ingestion of large doses of PCBs led to mild liver damage, and in some cases, death (ATSDR, 2001). Chronic (weeks or months) ingestion of lower doses of PCBs lead to anemia; acne-like skin conditions; liver, stomach and thyroid gland injuries; immune system effects; behavioural alternations; and impaired reproduction (ATSDR, 2001). PCBs are not known to cause birth defects (ATSDR, 2001).

49.1 Assessment of Carcinogenicity

Human studies suggest 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 (2009) suggests that currently available scientific evidence demonstrates that exposure to PCBs can cause cancer in experimental animals; however, the available epidemiological evidence has not demonstrated an association between exposure to PCBs and the incidence of disease in the human population. As such, Health Canada does not classify PCBs as carcinogens and therefore, PCBs were evaluated as non-carcinogens in this assessment.

49.2 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).

49.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

49.3.1 Oral Exposure

49.3.1.1 Non-Carcinogenic Toxicity Reference Values

Health Canada (2004b) has the TDI for PCB set at 0.001 mg/kg-day. This value is based on laboratory experiments using female rhesus monkeys (Grant, 1983), rather than rats (the original Health Canada TDI from the early 1970s was based on rats) because studies have showed that the rhesus monkeys' reproductive system was more susceptible to the toxic effects of PCB exposure than that of a rat.

The US EPA (1996) and ATSDR (2000) both provide a toxicity reference value for PCB mixture Aroclor 1254. These a established an oral reference dose (RfD) for Aroclor 1254 of 2×10^{-5} mg/kg-day based on immunological effects (such as ocular exudate, inflamed and prominent Meibomian glands, distorted growth of finger and toe nails, and decreased IgG and IgM response to sheep erythrocytes) in monkeys after 23 and 55 months of exposure (Tryphonas et al. 1989; 1991a; 1991b). The RfD was calculated from a lowest observable adverse effect level (LOAEL) of 0.005 mg/kg-day. A total uncertainty factor of 300 was applied (10-fold factor to account for sensitive individuals, 10-fold factor for LOAEL to NOAEL extrapolation and a factor of 3 for interspecies extrapolation).
For the purposes of this assessment, the US EPA (1996) and ATSDR (2000) TRV of 2.0×10^{-5} mg/kg-day was chosen because it was the most conservative value.

49.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, PCBs are not being evaluated as a carcinogen; therefore, a carcinogenic oral toxicological reference value has not been selected.

49.3.2 Inhalation Exposure

49.3.2.1 Non-Carcinogenic Toxicity Reference Values

49.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.1 µg/m^3 for PCBs was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008). This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009). TCEQ is an agency recognized by MOE (2004) as a source of air quality guidelines.

A 24-hour exposure benchmark of 0.15 µg/m^3 for PCBs was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

49.3.2.1.2 Chronic Inhalation Toxicity Reference Values

No chronic non-carcinogenic inhalation TRV for PCBs was identified for use in the risk assessment.

49.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

In this risk assessment, PCBs are not being evaluated as a carcinogen; therefore, a carcinogenic inhalation TRV has not been selected.

49.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004a). The relative dermal absorption fraction (RAF) was set as 0.14 (RAIS, 2006). With regards to the inhalation pathway, it has been conservatively assumed that PCBs are completely absorbed (i.e. absorption factor is 1).

49.5 Conclusion

The following tables present PCB TRVs selected for use in this risk assessment.

Table 49-1 Polychlorinated Biphenyls (PCB)Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Polychlorinated Biphenyls (PCB)	Non-carcinogenic TRV	2.0×10^{-5}	Immunological Effects	RfD	US EPA, 1996
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 49-2 Polychlorinated Biphenyls (PCB)Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Polychlorinated Biphenyls (PCB)	1-Hour	0.1	Health Based	Benchmark	TCEQ, 2008
	24-Hour	0.15	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	NV			

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$), NV – No Value

49.6 References

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50.0 SELENIUM

Selenium is a naturally occurring element that is considered to be an essential micronutrient for humans. The primary route of exposure is dietary with the majority of the selenium being excreted via urine (US EPA, 1991; Health Canada, 1992; IOM, 2000; ATSDR, 2003a).

Exposure to higher levels of selenium can cause adverse health effects. These effects are dependent on the route and duration of exposure. Short-term oral exposure to high levels of selenium can cause nausea, vomiting, and diarrhea. Chronic oral exposure can lead to a disease call selenosis, whose symptoms include hair loss, nail brittleness, and neurological abnormalities such as numbness and odd sensations in the extremities (ATSDR, 2003b). Short-term inhalation exposure to high levels of selenium or selenium dioxide can cause respiratory tract infection, bronchitis, difficulty breathing, and stomach pains. Chronic inhalation exposure can cause respiratory irritation, bronchial spasms and coughing (ATSDR, 2003b).

Animal studies indicate the very high levels of selenium can affect sperm production and the female reproductive system, however this has not been determined for human exposure (ATSDR, 2003b).

50.1 Assessment of Carcinogenicity

Selenium is classified as Group 3, not classifiable as a carcinogen, by IARC (1998). Several studies and investigations have remained inconclusive as to the carcinogenic potential of selenium (Health Canada, 1992). Following the IARC classification, the United States Environmental Protection Agency (US EPA, 1993) classified one form of selenium, selenium sulphide, a main ingredient in anti-dandruff shampoo, as a probable human carcinogen. Selenium sulphide, however, is not readily absorbed through the skin, does not readily dissolve in water, and binds tightly with soil, therefore limiting the potential routes of exposure (ATSDR, 2003a).

Selenium was not evaluated as a carcinogenic substance for the current assessment.

50.2 Susceptible Populations

Persons with selenium-deficient diets have exhibited increased selenium absorption via the gastrointestinal tract (ATSDR, 2003a). Given that large amounts of ingested selenium have reportedly resulted in some adverse health effects, those with selenium-deficient diets who then ingest large amounts may be more susceptible to toxic effects than others.

50.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

50.3.1 Oral Exposure

50.3.1.1 Non-Carcinogenic Toxicity Reference Values

A non-carcinogenic oral TRV was not available from Health Canada at the time of the assessment.

The US EPA has suggested an RfD of 0.005 mg/kg/d for selenium based on a study by Yang et al. (1989a,b) where a human epidemiological study was conducted and a chronic NOAEL and LOAEL determined through regression analysis (US EPA, 1991). Yang et al. studied a population of approximately 400 individuals living in three areas of China, with low, medium and high selenium levels in the soil and food supply. Subjects were evaluated for clinical and biochemical signs of selenium intoxication. Based upon blood selenium levels shown to reflect clinical signs of selenium intoxication (including the characteristic "garlic odor" of excess selenium excretion in the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions and CNS abnormalities), a whole blood selenium concentration of 1.35 mg/L corresponding to 1.261 mg of daily selenium intake was noted as the LOAEL and the next lowest whole blood selenium concentration of 1.0 mg/L, corresponding to 0.853 mg selenium/day, was noted as the NOAEL. When divided by the average body mass of the study population (55kg), and by dividing further by an uncertainty factor of 3 to account for sensitive individuals, the US EPA RfD was derived.

ATSDR (2003a) have also derived an oral TRV of 0.005 mg/kg/day based on another study by Yang et al. (1994). This more recent study examined a group of five individuals recovering from selenosis, who were drawn from the larger population evaluated in the Yang et al (1989a,b) study. Due to improving living conditions and reduced selenium ingestion, blood selenium levels in these individuals had fallen from 1.35 mg/L to 0.97 mg/L. This corresponded to 0.819 mg selenium/day intake associated with recovery. This formed the NOAEL on which the chronic oral TRV was based.

For this assessment, an oral TRV of 0.005 mg/kg/d was selected from selenium.

50.3.1.2 Carcinogenic Toxicity Reference Values

Selenium was not evaluated as a carcinogenic substance for the current assessment; therefore, a carcinogenic oral TRV was not selected.

50.3.2 Inhalation Exposure

50.3.2.1 Non-Carcinogenic Toxicity Reference Values

50.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 2 µg/m^3 for selenium was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 5 mg/m3 based on the following critical effects: eye and upper respiratory tract irritation. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 10 µg/m^3 for selenium was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

50.3.2.1.2 Chronic Inhalation Toxicity Reference Values

No Chronic inhalation TRVs were available from Health Canada or US EPA at the time of the assessment.

An annual exposure limit of 0.2 µg/m^3 for selenium was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 1.3.2.1.1. To derive a long-term ESL for selenium, TCEQ further divides the short-term ESL by an additional safety factor of 10.

50.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Selenium was not evaluated as a carcinogenic substance in the current assessment; therefore, no carcinogenic chronic inhalation TRV was selected.

50.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.002 (Health Canada, 2004).

50.5 Conclusion

Selenium TRVs selected for use in this risk assessment are presented in the following tables.

Table 50-1 Selenium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Selenium	Non-carcinogenic TRV	0.005	Blood selenium levels shown to reflect clinical signs of selenium intoxication	RfD	US EPA, 1991
	Carcinogenic Slope Factor	NV			

NV: no value

Table 50-2 Selenium Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Selenium	1-Hour	2	Eye and upper respiratory tract irritation	Benchmark	TCEQ ESL, 2008
	24-Hour	10	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	0.2	Eye and upper respiratory tract irritation	Benchmark	TCEQ ESL, 2009

[a] Units: Non-carcinogenic COPC (µg/m^3)

50.6 References

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51.0 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).

Chronic exposure to high levels of silver can lead to a condition called arygria which, while permanent, appears to be only a cosmetic problem resulting in a blue-grey discolouration of the skin and other body tissues. Argyria results from the deposition of silver in the dermis and also from silver-induced production of melanin. Similar effects can also be seen with exposure to lower levels of silver (ATSDR, 1999). Inhalation of high levels of silver can result in breathing problems, lung and throat irritation and stomach pains (ATSDR, 1999). Dermal contact with silver can cause allergic reactions in some people, leading to rash, swelling and inflammation (ATSDR, 1999).

51.1 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). For this assessment, silver is being assessed as a non-carcinogen.

51.2 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).

51.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

51.3.1 Oral Exposure

51.3.1.1 Non-Carcinogenic Toxicity Reference Values

A non-carcinogenic oral TRV was not available from Health Canada at the time of the assessment.

An oral reference dose (RfD) of 0.005 mg/kg-day was provided for metallic silver by the U.S. EPA (1991) based on a route-to-route extrapolation from a 2 - 9.75 year human study where i.v. injections of silver arsphenamine (total dose was 4-20 g) were given to 10 men and 2 women (Gaul and Staud,

1935). The main endpoint of concern was argyria, a medically benign but permanent bluish-gray discoloration of the skin. The LOAEL for the onset of argyria was 4 g total dose. The fraction of silver in silver arsphenamine is 23%, so a LOAEL for metallic silver can be determined as roughly 1 g total dose. The US EPA applied an uncertainty factor of 3 to the i.v. LOAEL and assumed an adult mass of 70 kg and a lifespan of 70 years in the route-to-route calculation. US EPA gives this RfD a low confidence given study limitations and uncertainties in route-to-route extrapolations.

51.3.1.2 Cancer Toxicity Reference Values

Silver was not evaluated as a carcinogenic substance in this assessment; therefore; a carcinogenic oral TRV for silver was not selected.

51.3.2 Inhalation Exposure

51.3.2.1 Non-Carcinogenic Toxicity Reference Values

51.3.2.2 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.1 µg/m^3 for silver was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 10 µg/m^3 based on the following critical effects: Argyria. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 1 µg/m^3 for silver was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

51.3.2.3 Chronic Inhalation Toxicity Reference Values

No chronic non-carcinogenic inhalation TRVs were available from Health Canada or US EPA at the time of the assessment.

An annual exposure limit of 0.01 µg/m^3 for silver was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 1.3.2.1.1. To derive a long-term ESL for silver, TCEQ further divides the short-term ESL by an additional safety factor of 10.

51.3.2.4 Cancer Inhalation Toxicity Reference Values

Silver was not evaluated as a carcinogenic substance in this assessment; therefore; a chronic carcinogenic inhalation TRV for silver was not selected.

51.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.25 (Health Canada, 2004).

51.5 Conclusion

The following tables present silver TRVs selected for use in this risk assessment.

Table 51-1 Silver Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Silver	Non-carcinogenic TRV	0.005	Argyria	RfD	US EPA, 1991
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) , NE – Not Evaluated

Table 51-2 Silver Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Silver	1-Hour	0.1	Argyria	Benchmark	TCEQ ESL, 2008
	24-Hour	1	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	0.01	Argyria	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3)

51.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

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52.0 TETRACHLOROETHYLENE

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 found in some consumer products (ATSDR, 1997).

Other names for tetrachloroethylene include perchloroethylene (PCE) and tetrachloroethene. Tetrachloroethylene is a nonflammable liquid at room temperature that 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).

The effects of tetrachloroethylene on human health are dose dependant. At high concentrations, and in poorly ventilated areas, inhalation of tetrachloroethylene can lead to nervous system effects such as dizziness, headache, sleepiness, confusion, nausea, difficulty speaking and walking, unconsciousness and death (ATSDR, 1997). In animal studies conducted with tetrachloroethylene at concentrations much higher than those humans are generally exposed to, liver and kidney damage and fetal toxicity have also been documented (ATSDR, 1997). Studies show that women who work in dry cleaning industries, where exposure to tetrachloroethylene can be quite high, may have more menstrual problems and a higher rate of spontaneous abortions, but no causative relationship has been determined (ATSDR, 1997).

Repeated or extended skin contact with tetrachloroethylene can lead to skin irritation (ATSDR, 1997). The health effects of inhaling or ingesting low levels of tetrachloroethylene have not been determined (ATSDR 1997).

52.1 Assessment of Carcinogenicity

The US 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 and 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. As such, in this risk assessment, tetrachloroethylene is being evaluated as a carcinogen.

52.2 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).

52.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

52.3.1 Oral Exposure

52.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, tetrachloroethylene is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

52.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, tetrachloroethylene is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral TRV has not been selected.

52.3.2 Inhalation Exposure

52.3.2.1 Non-Carcinogenic Toxicity Reference Values

52.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

CalEPA (1999) derived an acute 1-hour REL of 20,000 µg/m^3 based on a study by Stewart et al. (1970). Stewart et al. (1970) exposed 3 human subjects to 700,000 µg/m^3 of tetrachloroethylene for a duration of 3 hours. Central nervous system effects were indicated by an abnormal modified Romberg test and symptoms including headache, mild irritation of the eyes, nose and throat, and light-headedness were observed at concentrations of 7.0 x 10^5 µg/m^3. As a result CalEPA established a LOAEL of 7.0 x 10^5 µg/m^3. A NOAEL was not established from the study. The LOAEL of 7.0 x 10^5 µg/m^3 was extrapolated to derive a 1-hour LOAEL of 1.2 x 10^6 µg/m^3. The CalEPA (1999) 1-hour REL was derived from the extrapolated 1-hour LOAEL by applying a cumulative uncertainty factor of 60 (6 for the use of a LOAEL and 10 to account for sensitive populations). The CalEPA REL of 20,000 µg/m^3 was selected as the 1-hour exposure limit for tetrachloroethylene for this risk assessment.

A 24-hour exposure benchmark of 360 µg/m^3 for tetrachloroethylene was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects (effects on liver kidney and lungs) with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

52.3.2.2 Chronic Inhalation Toxicity Reference Values

Health Canada (2004b) derived a TC of 360 µg/m^3 for tetrachloroethylene in 1996. This value was derived using the LOAEL of 6.8 x 10^5 µg/m^3 for adverse effects on the liver, kidney and lung observed from inhalation studies in animals (NTP, 1986). Tetrachloroethylene was administered by inhalation for 6 hours/day, 5 days/week for 103 weeks. In the NTP (1986) study, the lowest concentration of tetrachloroethylene at which adverse effects [reduced survival (in males), hepatotoxicity (in males), lung congestion and nephrotoxicity (in both males and females)] were observed was 6.8 x 10^5 µg/m^3. The LOAEL was adjusted for discontinuous exposure (6/24-hours, 5/7-days) and a safety factor of 1,000 for

intra- and interspecies variation was applied (MOE 2005). The TC of 360 µg/m^3 was derived for a human aged 5 to 11 using a body weight of 27 kg and a respiration rate of 12 m^3/day.

ATSDR (1996) derived a chronic inhalation MRL of 274 µg/m^3 based on a study by Ferroni et al. (1992). Ferroni et al (1992) studied neurobehavioral effects in 60 women exposed to tetrachloroethylene in dry cleaning shops for an average of 10.1 years. Thirty women who worked at a cleaning plant where solvents were not used served as controls. Tetrachloroethylene levels were measured in blood samples collected during the work day and in air samples collected over 4-hour periods during the workweek. Blood and air samples were taken during the summer and winter to allow for seasonal variation. The median tetrachloroethylene concentration in air was 1.01 x 10^5 µg/m^3, and the median tetrachloroethylene blood concentration was 145 mg/L. Neurobehavioral tests completed were: finger tapping with dominant and nondominant hands, simple reaction times, digit symbol, shape comparison in two versions to test vigilance and the response to stress. The researchers observed that tetrachloroethylene exposed workers had prolonged reaction times in all tests when compared to the control group (Ferroni et al, 1992). From these results ATSDR (1999) derived a LOAEL of 1.01 x 10^5 µg/m^3 based on the prolonged reaction times in exposed workers. This LOAEL was converted from an occupational exposure to a continuous exposure by multiplying by 8/24 hours and 5/7 days. Finally, a cumulative uncertainty factor of 100 (10 for the use of a LOAEL and 10 to protect sensitive populations) was applied to derive a MRL of 274 µg/m^3.

RIVM (2001) derived a chronic inhalation TRV of 250 µg/m^3 based on the results of a study by Mutti et al. (1992). Mutti et al. (1992) conducted a cross-sectional study of 50 workers exposed chronically (average of 10 years) to tetrachloroethylene in dry cleaning facilities. The median exposure concentration was 100,000 µg/m^3. Twentry-three urinary and serum markers of early nephrotoxic effects were measured in the study (Mutti et al, 1992). The researchers observed that, compared to a control population, the exposed workers had significantly higher frequencies of abnormal values for a number of the urinary and serum markers. The researchers concluded that the abnormal markers may represent clinically silent, but potentially progressive, renal disease which may indicate a risk of renal failure (Mutti et al., 1992). RIVM (2001) established a LOAEL of 100,000 µg/m^3 from this study. The LOAEL was adjusted for continuous exposure (back calculated from 40 hours/week to 168 hours/week) and a cumulative uncertainly factor of 100 was applied (10 to account for the use of a LOAEL and 10 for the protection of sensitive populations) to arrive at a TCA of 250 µg/m^3.

The Health Canada (2004b) TC of 360 µg/m^3 for tetrachloroethylene was used in this risk assessment.

52.3.2.3 Carcinogenic Inhalation Toxicity Reference Values

WHO (2006) derived a unit risk of 1.8 x 10^{-6} to 5.2 x 10^{-6} (µg/m^3)$^{-1}$ for tetrachloroethylene based on studies by Nagano et al (1998a,b). In one study F344 rats (groups of 50 per sex) were exposed to tetrachloroethene (>99% purity) at about 0, 3.4 x 10^5, 1.4 x 10^6, or 4.1 x 10^6 µg/m^3. The exposure duration lasted for 6 hours/day, 5 days/week, for 104 weeks. All organs were examined microscopically. There were treatment-related increases in mononuclear cell leukemia in both sexes. No other increases in tumour incidence were reported. The liver and kidney were microscopically normal at 3.4 x 10^5 µg/m^3. Liver toxicity was limited to the males. In the kidney, nuclear enlargement was seen in the proximal tubules of males at 1.4 x 10^6 µg/m^3 and above, while at 4.1 x 10^6 µg/m^3, both sexes showed increases in nuclear enlargement and atypical proximal tubular dilation. Males were much more susceptible than females to liver and kidney toxicity. (Nagano et al., 1998a,b).

In a corresponding study in BDF1 mice, in groups of 50 males and 50 females were exposed to tetrachloroethene (>99% purity) at about 0, 6.9 x 10^4, 3.4 x 10^5, or 1.7 x 10^6 µg/m^3. The exposure duration lasted for 6 h/day, 5 days/week, for 104 weeks. Dose-related increases were seen in the incidences of benign and malignant liver tumours in both sexes. In addition, the top-dose males had an increased incidence of benign tumours of the Harderian gland. Kidney pathology was limited to nuclear enlargement of the proximal tubule (at 3.4 x 10^4 µg/m^3 and above in both sexes) and atypical proximal tubular dilation at 1.7 x 10^6 µg/m^3 in the females. There was no evidence of liver toxicity in either sex at 6.9 x 10^4 µg/m^3, but at 3.4 x 10^5 mg/m^3 and above, dose-dependent liver toxicity was seen (Nagano et al., 1998a,b).

From these studies the WHO derived a carcinogenic inhalation unit risk of 5.2 x 10^{-6} (µg/m^3)$^{-1}$

52.4 Bioavailability

In this risk assessment, tetrachloroethylene is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that tetrachloroethylene is completely absorbed (i.e., absorption factor is 1).

52.5 Conclusion

The following tables present tetrachloroethylene TRVs selected for use in this risk assessment.

Table 52-1 Tetrachloroethylene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Tetrachloroethylene	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE – Not Evaluated

Table 52-2 Tetrachloroethylene Inhalation TRVs used in the risk assessment

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Tetrachloroethylene	1-Hour	20,000	Eye, nose and throat irritation. Headache high-headedness and loss of coordination	Benchmark	CalEPA REL, 1999
	24-Hour	360	Adverse effects on the liver kidney, lungs	Benchmark	MOE AAQC, 2008
	Annual Average	360	Effects on liver, kidneys and lungs	RfC	Health Canada, 2004b
	Carcinogenic Annual Average	5.2 x 10^{-6}	Nasal squamous tumours	UR	WHO, 2006

[a] Units: Non-carcinogenic COPC (µg/m^3) , Carcinogenic COPC (µg/m^3)$^{-1}$, UR (unit risk)

52.6 References

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. ToxFAQs for Tetrachloroethylene. September 1997.

CalEPA (California Environmental Protection Agency). 1999. Air Toxics Hot Spots Program Risk Assessment Guidelines, Part I: The Determination of Acute Reference Exposure Levels for Airborne Toxicants. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Air Toxicology and Epidemiology Section.

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Japanese Industrial Safety and Health Association, Kanagawa (in Japanese). Cited In: WHO 2006

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. NIOSH Publication 2005-149.

NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 311. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

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53.0 THALLIUM

Pure thallium is a bluish-white metal that is found in trace amounts in the earth's crust. In the past, thallium was obtained as a by-product from smelting other metals; however, it has not been produced in the United States since 1984. Thallium is used mostly in manufacturing electronic devices, switches, and closures, primarily for the semiconductor industry. It also has limited use in the manufacture of special glass and for certain medical procedures (ATSDR 1995).

Exposure to high levels of thallium can result in harmful human health effects. Inhalation of thallium over several years has been shown to lead to nervous system effects such as numbness of the extremities. Ingestion of large amounts of thallium in a short period of time can lead to diarrhea, hair loss, nervous system effects, effects on the lungs, heart, liver and kidneys, and possible death. Effects from chronic ingestion of low levels of thallium are not known (ATSDR, 1995).

Reproductive effects from thallium exposure have not been documented in humans. In animal studies, however, exposure of mothers to high levels of thallium resulted in adverse developmental effects. Animal studies also suggest that the male reproductive system may be susceptible to damage by low levels of thallium (ATSDR, 1995).

53.1 Assessment of Carcinogenicity

Health Canada, the International Agency for Research on Cancer, and the US EPA have not classified thallium as to its human carcinogenicity.

53.2 Susceptible Populations

People with preexisting kidney and/or liver damage, or people with a neurological disease may be more at risk (ATSDR, 1995).

53.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

53.3.1 Oral Exposure

53.3.1.1 Non-Carcinogenic Toxicity Reference Values

The US EPA (1990) derived an oral RfD of 0.00008 mg/kg/day based upon subchronic (90-day) toxicity of thallium sulfate in Sprague- Dawley rats (U.S. EPA, 1986). Groups (20 rats/sex/group) were treated by gavage with 0, 0.01, 0.05, and 0.25 mg/kg/day of aqueous thallium sulfate (approximately 0.008, 0.04, and 0.20 mg thallium/kg/day). In this study no mortality was observed and no differences were seen between the control group and the exposed group receiving thallium sulfate; therefore based on these results the oral RfD was derived from a NOAEL concentration of 0.25 mg/kg/day and an uncertainty factor of 3000. This value was selected as an oral toxicity reference value for this assessment.

53.3.1.2 Cancer Toxicity Reference Values

Thallium is not classified as a carcinogenic substance; therefore, a carcinogenic oral toxicological reference value has not been selected

53.3.2 Inhalation Exposure

53.3.2.1 Non-Carcinogenic Toxicity Reference Values

53.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 1 µg/m^3 for thallium was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 100 µg/m^3 based on the following critical effects: Alopecia. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour inhalation TRV for thallium was not available.

53.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 0.1 µg/m^3 for thallium was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 1.3.2.1.1. To derive a long-term ESL for thallium, TCEQ further divides the short-term ESL by an additional safety factor of 10.

53.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Thallium is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

53.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.01(Health Canada, 2004).

53.5 Conclusion

The following tables present thallium TRVs selected for use in this risk assessment.

Table 53-1 Thallium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Thallium	Non-carcinogenic TRV	0.00008	No observed Effects	RfD	US EPA, 1990
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day)
NE – Not Evaluated

Table 53-2 Thallium Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Thallium	1-Hour	1	Alopecia	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	0.1	Alopecia	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)
NV – No Value

53.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

ATSDR (Agency for Toxic Substances and Disease Registry), 1995. *Toxicological Profile for Thallium*. September 1995

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

TCEQ (Texas Commission on Environmental Quality) 2008. Effects Screening Levels. http://www.tceq.state.tx.us/implementation/tox/index.html.

US EPA (United States Environmental Protection Agency). 1986. Subchronic (90-day) toxicity of thallium sulfate in Sprague- Dawley rats. Office of Solid Waste, Washington, DC

US EPA (United States Environmental Protection Agency), 1990. Integrated Risk Information System (IRIS) Database: Thallium(I) sulfate (Oral RfD Assessment).

54.0 TIN AND TIN COMPOUNDS

Tin is a silvery-white metal that is found in the earth's crust (ATSDR, 2005a). Inorganic tin is not very toxic due to its poor absorption in the human digestive tract, however ingestion of large amounts of inorganic tin can cause stomach pain, anemia, and liver and kidney problems (ATSDR, 2005b). Organotins are more toxic. Exposure (oral, dermal, inhalation) to trimethyltin and triethyltin can interfere with the brain and nervous system, and in severe cases can lead to death. Other organotins, such as dibutlins and tributyltins have been shown to affect the immune system in animals, although this hasn't been shown in people. Animal studies also show that organotins such as dibutlins, tributyltins, and triphenyltins can affect the reproductive system. This hasn't been examined in people (ATSDR, 2005b). Dermal contact with organic or inorganic tin compounds can produce skin and eye irritation (ATSDR, 2005b).

54.1 Assessment of Carcinogenicity

The US EPA's IRIS program has not evaluated the carcinogenicity of tin. The Agency for Toxic Substances and Disease Registry (ATSDR, 2005a) state that there is no conclusive information available on the carcinogenic potential of tin.

54.2 Susceptible Populations

There are no specific populations that have been identified that are unusually susceptible to either inorganic tin or organotin compounds with respect to health effects (ATSDR, 2005a).

54.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

54.3.1 Oral Exposure

54.3.1.1 Non-Carcinogenic Toxicity Reference Values

An oral reference dose (RfD) of 0.6 mg/kg-day was provided for tin in the EPA's Health Effects Summary Tables (ORNL, 2004). The RfD was derived by the U.S. EPA based on a chronic study examining ingestion of tin by rats. The main endpoint of concern was the appearance of lesions on the liver. The U.S. EPA reported a no observable adverse effects level (NOAEL) of 600 mg/kg-day, and applied an uncertainty factor of 100 to derive the RfD.

ATSDR (2005a) developed a minimal risk level of 0.3 mg/kg-day for tin, based on intermediate duration (13 weeks) exposure to stannous chloride in Wistar rats. In the study conducted by De Groot et al. (1973), groups of Wistar rats were fed a diet including 0, 9.5, 32, 95, and 315 mg/kg/day stannous chloride. A NOAEL of 32 mg/kg-day was developed through observing decreased hemoglobin count, and modified by an uncertainty factor of 100 to account for extrapolation from animals to humans and human variability. The ATSDR MRL of 0.3 mg/kg-day was used as the TRV for tin in this assessment.

54.3.1.2 Carcinogenic Toxicity Reference Values

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

54.3.2 Inhalation Exposure

54.3.2.1 Non-Carcinogenic Toxicity Reference Values

54.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 20 µg/m^3 for tin was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 2000 µg/m^3 based on the following critical effects: pneumoconiosis, eye and upper respiratory tract irritation, headache and nausea. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

A 24-hour exposure benchmark of 10 µg/m^3 for tin was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

54.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 2 µg/m^3 for tin was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 1.3.2.1.1. To derive a long-term ESL for tin, TCEQ further divides the short-term ESL by an additional safety factor of 10.

54.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

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

54.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was assumed to be 0.1.

54.5 Conclusion

The following tables present tin TRVs selected for use in this risk assessment.

Table 54-1 Tin Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Tin	Non-carcinogenic TRV	0.3	decreased hemoglobin count	RfD	ATSDR, 2005a

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day)
NE – Not Evaluated

Table 54-2 Tin Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Tin	1-Hour	20	pneumoconiosis, eye and upper respiratory tract irritation, headache and nausea	Benchmark	TCEQ ESL, 2008
	24-Hour	10	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	2	pneumoconiosis, eye and upper respiratory tract irritation, headache and nausea	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3),
NV – No Value

54.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

ATSDR (Agency for Toxic Substances and Disease Registry). 2005a. Toxicological Profile for Tin.

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TCEQ (Texas Commission on Environmental Quality). 2008. Effects Screening Level Lists. Available at: http://www.tceq.state.tx.us/implementation/tox/esl/list_main.html

55.0 TOLUENE

Toluene is a clear, colourless liquid with a distinctive smell. It is a by-product in the manufacturing of styrene and is produced in the process of making gasoline and other fuels from crude oil (ATSDR, 2000). A good solvent, toluene is used in making paints, paint thinners, fingernail polish, lacquers, adhesives, rubbers and in printing and some leather tanning processes (ATSDR, 2000).

The inhalation of toluene can cause nervous system effects (ATSDR, 2001). Acute inhalation of low to moderate levels of toluene can lead to tiredness, confusion, weakness, memory loss, nausea, loss of appetite, loss of hearing, and loss of colour vision. These symptoms are usually limited to the period of exposure (ATSDR, 2001). Acute inhalation of high levels of toluene can lead to feelings of lightheadedness, dizziness, sleepiness, unconsciousness and possible death (ATSDR, 2001). High levels of toluene have also been shown to affect kidney function (ATSDR, 2001).

55.1 Assessment of Carcinogenicity

The US EPA (2005) has not categorized toluene according to carcinogenicity because of inadequate data for an assessment of human carcinogenic potential. IARC (1999) classifies toluene as Group 3, not classifiable as to human carcinogenicity. Health Canada classifies toluene as Group IV-C, probably not carcinogenic to humans (CEPA, 1992; Health Canada, 1996). Accordingly, toluene was assessed as a non-carcinogen in this assessment.

55.2 Susceptible Populations

Chronic users of alcohol or those taking medications that interfere with the pathways of toluene metabolism would be more susceptible to toluene toxicity, including toluene-induced hearing loss, than other members of the population (ATSDR, 2000). Nutritional status, including malnourishment, may also affect an individual's susceptibility to the toxic effects of toluene (ATSDR, 2000). Other individuals who may be more susceptible to these effects are those with pre-existing defects in heart rhythm, those with asthma or other respiratory difficulties, and those with a genetic predisposition to hearing loss (ATSDR, 2000).

55.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

55.3.1 Oral Exposure

55.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, toluene is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral TRV has not been selected.

55.3.1.2 Cancer Toxicity Reference Values

In this risk assessment, toluene is only being evaluated through the inhalation pathway and as toluene is not considered to be a carcinogenic substance, a carcinogenic oral TRV has not been selected.

55.3.2 Inhalation Exposure

55.3.2.1 Non-Carcinogenic Toxicity Reference Values

55.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

An acute reference exposure level (REL) of 37,000 µg/m^3 was established by the CalEPA (2008a) based on a study conducted by Andersen et al. (1983) in which nasal mucus flow, lung function, psychometric performance, and subjective responses were studied in 16 young healthy males exposed to toluene concentrations ranging from 10 to 100 ppm (40,000 µg/m³ to 400,000 µg/m³) for 6 hours. Critical effects including headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation were reported at 400,000 µg/m³. The subjects also reported that it became more difficult to participate in the battery of psychometric tests and that their reaction time felt impaired at 400,000 µg/m³. No significant objective changes compared to control exposures were observed in the performance test results. No symptoms were reported at 40,000 µg/m³ and 150,000 µg/m³, which was adopted as the NOAEL. The NOAEL was extrapolated from a 6-hour concentration to a 1-hour concentration of 370,000 µg/m³, and modified by an uncertainty factor of 10 to account for interspecies variability. This value was selected as the 1-hour TRV for this assessment.

A 24-hour guideline was not available at the time of this assessment.

55.3.2.1.2 Chronic Inhalation Toxicity Reference Values

An inhalation Tolerable Concentration (TC) of 3,800 µg/m^3 was developed by Health Canada (1996, 2004). This value was also based on the previously described study conducted by Andersen et al. (1983). The NOAEL of 150,000 µg/m³ was extrapolated to a continuous exposure by dividing by 6/24, and subsequently modified by an uncertainty factor of 10 to account for intraspecies variation.

A chronic RfC of 5,000 µg/m^3 derived by the US EPA IRIS (2005) was based on neurological effects observed in occupational workers exposed to toluene (Foo et al. 1990; Nakatsuka et al. 1992; Murata et al. 1993; Abbate et al. 1993; Vrca et al. 1995; Boey et al. 1997; Zavalic et al. 1998; Eller et al. 1999; Cavalleri et al. 2000; Neubert et al. 2001). The average NOAEL, for an occupational exposure scenario, based on the above mentioned occupational studies was 128,000 µg/m^3. A NOAEL (HEC) of 46,000 µg/m^3 was derived by adjusting for continuous exposure (5/7 days) and the human ambient default minute volume (10/20 m^3/day). An uncertainty factor of 10 was applied for intraspecies variability.

A chronic minimal risk level (MRL) of 300 µg/m^3 was established by ATSDR (2000) based on a study conducted by Zavalic et al. (1998) in which the colour vision abilities of three groups of toluene-exposed workers were assessed: 46 shoemakers exposed for an average of 16 years to a median toluene concentration of 32 ppm (120,000 µg/m^3); 37 rotogravure printing workers exposed for an average of 18 years to a median toluene concentration of 132 ppm (500,000 µg/m^3); and 90 control workers without any known exposure to solvents or neurotoxic agents. Average scores in a color confusion index (based on results of color vision tests and adjusted for age and alcohol intake) were significantly increased in the toluene exposed shoemakers and printers compared with scores for control workers.

Consequently, a chronic LOAEL was established at 120,000 µg/m^3. This LOAEL was time adjusted (by factors of 5/7 and 8/24) subsequently modified by an uncertainty factor of 100 for the use of a LOAEL (10) and intraspecies variability (10).

A chronic reference exposure level (REL) of 300 µg/m^3 was established by the CalEPA (2008b) based on a study conducted by Hillefors-Berglund et al. (1995) in which male rats were exposed to a range of toluene concentrations (0, 40, 80, 160 or 320 ppm) for 4 weeks, 6 hours/day, 5 days/week, followed by a post-exposure period of 29-40 days. A LOAEL was established at 80 ppm based on decreased brain (subcortical limbic area) weight and altered dopamine receptor (caudate-putamen) binding, and a NOAEL was established at 40 ppm (150,000 µg/m^3). This NOAEL was modified by time factors (5/7 and 6/24), and subsequently modified by an uncertainty factor of 100 for intraspecies uncertainty (10) and use of a subchronic study (10). An uncertainty factor to reflect interspecies uncertainty was not applied as the study was supported by human study data and it was noted that the effect levels were similar.

The US EPA RfC of 5,000 µg/m^3 was chosen over the lower Health Canada TDI for this assessment because it was based on a chronic occupational study rather than an subchronic experimental study. Furthermore, it was chosen over the lower ATSDR value because it is based on an RfC rather than a minimal risk level, and it was chosen over the CalEPA value as it was based on a human study rather than an experimental animal study.

55.3.2.2 Cancer Inhalation Toxicity Reference Values

Toluene is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

55.4 Bioavailability

In this risk assessment, toluene is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that toluene is completely absorbed (i.e. absorption factor is 1).

55.5 Conclusion

The following tables present toluene TRVs selected for use in this risk assessment.

Table 55-1 Toluene Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value (mg/kg/day)	Critical Effect	Reference Type	Source
Toluene	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

NE - Not Evaluated

Table 55-2 Toluene Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Toluene	1-Hour	37,000	Headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation	Benchmark	CalEPA, 2008a
	24-Hour	NV			
	Annual Average	5000	Neurological Effects	RfC	US EPA, 2005

[a] Units: Non-carcinogenic COPC (µg/m^3) , NV - No Value

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56.0 TRICHLOROFLUOROMETHANE

Trichlorofluoromethane is a chlorofluorocarbon commonly referred to as freon-11 or FC-11. Trichlorofluoromethane is the most common fluorocarbon used as a refrigerant. FC-11 was principally used as blowing agent for foams and packaging materials, and as refrigerant in large commercial chillers. CFCs are photo-dissociated by the ultraviolet radiation in the stratosphere, where chlorine in the molecule is released. The increase of stratospheric chlorine concentration associated with CFC emissions is responsible for the stratospheric ozone depletion phenomenon. CFCs are important greenhouse gases; their net 100-year global warming potential is 4,600 and 10,600 for FC-11 and FC-12 respectively.

Trichlorofluoromethane is a liquid, colourless, nearly odourless chlorofluorocarbon. There were various uses for this compound both in industry and in consumer products; however it was identified as one of the major greenhouse gases and production of this compound was banned in 1997. An average worldwide background concentration of FC-11 in ambient air has been estimated at approximately 0.25 ppb (Cunnold et al., 1986). Concentrations of up to 42 ppb have been detected in California near factories known to use large quantities of fluorocarbons (*e.g.*, as blowing agents) (Hester et al., 1974). Landfills and recycling facilities that shred foam insulation from disused refrigerators continue to be a source of FC-11 to the environment. Subsequent to the ban in 1997, stocks have been depleted and new sources of emission have declined as predicted (CalEPA, 1997).

56.1 Assessment of Carcinogenicity

Health Canada, the US EPA, and the IARC have not evaluated the carcinogenicity of trichlorofluoromethane. Chronic exposure experiments in animals have been negative for carcinogenicity (CalEPA, 1997). Little is known about possible teratogenic and mutagenic effects; however, the available data indicates that the compound is not mutagenic in biological assays (CalEPA, 1997). Accordingly, trichlorofluoromethane is being assessed as a non-carcinogenic COPC in this HHRA.

56.2 Susceptible Populations

No specific populations have been identified that are unusually susceptible to trichlorofluoromethane.

56.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

56.3.1 Oral Exposure

56.3.1.1 Non-Carcinogenic Toxicity Reference Values

The US EPA (1992) provides an oral reference dose (RfD) of 0.3 mg/kg-day for trichlorofluoromethane. The RfD was derived from cancer bioassays on rats and mice, utilizing survival and histopathological endpoints (NCI, 1978). Various doses of trichlorofluoromethane were administered by gavage over a period of 78 weeks (50 animals/species/sex/dose for each of two doses with 20 animals/species/sex for each of two control groups). A statistically significant positive association between increased dosage and accelerated mortality by the Tarone test in male and female rats and female mice was observed. In treated rats of both sexes, there were also elevated incidences of pleuritis and pericarditis not seen in controls. A LOAEL of 488 mg/kg-day was reported based on mortality in rats, time-adjusted to 349 mg/kg-day, and further modified by applying an uncertainty factor of 1000 (10 to account for use of a LOAEL; 10 to account for intraspecies uncertainty; and 10 to account for application of the LOAEL to sensitive human populations). This value was selected for the current assessment.

56.3.1.2 Carcinogenic Toxicity Reference Values

Trichlorofluoromethane is not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected

56.3.2 Inhalation Exposure

56.3.2.1 Non-Carcinogenic Toxicity Reference Values

56.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour inhalation TRV was not available from any regulatory agency at the time of this risk assessment.

A 24-hour exposure benchmark of 6,000 µg/m^3 for trichlorofluoromethane was selected from the Ontario Ministry of the Environment (MOE). This acute inhalation value was based on occupational health effects with appropriate safety factors applied in the derivation of the AAQC (Szakolcai, 2009). No additional information regarding benchmark derivation was provided.

56.3.2.2 Chronic Inhalation Toxicity Reference Values

A chronic inhalation TRV was not available from any regulatory agency at the time of this risk assessment.

56.3.2.3 Carcinogenic Inhalation Toxicity Reference Values

Trichlorofluoromethane is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation TRV has not been selected.

56.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was also conservatively assumed to be 1.0, in the absence of substantive data suggesting other bioavailability estimates. With regards to the

inhalation pathway, it has been conservatively assumed that trichlorofluoromethane is completely absorbed (i.e. absorption factor is 1).

56.5 Conclusion

The following tables present trichlorofluoromethane TRVs selected for use in this risk assessment.

Table 56-1 Trichlorofluoromethane Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Trichlorofluoromethane	Non-carcinogenic TRV	0.3	Survival and histopathology	RfD	US EPA, 1992
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day), NE – Not Evaluated

Table 56-2 Trichlorofluoromethane Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Trichlorofluoromethane	1-Hour	NV			
	24-Hour	6000	Health Based	Benchmark	MOE AAQC, 2008
	Annual Average	NV			

[a] Units: Non-carcinogenic COPC (µg/m^3)

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57.0 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).

Inhalation of high levels of vanadium can lead to harmful health effects including lung irritation, coughing, wheezing, chest pain, runny nose, sore throat, and effects on the eyes. These effects generally stop soon after contact with vanadium ceases (ATSDR, 1995).

No other significant health effects have been seen in people, however, animals that consumed very large quantities of vanadium have died, and high levels of vanadium in the water of pregnant animals has resulted in minor birth defects. Some animals that have been chronically exposed to high levels of vanadium have demonstrated minor kidney and liver changes (ATSDR, 1995).

57.1 Assessment of Carcinogenicity

The ATSDR was unable to locate any studies that 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, vanadium is considered to be non-carcinogenic for the purposes of this assessment.

57.2 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).

57.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below.

57.3.1 Oral Exposure

57.3.1.1 Non-Carcinogenic Toxicity Reference Values

The US EPA IRIS (1996) has developed an RfD of 0.009 mg/kg-day for exposure to vanadium pentoxide based on a single study in rats (Stokinger et al., 1953). In the study, an unspecified number of rats were exposed to dietary levels of 10 or 100 ppm vanadium for 2.5 years. The study authors reported a decrease in hair cystine content in test animals compared to controls during the study, however, there were no significant effects on growth rate or survival (US EPA, 1996). The lower dose level (10 ppm vanadium) was the reported NOAEL. 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). This thus EPA value was selected for the current assessment but it needs to be noted that EPA places low confidence in this RfD because of the lack of details in the reference study and the scarcity of data available on vanadium pentoxide.

57.3.1.2 Carcinogenic Toxicity Reference Values

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

57.3.2 Inhalation Exposure

57.3.2.1 Non-Carcinogenic Toxicity Reference Values

57.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 0.5 µg/m^3 for vanadium was selected from the Texas Commission on Environmental Quality (TCEQ, 2008). The TCEQ effects screening level (ESL) is derived from an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 50 mg/m^3 based on the following critical effects: lung irritation. ACGIH values are occupational values, therefore TCEQ further divides the TLV by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit.

WHO (2000) derived a guideline value (24-hour averaging time) of 1.0 µg/m^3 for vanadium. This guideline was based upon chronic upper respiratory tract symptoms experienced by occupational workers involved in the refining and/or processing of vanadium (Lewis 1959; Kiviluoto et al. 1979; Nishiyama et al. 1977). An uncertainty factor of 20 was applied to a LOAEL of 20 µg/m^3 as the adverse effect observed in the study was minimal and a susceptible human subpopulation has not been identified. The WHO (2000) 24-hour guideline discussed above (1.0 µg/m^3) was selected as the chronic inhalation TRV for this assessment. Although WHO (2000) lists 1.0 µg/m^3 as a 24-hour exposure limit, the limit is derived from chronic inhalation studies of occupational workers; therefore, it can also be considered as a chronic exposure limit.

57.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The WHO (2000) 24-hour guideline discussed above (1.0 µg/m^3) was adopted as the chronic inhalation exposure limit for non-carcinogenic effects for vanadium in the current assessment

57.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

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

57.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.1 (Health Canada, 2004).

57.5 Conclusion

The following tables present Vanadium TRVs selected for use in this risk assessment.

Table 57-1 Vanadium Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Vanadium	Non-carcinogenic TRV	0.009	Decrease hair cystine	RfD	US EPA, 1996
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day)
NE – Not Evaluated

Table 57-2 Vanadium Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Vanadium	1-Hour	0.5	Lung Irritation	Benchmark	TCEQ ESL, 2008
	24-Hour	1	Chronic upper respiratory tract symptoms	RfC	WHO, 2000
	Annual Average	1	Chronic upper respiratory tract symptoms	RfC	WHO, 2000

[a] Units: Non-carcinogenic COPC ($\mu g/m^3$)
NV – No Value

57.6 References

ACGIH (American Conference of Industrial Hygienists). 2007. TLVs and BEIs Book.

ATSDR (Agency for Toxic Substances and Disease Registry), 1995. *ToxFAQs for Vanadium.* September 1995.

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58.0 VINYL CHLORIDE

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

The effects of vinyl chloride on human health are dose dependant. Inhalation of high levels of vinyl chloride can lead to dizziness or sleepiness. Inhalation of increasingly larger amounts of vinyl chloride can lead to unconsciousness and death (ASTDR, 2006). The health effects of ingesting high levels of vinyl chloride are unknown. Dermal contact with vinyl chloride will cause numbness, redness and blisters (ASTDR, 2006).

Chronic exposure to vinyl chloride can lead to more severe effects. Chronic inhalation of high levels of vinyl chloride can lead to liver damage, nerve damage and immune reactions (ASTDR, 2006). Animal studies have shown that chronic exposure to vinyl chloride can damage the sperm and testes (ASTDR, 2006).

58.1 Assessment of Carcinogenicity

The US EPA (2000) lists vinyl chloride as group “A” carcinogen, a known human carcinogen. This grouping is based on (1) consistent epidemiologic evidence of a causal association between occupational exposure to vinyl chloride 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 vinyl chloride and its metabolites in numerous in vivo and in vitro test systems; and (4) efficient vinyl chloride 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 vinyl chloride exposure, the evidence for vinyl chloride carcinogenicity is considered strong.

The IARC (2006) lists vinyl chloride as a Group 1 chemical: describing it as carcinogenic to humans.

For this assessment, vinyl chloride is being assessed for carcinogenic and non-carcinogenic endpoints.

58.2 Susceptible Populations

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

58.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below. For the purposes of this risk assessment only inhalation risks from exposure to vinyl chloride were evaluated.

58.3.1 Oral Exposure

58.3.1.1 Non-Carcinogenic Toxicity Reference Values

In this risk assessment, vinyl chloride is only being evaluated through the inhalation pathway; therefore, a non-carcinogenic oral toxicological reference value has not been selected.

58.3.1.2 Carcinogenic Toxicity Reference Values

In this risk assessment, vinyl chloride is only being evaluated through the inhalation pathway; therefore, a carcinogenic oral toxicological reference value has not been selected.

58.3.2 Inhalation Exposure

58.3.2.1 Non-Carcinogenic Toxicity Reference Values

58.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour inhalation TRV of 20,000 µg/m^3 was provided for vinyl chloride by TCEQ (2009), the basis of which is mild headache and dryness of eyes and nose. This value was based on an inhalation study by Baretta et al. (1969) in which four to eight human volunteers were exposed by inhalation in a whole-body chamber to 1.53 x 10^5, 6.78 x 10^5, 1.27 x 10^6, or 1.28 x 10^6 µg/m^3 VC for up to 7.5 hours (3.5 hours of exposure, 30 minute break, then another 3.5 hour exposure) (Baretta et al. 1969). Subjective and neurological responses were measured before each subject entered the chamber, 15 minutes after they entered the chamber, and at 1 h intervals thereafter. Two out of seven subjects exposed to 1.27 x 10^6 for 3.5 h and two out of four exposed to 1.28 x 10^6 for 7.5 hours reported mild headache and dryness of their eyes and nose. A NOAEL of 6.78 x 10^5 was identified from this study. The NOAEL was adjusted by TCEQ (2009) by applying an uncertainty factor of 10 to account for human variability to arrive at an acute ReV) of 68,000 µg/m^3. The acute ReV was then used to calculate the acute ESL. At the target hazard quotient of 0.3, the acute ESL is 20,000 µg/m^3. All numbers were rounded to two significant figures at the end of all calculations (TCEQ, 2009).

An AAQC (24-hour averaging time) of 1.0 µg/m^3 was derived by the MOE (2008) (originally set in 1989) based on the tumourigenic effect of this compound. In 1989, the Ontario Ministry of Labour used the best estimate of metabolically corrected data from animal studies based on angiosarcoma in rats to recommend an air guideline for vinyl chloride for MOE. The geometric mean of three results obtained from Maximum Likelihood Estimates derived from a Quantitative Risk Model was used to derive the standard. The information was obtained from the Carcinogen Assessment Group and the Exposure Assessment Group of the US EPA; and Crump (1982) and was based on the studies of Maltoni et al. (1981); Buchter et al. (1980); and Gehring et al. (1978). A value of 0.2 µg/m^3 at a 1x10^{-6} risk was obtained and adopted as the annual average AAQC by the Ontario Ministry of Labour in 1989. The 24-hour (and 1-hour) AAQC of 1.0 µg/m^3 was calculated from the annual average AAQC, this value was selected as the 24-hour exposure limit for the current assessment.

58.3.2.1.2 Chronic Inhalation Toxicity Reference Values

The US EPA (2000) has developed an inhalation RfC of 100 µg/m^3 based on the NOAEL for liver effects observed in a chronic dietary study by Til et al. (1983, 1991) in rats. The rationale for basing an

inhalation RfC on an oral study was based on evidence for a mode of action common to exposures from either route (liver toxicity) and availability of PBPK models to perform route-to-route extrapolations. The critical effect, increases in the incidence of liver cell polymorphism and cysts, is reported in both oral studies and inhalation studies (10-month inhalation study of Sokal et al., 1980). In addition, the existing inhalation studies report no direct effects at the portal of entry (i.e., the respiratory tract) (US EPA, 2000).

Til et al. (1983, 1991) studied the chronic effects of vinyl chloride in the diets of Wistar rats. Concentrations of 0, 0.014, 0.13, and 1.3 mg/kg-day vinyl chloride was fed to rats (n=100/sex for the first 3 dose groups and n=50/sex for the high dose group) for a lifetime. Rats were weighed at 4-week intervals throughout the study. All males surviving 149 weeks and all females alive until week 150 were sacrificed. Mortality was slightly increased in the high-dose group near the end of the study. A variety of lesions were observed histologically at the highest dose level of 1.3 mg/kg-day. These included liver-cell polymorphism, and cysts. The incidence of female rats having many hepatic cysts was 3/98 in controls, 4/100 at 0.014 mg/kg, 9/96 at 0.13 mg/kg, and 24/49 at 1.3 mg/kg. The incidence of male rats with liver cell polymorphism characterized as moderate or severe was 5/99 in controls, 5/99 at 0.014 mg/kg, 8/99 at 0.13 mg/kg, and 13/49 at 1.3 mg/kg; the corresponding incidence in females was 16/98, 16/100, 12/96, and 24/49. The LOAEL based on these endpoints was at the highest dose of 1.3 mg/kg-day and the NOAEL was at the next highest dose of 0.13 mg/kg-day.

The study NOAEL was converted to a human equivalent inhalation concentration (NOAEL(HEC)) of 2500 µg/m^3 with the use of PBPK modeling. An uncertainty factor of 30 was applied (3 for interspecies extrapolation and 10 for intraspecies variability) to arrive at a chronic inhalation RfC of 100 µg/m^3. The overall confidence in the derived RfC was medium.

The US EPA RfC value of 100 µg/m^3 has been selected for evaluation of chronic non-carcinogenic inhalation effects in this risk assessment.

58.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Health Canada (2004) does not provide a carcinogenic inhalation TRV for vinyl chloride.

The US EPA (2000) developed a unit risk concentration (UR) of 8.8 x 10^{-6} (µg/m^3)$^{-1}$ from an inhalation study by Maltoni et al. (1981, 1984). Male and female Sprague-Dawley rats (30/sex/group) were exposed to one of 13 doses of vinyl chloride (control, 1.3 x 10^4up to 2.6 x 10^7 µg/m^3) by inhalation for 4 hours/day, 5 days/week for 52 weeks (Maltoni et al., 1981, 1984). Animals were observed throughout their lifetime (135 weeks). Tumor incidence of liver angiosarcomas and latency were concentration dependent. Hepatomas, angiomas, and neoplastic nodules were not statistically significantly increased in the Maltoni et al. (1981, 1984) studies; however, because hepatocellular tumors were significantly increased in a study by Feron et al. (1981), the US EPA (2000) concluded that all liver tumors observed in the Maltoni et al. (1981, 1984) studies, although not statistically significant, were likely the result of exposure to vinyl chloride as well, and should be included as a conservative approach. From the results of the Maltoni et al. (1981, 1984) study a continuous lifetime exposure during adulthood unit risk estimate of 4.4 x 10^{-6} (µg/m^3)$^{-1}$ was determined by the US EPA (200) using a linear, multistage model, and subsequently multiplied by two to account for continuous exposure from birth. This value was ground-truthed using a LED_{10}/linear model, which provided virtually identical results. The US EPA has strong confidence in this UR value of 8.8 x 10^{-6} (µg/m^3)$^{-1}$.

For this risk assessment the US EPA UR value of 8.8×10^{-6} $(\mu g/m^3)^{-1}$ was selected for evaluation of chronic carcinogenic inhalation effects in this risk assessment.

58.4 Bioavailability

In this risk assessment, vinyl chloride is only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that vinyl chloride is completely absorbed (*i.e.,* absorption factor is 1).

58.5 Conclusion

The following tables present Vinyl Chloride TRVs selected for use in this risk assessment.

Table 58-1 Vinyl Chloride Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Vinyl Chloride	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) , Carcinogenic COPC $(mg/kg/day)^{-1}$
NE – Not Evaluated

Table 58-2 Vinyl Chloride Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Vinyl Chloride	1-Hour	20,000	Mild headache and dryness of eyes and nose	Benchmark	TCEQ ESL, 2009
	24-Hour	1	Angiosarcoma in rats	Benchmark	MOE AAQC, 2008
	Annual Average	100	Liver cell polymorphism	RfC	US EPA, 2000
	Carcinogenic Annual Average	8.8×10^{-6}	Liver Cancer	UR	US EPA, 2000

[a] Units: Non-carcinogenic COPC $(\mu g/m^3)$, Carcinogenic COPC $(\mu g/m^3)^{-1}$

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59.0 XYLENES (TOTAL)

Xylene occurs in three forms, or isomers, which are named according to the positions of the two methyl groups on the benzene ring. These isomers are *ortho*-xylene (methyl groups in positions 1 and 2), *meta*-xylene (positions 1 and 3), and *para*-xylene (positions 1 and 4). Although xylene is primarily a synthetic chemical and is produced by chemical industries from petroleum, it also occurs naturally in petroleum and coal tar and is formed during forest fires, to a small extent (ATSDR, 2005). It is a colourless flammable liquid with a sweet odour. Xylene is one of the top 30 chemicals produced in the United States and is primarily used as a solvent in printing, rubber and leather industries (ATSDR, 2005).

There are no documented health effects from exposure to low levels of xylene (ATSDR, 2007). Acute (short term) exposure to high levels of xylene an lead to skin, eye, nose and throat irritation; lung problems and breathing difficulties; delayed reaction time, memory problems, stomach pain, and possible effects in the liver and kidneys. At very high levels it can lead to unconsciousness and death (ATSDR, 2007). Both chronic and acute exposure to high levels of xylene can cause headache, confusion, lack of muscle coordination, dizziness, and problems with balance (ATSDR, 2007).

59.1 Assessment of Carcinogenicity

The US EPA (2003) IRIS database reports that available data are inadequate to assess the carcinogenicity of xylenes. Health Canada (1996) list xylenes as Group IV, “Probably Not Carcinogenic to Humans.” The IARC (1999) lists xylene as Group 3, “Not Classifiable as to Human Carcinogenicity.”

For this risk assessment, xylenes are not evaluated as carcinogens.

59.2 Susceptible Populations

Studies indicate that pregnant women, fetuses and young children may be at greater risk of toxic effects from exposure to xylenes than other segments of the population (ATSDR, 2005). Ingestion of aspirin by a pregnant mother may also potentiate the xylenes’ toxic effects to herself and her fetus (ATSDR, 2005). Other segments of the population who may be more susceptible to adverse effects from exposure to xylenes include those with subclinical or clinical epilepsy, those who consume alcohol, those with subclinical or clinical renal, hepatic, or cardiac disease, and those with respiratory conditions such as asthma (ATSDR, 2005).

59.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, are outlined below. For the purposes of this risk assessment only non-carcinogenic inhalation risks from exposure to xylenes were evaluated.

59.3.1 Oral Exposure

59.3.1.1 Non-Carcinogenic Toxicity Reference Values

A non-carcinogenic oral TRV has not been selected for this assessment because xylenes are not being evaluated for the oral exposure pathway.

59.3.1.2 Carcinogenic Toxicity Reference Values

Xylenes are not classified as a carcinogenic substance; therefore, a carcinogenic oral TRV has not been selected.

59.3.2 Inhalation Exposure

59.3.2.1 Non-Carcinogenic Toxicity Reference Values

59.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour inhalation REL of 22,000 µg/m^3 was provided for xylenes by CalEPA (1999a). This concentration was derived from a human inhalation study by Hastings et al. (1984). The researchers exposed 50 healthy individuals to 4.3 x 10^5, 8.7 x 10^5, or 400 1.7 x 10^6 µg/m^3 mixed xylenes for 30 minutes to evaluate eye, nose, and throat irritation. The percent of subjects reporting eye irritation was 56% for controls (clean air), 60% at 4.3 x 10^5 µg/m^3, 70% at 8.7 x 10^5 µg/m^3, and 90% at 1.7 x 10^6 µg/m^3. The authors concluded there was no effect on eye irritation at 4.3 x 10^5 µg/m^3 because the incidence of irritation was as low as the control group. CalEPA also considered that when the data from Nelson et al. (1943), Carpenter et al. (1975), and Hastings et al. (1984), were taken together they were consistent with a human NOAEL for eye irritation of about 4.3 x 10^5 µg/m^3 for at least a 30-minute exposure. The NOAEL of 4.3 x 10^5 µg/m^3 was extrapolated to a 1-hour concentration of 215,000 µg/m^3. CalEPA (1999a) applied an uncertainty factor of 10 to protect sensitive populations. This value was adopted as the 1-hour exposure limit for the current risk assessment.

An AAQC (24-hour averaging time) of 730 µg/m^3 was derived by the MOE (2008) for neurological effects by slightly adjusting the chronic REL established by the CalEPA (1999b) (discussed in the following section).

59.3.2.1.2 Chronic Inhalation Toxicity Reference Values

A provisional TC of 180 µg/m^3 for xylenes (mixed isomers) was derived by Health Canada (2004) based on results of an experimental animal study by Ungvary and Tatrai (1985). Pregnant rats were exposed to xylenes via inhalation from days 7 to 15 of gestation, and both maternal toxicity and fetotoxicity were observed at this concentration. The lowest inhaled xylene concentration, for which developmental toxicity was observed in rats, was 2.5 x 10^5 µg/m^3. Health Canada (2004) therefore designated 2.5 x 10^5 µg/m^3 as a LOEL, despite the fact that documentation on the supporting study was determined to be incomplete. The LOEL was adjusted, according to the ratio of inhalation volume to body weight, from rats to human children (0.11 m^3/day/ 0.35 kg to 12 m^3/day / 27 kg) and a further uncertainty factor of 1000 was applied – a factor of 10 for interspecies variation, 10 for intraspecies variation, and 10 for the use of a LOEL instead of a NOEL in order to derive the provisional TC of 180 µg/m^3.

The US EPA IRIS (2003) provides an inhalation RfC of 100 µg/m^3, based on a subchronic inhalation study by Korsak et al. (1994) of male rats. Male rats were exposed to m-xylene, toluene, or a 1:1 mixture of the two compounds for 6 hours per day, 5 days per week, at a concentration of 0 or 4.3 x 10^5 µg/m^3 for 6 months, or 4.3 x 10^6 µg/m^3 for 3 months. A human equivalent NOAEL of 39,000 µg/m^3 and a human equivalent LOAEL of 78,000 µg/m^3 were established based on the critical effect of impaired motor coordination. A cumulative uncertainty factor of 300 (factor of 3 was applied to account for interspecies variability, a factor of 10 for intraspecies variability, a factor of 3 for use of a subchronic study, and a factor of 3 for uncertainties in the database) was applied to the NOAEL to derive the RfC of 100 µg/m^3:

CalEPA (1999b) derived a chronic REL of 700 µg/m^3 from an occupational inhalation exposure study conducted by Uchida et al. (1993). 175 Chinese workers involved in the production of rubber boots, plastic coated wire and printing processes employing xylene solvents were assumed to be exposed for 8-hours/day for 5-days/week to a mean concentration of 61,000 µg/m^3. The critical effects were a dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite documented in occupationally exposed factory workers; therefore, a LOAEL of 61,000 µg/m^3 was derived from this study. CalEPA (1999b) calculated a human exposure concentration of 22,000 µg/m^3 by accounting for an occupational inhalation rate (10/20 m^3/day) and adjusting for continuous exposure (5/7 days). A cumulative uncertainty factor of 30 (3 for the use of a LOAEL and 10 to account for intraspecies variation) was applied to arrive at a chronic REL of 700 µg/m^3.

ATSDR (2007) also derived their chronic MRL from the Uchida et al (1993) study discussed above. While ASTDR (2007) arrived at the same LOAEL of 61,000 µg/m^3 the uncertainty factors applied to the LOAEL differed from the CalEPA derivation. ATSDR (2007) did not adjust the LOAEL for continuous exposure because rapid clearance of xylene from the body did not justify such a conversion. A cumulative uncertainty factor of 300 was applied to the LOAEL (10 for the use of a LOAEL, 10 for the protection of sensitive populations, and 3 to account for the lack of supporting studies evaluating the chronic neurotoxicity of xylene) to arrive at a chronic inhalation MRL of 200 µg/m^3 (ATSDR, 2007).

The US EPA RfC value of 100 µg/m^3 has been selected for use in the risk assessment because it is the most conservative value.

59.3.2.2 Carcinogenic Inhalation Toxicity Reference Values

Xylenes are not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected.

59.4 Bioavailability

In this risk assessment, xylenes are only being evaluated through the inhalation pathway; as a result, oral and dermal bioavailability/absorption factors have not been determined. With regards to the inhalation pathway, it has been conservatively assumed that xylenes are completely absorbed (*i.e.,* absorption factor is 1).

59.5 Conclusion

The following tables present Xylenes (total) TRVs selected for use in this risk assessment.

Table 59-1 Xylenes Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Xylenes	Non-carcinogenic TRV	NE			
	Carcinogenic Slope Factor	NE			

[a] NE – Not Evaluated

Table 59-2 Xylenes Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Xylenes	1-Hour	22,000	Irritation of the eyes, nose and throat	Benchmark	CalEPA REL, 1999
	24-Hour	730	Neurological effects	Benchmark	MOE AAQC, 2008
	Annual Average	100	Impaired motor coordination	RfC	US EPA, 2003

[a] Units: Non-carcinogenic COPC (µg/m^3), NV – No Value

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60.0 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, 2005a). 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).

Although zinc is essential to human health, levels 10-15 times higher than the amount needed for good health can be toxic to humans (ATSDR, 2005b). Ingestion of large quantities of zinc, over a short period of time, can lead to stomach cramps, nausea, and vomiting. Chronic exposure to zinc via ingestion can cause anemia and decrease “good” cholesterol in the body. Rats who consumed large amounts of zinc became infertile, but this has not been demonstrated in humans (ATSDR, 2005b).

Inhalation of large amount of zinc (dust or fumes) can cause a short-term disease called metal fume fever. Long term effects of zinc inhalation are not known. Dermal contact with zinc acetate and zinc chloride is likely a skin irritant in people (ATSDR, 2005b).

60.1 Assessment of Carcinogenicity

Epidemiological studies of workers exposed to zinc have not shown a relationship between zinc exposure and the development of cancer (ATSDR, 2005a). 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, 2005a). 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, 2005).

60.2 Susceptible Populations

There is no specific information regarding the existence of human subpopulations that are sensitive to the toxic effects of zinc (ATSDR, 2005a).

60.3 Selection of Toxicity Reference Values

Numerous sources were consulted in order to obtain toxicological and benchmark values for COPCs. A summary of the reviewed studies, and the rationale for the selection of the TRVs used in the HHRA, is outlined below.

60.3.1 Oral Exposure

60.3.1.1 Non-Carcinogenic Toxicity Reference Values

The US EPA (2005) derived an oral RfD of 0.3 mg/kg-day (based on human clinical studies to establish daily nutritional requirements for zinc (Yadrick et al. 1989; Fischer et al. 1984; Davis et al. 2000; Milne et al. 2001). These studies examine dietary supplements of zinc and the interaction of zinc with other

essential trace metals (e.g., copper), to establish a safe daily intake level of zinc for the general population, including pregnant women and children, without compromising normal health and development. The critical effects upon which a LOAEL was determined were decreases in erythrocyte copper and zinc superoxide dismutase (ESOD) activity in healthy adult male and female volunteers. Because these studies identified physiological changes on similar sensitive endpoints (indicators of body copper status), at similar doses (0.81-0.99 mg Zn/kg-day), in a variety of human subject groups (postmenopausal females, adult females, and adult males), all four were selected as co-principal studies in the derivation of the RfD.

The principal studies identified lowest effect levels of 0.81 mg Zn/kg-day (Davis et al., 2000 and Milne et al., 2001), 0.94 mg Zn/kg-day (Fischer et al., 1984), and 0.99 mg Zn/kg-day (Yadrick et al., 1989). These values were averaged together to obtain the LOAEL of 0.91 mg/kg/d (e.g., 0.81+0.94+0.99=2.74/3=0.91 mg/kg-day). US EPA applied an uncertainty factor of 3 was applied to account for inter-individual variability to derive the RfD.

A similar RfD value was also derived by ATSDR (2005a) using the LOAEL derived by Yadrick et al. (1989) along with an uncertainty factor of 3 for intraspecies variation.

60.3.1.2 Carcinogenic Toxicity Reference Values

Zinc is not classified as a carcinogenic substance; therefore, a carcinogenic oral toxicological reference value has not been selected

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60.3.2 Inhalation Exposure

60.3.2.1 Non-Carcinogenic Toxicity Reference Values

60.3.2.1.1 Acute Inhalation Toxicity Reference Values (1-hour, 24-hour)

A 1-hour exposure limit of 50 µg/m^3 for zinc was selected for this risk assessment from the Texas Commission on Environmental Quality (TCEQ, 2008) based on the critical effect of metal fume fever. This 1-hour ESL value is derived after a thorough review of epidemiological and experimental toxicological data and of occupational exposure limits (OEL) from various agencies around the world, including Occupational Safety and Health Administration (OSHA), American Conference of Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Health (NIOSH). The majority of TCEQ ESLs are derived from OELs, therefore to account for occupational exposures OELs are further divided by a safety factor of 100 (i.e., 10 for extrapolation from workers to the general public; 10 for difference in exposure time) to derive a 1-hour exposure limit (Lee, 2009).

A 24-hour inhalation TRV was not available from any regulatory agency at the time of this assessment.

60.3.2.2 Chronic Inhalation Toxicity Reference Values

An annual exposure limit of 5 µg/m^3 for zinc was selected from TCEQ (2008). The TCEQ ESL selected is based on health effects outlined in 60.3.2.1.1. To derive a long-term ESL for zinc, TCEQ further divides the short-term ESL by an additional safety factor of 10.

60.3.2.3 Carcinogenic Inhalation Toxicity Reference Values

Zinc is not classified as a carcinogenic substance; therefore, a carcinogenic inhalation toxicological reference value has not been selected

60.4 Bioavailability

For this HHRA, the oral bioavailability factor for soil was conservatively assumed to be 1.0 (Health Canada, 2004). The relative dermal absorption fraction (RAF) was set as 0.02 (Health Canada, 2004).

60.5 Conclusion

The following tables present zinc TRVs selected for use in this risk assessment.

Table 60-1 Zinc Oral TRVs used in the HHRA

COPC	Toxicity Reference Value	Value [a]	Critical Effect	Reference Type	Source
Zinc	Non-carcinogenic TRV	0.3	Decreased in erthyrocyte Cu, Zn,-superoxide dismutase	RfD	US EPA, 2005
	Carcinogenic Slope Factor	NE			

[a] Units: Non-carcinogenic COPC (mg/kg/day) , NE – Not Evaluated

Table 60-2 Zinc Inhalation TRVs used in the HHRA

COPC	Duration	Value [a]	Critical Effect	Reference Type	Agency
Zinc	1-Hour	50	Metal fume fever	Benchmark	TCEQ ESL, 2008
	24-Hour	NV			
	Annual Average	5	Metal fume fever	Benchmark	TCEQ ESL, 2008

[a] Units: Non-carcinogenic COPC (µg/m^3) , NV – No Value

60.6 References

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