APPENDIX A

TOXICOLOGICAL PROFILES

LIST OF TOXICOLOGICAL PROFILES

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APPENDIX A:

TOXICOLOGICAL PROFILES

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A1-1.0 ARSENIC

Comprehensive toxicity profiles for arsenic have been established by the following regulatory agencies: U.S. EPA (1984); U.S. EPA IRIS (1993; 1998); Cal EPA (1999; 2000); WHO (2000); RIVM (2001); ATSDR (2007); and, Health Canada (2004a,b; 2006; 2008). The following profile represents a short summary of the relevant background information and human toxicity data for arsenic. A summary of the toxicity reference values selected for the HHRA is provided in Table A1-1.

Table A1-1 Summary Table of Toxicity Reference Values Selected for the HHRA

Route of Exposure	*Exposure Limit*	*Type of Limit*	*Toxicological Basis*	*Reference*	
				Study	*Regulatory*
Acute Effects					
Oral	5.0 µg/kg-day	MRL	Gastrointestingal effects and facial edema	Mizuta *et al*., 1956	ATSDR, 2007
Inhalation (24 hour)	0.3 µg/m^3	AAQC	Irritation, sensitization, immunosuppression, teratogenesis, genotoxicity and carcinogenicity in exposed individuals	Not provided	MOE, 2004; 2008
Chronic-Cancer (Non-threshold) Effects					
Oral	0.0015 (µg/kg-day)$^{-1}$	SFo	skin cancer	Tseng *et al.,* 1968; Tseng, 1977	U.S. EPA, 1998
Inhalation	0.0043 (µg/m^3)$^{-1}$	IUR*	lung cancer	Higgins *et al.,*1982; Enterline and Marsh, 1982; Brown and Chu, 1983a,b; Lee-Feldstein, 1983	U.S. EPA, 1998
	0.015 (µg/kg-day)$^{-1}$	SFi			
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	0.3 µg/kg-day	RfD	hyperpigmentation, keratosis, and possible vascular complications	Tseng *et al.,* 1968; Tseng, 1977	U.S. EPA, 1993
Inhalation	0.03 µg/m^3	REL	Decreased fetal weight; increased incidence of intrauterine growth retardation and skeletal malformation in mice	Nagymajtényi *et al*., 1985	Cal EPA, 1999
Dermal	NA		NA	NA	NA

[a] U.S. EPA indicates that the unit risk should not be used if the air concentration exceeds 2 µg/m^3, as it may not be appropriate at concentrations above this level

NA Not available
SFo Oral slope factor
IUR Inhalation unit risk
SFi Inhalation slope factor
RfD Reference dose
REL Reference exposure level
AAQC Ambient Air Quality Criteria

A1-1.1 Background Information

Arsenic occurs both naturally in the environment as a widely distributed component of the earth's crust and as a result of anthropogenic emissions (ATSDR, 2007). Arsenic may be found in four different oxidation states which dictate if it will bind to metals or non metals. These oxidation states are -3 (arsine), 0 (arsenic metal), +3 (arsenite) and +5 (arsenate). In differing oxidation states, arsenic is present in the environment in both the inorganic and organic forms of which are quickly absorbed by the body if ingested (Health Canada, 2006; ATSDR, 2007). The organic forms are rapidly eliminated from the body whereas the inorganic forms tend to accumulate more in the sulfhydryhl-rich tissues (Bertolero *et al*., 1987; Environment Canada, 1999; Health Canada, 2006; ATSDR, 2007). Major anthropogenic sources of arsenic include the burning of fossil fuels, waste incineration, ore refining facilities such as lead and copper smelting which release inorganic arsenic, and arsenical pesticides (Grayson, 1978; NTP, 2005; Health Canada, 2006; ATSDR, 2007; HSDB, 2007). Some examples of inorganic arsenic include arsine gas (AsH_3) which is one of the most toxic arsenic compounds, as well as arsenic trioxide (As_2O_3), arsenic trisulfide (As_2S_3), sodium arsenite ($NaAsO_2$), arsenic pentoxide (As_2O_5), sodium arsenate (Na_2HAsO_4) and calcium arsenate ($Ca_3(ASO_4)_2$ (Opresko, 1992). Compounds in which arsenic is in its trivalent (As^{+3}) form are typically more toxic than those compounds with different valence states (RAIS, 1997).

Exposure to arsenic within the general public is primarily through the ingestion of food such as seafood and water (NTP, 2005). However, much of the arsenic in food items such as shellfish, fish and seaweed is present in the less toxic organic forms. Arsenic in drinking water, however, is typically in the inorganic form and, therefore, is considered to be a major potential source of exposure (Vahter *et al*., 1983; JECFA, 1988; Environment Canada, 1999; Health Canada, 2006). Additional exposure to inorganic forms of arsenic may occur through incidental ingestion of contaminated soil and dust (Health Canada, 2006). Elevated occupational exposure to arsenic may occur in facilities that manufacture or use arsenic (*e.g*., copper or lead smelting, pesticide application) (ASTDR, 2007).

The range of arsenic concentrations in naturally occurring soils (*i.e*., soil considered unimpacted by anthropogenic sources) have been reported to be 0.2 to 40 µg/g, with an average concentration of approximately 8.7 µg/g (Walsh and Keeney, 1975; Kabata-Pendias and Pendias, 1984; Adriano, 1986). Near base-metal smelters, average concentrations in Canada of arsenic in soil are elevated and typically range from 50 to 110 µg/g with a maximum reported concentration of 2,000 µg/g (Environment Canada, 1999). Although arsenic levels in soil may be elevated near smelter sites, animal and *in vitro* studies have shown that exposure to inorganic arsenic *via* soils/dust relative to more soluble forms (*e.g*., arsenic salts) is greatly reduced (Freeman *et al*., 1993; 1995; Groen *et al*., 1994; Davis *et al*., 1996; Hrudey *et al*., 1996; Ng and Moore, 1996; Ruby *et al*., 1996; Hamel *et al*., 1998; 1999; U.S. EPA, 1997; Ng *et al*., 1998; Williams *et al*., 1998; Rodriguez *et al*., 1999; Turpeinen *et al*., 2003).

A1-1.2 Fate and Transport

Anthropogenically produced arsenic is released into the air adsorbed onto small particles approximately 1 µm in diameter and is emitted mainly from high temperature processes such as smelting, oil and coal combustion and incineration operations (Coles *et al*., 1979; Pacyna, 1987). Arsenic is largely released as arsenic trioxide and less often, in the form of arsine (U.S. EPA, 1982). In the atmosphere, arsenic can be present in both the trivalent state and as the organic derivative; methyl arsine but it can be oxidized to form the pentavalent state (U.S. EPA, 1984; Scudlark and Church, 1988). Photolysis of arsenic in the atmosphere is not significant

(U.S. EPA, 1979). Atmospheric fallout can serve as a significant source of arsenic to both aquatic and terrestrial environments.

Input of arsenic into water bodies *via* atmospheric deposition has been reported near industrial sources (Scudlark *et al*., 1994; Hoff *et al*., 1996; Golomb *et al*., 1997; Shahin *et al*., 2000). In water, arsenic can undergo various processes such as oxidation-reduction, ligand exchange, precipitation and biotransformation of which are dependent on pH, metal sulfides, sulphide ion concentrations, iron concentrations, temperature, salinity, distribution of biota (biofilms) and organic matter content (U.S. EPA, 1979; Sanders *et al*., 1994; Wakao *et al*., 1988; Welch *et al*., 1988; Farago, 1997; Redman *et al*., 2002). Generally, pentavalent arsenic will be present in surface water as it is an oxidizing environment, and trivalent arsenic will be present in groundwater which has a reducing environment (ATSDR, 2007).

Partitioning to the soil or sediment from the water is dependent on the chemical form of arsenic and its interactions with other materials present (*e.g*., biofilms, proportion of clays, iron oxides, *etc*.) (ATSDR, 2007). In soils where arsenic is present, it is typically found as a mixture of mineral phases including co-precipitated, sorbed and dissolved species of arsenic. The amount of dissolved arsenic in soil is dependent on particle size, and the amount of arsenic distributed in the various phases. Distribution of the phases may also be indicative as to the source of the arsenic (Roberts *et al*., 2007). Arsenic was found to be only sparingly soluble in soil sampled from a historical mining site in Anaconda, Montana (Davis *et al*., 1996).

At typical environmental pH levels, the trivalent form of arsenic is not strongly adsorbed compared to the pentavalent form to suspended solids or sediments in the water column. In some cases, arsenic will not adsorb to sediment or debris and will travel considerable distances in rivers (U.S. EPA, 1979). Adsorption of arsenic onto sediments and soils is largely influence by the proportion of clays, iron oxides, aluminum hydroxides, manganese compounds and organic compounds. Typically, arsenic in the trivalent state is found in sediment or flooded soils since these present a more reduced environment and arsenic in the pentavalent form can be found in aerobic soils (U.S. EPA, 1982; Sanders *et al*., 1994). Concentrations of arsenic are commonly greater in the upper layers of the soil since it is not readily mobile in soil; more mobile in sandy soil than in clay loam; indicating that leaching is not of great concern (Merwin *et al*., 1994; Sanok *et al*., 1995; ATSDR, 2007). Iron has been implicated as most strongly affecting adsorption of arsenic in soils (Janssen *et al*., 1997).

In terrestrial systems, plants accumulate arsenic *via* the roots and leaves; however, relative to the environmental concentrations of arsenic, plant levels are relatively low (U.S. EPA, 1982; Gebel *et al*., 1998; Pitten *et al*., 1999 In aquatic environments, biomagnification is not significant (U.S. EPA, 1979; 1982; 1983; 2003; Mason *et al*., 2000). Bioaccumulation of arsenic depends on the environmental setting, organism, trophic status, exposure concentration and route uptake of the arsenic (Williams *et al*., 2006). Specifically, bioconcentration of arsenic in aquatic environments occurs significantly with the algae and the lower invertebrates. Bioconcentration at the predatory level is dependent on the organisms diet (ATSDR, 2007).

A1-1.3 Toxicokinetics

In general, the more soluble the arsenic species the greater the potential for absorption (NAS, 1977; Hrudey *et al*., 1996). Typically, elemental arsenic (oxidation state of 0) is not absorbed by the body and is eliminated unchanged (HWC, 1989). Inorganic and organic forms of arsenic are typically well absorbed by the gastrointestinal tract, however, organic forms and arsenate (+5) are rapidly eliminated from the body. Arsenite (+3) tends to accumulate in the tissues (Bertolero *et al*., 1987). Dermal absorption of arsenic is believed to be low, evidence suggests that less

than 5% of soluble arsenic compounds would be dermally absorbed and negligible amounts of particulate bound (soil or dust) arsenic is likely to cross the skin. ATSDR (2007) has indicated that dermal absorption of arsenic (organic and inorganic) is not a route that is likely to contribute towards a significant level of concern.

Arsenic absorbed into the system; binds onto haemoglobin and is distributed to various tissues and organs such as the liver, kidneys, lungs, spleen and skin within 24 hours for metabolism (Wickstroem, 1972; Axelson, 1978; Malachowski, 1990). Arsenic does not cross the blood-brain barrier, but transplacental transfer of arsenic may occur (Gibson and Gage, 1982). Metabolism of inorganic arsenic occurs primarily in the liver *via* enzymatic methylation (WHO-IPCS, 2001; Vahter, 2002). During the biotransformation process arsenate (+5) is quickly reduced to arsenite (+3) which under-goes enzymatic methylation to produce two metabolic products, including: monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA) (U.S. NRC, 2001; Vahter, 2002). Extensive deposits of arsenic following chronic exposure can be subsequently found within the hair and nails (U.S. EPA, 1984).

Elimination of arsenic from the body occurs *via* urine within a 12 hour period after absorption, however, methylated products (MMA and DMA) can be excreted up to 2 to 3 days later (Buchet and Lauwerys, 1985; Lovel and Farmer, 1985; Malachowski, 1990). A small fraction of excreted arsenic compounds occurs in the feces, bile, sweat and breast milk as well as skin, hair and nails (ICRP, 1975; Malachowski, 1990; Hrudey *et al*., 1996; Kurttio *et al*., 1999; ATSDR, 2007).

A1-1.4 Biomonitoring

Exposure to total arsenic can be determined from urine, blood, hair, and nail samples. Other methods can be employed to distinguish between inorganic and organic arsenic derivatives (ATSDR, 2007). Determination of recent exposure to arsenic is most readily and reliably obtained through urine samples (Millham and Strong, 1974; Pinto *et al*., 1977; Enterline *et al*., 1987a; Polissar *et al*., 1990). Blood samples are commonly used to evaluate the levels of an individual who has had an acute exposure to arsenic. This method is not used for assessing chronic exposure to low levels of arsenic (Heydorn, 1970; Valentine *et al*., 1979, 1981; Driesback, 1980; Hindmarsh and McCurdy, 1986). Lastly, to determine exposure to arsenic from as recently as one month to up to 10 months, hair and nail samples may be analyzed, however external contamination with these samples is a high concern (Milham and Strong, 1974; U.S. EPA, 1977; Valentine *et al*., 1979; 1981; Bencko *et al*., 1986; Choucair and Ajax, 1988; Yamauchi *et al*., 1989; Agahian *et al*., 1990).

A1-1.5 Chemical and Physical Properties

Table A1-2 Chemical and Physical Properties of Arsenic

Chemical/Physical Property	*Value*	*Reference*
Colour/Form	Silver-gray or tin white; solid	HSDB, 2007
Dissociation Constant (pKa)	No data	ATSDR, 2007
Henry's Law Constant	Not provided	ATSDR, 2007
Log K_{ow}	No data	ATSDR, 2007
Molecular Weight	74.9216	HSDB, 2007
Vapour Pressure	7.5E-03 mm Hg at 280ºC	HSDB, 2007
Water Solubility	Insoluble	HSDB, 2007
Odour	Odourless	HSDB, 2007

A1-2.0 TOXICOLOGICAL SUMMARY: HUMAN HEALTH EFFECTS

Inhalation

Acute Effects

Inhalation of inorganic arsenic will commonly cause irritation to the throat and lungs (RAIS, 1997). Acute inhalation exposure may damage mucous membranes leading to rhinitis, pharyngitis and laryngitis (U.S. EPA, 1984). It is estimated that these effects would not occur from short-term exposures to arsenic concentrations less than 100 µg/m^3 (RAIS, 1997). At very high exposure levels, perforations of the nasal septum have been reported to be related to inorganic arsenic (ATSDR, 2007). Gastrointestinal effects are not typically associated with arsenic poisoning by inhalation (Pinto and McGill, 1953). However, nausea, vomiting, and diarrhoea in workers with acute arsenic poisoning following occupational inhalation exposure have been reported (Pinto and McGill, 1953; Beckett *et al*., 1986; Bolla-Wilson and Bleecker, 1987; Ide and Bullough, 1988; Morton and Caron, 1989). It has been suggested that mucociliary transport of arsenic dust from the lungs to the gut could be responsible for gastrointestinal effects (ATSDR, 2007). Some studies have also reported that arsenic can produce effects on the cardiovascular system (ATSDR, 2007). On the other hand, it was reported that none of these studies provided conclusive evidence that the observed increase in risks was due to arsenic exposure (ATSDR, 2007). Furthermore, neurological effects have been reported in epidemiological studies (ATSDR, 2007). No deaths have been reported upon acute human exposure to inorganic arsenic *via* inhalation (ATSDR, 2007). ATSDR (2007) suggested that mortality was not of concern for humans following acute arsenic exposure, even at very high exposure levels (1 to 100 mg/m^3).

Chronic Effects

Adverse health effects have been reported as a result of chronic inhalation exposure to arsenic. Long-term exposure to lower concentrations of arsenic *via* inhalation may result in circulatory and peripheral nervous disorders (RAIS, 1997). Targets of chronic arsenic toxicity have been reported to include the respiratory (Lundgren, 1954), circulatory (Lagerkvist *et al*., 1986), nervous (Blom *et al*., 1985), and reproductive systems (Nordström *et al*., 1979). The epidemiological studies that quantified these effects have been brought into question because of expected exposure of the subjects to other compounds (Cal EPA, 2000).

Oral

Acute Effects

Acute oral exposure to concentrations of 1.2 and 21 mg/L of arsenic in well water has been found to lead to symptoms of abdominal pain, vomiting, diarrhoea, pain to the extremities and muscles and well as weakness with flushing of the skin as well as the appearance of a papular erythematous rash, hyperkeratosis of the palms and soles and deterioration of motor and sensory responses (Feinglass, 1973; Wagner *et al*., 1979; Fennel and Stacy, 1981; Murphy *et al*., 1981; Wesbey and Kunis, 1981).

Chronic Effects

Chronic oral exposure to inorganic arsenic in contaminated drinking water may result in dermal lesions such as hyperpigmentation, warts, hyperkeratosis of the palms and soles in adults

exposed to 700 µg/day over a 5 to 15 year period or 2,800 µg/day over a 6 month to 3 year period (U.S. EPA, 2001). Neurotoxicity is also associated with arsenic exposure, leading to peripheral neuropathy of the sensory and motor nerves (RAIS, 1997). Effects include numbness, reduced sense of touch, pain, temperature, as well as a weakening of the muscles (Heyman *et al*., 1956; Mizuta *et al*., 1956; Tay and Seah, 1975; Hindmarsh *et al*., 1977; Valentine *et al*., 1981; Hindmarsh and McCurdy, 1986). There is also some indication that arsenic may have reproductive effects, such as an increased occurrence of spontaneous abortions and reduced birth weight (Nordström *et al*., 1978a,b). In addition, oral exposure to inorganic arsenic may result in nausea, vomiting, and diarrhoea after repeated exposure to lower doses (ATSDR, 2007). These effects were reported to be caused by the direct irritation of the gastrointestinal mucosa by inorganic arsenicals (ATSDR, 2007). Chronic exposure to inorganic arsenic has also been associated with effects on the vascular system. The most serious of these effects is "Blackfoot Disease," a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (ATSDR, 2007).

One of the largest epidemiology studies conducted was by Tseng *et al*. (1968) and Tseng (1977) who observed an increased frequency in dermal lesions ("blackfoot disease") in addition to an increased skin cancer incidence in a Taiwanese farming community who were exposed to varying levels of arsenic (≥ 0.60 mg/L, 0.3 to 0.59 mg/L, 0.01 to 0.29 mg/L) in their drinking water. Adverse effects to the skin, respiratory, cardiovascular and digestive systems have also been observed in children (< 16 years old) who were exposed to mean arsenic concentrations of 0.6 mg/L in drinking water. The rate of effects decreased after levels were decreased to 0.08 mg/L but were still greater than the control group (Zaldivar and Ghai, 1980; Zaldivar, 1980). Infants who were exposed to an estimated amount of 3 mg/day of arsenic for two months through milk experienced effects to their central nervous system (CNS) which including hearing loss, eye damage, epilepsy, *etc*. as well as other effects such as melanoma and hyperkeratosis (Hammamoto, 1955; U.S. EPA, 1984).

A1-2.1 Carcinogenicity

Arsenic has been classified as carcinogenic to humans by Health Canada, 1994; IARC, 2004; U.S. EPA IRIS, 1998; NTP, 2005; and, ACGIH, 2006. In 1993, ACGIH reviewed its assessment for arsenic and confirmed its human carcinogenicity. The eleventh edition of the Report on Carcinogens (ROC) published by NTP (2005) has also classified arsenic as a known human carcinogen. For the purposes of this risk assessment arsenic was evaluated as a human carcinogen for both oral and inhalation exposure.

There is clear evidence that exposure to inorganic arsenic through the inhalation or oral route increases the risk of cancer in humans (ATSDR, 2007). Occupational exposure of workers in copper smelters or mines to arsenic trioxide has resulted in an increased risk of lung cancer (U.S. EPA IRIS, 1998; MOE, 2004; ATSDR, 2007). Elevated lung cancer incidence rates have also been observed in chemical plant workers exposed to arsenate. Residents living near smelters or chemical plants may also have an increased risk of lung cancer; however, the reported increases are not clearly detectable in all cases (ATSDR, 2007). Long-term exposure to 0.07 mg/m^3 or greater has been shown to increase the incidence of lung cancer (ATSDR, 2007). Epidemiological studies and case reports provide evidence that the ingestion of inorganic arsenic increases the risk of developing skin cancer (U.S. EPA IRIS, 1998; ATSDR, 2007). Squamous cell carcinomas are the most common tumours observed. Additional evidence is available to suggest that chronic exposure to arsenic may result in the development of bladder cancer (ATSDR, 2007). In addition, chronic oral exposure to arsenic may be linked to the formation of respiratory tumours (ATSDR, 2007).

A1-3.0 TOXICOLOGICAL REFERENCE VALUES (TRVS)

Carcinogenic TRVs

Health Canada (2004a; 2008) has derived a unit risk value of 0.0064 $(\mu g/m^3)^{-1}$ and an inhalation slope factor of 0.028 $(\mu g/kg\text{-}day)^{-1}$ based on an epidemiology study of an occupationally exposed cohort. The critical effect was lung cancer and the 5% tumorigenic concentration was 7.83 $\mu g/m^3$. The oral slope factor of 0.0018 $(\mu g/kg\text{-}day)^{-1}$ was based on studies by Chen *et al*. (1985); Wu *et al*. (1989); Morales *et al*. (2000) which are based on an epidemiology study of a naturally exposed cohort to drinking water (Health Canada, 2006).

Cal EPA (2005) has selected a inhalation unit risk factor of 0.0033 $(\mu g/m^3)^{-1}$ based on Enterline *et al*. (1987b) study on occupational exposure to low levels of arsenic (Anaconda, Tacoma and Ronnskar smelters) and the increased incidence of lung tumors and including adjustments to account for arsenic exposure from smoking.

U.S. EPA IRIS (1998) derived an inhalation unit risk of 0.0043 $(\mu g/m^3)^{-1}$ for an increased incidence of lung cancer in occupationally exposed males employed in smelters (Enterline and Marsh, 1982; Higgins, 1982; Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983). The unit risk is the upper-bound (95% confidence limit) lifetime cancer risk that is estimated to result from continuous exposure to a carcinogen (U.S. EPA, 1997). An absolute-risk linear model was used to derive the unit risk of each study. The geometric mean of the unit risk was calculated for each data set that used a distinct exposed population (*e.g*., Anaconda smelter and ASARCO smelter). The final estimate of the unit risk was calculated using the geometric mean of the unit risk from the Anaconda and ASARCO smelter data sets. The increase in age-specific mortality rate of lung cancer in these populations was attributed to cumulative exposure. The U.S. EPA value was adopted as the inhalation unit risk to evaluate the long-term human health effects of arsenic exposure as it is the most widely accepted and technically defensible toxicity reference value available for arsenic (Table A1-3). However, the unit risk should not be used if the air concentration exceeds 2 $\mu g/m^3$, as it may not be appropriate at concentrations above this level. RIVM (2001) derived a TCA for arsenic of 1.0 $\mu g/m^3$ for the occurrence of lung cancer in individuals exposed to trivalent arsenic. An uncertainty factor of 10 for intraspecies variation was applied to the LOAEL of 10 $\mu g/m^3$.

The cancer potency for arsenic *via* oral consumption has been defined by an oral slope factor of 0.0015 $(\mu g/kg\text{-}day)^{-1}$ by the U.S. EPA IRIS (1998) which represents the upper-bound estimate (95% confidence limit) of the slope of the dose-response curve in the low dose region for carcinogens (U.S. EPA, 1997). The dose-response curve is based on the data from the Tseng *et al*. (1968) and Tseng (1977) studies in which a Taiwanese farming community (population approximately 40,000) were exposed to differing levels of arsenic (high levels (≥0.60 mg/L), medium (0.3 to 0.59 mg/L) and low (0.01 to 0.29 mg/L)) in their drinking water originating from artesan wells and elevated incidences of skin cancer were detected in comparison to the control group. 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 U.S. males and females and it was assumed that the skin cancer risk in the U.S. 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. This value, which was also adopted by Cal EPA (2005), was adopted as the oral slope factor to evaluate long-term human health effects of exposure to arsenic as it is the most widely accepted and technically defensible toxicity reference value available for arsenic.

The cancer potency estimate for arsenic, as assessed by all major regulatory agencies, including Health Canada, WHO, Cal EPA and U.S. EPA, is based upon Taiwanese epidemiological studies of drinking water exposure in the 1970's (*i.e.*, Tseng *et al.*, 1968; Tseng, 1977) in which populations were exposed to inorganic arsenic primarily in their drinking water.

Several weaknesses of these studies have been cited in the scientific literature, including poor nutrition in the study population, possible genetic predisposition to adverse effects, unquantified exposures to arsenic from other sources, and possible bias in examiners (U.S. EPA, 1998). Despite these shortcomings, regulatory agencies continue to rely on these studies as the basis for oral slope factors since evidence of carcinogenicity in humans is considered to be superior to animal studies when classifying carcinogens. Among the concerns raised in relation to the Taiwanese studies are the following:

- Adequacy of the model used by U.S. EPA to derive the slope factor;
- Accuracy and reliability of the exposure data (Brown *et al.*, 1997a,b). The selection of exposure groups based on average concentrations of inorganic arsenic in Taiwanese village wells is a key source of uncertainty in these studies (Brown *et al.*, 1997a; Chappell *et al.*, 1997). Villages were represented by average well water concentration, although there were large variations in arsenic concentrations across individual wells. This precludes any ability to assess individual rates of exposure to those who developed cancers because of the lack of linkage with well water concentrations of arsenic, and well usage rates. The considerable variation in inorganic arsenic concentrations within the wells was recognized by Tseng *et al*. (1968), but was not addressed in the exposure estimation. Furthermore, concentrations of arsenic in the wells were measured in the early 1960s, and for many villages, only 2 to 5 analyses were conducted, and for other villages, only one analysis was performed. Also, tap water was supplied to many areas after 1966, and the arsenic-containing wells were only used in dry periods, which would greatly limit arsenic exposures. This was not accounted for. In addition, due to study design, particular wells used by subjects with skin cancer could not be identified and arsenic intake could only be assigned at the village level (U.S. EPA, 1998);
- Unique host and environmental factors among Taiwanese populations that are not applicable elsewhere (Carlson-Lynch *et al.*, 1994);
- A possible threshold for arsenic carcinogenicity and nonlinearities in the dose-response curve (Abernathy *et al.*, 1996; Slayton *et al.*, 1996);
- Differences in health and nutrition between Taiwan and other countries that might lead to higher cancer risks in Taiwan for the same level of exposure (Beck *et al.*, 1995). The importance of nutritional status in arsenic toxicology, as well as the actual nutritional status of the study population, has been debated in the literature. In general, poor nutritional status can lead to increased susceptibility to the toxic action of many chemicals. In the case of arsenic, there may be an additional role of nutrition in relation to carcinogenicity. The biomethylation of arsenic has been postulated to play a role in its genotoxicity and carcinogenicity. The status of the methyl donor pool, which is dependent on dietary intake of proteins and amino acids such as cysteine and methionine, may play a significant role in susceptibility to arsenic carcinogenicity. Indeed, Hsueh *et al*. (1995) found that malnutrition, indexed by a high consumption of dried sweet potato as a staple food, was a risk factor for skin cancer. However, Smith *et al*. (1995) reviewed the Taiwanese intake of protein, and found it adequate by current standards. Beck *et al*. (1995), in rebuttal, pointed out that current standards dictate intakes required for normal bodily processes, and may not be adequate to methylate an excessive and sustained intake of arsenic;
- The possibility that arsenic is an essential nutrient at lower doses (NRC, 1999); and,

- Uncertainty regarding the amount of water consumed daily by Taiwanese males (U.S. EPA, 1998).

Multiple studies in Asian populations (Taiwan, Bangladesh and elsewhere) exposed to arseniasis-endemic areas have confirmed a dose-response association of lung, bladder and skin cancer and arsenic exposure. Among these populations, it has been difficult to elucidate the dose-response relationship at lower exposure levels (less than 100 µg/L for drinking water) until recently (see Chen *et al*., 2010). The following review identifies the uncertainties relating to low-level arsenic exposures (almost exclusively *via* drinking water) that have been experienced by populations primarily in North and South America.

Several studies of populations that experienced long-term exposure to arsenic have given mixed results when investigated for associations with bladder cancer. The reasons for the differences noted from earlier studies in Taiwan and the apparent lack of association in the population of bladder cancer patients in Utah (Bates *et al*., 1995) were not apparent. Arsenic ingestion was not related to bladder cancer risk in the non-smoking population. Among smokers, some support for an etiologic role for arsenic came from the higher risk noted primarily among persons who were exposed during a ten year period at least 30 years prior to diagnosis of bladder cancer (Bates *et al*., 1995).

A number of arsenic studies have used an ecologic design, in which the geographic distribution of particular diseases, or causes of death, is compared with the geographic distribution of arsenic levels in the drinking water (Cantor and Lubin, 2007). The ecologic studies conducted in high-exposure areas consistently show strong associations and dose-response relationships with arsenic in drinking water for lung, skin, bladder, and kidney cancers (NRC, 2001). Thus, characterization of arsenic as a human carcinogen is formally based on data from epidemiologic studies conducted among populations exposed levels of arsenic in drinking water above 150 or 200 µg/L. In such studies excess relative risks per unit exposure among different populations are consistent across studies and dose-response relationships are generally linear (Cantor and Lubin, 2007).

By contrast, findings from epidemiologic studies among populations at lower levels of exposure are quite mixed, and generally do not reveal risks of bladder, lung, or other cancers that would be expected from linear extrapolation of findings from the high-exposure studies (Cantor and Lubin, 2007).

Lamm *et al*. (2004) combined county-specific white male bladder cancer mortality data for the period 1950 to 1979 from the National Cancer Institute and U.S. EPA with county-specific arsenic groundwater data. This ecologic study of drinking water arsenic and bladder cancer mortality in the United States included over 4500 bladder cancer deaths and over 75 million person-years of observation (Lamm *et al*., 2004). The authors identified 26 states and 133 counties that had reported both arsenic concentrations in drinking water of 3 µg/L or greater and provided bladder cancer mortality data.

In the U.S. ecologic study SMRs for each county were prepared and examined by linear regression in a meta-analysis. No evidence of an arsenic-dependent rate increase in mortality was observed in an arsenic exposure range of 3 to 60 µg/L (Lamm *et al*., 2004). Statistical analysis revealed that among white U.S. males, arsenic exposure between 1950 and 1979 did not adversely affect an increase in bladder cancer mortality (slope estimate indistinguishable from zero). Lamm *et al*. (2004) concluded that no arsenic-related increase in the lifetime bladder cancer mortality rate was observed for counties that depended exclusively on

groundwater containing median arsenic concentration of 3 to 60 µg/L for their drinking water supplies.

Studies of effects of low level arsenic exposures are prone to exposure misclassification. Relatively small errors in assessment of historical exposure to arsenic during relevant exposure periods can have profound effects on the risk that is observed (Cantor and Lubin, 2007). Although the U.S. study was criticized on the basis of the study design (lack of individual exposure data), and the regression analysis used (Taeger *et al*., 2004); Lamm *et al*. (2004) maintained that the size of the study confirmed their findings. Furthermore, the population numbers in studies involving low-exposure populations (*e.g*. incidence of bladder cancer cases) have been small, thus limiting statistical power to detect lower levels of risk. In most cases, difficulties in estimating historical exposure as well as the highly variable nature of the exposure assessments has increased the uncertainty of outcomes related to low doses of arsenic.

Risk estimates from several studies of bladder cancer and low levels of arsenic ingestion include six case-control studies of incident bladder cancer (Bates *et al*., 1995, 2004; Kurttio *et al*., 1999; Steinmaus *et al*., 2003; Karagas *et al*., 2004; Michaud *et al*., 2004) and a cohort mortality study that included bladder cancer as one of many outcomes (Lewis *et al*., 1999).

Bates *et al*. (1995) studied a population in Utah (117 bladder cancer cases with 266 controls) with long-term As levels based on cross-sectional sampling of public water systems. No association was reported among never smokers; while for smokers, mortality was elevated for exposures >10 years OR = 2.92 [1.1-8.0]. Kurttio *et al*. (1999) found no association between As and bladder cancer among never smokers, but reported an OR of 6.91 for smokers with a daily exposure ≥ 1 µg/day. Steinmaus *et al*. (2003) also found no association between exposure to As and bladder cancer among never smokers. Among smokers, the highest risk was for exposures in excess of 40 years. In New Hampshire, Karagas *et al*. (2004) found no association between arsenic exposure and bladder cancer in never smokers, but an OR = 2.17 [0.92 to 5.11] among smokers or former smokers based on As in toenail clippings (>0.33 µg/g). This suggested that low to moderate arsenic levels may act as a co-carcinogen for bladder cancer incidence when combined with smoking. Michaud *et al*. (2004) also examined toenail clippings of male smokers who were bladder cancer patients, but found no evidence of an association. Finally, in Utah, Lewis *et al*. (1999) reported a standardized mortality ratio (SMR) of 0.36 for exposures of less than 1000 ppb-years and an SMR of 0.95 for members of the general population who experienced slightly greater concentrations of arsenic exposure (≥ 5000 ppb-years).

Chen *et al*. (2005) found that arsenic methylation capability played an important role in reducing the risk of bladder cancer for both non-smokers and smokers. Among male non-smokers, the risk of bladder cancer was markedly higher (seven-fold) in subjects with environmental tobacco smoke (ETS) exposure [95% CI, 1.87-27.4] when compared to subjects without ETS exposure. However, individuals who demonstrated the ability to methylate arsenic (MMA or DMA in urine) showed reduced risks for bladder cancer.

In a Taiwanese population that received exposures to arsenic in drinking water, non-smokers who showed a greater ability to methylate arsenic (high primary methylation index or PMI) experienced a lower risk of bladder cancer. Subjects who were regularly exposed to ETS were at lower risk (OR = 0.37 [CI, 0.14-0.96]) when compared to subjects not exposed to ETS.

For example, no association was established for low level arsenic exposure and bladder cancer risk in a Finnish population followed up for as long as 14 years (Michaud *et al*., 2004) . This

suggests that arsenic exposure is unlikely to explain a substantial excess of bladder cancer in Finland or in countries with low arsenic exposure (Michaud *et al*., 2004).

Table A1-3 Carcinogenic Exposure Limits for Arsenic

Exposure Value	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Source*	*Derivation Date*
Inhalation ($\mu g/m^3)^{-1}$						
Unit risk	0.0064	Lung cancer	Occupational exposure	Higgins *et al*., 1982	Health Canada, 2004a; 2008	1993
Unit risk	**0.0043[a]**	**Lung cancer**	**Occupational exposure**	**Enterline and Marsh, 1982; Higgins, 1982; Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983**	**U.S. EPA IRIS, 1998**	**1995**
Unit Risk	0.0033	Lung tumor incidence	Occupational exposure	Enterline *et al*., 1987b	Cal EPA, 2005	Not provided
Unit Risk	0.0015	Lung cancer	Occupational exposure	Pinto *et al*., 1977; Lee-Feldstein, 1983; Viren and Silvers, 1994	WHO, 2000	2000
Slope factor $(\mu g/kg\text{-}day)^{-1}$	0.028	Lung cancer	Occupational exposure	Higgins *et al*., 1982	Health Canada, 2004a; 2008	1993
TCA ($\mu g/m^3$)	1.0	Lung cancer	Human inhalation exposure to trivalent arsenic LOAEC: 10 $\mu g/m^3$	Not provided	RIVM, 2001	Not provided
Oral $(\mu g/kg\text{-}day)^{-1}$						
Slope factor	0.0018	Bladder, lung and liver cancer	Naturally exposed cohort (epidemiological study; oral drinking water)	Chen *et al*., 1985; Wu *et al*., 1989; Morales *et al*., 2000	Health Canada, 2008	2006
Slope factor	0.0017	Not provided	Derived from Canadian Guidelines for Drinking Water Quality supporting document[b]	Not provided	Health Canada, 2004a	2002

Table A1-3 Carcinogenic Exposure Limits for Arsenic						
Exposure Value	***Exposure Limit***	***Critical Effect***	***Description of Study***	***References***	***Source***	***Derivation Date***
Slope factor	**0.0015**	**Skin cancer prevalence rates**	**Human studies (data extrapolation)**	**Tseng *et al*., 1968; Tseng, 1977**	**U.S. EPA IRIS, 1998**	**1995**
Slope Factor	0.0015	Skin cancer incidence	Cal EPA adopted the U.S. EPA IRIS (1998) oral slope factor	Tseng *et al*., 1968; Tseng, 1977	Cal EPA, 2005	Not provided

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment.
[a] If the air concentration exceeds 2 µg/m^3 the inhalation unit risk factor of 4.3 x 10^{-3} (µg/m^3)$^{-1}$ should not be utilized.
[b] Although the TRV from the Canadian Guidelines for Drinking Water Quality supporting document is presented, it is recommended that the comparable TRV from the more recent assessment (Health Canada, 1996) be used for risk characterization
TCA Tolerable concentration in air (inhalation exposure)

Non-Carcinogenic TRVs

An acute REL (4 hour exposure time) of 0.19 µg/m^3 was derived for arsenic by Cal EPA (1999) for decreased fetal weight in mice during a developmental study (Nagymajténi *et al*., 1985). Mice were exposed to arsenious acid *via* inhalation for 4 hours on gestation days 9 through 11. 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 TRV for arsenic. A chronic REL value of 0.03 µg/m^3 was used as set by Cal EPA (2000) which represents the value below at which an adverse effect will occur (Collins *et al*., 2005). This value was derived from a study that examined maternal inhalation exposure in CFLP mice to 200 µg/m^3 of arsenic or 260 µg/m^3 of As_2O_3 for a 4 hour period per day during days of gestation. Reduction in fetal weight was observed with increased dose (Nagymajtenyi *et al*., 1985). The REL value derived in this study is supported with data from other animal studies (Kamil'dzhanov, 1982; Aranyi *et al.*, 1985). However, limitations of this REL include lack of human inhalation data, no observations at any concentration at which no observed effect was noted, as well as lack of comprehensive, long term, and multiple species studies. Also at lower doses, results from this study may not apply (Cal EPA, 2000).

MOE (2004) 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 limit for arsenic for the current assessment (Table A1-4). Cal EPA (2000) utilized the same study in order to derive a chronic REL of 0.03 µg/m^3 based on decreased fetal weight, retardation and malformations in mice from discontinuous inhalation exposure to arsenic. This value was selected for the current assessment (Table A1-4).

ATSDR (2007) has derived acute and chronic MRLs for inorganic arsenic. Due to the lack of suitable data, an intermediate oral MRL could not be derived. The acute oral MRL of 5 µg/kg-day was selected and is based on a LOAEL of 50 µg/kg-day for gastrointestinal effects and facial edema of a group of Japanese people who ingested arsenic contaminated soy sauce for a period of 2 to 3 weeks (Mizuta *et al*., 1956). An uncertainty factor of 10 was chosen based on a factor of 10 for the use of the LOAEL and 1 for human variability. In addition to the acute oral MRL, a chronic oral MRL of 0.3 µg/kg-day has also been derived by ATSDR (2007). It is based on a NOAEL of 0.8 µg/kg-day which was determined from the dermal effects seen in a

Taiwanese farming community that was exposed to arsenic in their drinking water (Tseng, 1977; Tseng *et al*., 1968). An uncertainty factor accounting for human variability of 3 is used (ATSDR, 2007). For the current assessment, an acute oral MRL of 5 µg/kg-day was selected as the acute oral exposure limit (Table A1-4).

The U.S. EPA IRIS (1993) derived an RfD of 0.3 µg/kg-day for inorganic arsenic based on hyperpigmentation, keratosis and possible vascular complications observed in a Taiwanese farming population exposed to arsenic *via* well water (Tseng *et al*., 1968; Tseng, 1977). The study NOAEL of 0.9 µg/L was the arithmetic mean of arsenic concentrations between 1 and 17 µg/L. This also included arsenic intake from food. This was converted to a NOAEL of 0.8 µg/kg-day using a drinking water consumption rate of 4.5 L and a body weight of 55 kg. An uncertainty factor of 3 was applied for the lack of data to exclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL accounted for all sensitive individuals. ATSDR (2007) and Cal EPA (2000) have also derived/adopted chronic oral exposure limits of 0.3 µg/kg-day. This value was selected as the chronic oral exposure limit for the current assessment (Table A1-4).

Cal EPA (2008) has recently released new arsenic non-cancer TRVs for the inhalation and oral routes of exposure based on neurobehavioural effects in children exposed *via* drinking water ingestion. The derived values are more conservative than any other existing non-cancer TRVs for arsenic. Both the oral and inhalation TRVs developed by Cal EPA (2008) are based on studies cited in Tsai *et al* (2003) and Wasserman *et al* (2004). Both of these studies focus on neurobehavioural endpoints, associated with consumption of arsenic-contaminated groundwater.

The Tsai *et al.* (2003) study is limited in that the sample size is quite small (49 children) and the standard deviation for such parameters as arsenic concentrations in well water and well water intake are larger than the mean, indicating large variability in the data. In addition, the Wasserman *et al.* (2004) study discounts the Tsai study as not controlling for important covariates and inconsistent results.

The Wasserman *et al*. (2004) study also reports experimental parameters (such as Arsenic well water levels, urinary Arsenic levels *etc*.) with standard deviations that are large or larger than the mean values, again indicating high amounts of variability. Additionally, the Wasserman *et al.* (2004) study has a few key limitations, including that the following:

- Well water concentration of Arsenic may not be a good indicator of exposure level since wells with over 50 ppb arsenic were labelled with skull and cross bones in 2001, in an attempt to limit use of the waters from these wells. Children were assessed after that time frame (2002), although home well concentrations were assumed for drinking water concentration;
- Interestingly, urinary arsenic measurements were taken at the assessment time, and therefore would provide proper indication of the child's overall arsenic exposure at time of assessment (including diet, smoking in the home, drinking water *etc*., which were not controlled for); however, there was no statistically significant association between urinary Arsenic and intelligence measurements; and,
- The testing of intelligence was modified to account for cultural issues. This makes parallels to the standard IQ test difficult, and the authors warn that the dose-response relationship in US children could be different given differences in education and the prevalence of malnutrition in Bangladesh.

Health Canada was consulted to obtain their opinion of these studies, and to understand whether these studies had been, or are currently being considered in the review of arsenic toxicity by Health Canada. R. Charron (Health Canada, 2009 pers. comm.) identified a number of the weaknesses that question the robustness of these studies, and suggest that these studies may not have adequately controlled for confounding variables. Mr. Charron also noted the high degree of variability and inconsistency in the results of these two studies. Mr. Charron indicated that until further research confirms the outcomes of these two studies, Health Canada would not rely heavily on these studies. Based on these comments, and an internal review of these studies, it was decided to reject these TRVs for the current HHRA.

A1-4.0 RELATIVE DERMAL BIOAVAILABILITY

The relative dermal bioavailability for arsenic in soil is 0.03 (Health Canada, 2004b). The permeability co-efficient in water is 0.001 cm/hr (U.S. EPA, 2004).

Table A1-4 Non-Carcinogenic Toxicological References Values for Arsenic

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
Inhalation (µg/m^3)									
REL; 4 hour exposure time	Acute	0.19	Decreased fetal weight in mice	Mouse developmental study (maternal inhalation exposure for 4 hours)	Nagymajtényi *et al*., 1985	LOAEL: 0.19 mg/m^3	1,000	Cal EPA, 1999	1999
AAQC; 24 hour averaging time	**Acute/ Chronic**	**0.3**	**Irritation, sensitization, immunosuppression teratogenesis, genotoxicity and carcinogenicity in exposed individuals**	**Not provided**	**Not provided**	**Not provided**	**Not provided**	**MOE, 2004; 2008**	**1981**
REL	**Chronic**	**0.03**	**Decreased fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations in mice**	**Mouse discontinuous inhalation exposure**	**Nagymajtényi *et al*., 1985**	**LOAEL: 0.33 mg/m^3**	**1,000**	**Cal EPA, 2000**	**2000**
Oral (µg/kg-day)									
MRL	**Acute**	**5.0**	**Gastrointestinal effects and facial edema**	**Japanese people who ingested arsenic-contaminated soy sauce for two to three weeks**	**Mizuta *et al.*, 1956**	**LOAEL: 0.05 mg/kg-day**	**10**	**ATSDR, 2007**	**Not provided**
RfD	**Chronic**	**0.3**	**Hyperpigmentation, keratosis and possible vascular complications**	**Human studies**	**Tseng *et al*., 1968; Tseng, 1977**	**NOAEL: 0.0008 mg/kg/day; LOAEL: 0.014**	**3**	**U.S. EPA IRIS, 1993**	**1991**

Table A1-4 Non-Carcinogenic Toxicological References Values for Arsenic

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
						mg/kg-day			
MRL	Chronic	0.3	Dermal effects and possibly vascular complications	Taiwanese farming population exposed from well water	Tseng *et al*., 1968; Tseng, 1977	NOAEL: 0.0008 mg/kg-day	3	ATSDR, 2007	Not provided
REL	Chronic	0.3	Hyperpigmentation, keratosis, and possible vascular complications	Adopted the U.S. EPA IRIS (1993)	Tseng *et al*., 1968; Tseng, 1977	NOAEL: 0.0008 mg/kg-day	3	Cal EPA, 2000	2000 (adopted)
TDI	Chronic	1.0[a]	Hyperpigmentation	Based on the PTWI proposed by WHO (1989)	Not provided	NOAEL: 2.1 µg/kg-day	2	RIVM, 2001	2001 (adopted)
PTWI	Chronic	2.0 (0.015 µg/kg-wk)	Not provided	Not provided	JECFA, 1983	Not provided	Not provided	JECFA, 1989; WHO, 1989	1989

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment
MRL Minimal risk level
TDI Tolerable Daily Intake
AAQC Ambient Air Quality Criteria
REL Reference Exposure Levels
RfD Reference Dose
PTWI provisional tolerable weekly intake
[a] The original value adopted in 1991 (Vermeire *et al*., 1991) was the PTWI derived by JEFCA (1989); however, an additional safety factor (2) was added in 2001

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APPENDIX A:

TOXICOLOGICAL PROFILES

Table of Contents

List of Tables

A2-1.0 CADMIUM

Cadmium has been reviewed by Health Canada (1986; 2004a; 2008); JECFA (1989); WHO (1990; 1992; 2000; 2005); U.S. EPA IRIS (1992; 1994); ATSDR (1999); Cal EPA (2000, 2005a,b); European Commission (2000); RIVM (2001); and, MOE (2006, 2008). The following profile represents a short summary of the relevant background information and human toxicity data for cadmium. A summary of the toxicity reference values selected for the HHRA is provided in Table A2-1.

Table A2-1 Summary Table of Toxicity Reference Values Selected for the HHRA

Route of Exposure	*Exposure Limit*	*Type of Limit*	*Toxicological Basis*	*Reference*	
				Study	*Regulatory*
Acute Effects					
Oral	4.1 µg/day	MADL	Reproductive toxicity	Not provided	Cal EPA, 2006
Inhalation (24 hour)	0.25 $\mu g/m^3$	URT	Kidney effects/cancer	Not provided	MOE, 2006; 2008
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	0.0098 $(\mu g/m^3)^{-1}$	Unit Risk	Detection of lung tumours	Takenaka *et al.,* 1983; Oldiges *et al*., 1984	Health Canada, 2004a; Health Canada, 2008
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	1 µg/kg/day	pTDI	Renal tubular dysfunction	WHO 2001; 2004 based upon Friberg *et al*., 1971	Health Canada, 2008
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA

NA Not applicable
MADL Maximum Allowable Daily Level
TDI Tolerable Daily Intake
URT Upper Risk Threshold
$_P$TDI Provisional Tolerable Daily Intake

A2-1.1 Background Information

Cadmium is a malleable, silvery-white metal. In the environment, cadmium exists in association with other elements, predominantly occurring as cadmium oxide (CdO), cadmium chloride ($CdCl_2$), cadmium sulphate ($CdSO_4$), and cadmium sulphide (CdS) (MOE, 2006). Cadmium and its compounds are relatively stable in the environment, and are not readily degraded. Cadmium bioaccumulates to a great extent in terrestrial and aquatic food chains (ATSDR, 1999). The solubility of cadmium in water varies depending on its form, with cadmium chloride and cadmium sulphate being the most soluble. In the atmosphere, cadmium occurs most commonly as cadmium oxide, while cadmium chloride exists to a lesser extent resulting from incineration. The vapour pressure of cadmium is very low; however, cadmium emitted from combustion processes is subject to long-range transport (ATSDR, 1999).

Cadmium compounds are used in the manufacture of industrial and consumer products. Primary uses include electrodes in batteries, pigments in plastic products, heat stabilizers for polyvinyl chloride, anti-corrosive metal coatings, and alloy components (ATSDR, 1999; MOE, 2006). Cadmium is released into the environment through industrial activity. It is a by-product of zinc and sulphide-ore processing, and is released from metal (zinc, lead, copper) mining processes (ATSDR, 1999). Fumes produced from the roasting of zinc ores and concentrates as well as from the precipitates obtained during the purification of zinc sulphate contain by-products of cadmium which may be recovered (ATSDR, 1999; CCME, 1999). Industries

associated with the manufacture of cadmium products are also a source of cadmium, as well as fossil fuel combustion, cement production, sewage sludge and domestic waste disposal, and phosphate fertilizer use (MOE, 2006). Cadmium occurs naturally in the earth's crust, and natural sources include volcanic eruptions, forest fires, and rock erosion (ATSDR, 1999).

Human exposure to cadmium occurs through the intake of food, water or accidental ingestion of contaminated dust or soil (Health Canada, 1986; NTP, 2005). Additional exposure may also occur through the inhalation of cigarette smoke, occupational sources, and ambient air (ATSDR, 1999; NTP, 2005). For non smokers, the principal source of cadmium is food. In the U.S. and Canada, food items have been found to contain approximately 2 to 40 ng/g cadmium (Dabeka and McKenzie, 1992, 1995; NTP, 2005). For smokers, cigarettes can be the principal source of cadmium (Friberg *et al*., 1986; NTP, 2005). Exposure to cadmium through drinking water and ambient air tends to be quite low (ATSDR, 1999). Cadmium concentrations in drinking water generally range from 0.01 to 1 µg/L and in more polluted areas, can be elevated up to 25 µg/L (Lauwerys *et al*., 1990; WHO, 1992; 2000). In air, concentrations of cadmium were found to range between 0.1 and 20 ng/m^3 for remote and urban areas in Europe, respectively (WHO, 2000). In soils, background concentrations in Canada range from non detectable to 8.1 µg/g (Whitby *et al*., 1978; Frank *et al.*, 1986). In areas near lead-zinc smelters such as in British Columbia, in the Columbia River Valley near the Comino smelter, average concentrations within a 10 km radius were 17.1 µg/g and in Flin Flon, Manitoba near the copper smelter, concentrations in garden soils were 3.2 to 13 µg/g (John, 1975; Pip, 1991). The Rouyn-Noranda smelter in Quebec, had cadmium levels within a 1 to 3.7 km radius of 54 to 66 µg/g in the top 15 cm (CCME, 1999). Cadmium is easily mobilized and assimilated into plants, and therefore, the consumption of food crops is typically an exposure pathway of concern (CCME, 1999).

A2-1.2 Fate and Transport

Cadmium is present in the atmosphere as suspended particulate matter in the oxide, sulphate and chloride forms which can travel large distances (*e.g*., >1,000 km) over a period of 1 to 10 days (Elinder, 1985a; Keitz, 1980). In the air, cadmium is stable and will not undergo photochemical reactions. Deposited cadmium onto surface waters is more mobile in this environment compared to other heavy metals (ATSDR, 1999). In water, cadmium is found as cadmium (+2) ion, Cd(OH), CdCO and in complexes; particularly with organic matter (McComish and Ong, 1988; NTP, 1991). Cadmium has a strong affinity for humic acids followed by CO_3^{2-}, OH^-, Cl^- and SO_4^{2-} and concentrations the water will be inversely proportional to the pH and the concentration of organic material present (Callahan *et al*., 1979). In aqueous environments, photolysis and biomethylation are not significant factors (Callahan *et al*., 1979; U.S. EPA, 1983). Cadmium partitioning to the sediment or soil is dependent on the amount of precipitation and sorption to mineral surfaces, hydrous metal oxides and organic materials which increases as the pH increases (Callahan *et al*., 1979). Sediment bacteria will also assist in the partitioning of cadmium from the water to the sediment (Burke and Pfister, 1988). Typically, concentrations in the sediment are at least one order of magnitude or higher than in the water column. Cadmium can redissolve into the water, depending on the pH, salinity and redox potential of the environment (Callahan *et al*., 1979; Eisler, 1985; Feijtel *et al*., 1988; Muntau and Baudo, 1992). Partitioning of cadmium to the air does not occur since no volatile compounds involving cadmium are formed in the water (Callahan *et al*., 1979). In soils, pH, oxidation-reduction and the formation of complexes are key factors affecting the mobility of cadmium (McComish and Ong, 1988; Bermond and Bourgeois, 1992; Herrero and Martin, 1993). Increasing pH levels will increase absorption which may make it unavailable for other sources, particularly if bound to organic materials rather than inorganic materials (Herrero and

Martin, 1993; McBride, 1995). Typically, 90% of cadmium found in soils lies in the top 15 cm (Anonymous, 1994 (Cited In: ATSDR, 1999).

Aquatic and terrestrial biota bioaccumulate cadmium (Health Canada, 1986; ATSDR, 1999). In crops, bioaccumulation varies from plant to plant (Kristensen *et al*., 1996) due to differences in the uptake of cadmium from the soil by the root system and differences in direct foliar uptake of surface deposited cadmium (ATSDR, 1999). Cadmium tends to accumulate primarily in the leaves of plants (He and Singh, 1994; Alloway *et al*., 1990). In the food chain, animals and humans will preferentially bioaccumulate cadmium in the liver and kidneys compared to the muscle tissues (ATSDR, 1999). The presence of acidic soil, in areas where acid rain is a concern, has been associated with enhanced cadmium uptake by plants and thus increased potential for bioaccumulation; potential leaching of cadmium into a water source is also enhanced at low pH levels (Callahan *et al*., 1979; Elinder, 1985a; 1992).

A2-1.3 Toxicokinetics

Absorption of cadmium through inhalation occurs in the alveoli if the particles are <0.1 µm. Therefore, cadmium from cigarette smoke has a greater potential for absorption than from aerosols due to the smaller particle size. On average, 50% of particles <0.1 µm will be deposited at the alveoli and 50 to 100% of these particles will be absorbed (Nordberg *et al*., 1985). Absorption does not appear to be dependent on solubility but rather dependent on the different forms of cadmium (Glaser *et al*., 1986; Rusch *et al.*, 1986). Ingested cadmium, largely passes through the gastrointestinal tract without being absorbed except for some of the cadmium which is trapped in the intestinal mucosa (Kjellstrom *et al*., 1978; Foulkes, 1984). Dermal absorption was studied in one *in vitro* study using human skin (Wester *et al.*, 1992) and does not appear to be a concern unless the skin is in contact for several hours with the cadmium compound (ATSDR, 1999).

Once absorbed, cadmium is distributed to all tissues however the liver and the kidney contain the greatest concentrations; approximately 40 to 80% of the entire body burden (Sumino *et al.*, 1975; Chung *et al.,* 1986; WHO, 2000). In the liver cadmium concentrations rise to 1 to 2 µg/g (wet weight) in adults of 20 to 25 years old and then slightly increase thereafter (Hammer *et al.,* 1973; Sumino *et al.*, 1975; Chung *et al.,* 1986; Lauwerys *et al.,* 1984). In the kidneys, concentrations of 40 to 50 µg/g (wet weight) are found in adults of 50 to 60 years old and concentrations either plateau or decline thereafter (Hammer *et al.,* 1973; Lauwerys *et al.,* 1984; Chung *et al.,* 1986). The placenta acts as a partial barrier to fetal exposure to cadmium; although levels of exposure have been found to vary (Kuhnert *et al*., 1982; Truska *et al.,* 1989). Cadmium levels in cord blood are half of what is present in the maternal blood (Lauwerys *et al.,* 1978; Kuhnert *et al.,* 1982; Truska *et al.,* 1989). Human milk contains 5 to 10% of the cadmium levels that are in the blood (Radisch *et al.,* 1987).

In terms of metabolism, cadmium does not undergo oxidation, reduction or alkylation (ATSDR, 1999). Cadmium (+2) does bind to proteins such as albumin and metallothionein to circulate in the plasma (Nordberg *et al.,* 1985; Foulkes and Blanck, 1990). Cadmium blood levels in the general population are generally <0.5 µg/100 mL (WHO, 2000)

Much of the cadmium that enters the body is excreted in the feces or urine (Kjellstrom and Nordberg, 1978).

A2-1.4 Biomonitoring

Exposure to cadmium can be measured in the blood, urine, feces, liver, kidney and hair (ATSDR, 1999). Recent cadmium exposure can be determined by measuring blood cadmium levels (Ghezzi *et al*., 1985; Jarup *et al*., 1988; Roels *et al*., 1989; Lauwerys *et al*., 1994). In populations not exposed to significant amounts of cadmium, blood cadmium levels range from 0.4 to 1.0 µg/L for non smokers and from 1.4 to 4 µg/L for smokers (Elinder, 1985b; Sharma *et al*., 1982). Environmentally exposed populations may have blood cadmium levels of 10 µg/L (Kido *et al*., 1990a,b; Shiwen *et al*., 1990). To detect chronic exposure to cadmium, urinary cadmium levels can be measured (Bernard and Lauwerys, 1986). Once cadmium-induced renal damage occurs however, urinary cadmium levels may increase sharply in response to intrarenal cadmium release and a decrease in renal reabsorption of cadmium (Roels *et al*., 1981; Lauwerys *et al*., 1994). Under these circumstances, urinary cadmium can also be reflective of recent exposure (Lauwerys *et al*., 1994). In non-smokers, average urinary cadmium has been measured at 0.35 µg/g creatinine and in environmentally or occupationally exposed populations, levels were up to 50 µg/g creatinine (Roels *et al*., 1981; Falck *et al*., 1983; Lauwerys and Malcolm, 1985; Tohyama *et al*., 1988; Mueller *et al*., 1989). Fecal matter can be measured for dietary exposure to cadmium since cadmium is poorly absorbed by the gastrointestinal tract (Kjellstrom *et al*., 1978; Adamsson *et al*., 1979). Liver and kidney tissues can also be measured to determine extent of cadmium exposure since these tissues preferentially bioaccumulate cadmium (ATSDR, 1999). Generally, cadmium concentrations measured from the kidney cortex peak around 50 to 60 years of age in an individual and have been measured to range from 25 to 40 µg/g in 60 year old north Americans who were environmentally exposed. Liver cadmium concentrations continue to increase over time and have been measured at 1 to 3 µg/g wet weight (Elinder, 1985b; ATSDR, 1999).

Cadmium concentrations measured from hair samples is controversial due to the potential for contamination (Huel *et al*., 1984; Shaikh and Smith, 1984; Wilhelm *et al*., 1990; Frery *et al*., 1993; Lauwerys *et al*., 1994). While correlations have been found between cadmium levels in mother and infant hair (Huel *et al*., 1984) and scalp and pubic hair (Shaikh and Smith, 1984), Frery *et al*. (1993) found that hair analysis was only reliable for determining high exposure to cadmium rather than low level exposure.

A2-1.5 Chemical and Physical Properties

Table A2-2 Chemical and Physical Properties

Chemical/Physical Property	***Value***	***Reference***
Colour/Form	Silver-white	Merck, 1989
Dissociation Constant (pKa)	Not provided	ATSDR, 1999
Henry's Law constant	No data	HSDB, 1996
Log K_{ow}	No data	HSDB, 1996
Molecular Weight	112.41	HSDB, 1996
Vapour Pressure	1 mm Hg at 394 ºC	HSDB, 1996
Water Solubility	Insoluble	Merck, 1989
Odour	Odourless	HSDB, 1996

A2-2.0 TOXICOLOGICAL SUMMARY: HUMAN HEALTH EFFECTS

Inhalation

Acute Effects

Symptoms of cadmium poisoning from occupational exposure to dust fumes include nausea, headache, vomiting, chills, weakness, diarrhoea, and pulmonary edema (Spolyar *et al.,* 1944). Pneumonitis has been documented at concentrations as low as 500 to 2,500 µg/m^3 over a 3 day exposure period (Hygienic Guides Committee, 1962). Beton *et al.* (1966) reported effects to the respiratory (pulmonary edema, pneumonitis) and renal systems (kidney necrosis) from a 5 hour occupational exposure to 8.6 mg/m^3 of cadmium oxide. At this concentration, the death of five workers resulted from respiratory failure (JECFA, 1989). WHO (2000) suggested a critical concentration of 5 µg/m^3 for occupational exposure (8 hour) to cadmium *via* inhalation.

Chronic Effects

There is ample evidence that chronic exposure to cadmium *via* inhalation affects the renal and respiratory systems. Incidence of proteinuria (9.2 to 100%), defined as proteinuria exceeding the 95th percentile of a population, has been reported at levels ranging from 23 to 67 µg/m^3 over a standardized occupational exposure of 30 years (Falck *et al*., 1983; Elinder*,* 1985b; Jarup *et al.,* 1988). Lauwerys *et al.* (1974) similarly report a LOAEL of 21 µg/m^3 (respirable cadmium) for proteinuria (68%) and declined measures in pulmonary function (*e.g.,* peak expiratory flow rate, forced vital capacity) in 22 men occupationally exposed to cadmium over 27.8 years. In the same study, proteinuria (15%) was observed in men exposed to respirable cadmium (88 µg/m^3) for 8.6 years. Kjellstrom *et al.* (1977) also found increased secretion of ß$_2$-microglobulin in battery factory workers exposed to cadmium in the workplace at concentrations estimated to range between 28 and 53 µg/m^3.

Protective gear (*e.g.,* mask) was not worn by the workers, and it was estimated that the lower end of the cumulative exposure concentration range would be 170 µg/m^3 if protective gear was worn. Ellis *et al.* (1985) calculated the probability of renal dysfunction (7%) at a concentration of 100 µg/m^3 for occupational exposure, and this was also quoted by Thun *et al.* (1991). Friberg *et al.* (1974) reported emphysema and renal disturbance resulting from chronic exposure at higher concentrations, ranging from 3,000 to 15,000 µg/m^3. Based on a review of available studies, European Commission (2000) and WHO (2000) cite the lowest estimate of the critical cumulative exposure to cadmium of 100 µg/m^3 for renal effects (proteinuira). Extrapolation to continuous lifetime exposure translates to 0.3 µg/m^3 (WHO, 2000).

Friberg (1950) reported deaths of two workers as a result of chronic occupational exposure at an average concentration of 6,800 µg/m^3. This was related to pneumonia and emphysema in one of the workers. Data available in regards to the developmental and reproductive effects of cadmium are sparse. A study by Salpietro *et al.* (2002) found that birth weight was inversely proportional to cadmium concentrations in cord blood resulting from inhalation exposure in pregnant women.

Oral

Chronic Effects

Renal damage resulted from exposure to an unknown form of cadmium from rice produced in a contaminated region of Japan (Nogawa *et al.,* 1989). It was estimated that elevated urinary $ß_2$-microglobulin would occur after a total intake of 2,000 mg cadmium over a lifetime, which corresponds to a 50 year dose of 2 µg/kg/day for a 53 kg person (ATSDR, 1999). Renal effects were also documented in a study by Shiwen *et al.* (1990), which found tubule interstitial lesions at 78 µg/kg/day resulting from environmental exposure estimated over 25 years. At this concentration, muscular, skeletal, and haematological effects were not found. The highest renal level of cadmium not associated with significant proteinuria was reported as 200 µg Cd/g wet weight of human renal cortrex by the U.S. EPA (1985a).

Other effects from chronic oral exposure to cadmium and its compounds have not been clearly demonstrated in scientific studies. Itai-itai syndrome, characterized by osteoporosis and osteomalacia, was documented in Japan in the mid-fifties, where cadmium intake in endemic areas was estimated at 600 µg/day (Schroeder, 1965). However, a clear dose-response effect was not demonstrated (RIVM, 2001). A relationship between chronic oral cadmium exposure and hypertension has been suggested in various studies, but results have proved to be inconclusive (Schroeder, 1965; Perry, 1969; NIOSH, 1977).

A2-2.1 Carcinogenicity

Cadmium and its compounds are classified by the IARC (1993) as Group 1 carcinogens. This indicates that cadmium is carcinogenic to humans based on sufficient evidence in humans and experimental animals (ATSDR, 1999; European Commission, 2000; MOE, 2006). NTP (2005) classified cadmium and compounds as being “known carcinogens”, indicative of sufficient information from human studies to indicate a causal relationship. This was recently updated from a less stringent classification of being “reasonably anticipated to be carcinogens,” based on limited evidence of carcinogenicity in humans (NTP, 2005). In the updated classification, NTP (2005) considered evidence from several epidemiological studies with associations between exposure and cancer of the prostate, bladder, and kidney. Cal EPA (2005a) classified cadmium as being known to cause cancer, based on extrapolation from human lung cancer data resulting from occupational exposure in a study by Thun *et al.* (1985). The U.S. EPA (1985b) listed cadmium and its compounds in Group B1, denoted as “probable human carcinogens “ due to sufficient evidence of lung cancer in laboratory animals (Takenaka *et al.,* 1983), but limited evidence of lung cancer in humans resulting from occupational exposure (Thun *et al.,* 1985). European Commission (2000) classified cadmium chloride, cadmium oxide, and cadmium sulphate as Group 2 carcinogens, being substances which “should be regarded as if they are carcinogenic to man”. Cadmium sulphide was classified in Group 3, indicating that it was a cause for concern in humans owing to possible carcinogenic effects, but lacking in evidence for a satisfactory assessment (European Commission, 2000). Cadmium and its compounds were classified as Group 2 Carcinogens by Health Canada (1996), listed as being “probably carcinogenic to humans” (MOE, 2006). For the current assessment cadmium was assessed as a human carcinogen *via* inhalation only.

A number of epidemiological studies have related respiratory cancer standard mortality ratios to cadmium exposure. Significantly increased risks of respiratory cancer deaths have been observed in occupational workers exposed to cadmium *via* inhalation (Lemen *et al*., 1976; Thun *et al*., 1985; Sorahan and Waterhouse, 1983; Varner, 1983; Armstrong and Kazantzis, 1983).

However, the strongest evidence of cadmium-induced carcinogenicity in humans is the study conducted by Thun *et al*. (1985) in which follow-up of an earlier study (Lemen *et al*., 1976) was conducted on a cohort of cadmium smelter workers. Thun *et al.* (1985) demonstrated a clear dose-response relationship between cumulative cadmium exposure *via* inhalation and the risk of death due to lung cancer. In addition, cadmium may also have a possible effect on prostate cancer (Lemen *et al*., 1976).

A2-3.0 TOXICOLOGICAL REFERENCE VALUES (TRVS)

Carcinogenic TRVs

Health Canada (2004a) derived an inhalation unit risk of 0.0098 $(\mu g/m^3)^{-1}$. This value was based upon the detection of lung tumours in a rat study (Takenaka *et al.,* 1983; Oldiges *et al*., 1984). Based on the Takenaka *et al*. (1983) study, WHO (2000) derived a unit risk of 0.092 $(\mu g/m^3)^{-1}$. The study involved inhalation of cadmium chloride in doses of 12.5, 25 and 50 $\mu g/m^3$ over a period of 23 hours/7 days a week for a duration of 18 months. U.S. EPA IRIS (1992) derived a unit risk of 0.0018 $(\mu g/m^3)^{-1}$ from the epidemiological data from the Thun *et al*. (1985) study, however this value was not considered reliable due to multiple confounding factors. The value derived by Health Canada was selected as the inhalation unit risk for cadmium in the current assessment (Table A2-3).

The MOE (2006) proposed a chronic Ambient Air Quality Criteria (AAQC) (annual averaging time) of 0.005 $\mu g/m^3$ which was based on the scientific approach used by the European Commission (2000). The value was derived by applying an uncertainty factor of 50 (5 use for a LOAEL and 10 for interspecies variability) to an adjusted LOAEL of 0.27 $\mu g/m^3$ for proteinuria associated with proximal tubular dysfunction and lung cancer as a result of workplace exposure (Thun *et al*., 1991). This value, which was consistent with the chronic inhalation RfC for cadmium recommended by the European Commission (2000) and WHO (2000), was not selected as the chronic inhalation exposure limit in the current assessment since it was based on a cancer endpoint , which is addressed through the Health Canada unit risk value (Table A2-3).

Table A2-3 Carcinogenic Exposure Limits for Cadmium

Reported Exposure Limit	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Source*	*Derivation Date*
Inhalation ($\mu g/m^3)^{-1}$						
Unit Risk	**0.0098**	**Detection of lung tumours**	**Rat study**	**Takenaka *et al.*, 1983; Oldiges *et al*., 1984**	**Health Canada, 2004a; Health Canada, 2008**	**1994**
Slope Factor $(\mu g/kg\text{-}day)^{-1}$	0.0429					
AAQC (proposed); annual averaging time	0.005	Kidney and cancer effects	Accepted the scientific approach adopted by European Commission (2000)	Thun *et al.,* 1991	MOE, 2006; 2008	2006
Unit Risk	0.092	Detection of lung tumours	Rat study	Takenaka *et al.,* 1983	WHO, 2000; U.S. EPA IRIS, 1992	1992
Unit Risk	0.0042	Lung cancer data	Occupational exposure (male)	Thun *et al.,* 1985	Cal EPA, 2005a	Not provided
Slope Factor $(\mu g/kg\text{-}day)^{-1}$	0.015					
Unit risk	0.0018	Lung, trachea, bronchus cancer deaths	Occupational exposure (human, male)	Thun *et al.,* 1985	U.S. EPA IRIS, 1992	1992

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment.

Non-Carcinogenic TRVs

The MOE (2006) has proposed a 24 hour AAQC for cadmium of 0.025 µg/m^3. This value was based upon the proposed annual average AAQC adjusted by a factor of 5. This value comes into effect in Ontario after February 2013. Until February 2013, the upper risk threshold value of 0.25 ugm^3 has effectively been adopted as the AAQC. This value was adopted as the 24 hour exposure limit for cadmium in the current assessment (MOE, 2008). In addition, MOE (2006) proposed a chronic AAQC (annual averaging time) of 0.005 µg/m^3 which was based on the scientific approach used by the European Commission (2000). The value was derived by applying an uncertainty factor of 50 (5 for use of a LOAEL and 10 for interspecies variability) to an adjusted LOAEL of 0.27 µg/m^3 for proteinuria associated with proximal tubular dysfunction and lung cancer as a result of workplace exposure (Thun *et al*., 1991). This value, which was consistent with the chronic inhalation RfC for cadmium recommended by the European Commission (2000) and WHO (2000), was not selected as the chronic inhalation exposure limit in the current assessment since it was based on a cancer endpoint, which is addressed through the Health Canada unit risk value.

ATSDR (1999) has not derived an acute oral minimal risk level (MRL) for the consumption of cadmium. A chronic oral MRL of 0.2 µg/kg-day based on renal effects on humans in a study by Nogawa *et al*. (1989) has been established (ATSDR, 1999). Cal EPA (2006) has derived a maximum allowable daily level (MADL) of 4.1 µg/day based on the oral intake of cadmium. The MADL was calculated by dividing the NOEL by 1,000. This value was adopted as the exposure limit for the acute oral pathway in the current assessment (Table A2-4). The U.S. EPA IRIS (1994) derived a chronic oral RfD for water consumption of 0.5 µg/kg-day. This value was based upon a NOAEL of 5 µg/kg-day for significant proteinuria in human studies involving chronic exposures (U.S. EPA, 1985a). An uncertainty factor of 10 was applied to account for interhuman variability. The U.S. EPA IRIS (1994) also derived a chronic oral RfD for diet of 1 µg/kg-day. 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. Health Canada (2008) have recommended a similar value for their provisional tolerable weekly intake (pTDI). This value, which was consistent with the chronic inhalation RfC for cadmium utilized by WHO (2005), was selected as the chronic oral exposure limit in the current assessment (Table A2-4).

A2-4.0 RELATIVE DERMAL BIOAVAILABILITY

The relative dermal bioavailability for cadmium in soil is 0.14 (Health Canada, 2004b). The permeability co-efficient for water is 0.00000058 cm/hr (U.S. EPA, 2004).

Table A2-4 Non-Carcinogenic Toxicological Exposure Limits for Cadmium									
Reported Exposure Limit	***Duration***	***Exposure Limit***	***Critical Effect***	***Description of Study***	***References***	***Endpoint***	***Uncertainty Factor***	***Source***	***Derivation Date***
Inhalation (µg/m^3)									
AAQC (URT); 24 hour averaging time	**Acute/ Chronic**	**0.25**	**Not provided**	**Not provided**	**Not provided**	**Not provided**	**Not provided**	**MOE, 2006; 2008**	**2006**
Annual guideline value	Chronic	0.005	Proteinuria associated with proximal tubular dysfunction, lung cancer	Exposure in the Workplace	Thun *et al.,* 1991	LOAEL (ADJ): 0.27 µg/m^3	50	WHO, 2000	1999
AQG	Chronic	0.005	Proteinuria associated with proximal tubular dysfunction, lung cancer	Exposure in the Workplace	Thun *et al.,* 1991	LOAEL (ADJ): 0.27 µg/m^3	50	European Commissio n, 2000	2000
REL	Chronic	0.02	Kidney effects and respiratory effects	Human occupational exposure	Lauwerys *et al.*, 1974	NOAEL (HEC): 0.5 µg/m^3	30	Cal EPA, 2000	2000
Oral (µg/kg-day)									
MADL (µg/day)	**Acute**	**4.1[a]**	**Reproductive toxicity**	**Value derived using the NOEL divided by 1,000 (for safe drinking water standards)**	**Not provided**	**Not provided**	**Not provided**	**Cal EPA, 2006**	**Not provided**
MRL	Chronic	0.2	Renal effects	Human studies	Nogawa *et al.,* 1989	NOAEL: 2.1 µg/kg-day	10	ATSDR, 1999	1999
RfD (water)	Chronic	0.5	Significant proteinuria	Human studies	U.S. EPA, 1985a	NOAEL: 5 µg/kg-day	10	U.S. EPA IRIS, 1994	1985

Table A2-4 Non-Carcinogenic Toxicological Exposure Limits for Cadmium									
Reported Exposure Limit	***Duration***	***Exposure Limit***	***Critical Effect***	***Description of Study***	***References***	***Endpoint***	***Uncertainty Factor***	***Source***	***Derivation Date***
TDI	Chronic	0.5	Renal tubular dysfunction	Prevention of kidney cadmium levels from exceeding 50 mg/kg in the renal cortex after continuous exposure for 50 years	Based upon the TDI established in by WHO-JECFA,1989; Vermeire *et al*., 1991	TDI: 1.0 µg/kg/day	2	RIVM, 2001	1999/2000
chRD	Chronic	0.011	Renal tubular dysfunction	Adult human study	Buchet *et al*., 1990	LOAEL 1 µg/kg-day	90	Cal EPA, 2005b	2005
pTDI	**Chronic**	**1**	**Renal tubular dysfunction (proximal tubule epithelial cell damage), manifested as low molecular weight proteinuria**	**Epidemiological occupational exposure**	**WHO 2004; 2001; based upon Friberg *et al*., 1971**	**NOAEL: 2.5 µg/g creatinine in urine**	**Not provided**	**Health Canada, 2008**	**Not provided**

Table A2-4 Non-Carcinogenic Toxicological Exposure Limits for Cadmium

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
RfD (food)	Chronic	1.0	Significant proteinuria	Human studies	U.S. EPA, 1985a	NOAEL: 10 µg/kg-day	10	U.S. EPA IRIS, 1994	1985
PTWI	Chronic	1.0 (7.0 µg/kg-wk)	Kidney effects: proteinuria	Value was established to prevent kidney cadmium levels from exceeding 50 mg/kg in the renal cortex after continuous exposure for 50 years	Task Group on Metal Toxicity, 1976	Not provided	Not provided	JECFA, 1989; WHO, 2005	1988

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment
[a] If a source/product results in multiple routes of exposure, therefore, the total exposure needs to be considered (Cal EPA, 2006).
MADL Maximum Allowable Daily Intake Level
MRL Minimal Risk Level
chRD Child Specific Reference Dose
TDI Tolerable Daily Intake
AAQC Ambient Air Quality Criteria
REL Reference Exposure Levels
RfD Reference Dose
AQG Air Quality Guideline
PTWI Provisional Tolerable Weekly Intake
URT Upper Risk Threshold

A2-5.0 REFERENCES

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APPENDIX A:

TOXICOLOGICAL PROFILES

Table of Contents

List of Tables

A3-1.0 COPPER

Copper has been reviewed by Health Canada (1990; 1992; 2004a,b; 2008); U.S. EPA IRIS (1991); Cal EPA (1999); IOM (2000); RIVM (2001); ATSDR (2004); and, MOE (2008). The following profile represents a short summary of the relevant background information and human toxicity data for copper. A summary of the toxicity reference values selected for the HHRA is provided in Table A3-1.

Table A3-1 Summary Table of Toxicity Reference Values Selected for the HHRA

Route of Exposure	*Exposure Limit*	*Type of Limit*	*Toxicological Basis*	*Reference*	
				Study	*Regulatory*
Acute Effects					
Oral	10 µg/kg-day	MRL	Gastrointestinal disturbances in women	Pizarro *et al*., 1999	ATSDR, 2004
Inhalation (1 hour)	100 µg/m^3	REL	Metal fume fever	Whitman, 1957; 1962; Gleason, 1968; ACGIH, 1991	Cal EPA, 1999
Inhalation (24 hour)	50 µg/m^3	AAQC	Health Effects	Not provided	MOE, 2008
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	90 (0-6 mo) 90 (7 mo-4 yrs) 100 (5-11yrs) 100 (12-19 yrs) 100 (20+) µg/kg-day	UL	Hepatoxicity, gastrointestinal effects	Pratt *et al.,* 1985; O'Donohue, *et al*., 1993	Health Canada, 2008
Inhalation	1.0 µg/m^3	TCA	Respiratory and immunological effects	Not Provided	RIVM, 2001
Dermal	NA		NA	NA	NA

NA Not applicable
REL Reference exposure level (derived from oral RfD)
AAQC Ambient Air Quality Criteria
TCA Tolerable Concentration in Air
UL Tolerable Upper Intake Level

A3-1.1 Background Information

Copper is a reddish-brown, odourless metal with four oxidation states (0, I, II and III). It occurs naturally in the environment in its metallic form or in minerals. In the environment, copper exists predominantly in the copper (II) oxidation state or as the cupric ion (ATSDR, 2004). Copper binds readily to organic and inorganic matter in soil, water and sediments, and is rarely present in its free form. Cu (II) is soluble in water, and in mildly acidic solutions (Cal EPA, 1999). Copper has a low potential for bioaccumulation in biota.

Copper is an important metal because of its durability, malleability, ductility, and thermal and electrical conductivity (ATSDR, 2004). Copper is primarily used in its metal form or as an alloy in construction, electrical products and systems, transportation equipment, and industrial equipment. Copper compounds are also used as fungicides, algicides, and repellents. Copper

sulphate is the mostly widely produced copper compound, and is utilized in various industrial and agricultural applications.

Copper is released into the environment as a result of mining activities (copper and other metals), combustion of fuels and wastes, wood production, fertilizer use and production, and landfills. The major release of copper to land is from tailings and overburdens from mines and sewage sludge. Natural sources of copper result from volcanoes, fires, decomposition of organic material, and sea spray (ATSDR, 2004). Mean copper concentrations in soils across the U.S. are dependent on the soil type and the land use and can range from 14 to 41 mg/kg (dry weight) (Fuhrer, 1986; Chen *et al*., 1999). In areas near smelter operations, where copper emissions are elevated, copper concentrations have been found to be approximately 2,480 ppm in the first 5 cm of top soil (Davis and Bennett, 1985). In the vicinity of the Sudbury smelter, maximum wetland soil/sediment copper concentrations were 6,912 ppm (Taylor and Crowder, 1983). In all cases near smelter operations, copper concentrations have been found to decrease with distance to the main stack (Taylor and Crowder, 1983; ATSDR, 2004).

Copper is an essential element in living organisms. Human exposure occurs primarily through regular consumption of food and water, and less readily through inhalation and dermal contact with air, water and soil (ATSDR, 2004). However, increased copper exposure tends to occur through drinking water. In the U.S., typical copper concentrations in drinking water are a few ppbs to 10 ppm. Increased exposure may also occur in smelter/mining areas where there are copper emissions through the inhalation of dust containing elevated levels of copper (ATSDR, 2004).

A3-1.2 Fate and Transport

Copper is released to the atmosphere adsorbed to particulate matter (PM) (Perwak *et al*., 1980). In the atmosphere, copper exists in the oxide form, particularly if it has originated from a combustion source (Schroeder *et al*., 1987). Copper can remain bound to PM in the troposphere for approximately seven to thirty days, during which time it may travel a considerable distance from its source (Perwak *et al*., 1980). Removal from the atmosphere occurs *via* gravitational settling as well as wet and dry deposition. The rate of removal is dependent on various factor including particle size, turbulence, and wind velocity (ATSDR, 2004). Copper particles settling onto surface waters will adsorb to organic matter, hydrous iron, manganese oxides and clay. Within the first hour, much of the copper will be adsorbed; however, a final equilibrium with the water column can be reached within 24 hours (Harrison and Bishop, 1984). Copper will also form complexes to organic matter and iron oxides in runoff similarly as it does in surface waters (Davies-Colley *et al*., 1984). A common form of copper in water is Cu (II) however if a stabilizing ligand is present, copper can be found as Cu_2S, CuCN and CuF (Kust, 1978; U.S. EPA, 1979). Ammonia and chloride ions tend to form stable ligands with copper, however, stable ligands can also be formed with the $–NH_2$, -SH and –OH groups of humic acids. Formation of these ligands will affect future adsorption, precipitation and oxidation-reduction reactions (U.S. EPA, 1979). In freshwater and seawater at pH levels ranging between 6.5 to 7.5, the major species of copper found include Cu^{2+}, $Cu(HCO_3)$ and $Cu(OH)_2$ (Stiff, 1971; Long and Angino, 1977). In general, the amount of dissolved copper is dependent on pH, oxidation-reduction potential, presence of competing cations and salts (ATSDR, 2004).

In sediment and soils, copper can adsorb to organic matter, carbonate minerals, clay minerals and/or hydrous iron and manganese oxides (U.S. EPA, 1979; Tyler and McBride, 1982; Fuhrer, 1986; Janssen *et al*., 1997; Petruzzelli, 1997). At pH levels greater than five, copper has been

found to adsorb to soils but at pH levels less than five copper remains in porewater and is mobile in the soil; therefore, increasing the occurrence of leaching into groundwater (Perwak *et al*., 1980; Luncan-Bouche *et al*., 1997). At sites where acid rain is a concern due to the SO_x emissions (*e.g*., smelter sites), soil pH levels may be lower therefore increasing the leachability of copper (Amrhein *et al*., 1992).

Copper has not been found to biomagnify at higher levels in the food chain, although there is some concern of bioconcentration at lower levels (*i.e.*, within molluscs) (Perwak *et al*., 1980; Bradley and Morris, 1986). In plants, copper is an essential nutrient and its uptake is dependent on the concentration and bioavailability of copper in the soil. Other factors that will influence copper uptake in plants includes root surface area, plant genotype, stage of plant growth, weather conditions, and interaction with other nutrients (Gupta, 1979; Clemens, 2001).

A3-1.3 Toxicokinetics

To date, no studies have been located which determine the rate and extent of absorption following inhalation exposure of copper to humans (ATSDR, 2004). Oral consumption of copper, leads to absorption into the system from the stomach and the small intestine. The site of maximum copper absorption for humans is unknown, however, it is suspected to be in the stomach and the duodenum (Bearn and Kunkel, 1955). Copper may be absorbed as ionic copper or bound to amino acids and a small concentration of copper is transported from the mucosal side of the intestine to the serosal side (Gitlin *et al*., 1960; Crampton *et al*., 1965). A greater portion of copper is absorbed *via* the absorptive surface and mucosal uptake followed by binding to metallothionein or another binding protein in the intestine (Evans and LeBlanc, 1976). Factors affecting copper absorption include the amount of copper in the diet, competition with other metals and age (Farrer and Mistilis, 1967; Hall *et al*., 1979; Haschke *et al*., 1986; Hoogenraad *et al*., 1979; Prasad *et al*., 1978; Strickland *et al*., 1972; Davies and Campbell, 1977; Turnlund *et al*., 1988; 1989; Varada *et al*., 1993). Generally, copper metabolism involves transfer to and from different organic ligands such as sulfhydryl and imidazole groups on amino acids and proteins. Specific binding proteins for uptake, storage and release have been identified for copper. In the liver, copper is bound to metallothionein and amino acids and can induce metallothionein synthesis as well as ceruloplasmin biosynthesis (Evans *et al*., 1970; Haywood and Comerford, 1980; Mercer *et al*., 1981; Wake and Mercer, 1985). From this point, copper can be slowly released from metallothionein to the bloodstream thereby eliminated *via* the bile or excreted when the mucosal cell is degraded (ATSDR, 2004). Dermal exposure to copper does not result in a great amount of exposure due to poor absorption of the copper through the skin as seen with *in vivo* and *in vitro* data (ATSDR, 2004; Pirot *et al*., 1996a,b).

A3-1.4 Biomonitoring

Exposure to levels of copper can be measured in the blood serum, urine, hair, toenails and liver (ATSDR, 2004). Chuttani *et al*. (1965) found increased serum levels; 239 to 346 µg/100 mL in individuals exposed to a single dose (1 to 30 g) of copper sulphate compared to non-exposed individuals; 151.6 µg/100 mL. However, increased serum levels may only be indicative of recent exposure (ATSDR, 2004). Exposure to copper may also be assessed through the examination of hair and toenails. Due to differing growth rates of hair and toenails, the first 2 cm of a hair strand (closest to the scalp) can be analyzed to measure copper exposure within the past two months and toenails can be used to determine exposure over the past 12 to 18 months (Hopps, 1977; Fleckman, 1985). In cases of excess copper intake, the liver has been a primary target and there have been reports of changes in the serum enzymes resulting from liver damage (Chuttani *et al*., 1965; Haywood, 1980; Haywood and Comerford, 1980; Epstein *et al*., 1982; NTP, 1993; Sugawara *et al*., 1995; Muller *et al*., 1998). In addition, increased levels of

bilirubin have also been detected however, changes in the liver are not necessarily unique to increased copper intake. Gastrointestinal issues including nausea, vomiting and abdominal pain have also been associated with excess intakes of copper. Although rare, copper deficiency may occur and indicators include hypochronic anemia, abnormalities of connective tissues and central nervous system disorders (ATSDR, 2004).

A3-1.5 Chemical and Physical Properties

Table A3-2 Chemical and Physical Properties of Copper

Chemical/Physical Property	*Value*	*Reference*
Colour/Form	Reddish	Lewis, 1997
Dissociation Constant (pKa)	Not provided	ATSDR, 2004
Henry's Law constant	No data	ATSDR, 2004
Log K_{ow}	No data	ATSDR, 2004
Molecular Weight	63.546	Lide, 2000
Vapour Pressure	1 (1,628 ºC)	Lewis, 2000
Water Solubility	Insoluble	Stewart and Lassiter, 2001
Odour	No data	ATSDR, 2004

A3-2.0 TOXICOLOGICAL SUMMARY: HUMAN HEALTH EFFECTS

Inhalation

Acute Effects

Occupational exposure to copper has resulted in "metal fume fever"; an acute (4 to 36 hour) illness characterized by fever, metallic taste in the mouth, aching muscles, headache, and dryness of the mouth and throat (ATSDR, 2004). Gleason (1968) observed symptoms of metal fume fever in workers exposed to 30 to 120 µg/m^3 copper dust for a number of weeks. A "sweet taste in the mouth" (consistent with symptoms of metal fume fever) was observed in workers upon exposure to 1,000 to 3,000 µg/m^3 copper fume for unspecified short periods of time (Whitman, 1957). Upper respiratory irritation occurred in addition to metal fume fever in workers exposed to copper cutting brass pipe with an electric cutting tool for 1 to 10 hours (Armstrong *et al.,* 1983). Ocular irritation was observed in factory workers exposed to copper dust for an unspecified duration (Askergren and Mellgren, 1975). In the majority of studies identified, co-exposure to other metals in addition to copper occurred (Cal EPA, 1999; ATSDR, 2004). An acute inhalation exposure level for copper was developed using the studies by Whitman, 1957; 1962; Gleason, 1968.

Chronic Effects

Copper irritates the respiratory system. Copper is considered the cause of "vineyards sprayer's lung" which is observed in workers spraying using an agent containing 1 to 2.5% copper sulphate (neutralized with lime) (Pimentel and Marquez, 1969). Symptoms include intra-aveolar desquamation of macrophages, formation of histiocytic and noncaseating granulomas with inclusions of copper (Pimentel and Marquez, 1969; Plamenac *et al.,* 1985). These studies were primarily based on case reports, and lack concentration-specific information. Suciu *et al.* (1981) reported pulmonary fibrosis and nodulation in workers exposed to concentrations of copper ranging from 111 to 434 mg/m^3 over a period of 1 to 3 years. Askergren and Mellgren (1975) observed vascularity and superficial epistatic vessels in the nasal mucosa of sheet metal workers exposed to unquantified concentrations of patina dust (a mixture of copper-containing compounds).

Several effects occurred in workers exposed to copper dust concentrations ranging from 111 to 434 mg/m^3 as a result of sieving copper for 1 to 3 years (Suciu *et al.,* 1981). Hepatic (hepatomegaly), neurological (headaches, vertigo, drowsiness), endocrine (seven cases of arterial hypertension, enlargement of sella turcica and nonsecretive hypophyseal), and reproductive (sexual impotence in 16% of workers) effects have been reported (Suciu *et al.,* 1981). The significance of health impairment by these endocrine and reproductive effects was not assessed in the study. Gastrointestinal (diarrhoea) effects were also observed with copper intoxication, but these may have been attributed to oral exposure. No reproductive or developmental effects in humans were reported to result from chronic inhalation exposure (Cal EPA, 1999; ATSDR, 2004).

Haematological effects such as decreased haemoglobin and erythrocyte levels were reported in workers exposed to copper concentrations of 640 µg/m^3 for an unspecified period of time (Finelli *et al*., 1981). However, workers were exposed to other metals and this was not taken into consideration in the study.

Oral

Chronic Effects

No human studies were located that identified adverse effects of chronic oral exposure to copper. The animal and human studies located relate to the acute and intermediate (15 to 364 days) effects of copper exposure (ATSDR, 2004).

A3-2.1 Carcinogenicity

IARC, ACGIH, NTP, U.S. EPA, Cal EPA and OSHA have not classified the carcinogenicity copper. For the purposes of this risk assessment copper was assessed as a non-carcinogen.

A3-3.0 TOXICOLOGICAL REFERENCE VALUES (TRVS)

Carcinogenic TRVs

Carcinogenic TRVs were not required as copper was evaluated as a non-carcinogen within the current assessment.

Non-Carcinogenic TRVs

The Cal EPA (1999) derived an acute REL for a 1 hour exposure of 100 µg/m^3 for copper. The critical effect was metal fume fever observed in workers occupationally exposed to copper for an unknown exposure duration (Whitman, 1957; 1962; Gleason, 1968; ACGIH, 1991). An uncertainty factor of 10 for intraspacies variation was applied to the study NOAEL of 1,000 µg/m^3. This value was adopted as the 1 hour acute exposure limit for copper for the current assessment (Table A3-3).

MOE (2008) lists an AAQC (24 hour average) of 50 µg/m^3 for copper, based on the protection of human health effects. No further information regarding the basis of this exposure limit was available; however, it was selected as the 24 hour TRV for copper.

RIVM (2001) derived a chronic TCA of 1.0 µg/m^3 for copper based on respiratory and immunological effects observed in rabbits during a sub-acute (6 weeks) inhalation study. The

study NOAEL of 600 µg/m^3 was adjusted for continuous exposure (6 to 24 hours, 5 to 7 days) and a safety factor of 100 for interspecies and intraspecies variation was applied. This value was selected as the chronic exposure limit for copper (Table A3-3).

ATSDR (2004) derived an acute oral minimal risk level (MRL) of 10 µg/kg-day and an intermediate oral MRL of 10 µg/kg-day to be protective of health effects from copper levels in drinking water. The acute MRL is based on a study where gastrointestinal disturbances were experienced in women who were ingesting 73.1 µg/kg-day of copper in drinking water over a 2 week period. A NOAEL of 27.2 µg/kg-day was derived and an MRL was calculated using an uncertainty factor of 3 to account for human variability. An intermediate MRL was derived based on the study where gastrointestinal disturbances in men and women were detected who were consuming 91 µg/kg-day of copper in drinking water over a 2 month period. A NOAEL of 42 µg/kg-day was determined and an MRL was calculated using an uncertainty factor of 3 for human variability. In the current assessment, 10 µg/kg-day MRL value was chosen as the acute oral exposure limit (Table A3-3).

IOM (2000) derived a series of tolerable daily intake levels (ULs) for different age groups. The ULs range from 1,000 for 1 to 3 year olds to 10,000 µg/day for adults (male weight: 76 kg; female weight: 61 kg). The ULs were determined using human studies by Pratt *et al*. (1985) and O'Donohue *et al*. (1993) where hepatotoxicity and gastrointestinal effects where noted in individuals consumping copper gluconate capsules for a given duration. Health Canada has indicated that the agency will officially adopt upper intake level (ULs) as toxicity reference values for all essential elements (Roest and Petrovic, 2005 pers. comm.) for contaminated sites human health risk assessments. The UL values adopted by HC are equal to those of IOM but have been adjusted for the duration of the life stage and body weight (Health Canada, 2008). These values were selected as the chronic exposure limit for the current assessment (Table A3-3).

A3-4.0 RELATIVE DERMAL BIOAVAILABILITY

The relative dermal bioavailability for copper in soil is 0.1 (Health Canada, 2004a). The permeability co-efficient in water is 0.003 cm/hr (U.S. EPA, 2004).

Table A3-3 Non-Carcinogenic Toxicological Exposure Limits for Copper

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
Inhalation (µg/m^3)									
REL; 1 hour exposure time	**Acute**	**100**	**Metal fume fever**	**Occupational**	**Whitman, 1957; 1962; Gleason, 1968; ACGIH, 1991**	**NOAEL: 1,000 µg/m^3**	**10**	**Cal EPA, 1999**	**1999**
Air Standard; 24 hour averaging time	**Acute/Chronic**	**50**	**Health effects**	**Not provided**	**Not provided**	**Not provided**	**Not provided**	**MOE, 2008**	**Not provided**
TCA	**Chronic**	**1.0**	**Respiratory and immunological effects**	**Sub-acute inhalation rabbit study**	**Not provided**	**NOAEC: 600 µg/m^3**	**100**	**RIVM, 2001**	**1999/2000**
Oral (µg/kg-day)									
MRL	**Acute**	**10**	**Gastrointestinal disturbances in women**	**Two week drinking water study**	**Pizarro *et al*., 1999**	**NOAEL; 27.2 µg Cu/kg-day**	**3**	**ATSDR, 2004**	**2004**
MRL	Intermediate	10	Gastrointestinal disturbances in men and women	Two month drinking water study	Araya *et al.,* 2003	NOAEL: 42 µg Cu/kg-day	3	ATSDR, 2004	2004
TDI	Chronic	30	Dietary copper intakes that "seem to be adequate and safe"	From CCME (1999) Soil Quality Guidelines	Health Canada, 1990	Not provided	Not provided	Health Canada, 2004b	1990

Table A3-3 Non-Carcinogenic Toxicological Exposure Limits for Copper

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
UL (µg/day)	Chronic	1,000 (1-3 yrs); 3,000 (4-8 yrs); 5,000 (9-13 yrs); 8,000 (14-18 yrs); 10,000 (≥19 yrs) (76 kg male, 61 kg female)[a]	Hepatoxicity, gastrointestinal effects	Ingestion of copper capsules (2 years (O'Donohue *et al*., 1993); 12 weeks (Pratt *et al.*, 1985)	Pratt *et al.,* 1985; O'Donohue, *et al*., 1993	NOAEL: 10,000 µg/day	None	IOM, 2000	2000
UL (µg/kg-day)	**Chronic**	**90(0-6 mo) 90(7mo-4 yrs) 100(5-11 yrs) 100(12-19 yrs) 100(20+, 70.7 kg)**						**Adjusted IOM (2000) values for life stage duration and body weight**	**Health Canada, 2008**
TDI	Chronic	140	Based on the maximum daily intake of the population	Not provided	Not provided	Not provided	Not provided	RIVM, 2001	1991

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment
MRL Minimal risk level
TDI Tolerable Daily Intake
REL Reference Exposure Levels
TCA Tolerable Concentration in Air
UL Upper Intake Level
[a] Health Canada has indicated that in 2005/2006, the agency will officially be using ULs as toxicity reference values for all essential elements (Roest and Petrovic, Health Canada, 2005 pers. comm.) for contaminated sites human health risk assessments

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APPENDIX A:

TOXICOLOGICAL PROFILES

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A4-1.0 LEAD

Comprehensive toxicity profiles for lead have been established by the following regulatory agencies: JECFA (1987); MOE (1994; 2006; 2007; 2008); WHO (1995; 2000); CCME (1999); RIVM (2001); Cal EPA (2001; 2005a,b); ATSDR (2007) and U.S. EPA (2007a,b; 2008). The following profile represents a short summary of the relevant background information and human toxicity data for lead. A summary of the toxicity reference values selected for the HHRA is provided in Table A4-1.

Table A4-1 Summary Table of Toxicity Reference Values Selected for the HHRA

Route of Exposure	*Exposure Limit*	*Type of Limit*	*Toxicological Basis*	*Reference*	
				Study	*Regulatory*
Acute Effects					
Inhalation (24 hour)	0.5 ug/m3	AAQC	neurological effects in children; weight of evidence	Not provided	MOE, 2007; 2008
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	3.6 µg/kg/day	pTDI	Behavioural effects and learning disabilities in children	Based upon the $_{P}$TWI derived by; Ziegler *et al.,* 1978 ; Ryu *et al.,* 1983; JECFA, 1987	Health Canada, 2004a; 2008
Inhalation (3 month averaging time)	0.15 ug/m3	AAQC	Protective of children and other at-risk populations	--	U.S. EPA, 2008
Dermal	NA		NA	NA	NA

NA Not applicable
pTDI Provisional Tolerable Daily Intake
AAQC Ambient Air Quality Criteria
$_{P}$TWI Provisional Tolerable Daily Intake

A4-1.1 Background Information

Lead is a naturally occurring metallic element that occurs in a variety of minerals, often in close association with zinc (CCME, 1999). Common lead-containing minerals include galena (lead sulphide), anglesite (lead sulphate), and cerussite (lead carbonate) (Schoof, 2003). While most of the lead found in the environment is the result of mining and smelting operations as well as combustion sources (Corrin and Natusch, 1977; U.S. EPA, 1986; Environment Canada, 1996; Spear *et al*., 1998), there are also significant natural sources including volcanoes, forest fires, sea spray, and weathering of lead-containing minerals (Environment Canada, 1996). Due to several desirable properties, including the ability to resist corrosion, lead has historically been used in a wide variety of products in both industrial applications and residential uses. Particularly lead-storage batteries for vehicles and general industry (*e.g*., piping, cable covering, bearing metals for machinery, and sheet lead, *etc*.) (ATSDR, 2007). Organic forms of lead have traditionally been used as additives in vehicle fuels (ATSDR, 2007).

Occupationally exposed populations are primarily exposed to lead through inhalation (with some lead ingestion), whereas the general population may be exposed to lead via food items, cigarette smoke, contaminated dust and/or soil present in food items as well as exposure to ink, paint and plaster which may contain lead (CCME, 1999; ATSDR, 2007). Absorption of lead into the body from these items can occur through inhalation, ingestion, dermal contact and for

foetuses, exposure through the placenta. In Ontario, Canada, lead levels in drinking water ranged from 1.1 to 30.7 µg/L with a median of 4.8 µg/L. This contributes to an average lead consumption from 1.5 L of drinking water of 7.2 µg for adults and 2.9 µg for children. Lead can be present in food items inadvertently through lead-soldered cans or through fall out of lead emissions onto the fruits and vegetables. For children, lead in soils and household dust can be a significant contributor towards exposure (U.S. EPA, 1986). In Canadian soils, background lead levels have been reported to range from 12 to 25 mg/kg.

Specifically, in the cordilleran region, lead levels have been detected at 16 mg/kg whereas in the Appalachian and Canadian shield levels have been at 21 mg/kg. Similarly, background lead levels for soils in the U.S. have been measured to range from < 10 to 30 µg/g (ATSDR, 2007). Conversely, soils in a boreal forest located less than 10 km from a copper-zinc smelter in Manitoba contained elevated lead levels (values not specified) in addition soils sampled from a distance of 35 km from the emission stack were also elevated (Hogan and Wotton, 1984). In Missouri, soils next to the smelter had greater concentrations of lead which were approximately 60,000 mg/kg (Palmer and Kucera, 1980). Soils which also contained elevated levels of lead were those beside roadways which have been found to be 30 to 2,000 mg/kg higher than natural levels but which decrease significantly the further away from the roadway (U.S. EPA, 1986). In Minneapolis/St. Paul, lead levels in the soils were 60 times higher (423 mg/kg) than those in rural Minnesota (6.7 mg/kg). Elevated lead levels near roadways have been attributed to the combustion of leaded gasoline (ATSDR, 2007). Other sources of lead include lead paint which results in lead levels greater than 10,000 mg/kg in soils next to homes with exterior lead pain (U.S. EPA, 1986).

A4-1.2 Fate and Transport

Lead is persistent in both water and soil. Elemental lead occurs rarely in the ambient environment; the most common form of lead in the environment is Pb^{2+}. Particulate-bound lead emitted from mining operations, smelters, and combustion sources occurs primarily in the form of lead-sulfur compounds such as $PbSO_4$, $PbO{\cdot}PbSO_4$, and PbS (Corrin and Natusch, 1977; U.S. EPA, 1986; Spear *et al*., 1998). However, in the atmosphere, lead exists primarily in the form of particulate-bound $PbSO_4$ and $PbCO_3$ (ATSDR, 2007; MOE, 2006). The average residence time of lead in the atmosphere prior to being deposited *via* wet or dry processes is 10 days (ATSDR, 2007; NAS, 1980). Generally, most of the lead is deposited within close proximity to emission sources on account of large particle size (>2 µm diameter) (WHO, 1995; ATSDR, 2007). Airborne lead particles associated with fine particles (<2 µm diameter),which account for 20% of the total lead particles emitted are transported at long-range, and have been detected in remote areas such as Greenland and areas in Canada far from any point sources (Evans and Rigler, 1985; WHO, 1995). Once in the environment, lead may transform, but does not degrade and cannot be destroyed (ATSDR, 2007).

Soil is a major sink for lead deposited from the atmosphere. The transport and bioavailability of lead in soils is largely a function of pH, organic matter, mineral composition, microbial activity, ion exchange capacity, and presence of inorganic colloids and iron oxides (CCME, 1999; ATSDR, 2007). Since lead is relatively immobile due to the complexes it forms with organic matter it has a long retention time in soil, therefore, causing it to remain in the upper surface horizons (5 cm) of the soil profile (WHO, 1995; U.S. EPA, 2006). Only a small proportion of lead in the upper portion of the soil is transported to surface or ground water. Mobility of lead in the soil is related to the solubility of lead, which is dependant on pH. Lead sorbed onto organic matter is readily dissolved in acidic conditions (U.S. EPA, 2006). In the pH range of 4 to 6, organic-lead complexes are soluble, and are subject to leaching and uptake by plants (WHO,

1995). Labile forms of lead are also associated with high chlorine content in soils, and colloid soil particles, such as Fe-Mn oxides (U.S. EPA, 2006).
In addition to the complexes formed and the pH of the soil, the mobility of lead in the soil also varies with the different forms of lead released into the environment. For example, lead chlorides, acetates, and nitrates are highly soluble, thus are readily transported through the soil (CCME, 1999). Metallic lead is insoluble, but can be oxidized into a more soluble form. Soil properties also affect the speciation of lead within the soil. In aerobic soils, lead compounds undergo weathering and may become more stable over time (CCME, 1999). In anaerobic soils, much of the sulphate is reduced to sulphide, thus the predominant form of lead in these soils is lead sulphide - a highly stable, insoluble and relatively non-reactive lead species. It is generally believed however, that the amount of free Pb^{2+} in solution best represents what is actually bioavailable to organisms (CCME, 1999). Generally, lead does not bioaccumulate in terrestrial or aquatic food chains (ATSDR, 2007).

Lead enters aquatic ecosystems through atmospheric deposition, runoff, and industrial wastewater. It exists in the form dissolved lead, suspended particulate, or sediment. The ratio of lead in suspended solids to the dissolved form in streams ranges from 4:1 to 27:1 (WHO, 1995; ATSDR, 2007). Lead partitions rapidly between sediment and water, depending on pH, salt content, and presence of organic matter (WHO, 1995). For example, in water with pH >5.4, solubility is greater in soft water (500 µg/L) as compared to hard water (30 µg/L) (ATSDR, 2007). The solubility of lead is also limited by sulfate ions in water with pH <5.4, and by lead carbonates in water with pH >5.4. The solubility of lead compounds increases due to complexation with organic compounds (*e.g.,* humic and fulvic acids) in surface waters (WHO, 1995).

The predominant chemical forms of lead in waterways are undissolved particles of PbO and $PbCO_3$ (WHO, 1995; MOE, 2006; ATSDR, 2007). At pH <7.5, lead exists as the divalent cation ($Pb2^+$), and complexes with organic matter to form $PbCO_3$ in alkaline water (ATSDR, 2007). Lead does not volatilize readily into the atmosphere from water. In sediment, lead is stable and has a long residence time, and this medium is major sink for lead (U.S. EPA, 2006). There are conflicting studies pertaining to the mobility of lead in sediments. Lead preferentially sorbs to small particles, and to sediment with high organic matter content. Iron and managnese oxides sequester lead, and this increases resuspension of lead into the water (U.S. EPA, 2006). Resuspension also occurs as a result of physical processes, releasing lead into the water in the form of suspended particulates (MOE, 2006). Lead does not biomagnify in aquatic ecosystems. In the aquatic food chain, lead concentrations are the greatest in benthic organisms and algae in comparison to top predators (ATSDR, 2007).

A4-1.3 Toxicokinetics

Absorption of lead via inhalation is dependent on the particle size, solubility and location of the deposited lead particles within the respiratory tract. Larger particles (>2.5 µm) are deposited in the ciliated airways and then transferred to the esophagus by mucociliary transport to be eventually swallowed. Smaller particles (<1 µm) are deposited into the alveolar region and absorbed after extracellular dissolution or after ingestion by phagocytic cells (ATSDR, 2007). If ingested, the degree of absorption of lead will be dependent on factors/status such as age, diet, and pregnancy as well as particle size, solubility and species of lead. In addition, the amount of lead absorbed may vary with the amount of lead ingested (ATSDR, 2007). Specifically, studies have shown that absorption of Pb is greater in children than in adults (Alexander *et al*., 1974; Ziegler *et al*., 1978; Rabinowitz *et al*., 1980; Heard and Chamberlain, 1982; James *et al*., 1985; Watson *et al*., 1986). In terms of dietary status, it was shown that absorption of lead is decreased significantly in individuals who have consumed a meal with the ingested lead

(Rabinowitz *et al*., 1980; Heard and Chamberlain, 1982; Blake and Mann, 1983; Blake *et al*., 1983; James *et al*., 1985; Maddaloni *et al*., 1998). As well, children and adults who were iron and calcium deficient also showed higher blood lead levels (Ziegler *et al*., 1978; Heard and Chamberlain, 1982; Blake and Mann, 1983; Mahaffey and Annest, 1986; Mahaffey *et al*., 1986; Marcus and Schwartz, 1987). Although increased blood lead levels have been observed in pregnant women, there is no direct evidence that it is due as a result of increased absorption but rather because of increased bone lead mobilization (Rothenberg *et al*., 1994; Lagerkvist *et al*., 1996; Schuhmacher *et al*., 1996; Gulson *et al*., 1997; 1998b; 2004).

The distribution of absorbed lead was found to be the same regardless of the route of entry into the body, in both children and adults (Chamberlain *et al*., 1978; Kehoe, 1987). In blood, most of the circulating lead (99%) is found in red blood cells, primarily bound to plasma proteins. Lead that is not protein-bound is found in complexes with sulfhydryl compounds and other ligands (Ong and Lee, 1980; Al-Modhefer *et al*., 1991; Schutz *et al*., 1996; Bergdahl *et al*., 1997; 1999; Hernandez-Avila *et al*., 1998; Manton *et al*., 2001; Smith *et al*., 2002). The half-life of lead in blood is approximately 30 days (Griffin *et al*.,1975; Rabinowitz *et al*., 1976; Chamberlain *et al*., 1978), therefore blood lead levels do not accurately reflect exposure that occurred more than six weeks prior to testing (Patrick, 2006). Lead in the body continues to circulate until it is either excreted or deposited in soft tissues including the liver, renal cortex, aorta, brain, lungs, and spleen, as well as the bones where the total body burden of lead is mainly stored (Hu *et al*., 1996a).

The half-life of lead in human bone is estimated to be up to 30 years (Ibrahim *et al*., 2006). In adults approximately 80 to 90% of retained lead is stored in bone. For children, less (~70%) is stored in bone, indicating that significantly more lead burden in children is in the soft tissues (Patrick, 2006). During infancy and childhood deposition of lead occurs in trabecular bone (high turnover); while in adulthood, both trabecular and cortical (tibia) bones are sites of deposition (Patrick, 2006). Lead stored in the bone generally increases in concentration with age and can be released back into blood over time (Schroeder and Tipton, 1968; Barry, 1975; 1981; Gross *et al*., 1975). Conditions that increase bone turnover (pregnancy, lactation, postmenopausal osteoporosis, hyperthyroidism and *cis*-platin chemotherapy) can mobilize stores of lead into circulation (Patrick, 2006). Bone lead can be transferred to a fetus during production of the fetal skeleton (Franklin *et al*., 1997; Gulson *et al*., 1997; 1999; 2003). Maternal lead can also be transferred to the fetus *via* cord blood or through breastfeeding (Goyer, 1990; Graziano *et al*., 1990; Carbone *et al*., 1998; Gulson *et al*., 1998a; Ettinger *et al*., 2006).

Metabolism of inorganic lead occurs *via* the formation complexes with both protein and non protein ligands such as albumen and non protein sulfhydryls as well, will form complexes with ALAD; an intracellular ligand in red blood cells. Lead may also form complexes with proteins in the cell nucleus and cytosol (ATSDR, 2007). The complexes that lead forms often cause interference with numerous physiological processes including haeme biosynthesis by inhibition of δ-aminolevulinic acid dehydratase (δ-ALAD), probably through its high affinity for the zinc-binding site in the enzyme. Although lead displaces zinc more readily in one of the alloenzymes of the protein, the relationship between the δ-ALAD genotype and sensitivity to lead at different blood lead concentrations remains unclear. Lead also causes an increase in zinc protoporphyrin, by a mechanism which is not fully established. Lead inhibits pyrimidine5′-nucleotidase, resulting in accumulation of nucleotides, and subsequent haemolysis and anemia (IARC, 2004).

Final excretion of lead from the body occurs primarily through urine and feces but may also include, although in minor amounts, sweat, saliva, hair, nails and breast milk (Hursh and Suomela, 1968; Hursh *et al*., 1969; Griffin *et al*., 1975; Rabinowitz *et al*., 1976; Chamberlain *et al*., 1978; Kehoe, 1987; Stauber *et al*., 1994).

A4-1.4 Biomonitoring

Human blood, hair, teeth, bone and urine are used as biomarkers of lead exposure. Blood is the most widely used and reliable indicator of lead exposure. Blood lead is typically used for short-term exposures on account of its relatively short half-life, which is approximately 36 days (ATSDR, 2007). Generally, time-integrated or longitudinal blood measurements are more reliable than a single blood measurement. For example, in a single blood measurement, low-level chronic exposure cannot be differentiated from short-term high-level exposure (WHO, 1995). Average blood levels in the general population, as reported in the National Health and Nutritional Examination Survey (NHANES IV), were 1.7 µg/L and 1.46 µg/L in children (1 to 5 years) and adults (≥20 years), respectively in 2001 to 2002 (CDC, 2005). Mean levels from occupational exposure are slightly greater than in the general population. The mean PbB level in adults from twelve workplace categories was 2.42 µg/L, with the highest means in construction workers (4.4 µg/L) and vehicle mechanics (4.8 µg/L) (Yassin *et al.,* 2004).

Bone is a good biomarker of cumulative lead exposure because it accumulates in the bone over a lifetime, with a half-life ranging from 12 to 27 years (U.S. EPA, 2006). A high proportion of the total body burden of lead occurs in bone, ranging from 90% in adults to 70% in children. Lead accumulates predominantly in trabecular bone in children, and in both trabecular and cortical bones in adults. Generally, cortical bone is a better indicator of lead exposure due to blood-bone lead exchange rates. Bone lead is remobilized and can contribute from 40 to 70% lead to the blood (U.S. EPA, 2006). During pregnancy, lactation, menopause and in cases of osteoporosis, bone lead is also mobilized and increases the lead levels in the blood (U.S. EPA, 2006). Like bones, teeth are also useful in assessing long-term lead exposure. Tooth enamel is indicative of *in utero* exposure, while dentin lead reflects exposure postnatal exposure up until the time that the tooth is shed (U.S. EPA, 2006). Unlike bone, lead in teeth does not significantly contribute to lead body burden. Due to the high variability in lead levels from tooth analysis as well as moderate correlations between blood and tooth lead, teeth are not used as a biomarker for regulatory policy of lead exposure or toxicity (Mushak, 1991; U.S. EPA, 2006).

Urinary lead has been used as in indicator of current lead exposure. It is not regarded as a reliable biomarker due to low and fluctuating levels of lead (WHO, 1995). However, after administration of a chelating agent ($CaNa_2$-ETDA), urinary lead is considered to be an excellent measure of the toxic fraction of the total body burden of lead. Chelatable lead that is excreted in urine is representative of lead removal from soft tissues, blood, and bone (WHO, 1995). It has been used to confirm elevated lead body burden (ATSDR, 2007). Average levels of lead in urine in the general population, as reported in the National Health and Nutritional Examination Survey (NHANES IV), were 0.92 and 0.66 µg Pb/g-creatinine in children (6 to 11 years) and adults (≥20 years), respectively in 2001 to 2002 (CDC, 2005).

Levels of lead in hair have been used as an indictor of exposure in children and also in some epidemiological studies (WHO, 1995; U.S. EPA, 2006). Lead has been correlated with liver and kidney concentrations in occupational studies (Gerhardsson *et al.,* 1995a). Overall, lead in hair is not considered to be a useful biomarker of lead exposure. This is primarily due to variations caused by different hair colors, textures, growth phases, and chemical treatments (WHO, 1995). Levels of lead measured in hair are variable. Average levels were reported at 2.42 µg/g in the adult general population in the U.S. (DiPietro *et al*., 1989). Levels were higher in children

residing in towns in close proximity to smelter and battery operations in Russia (5.4 µg/g) (Esteban *et al.,* 1999). Levels of 8.0 and 2.6 µg/g were reported in active and retired workers, respectively (Gerhardsson *et al.,* 1995a).

Numerous studies have associated blood lead levels with deleterious health effects. Various agencies (U.S. EPA, 2004; CDC, 2005) have identified 10 µg/dL as a level of concern. This is not a definitive toxicological threshold, but is indicative of the need to mitigate risk in individuals already exposed (Wilson *et al.,* 2005). Levels of lead in environmental media are typically used to predict blood lead concentrations for human health assessments of lead-contaminated sites (ATSDR, 2007). As a result, blood lead concentrations can be used to evaluate health effects or derive suitable guidelines. Tools developed by regulatory agencies that are used to relate environmental lead exposure to blood lead concentrations include the ATSDR slope factor approach, the U.S. EPA IEUBK model, and the Leggett and O'Flaherty models (U.S. EPA, 2006; ATSDR, 2007).

A4-1.5 Chemical and Physical Properties

Table A4- 2 Chemical and Physical Properties

Chemical/Physical Property	*Value*	*Reference*
Colour/Form	Bluish-gray/solid	HSDB, 2007
Dissociation Constant (pKa)	Not provided	ATSDR, 2007
Henry's Law constant	No data	HSDB, 2007
Log K_{ow}	No data	HSDB, 2007
Molecular Weight	207.2	HSDB, 2007
Vapour Pressure	1.77 mm HG at 1,000 ºC	HSDB, 2007
Water Solubility	Insoluble at 25 ºC	HSDB, 2007
Odour	Odourless	HSDB, 2007

A4-1.6 Toxicological Summary: Human Health Effects

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). Generally, effects from chronic exposure are primarily neurological, renal, hematological, reproductive, and developmental (ATSDR, 2007; CDC, 1991). Well-characterized human health effects include neurotoxicity and renal toxicity, which can be severe at blood lead levels greater than 120 µg/dL (U.S. EPA, 1986). Severe lead exposure in children (PbB above 380 µg/dL) can cause coma, convulsions, and even death.

Clinical signs of lead toxicity, generally manifested as neurotoxicity and anaemia, are evident at PbB levels of 70 µg/dL and greater (IARC, 2004). 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 (U.S. EPA IRIS, 2004). The effects in children often manifest as decreased IQ and memory, decreased gestation period, and retarded growth rate. While the debate as to whether or not a threshold exists for the cognitive effects of lead in children continues, there is consistent information from the available lead health effects literature indicating that childhood PbB levels >10 µg/dL are linked to decreased intelligence and impaired neurobehavioral development (WHO, 1995; CDC, 2004; Lanphear *et al*., 2005; U.S. EPA IRIS, 2004; ATSDR, 2007).

Anaemia and altered blood enzyme levels or activity have been commonly correlated to elevated PbB concentrations in the scientific literature. However, haematological effects are less sensitive endpoints for lead toxicity than neurological, neurodevelopmental, and neurobehavioural effects. The severity of anaemia resulting from lead exposure is linearly related to PbB concentrations (Landrigan, 1989). Anaemia, resulting from reduced hemoglobin production and damage to erythrocytes, has been observed in adults with blood lead levels of 80 µg/dL and in children at PbB levels of greater than 70 µg/dL (U.S. EPA, 1986; Goyer, 1989).

A4-1.6.1 Pediatric Toxicity

Central neurotoxicity is the most common manifestation of pediatric lead toxicity (Ibrahim *et al.*, 2006). At lower levels (1 to 50 µg/dL) lead may cause subtle cognitive and behavioral changes; however these may be difficult to differentiate from normal developmental variance (Canfield *et al.*, 2003). At moderate levels (50 to 70 µg/dL) children may display a global decrease in activity (Ibrahim *et al.*, 2006). These symptoms have been classified as pre-encephalopathic symptoms and are most prominent between one and five years of age. Conditions of severe lead toxicity (>70 µg/dL) in children produce a variety of encephalopathic symptoms including with coma, seizures, altered mental status, and symptoms consistent with increased intracranial pressure (Ibrahim *et al.*, 2006). Typically, children at stages when they are most actively investigating their environment using oral sensory stimulation (between the ages of 15 and 30 months) are most commonly the victims of lead-related encephalopathy.

Other symptoms of childhood lead toxicity include anemia; peripheral motor neuropathy; GI complaints, such as anorexia, vomiting, and abdominal pain; and growth delay (Ibrahim *et al.*, 2006). Lead readily crosses the placenta and has been reported to cause fetal toxicity (Lockitch, 1993). Acute lead exposure resulting in central neurotoxicity disrupts the intercellular junction, interfering with cellular calcium metabolism. This may render the blood-brain barrier less effective and thereby causing the capillaries leak, leading to an increase in intracranial fluid and a resultant increase in intracranial pressure (Ibrahim *et al.*, 2006).

Other main toxic effects of lead in children include effects on the function of the haematologic system through (1) reduction of erythrocyte lifespan; and, (2) decreased hemoglobin biosynthesis. Lead also interferes with several enzymes in the haeme synthesis pathway (Ibrahim *et al.*, 2006).

A4-1.6.2 Adult Toxicity

Lead poisoning in adults generally is related to occupational respiratory exposures. Lead-induced hypertension is the most common symptom attributed to lead exposure in adults, but patients can also develop anemia, gastric colic, muscle and joint pain, decreased fertility, renal failure, and peripheral motor neuropathy (Hu *et al.*, 1996a; Ibrahim *et al.*, 2006; Patrick, 2006). Adults affected by lead commonly suffer from subtle neurologic deficits, such as fatigue and mood swings.

A4-1.6.3 Renal Damage and Lead

Renal manifestations of acute lead poisoning include increased glucose, amino acids and phosphate in urine. Long-term environmental exposures or the chronic release of deposited bone lead is presumed to be responsible for progressive development of renal failure. Lead nephropathy has been documented in occupationally exposed workers. Proximal tubular damage, glomerular sclerosis and interstitial fibrosis have all been reported (Patrick, 2006). . Chronic exposure to low concentrations of lead is associated with increased urinary excretion of

low-molecular-weight proteins and lysosomal enzymes. Chronic exposure to high concentrations of lead results in interstitial fibrosis, glomerular sclerosis, tubular dysfunction, ultimately leading to chronic renal failure (Ekong *et al.*, 2006).

The relationship between lead and chronic kidney disease (CKD) has been reviewed by Ekong *et al.* (2006). Findings of their review suggested that significant associations were limited to susceptible populations (diabetics and hypertensives) (Tsaih *et al.*, 2004; Ekong *et al.*, 2006). Hypertensive subjects also emerged as a susceptible group in National Health and Nutrition Examination Survey data (Muntner *et al.*, 2003). Higher blood lead levels remain associated with a higher burden of chronic kidney and peripheral arterial diseases among the overall population and with hypertension among non-Hispanic blacks and Mexican Americans with end stage renal disease (ESRD) (Muntner, *et al.*, 2005; Muntner *et al.*, 2007).

Additional epidemiology studies have indicated an association between lead exposure and adverse renal effects. Evidence of renal tubular dysfunction in children living in the vicinity of lead smelters has been reported (Bernard *et al.,* 1995; Verberk *et al.,* 1996). Renal tubular dysfunction is also seen in males with osteoporosis who have been occupationally-exposed to lead (Sun *et al*., 2008). Renal damage and osteoporosis was demonstrated by the stable relationship between concentrations of various enzymes serving as biomarkers that increased concomitantly with a decrease in bone density. Evidence of osteoporosis was initially associated with BPb >8 µg/dL and an elevation in serum concentrations of alkaline phosphatase. Changes in other enzyme functions specifically associated with increased risk of osteoporosis and increased bone metabolism were associated with BPb in excess of 10 µg/dL in the population (n=211) (Sun *et al.*, 2008).

A4-1.6.4 Hypertension and Lead

There is currently scientific debate as to whether there is a causal relationship between PbB and adverse cardiovascular outcomes such as hypertension (ATSDR, 2007). Occupationally exposed populations with PbB levels of between 30 to 120 µg/dL experienced hypertension, increased heart rate and increased blood pressure (Pollock and Ibels, 1986; Weiss *et al*., 1986, 1988; de Kort *et al*., 1987; Marino *et al*., 1989). However, these studies all had small cohort sizes (n<100) and failed to control for at least one confounding factor (ATSDR, 2007). A number of other studies have failed to find a strong correlation between PbB and cardiovascular effects (WHO, 1995; ATSDR, 2007). Other studies that have investigated cardiovascular endpoints associated with lead (Jain *et al*., 2007) have been recently reviewed (Navas-Acien *et al*., 2007). Despite the uncertainties, these authors inferred a causal relationship between lead exposure and hypertension; however, the shape of the concentration-response relationship for lead and blood pressure is incompletely characterized. The lowest level of lead exposure not associated with alteration of blood pressure is unknown, although in the available studies there seems to be no evidence of a threshold effect (Hertz-Picciotto and Croft 1993; Schwartz *et al*., 2001; Navas-Acien *et al*., 2007).

In a cohort of middle-aged to elderly men selected for the Normative Aging Study, a family history of hypertension was the factor most strongly associated with hypertension (Hu *et al.*, 1996a). Other important factors associated with hypertension in this cohort were body mass index and tibia lead (Hu *et al.*, 1996a). Additional factors such as smoking, alcohol consumption, dietary sodium and calcium and age did not significantly influence risk of hypertension in this population. Hu *et al.* (1996a) concluded that the hypertensive effect of lead may be a cumulative lifetime dose. There was general consensus that overall the data support an association between increasing blood lead and blood pressure (Nawrot *et al.*, 2002; Navas-Acien *et al.*, 2007). Since studies have shown that patella lead is significantly correlated with

blood lead (Hu *et al.*, 1996b; Weaver *et al.*, 2005), patella lead might also be expected to be positively associated with changes in blood pressure.

Investigation of the association between bone lead levels and adverse cardiovascular outcomes has been examined in efforts to determine whether lead-associated elevations in blood pressure reflect acute responses to blood concentrations or rather chronic effects associated with cumulative dose (Glenn *et al.*, 2006). Contrasting results have been found. Glenn *et al.*, (2006) investigated changes in systolic blood pressure associated with lead in blood and bone in a lead-exposed occupation cohort (n=575) and found that while both cross-sectional and longitudinal blood lead variables predicted a relatively small increase in systolic blood pressure (1 mm Hg per 10 µg/dL increase in BPb) associated with this acute pathway, average annual change in diastolic blood pressure was not predicted by tibia lead dose (the chronic accumulation of lead in the cortical bone). Navas-Acien *et al.*, (2008) however, concluded from a meta-analysis of data from eight studies (3 prospective studies and 5 cross-sectional studies) examining the relation between lead detected in tibia and patella bone and changes in blood pressure, that systolic blood pressure and hypertension risk *were* associated with lead levels in tibia bone, although the magnitude of the summary estimates was small. A 10 µg/g increase in tibia lead described in the five cross-sectional studies produced increases in blood pressure of 0.26 mm Hg for systolic and 0.02 mm Hg for diastolic. The relative contribution of bone and blood lead levels was not examined, nor was the evaluation of non-linear dose-response relationships, as the study was conducted using published literature (Navas-Acien *et al.*, 2008).

A4-1.6.5 Cardiovascular Disease Outcomes Plausibly Associated with Lead

Exposure to lead is associated with cardiovascular effects and with changes in endocrine and immune functions. Many of the effects of lead exposure in humans have been confirmed in experimental systems. At the cellular level, lead has mitogenic properties; it affects various regulatory proteins, including those that depend on the presence of zinc.

A longitudinal study of middle-aged and elderly men followed over a period of 10 years reported that the risk of future ischemic heart disease (IHD) increases significantly with increasing bone and blood lead levels, after adjusting for potential confounders (Jain *et al.*, 2007). When blood lead level was examined, the proportion of IHD cases with a blood lead level ≥5 µg/dL was significantly higher than non-cases. A higher proportion of cases were in the highest tertile of tibia and patella lead level compared with non-cases (for tibia lead: 38.1% cases compared with 32.7% non-cases; for patella lead: 49.2% cases compared with 30.8% non-cases). No dose response was established for tibia and patella lead levels bringing the value of this metric as a predictor of cardiovascular risk at lower dose (bone Pb accumulation) levels into question.

A4-1.6.6 Osteoporosis and Lead

Evidence for osteoporosis in addition to renal damage was provided by the stable relationship between concentrations of enzymes that increased concomitantly with a decrease in bone density (Sun *et al.*, 2008). Evidence of renal tubular dysfunction (but not glomerular dysfunction) was associated with lead-exposed individuals who also experienced osteoporosis (p=0.004) (Sun *et al.*, 2008). Results showed that there was a dose-response relationship between BPb and indicators of renal dysfunction/osteoporosis that was supported by calculated $BMDL_{05}$ values for alkaline phosphatase, urinary *N*-acetyl-β-D-glucosaminidase (NAG), serum ostocalsin and urinary hydroxyproline. Each of these indicators appeared prior to concentrations of blood Pb associated with osteoporosis (14.17 µg/dL). Changes in other enzyme functions specifically associated with increased risk of osteoporosis and increased bone metabolism were associated with BPb in excess of 10 µg/dL (Sun *et al.*, 2008).

A4-1.6.7 Neurotoxicity and Lead

A considerable body of evidence suggests that children are more sensitive than adults to the neurotoxic properties of lead. Although clinical symptoms of toxicity generally become apparent at blood lead concentrations of 70 µg/dL, many important neurological disturbances occur at much lower concentrations. These include electrophysiological anomalies of evoked brain potential in response to auditory stimuli and reduced peripheral nerve conduction (Ibrahim *et al.*, 2006).

Both cross-sectional and prospective studies of children have found impairments in cognition, attention, and language function at low concentrations of lead. In studies with larger samples, better measures of lead burden and neurobehavioural function, and more advanced statistical techniques, effects are detectable at BPb concentrations below 10 µg/dL. The relative effect is greater below 10 µg/dL than above this level (Canfield *et al.*, 2003). Recently, attention has shifted from the impact of lead on cognition to its effects on behaviour. Exposure to lead has been found to be associated with attention deficit disorders, aggression, and delinquency

The reliance on blood lead level as the index of exposure presumes that whole blood lead level is a precise and valid surrogate index of brain lead level (Bellinger, 2007). This generalization leads to some exposure misclassification since whole blood lead is less representative than plasma blood level when effects in different tissue compartments are assessed. As concern for exposure level shifts to the expected effects of lower and lower levels of Pb, the inferences of biological outcome for a specified dose are directly affected by the imprecision of tissue distribution, and the degree to which peripheral biomarkers can reflect dose at the critical target organ (Bellinger, 2007).

In a cross-sectional study of 400 six to 10 year olds, children with blood lead levels of 5 to 10 µg/dL scored lower than children with levels of 1 to 2 µg/dL on academic skills (not IQ) such as word reading, reading comprehension, listening comprehension, math reasoning and math calculations (Surkan *et al.*, 2007)

Childhood lead exposure has linked changes in brain morphology and gray matter volume to prolonged lead exposure through the use of brain imaging technology (Cecil *et al.*, 2008). The study's participants, now 19 to 24 years old, were recruited shortly after birth from areas of inner-city Cincinnati (Cincinnati Lead Study (CLS) cohort). Detailed blood lead histories were assembled prospectively, beginning before birth through age six years. Cecil *et al.* (2008) reported that increased childhood blood lead concentration was consistent with lead exposure resulting in permanent structural impairment of cortical development and maturation. The largest area of significant brain volume loss detected in adults was in medial portions of the prefrontal cortex; this loss was associated with childhood lead exposure. During the first five years of life, at least one of the quarterly blood lead assessments exceeded 10 µg/dL for 99% of the cohort. By adolescence, the mean blood lead concentrations for the cohort were 2.8 µg/dL (SD 1.3 µg/dL) (Cecil *et al.*, 2008). Dose-dependent decreases in cortical volume of gray matter were found in the ventrolateral prefrontal cortex, the anterior cingulate cortex, the postcentral gyri, the inferior parietal lobule, and the cerebellum. Reduced volumes in the prefrontal cortical areas were particularly striking in males (Bellinger, 2008; Cecil *et al.*, 2008).

In this same CLS cohort violent offenses, drug offenses, theft or fraud, obstruction of justice, serious motor vehicle offenses, and disorderly conduct since the age of 18 years were correlated with BPb. The covariate-adjusted rate ratios for number of arrests associated with each 5 µg/dL increment were modest, but statistically significant, for prenatal childhood blood lead and blood lead at six years of age (Wright *et al.*, 2008). Others have reported associations between increased lead exposures and attention deficit hyperactivity disorder (ADHD) (Braun *et al.*, 2006). Analysis of data from the third National Health and Nutrition Examination Survey (NHANES-III) found that children (boys) with higher blood lead concentrations were significantly associated with a diagnosis of ADHD. Children with blood lead concentrations greater than 2 µg/dL were at a 4.1-fold increased risk of ADHD (Braun *et al.*, 2006).

A4-1.6.8 Blood Lead and IQ

Canfield *et al.* (2003) found BPb was inversely and significantly associated with IQ. Each increase of 10 µg/dL in the lifetime average blood lead concentration was associated with a 4.6 point decrease in IQ (p=0.004). By contrast, children whose maximal lead concentrations remained below 10 µg/dL experienced a change in IQ greater than the rate of decline shown for children with higher BPb. In this subsample of 101 children with low level BPb, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 µg/dL (the same increment described above). Canfield *et al.* (2003) interpreted these results as putting a greater number of children at risk of loss of intellectual function, particularly those who were presumed "safe" based on recognized intervention criteria (BPb <10 µg/dL) who would now be expected to show greater susceptibility to the adverse effect of Pb on IQ.

In a similar study, Jusko *et al.* (2008) recruited children (n=174) born between July, 1994 and January, 1995 who had previously been enrolled in a residential dust-control trial and lived in Rochester, New York. Multiple venous blood samples were taken (at six, 12, 18, 24, 36, 48, 60, and 72 months of age). Associations between measured BPb and IQ were evaluated in the cohort. At the 6-year assessment 92% of children had measured blood lead concentrations <10 µg/dL. Fifty-five percent of children never had a measured blood lead concentration ≥10 µg/dL over the period from six to 72 months of age (Jusko *et al.*, 2008). Children with blood lead concentrations in the 5 to 9.9 µg/dL range had significantly lower IQ scores than children who had blood lead concentrations <5 µg/dL (Jusko *et al.*, 2008). Jusko *et al.* (2008) showed that peak exposure to Pb throughout early childhood (as indicated by blood lead levels) suggested BPb as low as ~2 µg/dL may be associated with declines in Full-Scale IQ.

A4-1.6.9 Alzheimer's disease and Lead

The pathological manifestations of Alzheimer's disease (AD) in humans are associated with old age. The process of amyloidogenesis associated with AD may become evident during aging, but the initiating event may have occurred much earlier in life during the early stages of brain development (Zawia and Basha, 2005). Early exposure to a toxicant (such as lead) may be linked to eventual development of AD (Wu *et al.*, 2008a). Chronic exposure has no bearing on this outcome. Therefore, according to Wu *et al.*, 2008a hypothesis no level of Pb exposure during neonatal development would be considered acceptable.

A4-1.6.10 Reproductive Outcomes and Lead

Studies on the reproductive and developmental toxicity of lead have not shown consistent effects, morphologically or quantitatively, on markers of male fertility. It is not clear whether the effects are caused by a direct interaction of lead with the reproductive organs, or by modulation of the endocrine control of reproduction, or both.

The association of BPb with spontaneous abortion in a cohort of pregnant women seeking prenatal care in Mexico City showed an odds ratio (OR) for spontaneous abortion before 21 weeks gestation was 1.13 for every incremental increase of 1 µg/dL in blood lead across the blood lead range of 1.4 to 29 µg/dL. Compared with the reference category of BPb <5 µg/dL, women whose blood lead levels were 5 to 9, 10 to 14, and >15 µg/dL had ORs for spontaneous abortion of 2.3, 5.4, and 12.2, respectively (test for trend, *p*=0.03) (Kosnett *et al.*, 2007). Women with a history of miscarriage had a comparatively higher mean plasma/blood Pb ratio relative to those with no history (Lamadrid-Figueroa *et al.*, 2007). When plasma/blood Pb ratio was treated as a continuous variable an increment of 0.1 percentage point in the plasma/blood Pb ratio is associated with a 12% greater incidence rate ratio (IRR) of abortion (IRR = 1.12; *p*=0.02) (Lamadrid-Figueroa *et al.*, 2007).

Pre-natal exposure to low levels of lead includes effects such as reduced birth weight, reduced gestational age and neurobehavioral deficits, or delays. The evidence for an association between PbB levels and reduced birth weight and gestational age is inconsistent, and therefore equivocal. Evidence in support of neurobehavioral deficits or delays has been much more consistent, with most studies indicating a positive association between low-level lead exposure and developmental neurobehavioral effects (ATSDR, 2007).

Bone resorption during pregnancy and lactation could result in increased BPb and exposure *in utero* as well as neonatal exposure during lactation (Ettinger *et al.*, 2006). A recent study of 310 lactating women determined that breast milk lead levels, although correlating with infant blood lead levels, were fairly low (0.21 to 8.0 µg/L) (Ettinger *et al.*, 2004). Bone lead measurements in mothers that were obtained at one month postpartum revealed progressive reductions in lead content one, four, and seven months postpartum. Mean breast milk lead levels were 1.4 (SD, 1.1), 1.2 (SD, 1.0), and 0.9 (SD, 0.8) µg/L respectively showing that levels of BPb undergo a significant decreasing trend as readily available deposits of lead are depleted over the course of lactation (p <0.00001) (Ettinger *et al.*, 2006).

Bone loss and significant bone turnover in lactating women were not related to postpartum maternal blood Pb levels (Sowers *et al.*, 2002). Blood lead concentrations of women who breast-fed (average of 36 weeks) were compared with women who chose bottle-feeding for their newborn infants (Sowers *et al.*, 2002). No significant differences in maternal blood lead concentrations between lactating and non-lactating women were revealed (although a trend to higher levels of BPb was noted in lactating women) (Sowers *et al.*, 2002). Despite the clear connection between bone loss and lactation, there was no evidence of a statistically significant association of bone loss with change in maternal blood lead concentration that would support a hypothesis of risk from lead to neonates from bone turnover. In fact, women who showed evidence of higher bone turnover had lower blood lead levels in breast milk (Sowers *et al.*, 2002).

There is no currently accepted intervention level of bone lead. It is important to recognize that there is no methodology or clinical management practice that would permit the reduction of lead deposited in bone. Nevertheless, mitigation of circumstances that might result in the remobilization of lead could be important actions for populations known to have elevated levels of lead in both types of bone.

Table A4-3 summarizes outcomes and TRVs associated with specific changes in blood or bone lead concentrations.

Table A4-3 Outcomes and TRVs Associated with Specified Changes in Blood or Bone Lead Concentrations

Outcome	*Measure associated with Pb*	*Incremental Change for Pb*	*Result of Incremental Change in Outcome*	*Reference*
Hypertension	↑ Systolic BP	10 µg/dL in BPb	1mm Hg	Glenn *et al.*, 2006
	↑ Systolic BP ↑ Diastolic BP	10 µg/g increase in tibia Pb	0.26 mm Hg for systolic [CI 0.02 to 0.50][A] 0.02 mm Hg for diastolic [CI - 0.15 to 0.19]	Navas-Acien *et al.*, 2008
	↑ Systolic BP	10 µg/g increase in tibia Pb	The summary odds ratio for hypertension: 1.04 [CI 1.01 to 1.07]	
	↑ Systolic BP	10 µg/g increase in patella Pb	Summary odds ratio for hypertension: 1.04 [CI 0.96 to 1.12]. **Not significant**	
	↑ Systolic BP	An increase from the lowest quintile to the midpoint of the highest quintile of tibia Pb of 8 to 37 µg/g	OR for hypertension of 1.5 [CI 1.1 to 1.8]	Hu *et al.*, 1996a
Hypertension	Glomerular filtration	One µg/dL higher BPb was associated with a reduction in glomerular filtration rate (GFR)	An inverse association between estimated glomerular filtration rate and blood lead has been observed at blood lead levels <5 µg/dL in renal patients. Reduction of (GFR) of 4.0 ml/min/1.73m^2 per 1 µg/dL BPb during a 4-year study of 121 chronic kidney disease (CKD) patients. Mean BPb was 4.9 µg/dL in the "high normal" group and 3.4 µg/dL in the "low normal" group)	Yu *et al.*, 2004; Ekong *et al.*, 2006; Muntner *et al.*, 2005
Ischemic Heart Disease	Mortality	Population chronic level BPb	Hazard Ratio BPb ≥5 µg/dL = 1.73 [95% CI 1.05–2.87] for IHD compared to BPb <5 µg/dL	Jain *et al.*,2007
All cause cardiovascular disease	Mortality	3.4-fold increase in BPb	Hazard Ratio of 1.53 [CI1.21 to 1.94] mortality	Menke *et al.*, 2006
Myocardial infarction			Hazard Ratio of 1.78 [CI1.18 to 2.67] MI mortality	
Stroke			Hazard Ratio of 1.59 [CI1.08 to 2.34] for stroke mortality	
All cause mortality			Hazard Ratio of 1.34 [CI1.16 to 1.54] for all cause mortality	
Osteoporosis	$BMDL_{05}$ BPb required to result in 5% increase over background	BPb >8 µg/dL	Elevation in serum concentrations of alkaline phosphatase	Sun *et al.*, 2008
		BPb >10 µg/dL	Changes in other enzyme functions specifically associated with increased risk of osteoporosis and increased bone metabolism	

Table A4-3 Outcomes and TRVs Associated with Specified Changes in Blood or Bone Lead Concentrations				
Outcome	***Measure associated with Pb***	***Incremental Change for Pb***	***Result of Incremental Change in Outcome***	***Reference***
Neurotoxicity	Academic performance	BPb 5-10 µg/dL *versus* BPb 1-2 µg/dL	Children six to ten-year-olds with blood lead levels of 5-10 µg/dL scored lower than children with levels of 1-2 µg/dL on academic skills (not IQ)	Surkan *et al.*, 2007
	Dose-dependent decreases in cortical volume of gray matter	During the first 5 years of life, at least one of the quarterly BPb exceeded 10 µg/dL for 99% of the cohort	At adolescence, mean BPb of cohort = 2.8 µg/dL (SD 1.3 µg/dL) Cincinnati Lead Study (CLS) cohort	Cecil *et al.,* 2008
	Violent offenses, drug offenses, theft or fraud, obstruction of justice, serious motor vehicle offenses, and disorderly conduct since the age of 18 years	Statistically significant increase per 5 µg/dL increment Prenatal childhood blood lead and blood lead at six years of age	Elevated risk for violence. Cincinnati Lead Study (CLS) cohort. Mean blood lead concentrations for the cohort were 2.8 µg/dL (SD 1.3 µg/dL)	Wright *et al.*, 2008
	ADHD (attention deficit hyperactivity disorder)	>2 µg/dL BPb	Children with blood lead concentrations greater than 2 µg/dL were at a 4.1-fold increased risk for diagnosis of ADHD.	Braun *et al.*, 2006 (NHANES-III)
	Intelligence quotient IQ	Increment of 10 µg/dL BPb for lifetime average	Each increment in the lifetime average blood lead concentration was associated with a 4.6 point decrease in IQ (p=0.004).	Canfield *et al.*, 2003

Table A4-3 Outcomes and TRVs Associated with Specified Changes in Blood or Bone Lead Concentrations				
Outcome	***Measure associated with Pb***	***Incremental Change for Pb***	***Result of Incremental Change in Outcome***	***Reference***
Neurotoxicity	Intelligence quotient IQ	Children whose maximal BPb remained below 10 µg/dL. Range of lifetime maximum 1-10 µg/dL	Change in IQ greater than the rate of decline shown for children with higher lifetime BPb. In this subsample of 101 children with low level BPb, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1-10 µg/dL	Canfield *et al.*,2003
	Intelligence quotient IQ	At the 6 year assessment 92% of children had measured blood lead concentrations <10 µg/dL. Fifty-five percent of children never had a measured blood lead concentration ≥10 µg/dL from 6 to 72 months of age	Children with blood lead concentrations in the 5-9.9 µg/dL range had significantly lower IQ scores than children who had blood lead concentrations <5 µg/dL BPb as low as ~2 µg/dL may be associated with declines in Full-Scale IQ	Jusko *et al.*, 2008
	Alzheimer's Disease The brains of 23 year old cynomolgus monkeys examined for β-amyloid plaques in the frontal cortex	BPb in the Pb treated monkeys (400 days) ranged from 10 to 26 µg/dL, but by adulthood both treated and untreated animals had similar blood lead levels. No differences were found in soft tissue concentrations of lead between treated and control groups	Increased frequency of markers of AD following *developmental exposure* to Pb suggests that such exposure can influence latent pathogenesis and AD in primates. Environmental levels of exposure to Pb early in life could contribute to development of AD later in life. Not related to chronic exposure. No level of Pb exposure during neonatal development would be considered acceptable	Wu *et al.*, 2008b
Breast Milk Exposure	Neonate exposure	Pb in breast milk or maternal blood	There is a clear connection between bone loss and lactation. No evidence of a statistically significant association of bone loss with change in maternal blood lead concentration that would support a hypothesis of risk from lead to neonates from bone turnover. In fact, women who showed evidence of higher bone turnover had lower blood lead levels in breast milk .	Sowers *et al.*, 2002

Table A4-3 Outcomes and TRVs Associated with Specified Changes in Blood or Bone Lead Concentrations

Outcome	*Measure associated with Pb*	*Incremental Change for Pb*	*Result of Incremental Change in Outcome*	*Reference*
Spontaneous abortion	Spontaneous abortion	Incremental increase of 1 µg/dL in BPb across the blood lead range of 1.4-29 µg/dL. Reference population: BPb <5 µg/dL	Odds Ratio (OR) for spontaneous abortion before 21 weeks gestation = 1.13 [CI, 1.01-1.30] Compared to women whose blood lead levels were 5-9, 10-14, and > 15 µg/dL Spontaneous abortion had ORs of 2.3, 5.4, and 12.2, respectively (test for trend, *p*=0.03).	Kosnett *et al.*, 2007
Spontaneous abortion	Spontaneous abortion	Plasma and blood lead measurements.	Pregnancy was responsible for a significant increase in the plasma Pb and the percent ratio of P-Pb/BPb. BPb concentrations were similar in women based on pregnancy (4.42 ± 0.58 µg/dL in pregnant women *versus* 5.88 ± 0.54 µg/dL in non-pregnant women; *p* >0.05). Plasma Pb in pregnant women presented significantly higher concentrations (0.055 ± 0.011 µg/dL *versus* 0.026 ± 0.004 µg/dL) and ratio percent P-Pb/BPb (1.56 ± 0.33% *versus* 0.46 ± 0.06%) compared with non-pregnant women (both *p* <0.01).	Montenegro *et al.*, 2008

[a] [CI] 95% Confidence Interval; Significance at *p*<0.05 for OR>1.0
BPb Whole blood lead concentration
P-Pb Plasma lead concentration
GFR Glomerular filtration rate
AD Alzheimer's Disease

A4-1.7 Carcinogenicity

The U.S. EPA IRIS (1993) classified inorganic lead as a probable human carcinogen (Group 2B) based on animals assays with significant increases in renal tumours after exposure to soluble lead salts; however, the human carcinogenicity data is inadequate. The U.S. EPA has determined that an estimate of carcinogenic risk from oral exposure (such as a slope factor) using standard methods would not adequately describe the potential risk for lead compounds. The U.S. EPA's Carcinogen Assessment Group made this determination given the current lack of understanding on various toxicological and toxicokinetic characteristics of lead. IARC (2004) classified inorganic lead compounds as probably carcinogenic to humans (Group 2A), based on limited evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in experimental animals. The IARC evaluation considers the evidence of carcinogenicity in humans and experimental animals, as well as other data relevant to the evaluation of carcinogenicity and its mechanisms. For example, IARC (2004) noted that while there appeared to be little evidence that lead is directly genotoxic, it may be indirectly genotoxic as a result of oxidative stress and the formation of reactive oxygen species. NTP (2005) concluded that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals. Health Canada has not formally classified lead compounds with respect to their carcinogenic potential.

It is well established that the most sensitive endpoint for lead (and the greatest potential risk) is the development of adverse neurological, neurodevelopmental and neurobehavioural effects in young children. As a result, virtually all regulatory agencies around the world have focused on these health outcomes of lead exposure, and not on the potential carcinogenic risks. This regulatory focus also reflects the fact that the concern for neurological, neurodevelopmental, and neurobehavioural effects is associated with a less than lifetime exposure duration (*i.e.*, toddlers, infants, young children), whereas carcinogenic effects are virtually always associated with much longer exposure durations over a lifetime.

In addition, it is important to recognize that the human carcinogenicity potential of lead compounds is largely inconclusive.

A4-1.8 Toxicological Reference Values (TRVs)

Carcinogenic TRVs

Cal EPA (2005a) considers lead compounds human carcinogens as they have derived both oral and inhalation slope factors and unit risks for lead (Table A4-4). These values are based on the study by Azar *et al*. (1973) in which groups of male and female rats were fed concentrations of 0, 10, 50, 100, 500, 1,000 and 2,000 ppm of lead acetate in their feed for a 2 year period. Kidney tumors (adenomas) were seen in the highest three concentrations in the male group and in 35% of the females that were fed the 2,000 ppm concentration of lead. An oral slope factor was calculated by converting the doses to human equivalent doses (HED), followed by fitting the male kidney tumor dose-response data to a linearized multistage model. The 95% UCLM was selected as the slope factor of 0.0085 $(mg/kg\text{-}day)^{-1}$. Inhalation unit risk of $2.4x10^{-6}$ $(\mu g/m^3)^{-1}$ was calculated using the oral slope factor with the assumption that an average adult human has a body weight of 70 kg and an average air intake of 20 m^3/day. Assuming equivalent absorption via inhalation and oral routes as well as that there is five times higher absorption with inhalation that through oral intake then the inhalation risk can be multiplied by five to get a final inhalation unit risk of $1.2x10^{-5}$ $(\mu g/m^3)^{-1}$ (Cal EPA, 2005a).

Currently Cal EPA is the only public regulatory agency known to have derived regulatory exposure limits for lead based on carcinogenic effects and the U.S. EPA has determined that an estimate of carcinogenic risk from oral exposure (such as a slope factor) using standard methods would not adequately describe the potential risk for lead compounds. As a result, lead was not evaluated in this manner.

Table A4-4 Carcinogenic Exposure Limits for Lead

Reported Exposure Limit	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Source*	*Derivation Date*
Inhalation ($\mu g/m^3$)$^{-1}$						
Unit risk	1.2E-05[a]	Rat kidney tumour incidence data	Lead acetate fed to male and female rats at concentrations of 0, 10, 50, 100, 500, 1,000 and 2,000 ppm for a 2 year period	Azar *et al.*, 1973	Cal EPA, 2005a	1996
Oral (µg/kg-day)$^{-1}$						
Slope factor	8.5E-06	Rat kidney tumour incidence data	Lead acetate fed to male and female rats at concentrations of 0, 10, 50, 100, 500, 1,000 and 2,000 ppm for a 2 year period	Azar *et al.*, 1973	Cal EPA, 2005a	1997

[a] Derived from the oral slope factor using a body weight of 70 kg and an inhalation rate of 20 m^3/day

Non-Carcinogenic TRVs

MOE (2007; 2008) proposed an acute 24 hours ambient air quality criteria (AAQC) of 0.5 µg/m^3 based on neurological effects in children.

The U.S. EPA, in 1978, developed an acute national ambient air quality standard (NAAQs) (three months averaging time) of 1.5 µg/m^3; based on keeping 99.5% of children from exceeding a blood lead level of 40 µg/dL. However, as of October 15th, 2008, the U.S. EPA has revised the NAAQs to a value of 0.15 µg/m^3 (3 month rolling average) to be protective of children and other at-risk populations. The U.S. EPA considered the available literature since the previous standard was released and has noted that there are no known safe levels of lead in the body and have seen that children may be greatly affected by this *via* neurological effects such as neurocognitive and neurobehavioral. To derive this new standard the key effect examined was IQ loss in children in the first seven years of life.

The U.S. EPA employed two procedures to predict risk from exposure to lead (Pb) in air. The first was an evidence-based analysis which employed data obtained from literature describing cohort or other studies that compared data for air concentrations of Pb to determinations of blood lead (BPb) in receptor populations. This produces an Air-to-Blood ratio (AB ratio). A slope factor was developed for IQ loss for each increment of BPb. The second was a risk assessment.

The components of the risk assessment model included:

The Critical Exposure Path for Pb was determined to be *via ingestion of indoor dust* and *inhalation*. Pb in ambient air penetrates buildings and is deposited as indoor dust. Additional residential Pb in dust originates outside and is tracked into the residence.

- Pb in paint was assumed to be part of the indoor dust;
- Dietary ingestion of Pb deposited to crops and Pb in drinking water were combined to serve as background; and,
- The exposure model combined (1) inhalation; (2) ingestion of indoor dust; and, (3) ingestion of outdoor soil.

Exposure Concentrations were focused on larger urban areas. Census blocks were characterized for demographics including the number of children zero to seven years and the monitored air concentration of Pb was applied to each census tract. An urban area was then constructed based on the census tracts and an exposed population distribution was created.

- Exposure Scenarios varied the averaging times of exposure (monthly or quarterly maximum) and the levels at 0.5, 0.2, 0.05 and 0.02 µg/m^3; and,
- This generated population-weighted distributions of BPb for each ambient level.

Concentration-Response Functions for BPb and IQ loss were created using NHANES data and pooled data (seven cohort studies) by Lanphear *et al*. (2005). The strongest association between BPb and IQ loss was for concurrent blood level (BPb closest to the time of IQ testing).

- The CRF for correlation of IQ loss with concurrent BPb chosen for the risk assessment was derived from a regression analysis that combined log-linear with low exposure linearization of the Lanphear *et al*. (2005) pooled analysis;

- The linearized portion of the curve accounted for the much greater sensitivity of IQ loss to small changes in BPb at low concurrent lead levels; and,
- The logarithmic regression accounted for the different rate of IQ loss above approximately 3.5 to 4 µg/dL of BPb in children aged zero to seven.

The conceptual model framework (Figure A4-1):

- Used multi-pathway BPb modeling to generate a single central tendency BPb for a metropolitan area (or smelter within a 2 km radius) (Gray);
- Applied a geometric standard deviation to establish a distribution of BPb for the population (Yellow);
- Applied the IQ loss CRFs to determine the distribution of IQ loss across the chosen population (Pink);
- Attribution of Pb to different pathways in the IEUBK model was very important; and,
- Equally important is the modeled estimates of conversion of lead in air to residential dust.

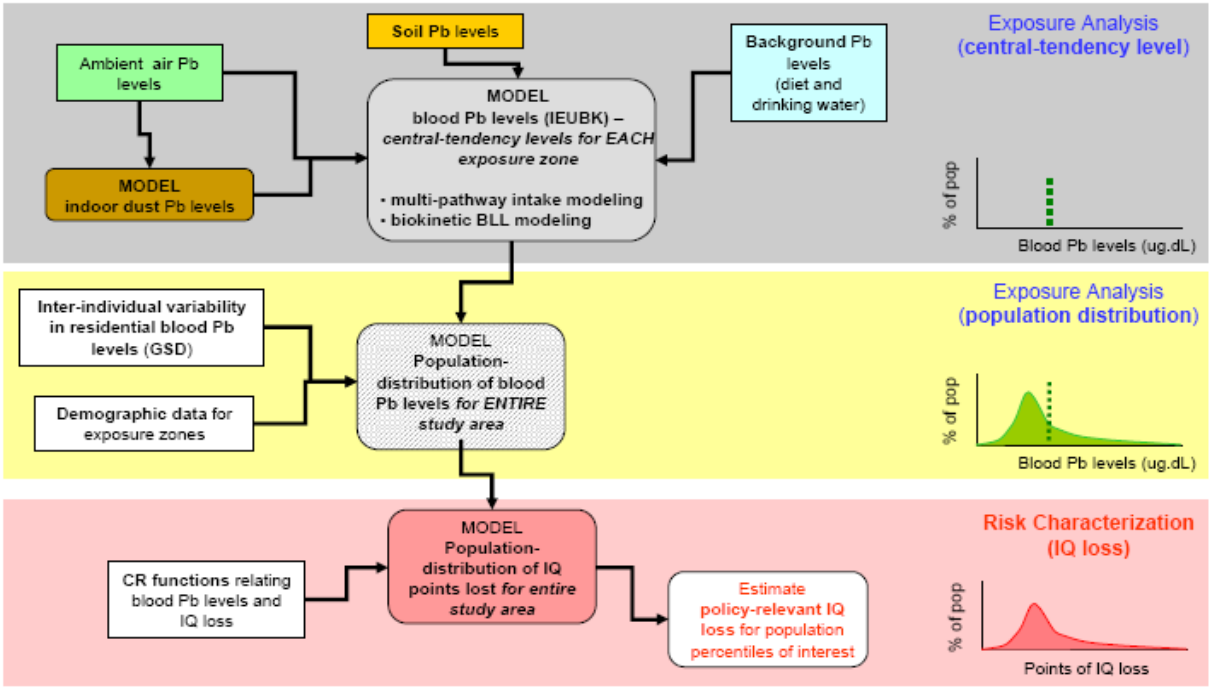

Figure A4-1 Conceptual Framework for U.S. EPA Risk Assessment for Lead In Air from a Presentation By Z. Pekar and J.Y Kim (Nov 12, 2008)

Some examples of the apportionment of Pb to different pathways used in total uptake for IEUBK modeling are given in Table A4-5.

Table A4-5 Pathway Contribution (Fraction of Total Uptake) to IEUBK Model Inputs[a]					
Diet	***Drinking water***	***Inhalation[b]***	***Indoor dust (air)***	***Indoor dust (other[b])***	***Outdoor soil/dust***
General urban case study (concurrent) 0.2 µg/m^3 , maximum monthly average					
17.9%	10.4%	0.5%	27%	6%	38.2%
General urban case study (concurrent) 1.5 µg/m^3 , maximum quarterly average					
10.4%	6.0%	3.3%	57.1%	1.1%	22.1%
Primary Pb smelter case study (concurrent) 1.5 µg/m^3, maximum quarterly average					
21.9%	12.8%	1.2%	30.8%	--	33.4%

[a] From U.S. EPA, 2007b Appendix I Exhibit I-2 to I-8 and Exhibit I-17.

[b] ***Other*** refers to contributions to indoor dust Pb from indoor paint, outdoor soil/dust, and additional sources (including historical air); and ***Inhalation*** refers to pathway contributions associated with outdoor ambient air Pb levels (either by inhalation of ambient air Pb or ingestion of indoor dust Pb predicted to be associated with outdoor ambient air Pb levels).

Evidence-based Analysis

The alternative approach (deterministic) for loss of IQ based on air to blood ratio determined by U.S. EPA (2008) is shown below.

Potential Level For Standard (µg/m^3)	Air-related Mean IQ Loss (points) for the subpopulation of children exposed at level of the standard IQ loss estimate is based on median slope of 4 C-R functions with blood Pb Levels closer to those of today's U.S. children (range shown for estimates based on lowest and highest of 4 slopes ***Air-to-Blood Ratio***		
	1:10	1:7	1:5
0.50	>5*	>5*	4.4 (3.9-7.4)
0.40		4.9 (4.4-8.2)	3.5 (3.1-7.4)
0.30	5.3 (4.7-8.8)	3.7 (3.3-6.2)	2.6 (2.3-4.4)
0.25	4.4 (3.9-7.4)	3.1 (2.7-5.1)	2.2 (2.0-3.7)
0.20	3.5 (3.1-5.9)	2.5 (2.2-4.1)	1.8 (1.6-2.9)
0.15	2.6 (2.3-4.4)	1.8 (1.6-3.1)	1.3 (1.2-2.2)
0.10	1.8 (1.6-2.9)	1.2 (1.1-2.1)	0.9 (0.8-1.5)
0.05	0.9 (0.8-1.5)	0.6 (0.5-1.0)	0.4 (0.4-0.7)
0.02	0.4 (0.3-0.6)	0.2 (0.2-0.4)	0.2 (0.2-0.3)

* For these combinations of standard levels and air-to-blood ratios, the appropriateness of the C-R function applied in this table becomes increasingly uncertain such that no greater precision than ">5" for the IQ loss estimate is warranted.

Health Canada (1992; 2004a; 2008) has selected a provisional total daily intake (pTDI) of 3.6 µg/kg-day which corresponds to a maximum acceptable blood lead concentration of 10 µg/dL based on JEFCA (1987) and the studies by Ryu *et* al. (1983) and Ziegler *et al*. (1978). Ziegler *et al*. (1978) conducted a metabolic balance study whereby infants who were between 14 to 746 days old were administered a lead dose of 1.72 to 22.61 µg/kg-day through their milk, formula or strained foods for a period of 72 hours. Results showed increased blood lead in the infants. 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 to 111 days old was 17 µg/kg-day and those who were 112 to 195 days old the dosage was 16 or 61 µg/kg-day. Again, significant increases in blood lead concentrations were measured. From the studies a NOAEL of 3.0 to 4.0 µg/kg-day was determined on the basis that increases in blood lead levels or body burden of lead would not occur at this level. The TDI was calculated using the provisional tolerable weekly intake (pTWI) set by JEFCA (1987) which is 25 µg/kg in young children. This pTWI has assumed that lead is a cumulative poison and that there should be no increase in the body burden of lead from any source to avoid any possible effects (Ziegler *et al*., 1978; Ryu *et al*., 1983).

The Ontario Ministry of the Environment (MOE, 1994) derived an intake level of concern (IOC_{pop}) for Ontario children that would be protective of a blood lead level of 10 µg/dL. Similar to Health Canada, the MOE estimated this intake to be 3.7 µg/kg-day. The MOE divided this value by a safety factor of two to account for variability among children to derive an IOC_{pop} of 1.85 µg/kg-day. This value was considered to represent the intake that corresponds to a blood lead level that is associated with a low risk to children's health (MOE, 1994).

As of 2003, Health Canada has adopted the value of 3.6 µg/kg-day as the pTWI for lead and the CCME uses this value as the basis for derivation of soil and drinking water guidelines that are protective of human health. As such, this value was selected as the exposure limit for lead in the current assessment (Table A4-6).

As previously indicated, 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 in the vast majority of studies. As a result, the Health Canada pTDI has been selected for systemic exposures and is used to evaluate both oral and inhalation exposure pathways.

A4-1.9 Relative Dermal Bioavailability

The relative dermal bioavailability for lead in soil is 0.006 (Health Canada, 2004b).

Table A4-6 Non-Carcinogenic Toxicological Exposure Limits for Lead									
Reported Exposure Limit	***Duration***	***Exposure Limit***	***Critical Effect***	***Description of Study***	***References***	***Endpoint***	***Uncertainty Factor***	***Source***	***Derivation Date***
Inhalation (µg/m^3)									
Proposed AAQC; 24 hours averaging time	**Acute**	**0.5**	**Blood lead level of 10 µg/dL**	**Based on neurological effects in children; weight of evidence**	**Not provided**	**Not provided**	**Not provided**	**MOE, 2007; 2008**	**2007**
CAAQS; 30 days averaging time	Chronic	1.5	Based impairment of hemopoietic system	Not provided	Not provided	Not provided	Not provided	Cal EPA, 2005b	1970
National Ambient Air Quality Standard; 3 months averaging time	Chronic	1.5	Based on keeping 99.5% of children from exceeding a blood level of 40 µg/dL	Not provided	U.S. EPA, 1977; Cal EPA, 2001	Not provided	Not provided	U.S. EPA, 2006; Cal EPA, 2001	1977; 1986
Approvable level (for site-specific use) - high exposure; 30 days averaging time	Chronic	0.12	Based on a 10% increase of the baseline average blood level in children in a high-exposure scenario	Not provided	Not provided	Not provided	Not provided	Cal EPA, 2001	Not provided
Proposed AAQC; 30 days averaging time	Chronic	0.2	Blood lead level of 10 µg/dL	Based on neurological effects in children; weight of evidence	Not provided	Not provided	Not provided	MOE, 2007; 2008	2007
Air Standard; annual averaging time (objective for 2008)	Chronic	0.25	Impairment of brain function	Designed for the protection of children	Not provided	Not provided	Not provided	UK DETR, 1999	Not provided
National Ambient Air Quality Standard; 3 months averaging time (revised October 2008)	**Chronic**	**0.15**	**Protective of children and other at-risk populations**		**U.S. EPA, 2008; U.S. EPA, 2007a,b**			**U.S. EPA, 2008**	**2008**
Approvable level (site-specific use) – averaged exposure; 30 days averaging time	Chronic	0.3	Based on a 5% probability of blood lead exceeding a blood level of 10 µg/dL in children in an average exposure scenario	Not provided	Not provided	Not provided	Not provided	Cal EPA, 2001	Not provided
Guideline value; annual averaging time	Chronic	0.5	Adults: elevated free erythrocyte proporphyrin; Children: Cognitive functioning, such as the psychometric IQ and changes in vitamin D metabolism.	Various international agencies	Rosen *et al.,* 1980; Mahaffey *et al.,* 1982	LOAEL: 100 to 150 µg/l blood lead levels (children)	Not provided	WHO, 2000	2000

Table A4-6 Non-Carcinogenic Toxicological Exposure Limits for Lead

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
Oral (µg/kg-day)									
IOC_{pop}	Chronic	1.85 (Based on 10 µg/dL as the blood lead level of concern or the TDI/2)	Behavioural effects and learning disabilities in children	To ensure that a child's blood lead levels do not exceed 10 µg/dL	Not provided	Not provided	2	MOE, 1994	1994
TDI	Chronic	3.6	Increased blood lead concentration	Based upon the PTWI derived by JECFA (1987)	Ziegler *et al.*, 1978 ; Ryu *et al.*, 1983	NOAEL	Not provided	RIVM, 2001	1999/2000
pTDI	**Chronic**	**3.6**	**Increased blood lead concentration**	**Based upon the PTWI derived by JECFA (1987)**	**Ziegler *et al.*, 1978 ; Ryu *et al.*, 1983**	**NOAEL: 3.0-4.0 µg/kg-day**	**Not provided**	**Health Canada, 2004a; 2008**	**1992**
PTWI	Chronic	3.6 (2.5 mg/kg-wk)	Increased blood lead concentration	Metabolic studies in infants and children	Ziegler *et al.*, 1978 ; Ryu *et al.*, 1983	NOAEL	Not provided	JECFA, 1987	1987

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment
pTDI Provisional Tolerable Daily Intake
TDI Tolerable Daily Intake
AAQC Ambient Air Quality Criteria
PTWI Provisional Tolerable Weekly Intake
IOCpop Intake of Concern

A4-2.0 REFERENCES

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APPENDIX A:

TOXICOLOGICAL PROFILES

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A5-1.0 MERCURY

Comprehensive toxicity profiles for mercury have been previously published by JECFA (1972); WHO (1978; 1990; 1991; 2000; 2004), Health Canada (1979; 2007a,b; 2008); U.S. EPA IRIS (1995a,b; 2001); ATSDR (1999); Cal EPA (1999); CCME (1999); OEHHA (1999); RIVM (2001); and, U.S. EPA (2001). The following profile represents a short summary of the relevant background information and human toxicity data for mercury. A summary of the toxicity reference values selected for the HHRA is provided in Table A5-1.

Table A5-1 Summary Table of Toxicity Reference Values Selected for the HHRA

Route of Exposure	*Exposure Limit*	*Type of Limit*	*Toxicological Basis*	*Reference*	
				Study	*Regulatory*
ELEMENTAL MERCURY					
Acute Effects					
Inhalation	NA		NA	NA	NA
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	NA	NA	NA	NA	NA
Inhalation	0.06 ($\mu g/m^3$)	TC (provisional) (mercury vapour)	Neurobehavioral effects	Ngim *et al*., 1992	Health Canada, 2008
Dermal	NA		NA	NA	NA
INORGANIC MERCURY					
Acute Effects					
Oral	7.0 (µg/kg-day)	MRL	Renal effects, increased incidence and severity of tubular necrosis	NTP, 1993	ATSDR, 1999
Inhalation (1 hour)	1.8 ($\mu g/m^3$)	REL	Behavioural deficits	Danielsson *et al*., 1993	Cal EPA, 1999
Inhalation (24 hours)	2.0 ($\mu g/m^3$)	AAQC	Health effects	Not provided	MOE, 2005, 2008
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	0.3 (µg/kg-day)	TDI (inorganic, ionic)	Kidney effects	Druet *et al*., 1978; Bernaudin *et al*., 1981; Andres, 1984	Health Canada, 2004a, 2008
Inhalation	1.0 ($\mu g/m^3$)	Annual average guideline (inorganic vapour)	Objective tremor, renal tubular effects and non-specific symptoms	WHO, 1991; Cardenas *et al.,* 1993	WHO, 2000
Dermal	NA		NA	NA	NA

Table A5-1 Summary Table of Toxicity Reference Values Selected for the HHRA					
Route of Exposure	***Exposure Limit***	***Type of Limit***	***Toxicological Basis***	***Reference***	
				Study	***Regulatory***
METHYL MERCURY					
Acute Effects					
Inhalation	NA		NA	NA	NA
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	0.47 (µg/kg-day) (general adult population) and 0.20 (µg/kg-day) (women of childbearing age, children (<12 yrs)	pTDI	Neurotoxicity and neurodevelopmental toxicity	Grandjean *et al*., 1997; Feeley and Lo, 1998	Health Canada, 2007a, 2008
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA

NA Not applicable
REL Reference exposure level (derived from oral Reference Dose)
AAQC Ambient Air Quality Criteria
TDI Tolerable Daily Intake
$_P$TWI Provisional Tolerable Daily Intake
TC Total Concentration
MRL Minimal risk level

A5-1.1 Background Information

Mercury occurs naturally in the environment and is most commonly found in rocks and soil as mercuric sulphide. Mercury occurs in three oxidation states in nature: metallic/elemental (Hg^0), mercurous (Hg^+), and mercuric (Hg^{2+}). Mercuric cations can form various organic and inorganic mercury compounds (ATSDR, 1999). Elemental mercury is mined and refined from its natural form. Inorganic forms of mercury, also known as mercury salts, are the result of the combination of elemental mercury with other elements (*e.g.,* chlorine, sulphur, oxygen). The mixture of mercury and carbon produces various forms of organic mercury including methylmercury, dimethylmercury, and phenyl mercury (ATSDR, 1999). Methylmercury is primarily produced by microorganisms, which can convert inorganic mercury to an organic form. In the past, organic forms of mercury were used as fungicides, but these uses are presently banned in North America and Europe due to evidence of adverse human health effects. Today, dimethylmercury is used in the preparation of resonance and mass spectrometry standards (ATSDR, 1999). Organic forms of mercury are generally volatile, and solubility differs greatly for the different forms (WHO, 1990). Methylmercury is soluble and highly bioaccumulative (ATSDR, 1999). Research has shown that methylmercury will biomagnify in aquatic food chains, and has been identified as the predominant form of mercury in fish.

Elemental/metallic mercury is an inflammable, odourless, heavy liquid metal that is silver in colour (ATSDR, 1999). Inorganic forms generally exist as white, crystalline solids, with the exception of mercurous oxide and sulphide, which occur as black powders, and mercuric sulphide which is red (Cal EPA, 1999). Metallic mercury is more volatile than inorganic mercury

(CCME, 1999). The solubilities of mercury compounds vary, with the solubility of elemental mercury being lower than that of certain inorganic compounds (*e.g.,* mercurous chloride, mercuric chloride) (WHO, 1991). Mercury is cycled through the environment *via* a number of processes, including degassing from the environment, atmospheric transport, deposition, sorption onto soils and sediments, and revolatilization into the atmosphere (ATSDR, 1999). Mercury vapour has the potential for long-range transport, with a residence time in the atmosphere of up to three years (WHO, 1991). More soluble forms of mercury exist in the atmosphere for a matter of weeks before they are deposited.

Mercury is used in a wide range of industrial applications as a result of certain chemical properties, namely fluidity, thermal conductivity, surface tension, and uniform volume expansion (ATSDR, 1999). Mercury is predominantly used in chemical and mining applications, such as in the extraction of gold, and in the production of polymers, chlorine gas, and caustic soda. Electrical applications include use in batteries, wires and switches, and thermostats, though these uses are being phased out. Mercury is used for medical applications, such as dental amalgams and thermometers. Phenyl mercuric acetate is used in ink and adhesive preparations, and as a fungicide in paints (ATSDR, 1999). Mercury salts have been used in skin-lightening creams and medications (*e.g.,* laxatives, teething powders), but have since been replaced with safer compounds (OEHHA, 1999).

Mercury is released into the atmosphere from mining and smelting, fossil fuel combustion, and waste incineration. Releases into aquatic and terrestrial ecosystems result from municipal waste (*e.g.*, used batteries), fertilizers, fungicides, and industrial wastewater (WHO, 1991). Mercury occurring naturally in the environment is distributed by rock weathering, wind, erosion, and volcanic activity. Average soil concentrations of mercury in areas of relatively minimal anthropogenic activity range from 0.01 to 0.4 mg/kg (Jonasson and Boyle, 1972; Gracey and Stewart, 1974; McKeague and Kloosterman, 1974; Environment Canada, 1979; OMEE, 1994). Frank *et al*. (1976) found that in agricultural soils, concentrations were more elevated ranging from 0.01 to 1.14 mg/kg. In Canadian lakes located near smelters, surface sediments ranged from 0.03 to 9.22 µg/g. Concentrations were greatest near the smelter, however, it was found that mercury concentrations in fish could not be correlated with the mercury content in sediments (Harrison and Klaverkamp, 1990).

Dental amalgams are the largest non-occupational source of metallic mercury vapour to humans (*via* inhalation and ingestion); however, the risk is deemed minimal due to the small amounts of mercury present in amalgams (ATSDR, 1999). Inhalation of metallic mercury vapour from the workplace is an additional route of human exposure. The major sources of exposure to inorganic mercury (mercuric chloride) are dermal (skin-lightening creams, soaps) and oral (medicines, such as calomel) (WHO, 1991). Human dietary intake is the most important route of exposure for methylmercury (Health Canada, 2007a).

A5-1.2 Fate and Transport

Mercury occurs naturally in the environment, and anthropogenic activity accounts for approximately 33 to 66% of total mercury releases (ATSDR, 1999). The fate of mercury in air, water, soil, and sediment is dependant upon the speciation of the compound, and the different chemical properties associated with the various forms. Approximately 95% of the total mercury found in the atmosphere is in the form of elemental/metallic mercury vapour (Hg^0) (ATSDR, 1999). This form of mercury has a high vapour pressure and low water solubility, thus is subject to long-range transport, with a residence time in the atmosphere ranging from 6 days to 2 years (average 1 year) (U.S. EPA, 1997; ATSDR, 1999). A small fraction of mercury in the atmosphere is associated with particulates, with residence times on the order of weeks (WHO,

1991). Mercury is transformed by oxidation and reduction with compounds in the atmosphere (*e.g.,* ozone) into inorganic forms, and enters other environmental media *via* wet and dry deposition.

Different inorganic forms of mercury with a range of solubilities exist in both aquatic and terrestrial ecosystems, with mercuric mercury (Hg^{2+}) being the dominant form of the compound (ATSDR, 1999; CCME, 1999 In soil and sediments inorganic mercury has limited mobility since it readily adsorbs onto organic matter in soil and sediments; therefore not readily leaching into ground or surface waters (CCME, 1999; OEHHA, 1999). This is largely due to adsorption onto soil and sediments, where inorganic mercury compounds form complexes with organic matter containing humic and fulvic acids (CCME, 1999). In general, the adsorption of mercury to soil increases with levels of iron and aluminum, and decreases with increasing pH and chloride ions (Ahmad and Qureshi, 1989; Schuster, 1991). Partition coefficients calculated for the relative affinity of inorganic mercuric mercury for sediment or soil over water show a strong preference for binding to soil and sediment (U.S. EPA, 1997). Since inorganic mercury does not easily desorb from soil or sediment, it enters aquatic systems through runoff. In water, mercury undergoes transformation processes similar to those in soil.

Inorganic forms of mercury in soils, sediments, and water are naturally transformed to organic methylmercury. Both aerobic and anaerobic bacteria are responsible for mercury methylation, with sulfur-reducing bacteria being the predominant species in the process (ATSDR, 1999). Similarly, some bacteria can demethylate methylmercury into metallic mercury which readily volatilizes into the environment (ATSDR, 1999). Generally, methylation rates increase with anaerobic and acidic conditions, and decrease with dissolved organic carbon levels (ATSDR, 1999). Methylmercury is mobile and bioavailable, therefore binding tightly to proteins in fish tissue, resulting in bioaccumulation in food chains (Health Canada, 2007a). Carnivorous fish have been found to biogmagnify to levels that are 10,000 to 100,000 times of that in the water (OEHHA, 1999). Most plants grown in areas with elevated mercury in soil do not accumulate the chemical, although studies have show that edible mushrooms accumulate mercury to a great extent (ATSDR, 1999). Inorganic mercury bioaccumulates to a much lesser extent (Health Canada, 2007a). Other organic forms of mercury, such as dimethylmercury, are rarely found in the environment.

Selenium levels in water affect the availability of mercury for biota (WHO, 1991). Like methylmercury, selenium is known to bioaccumulate in aquatic species (ATSDR, 1999). Selenium forms complexes with both organic methylmercury and inorganic mercuric mercury, reducing the bioavailability of mercury for uptake into the aquatic food chain. Turner and Rudd (1983) found that the addition of selenite to a Canadian lake reduced availability of mercury in the water resulting from pulp and paper effluent. In the study, the measure of solubility for the mercury selenide complex was found to be lower than that of inorganic mercuric sulfide that was initially present in the lake. In Swedish lakes, decreased levels of mercury were documented in fish as a result of artificially increased selenium levels from 0.4 to 2.4 µg/L over a 1 to 2 year period (Bjornberg *et al.,* 1988). Mercury concentrations declined by approximately 55% in pike (initial concentration 1,500 µg Hg/kg), and 70% (initial concentration of 560 µg Hg/kg) in perch. The elevated selenium levels were within acceptable levels for drinking water standards (WHO, 1990).

A5-1.3 Toxicokinetics

Absorption of metallic mercury after inhalation is quite high since it is highly lipophillic and can rapidly diffuse across alveolar membranes of the lungs into the blood (Hursh *et al*., 1976; Teisinger and Fiserova-Bergerova, 1965). No studies could be found indicating absorption of

mercury after inhalation to phenyl or methyl mercury, although there is indirect evidence that organic mercury can be absorbed through the lungs (Ostlund, 1969). Similarly, few studies could be found regarding the absorption of metallic or inorganic mercury after oral exposure (ATSDR, 1999). Some studies have shown that absorption is negligible (Sue, 1994; Wright *et al*., 1980). Conversely, organic mercury is much more readily absorbed, up to 95% as one study showed (Aberg *et al*., 1969). Other studies have also shown absorption to be quite high, although the amount absorbed was not expressed quantitatively (Al-Shahristani *et al*., 1976; Miettinen, 1973). Absorption following dermal exposure to mercury vapour is minimal; however, applications of ointments containing inorganic mercury have shown to have considerable absorption (Bourgeois *et al*., 1986; DeBont *et al*., 1986; Hursh *et al*., 1989). Minimal information regarding absorption after dermal exposure to organic mercury could be found however, dermal exposure to dialkylmercurials have been shown to have high absorption (Blayney *et al*., 1997; Nierenberg *et al*., 1988).

Since metallic mercury is quite lipophillic it is readily distributed throughout the body and can cross blood-brain and placental barriers after inhalation (Clarkson, 1989; Hursh *et al*., 1976). In the blood, metallic mercury is oxidized to the divalent form, which can exist in both diffusible and non diffusible forms; however, the non diffusible form is predominant and binds to proteins such as albumin and globulin (Berlin and Gibson, 1963; Cember *et al*., 1968; Clarkson *et al*., 1961). As well, the kidney is the major organ for mercury deposition since it contains metallothionein, which is stimulated by mercury (Rothstein and Hayes, 1964; Piotrowski *et al*., 1973; Cherian and Clarkson, 1976). Distribution of organic mercury is similar to that of metallic or inorganic mercury (ATSDR, 1999). Metabolism of mercury involves an oxidation-reduction cycle, whereby the mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs. It can be reduced to the metallic or monovalent form and released as exhaled metallic mercury vapour (ATSDR, 1999). Ultimately, mercury can be excreted *via* the urine, feces or expired air as well it can be excreted through breast milk (ATSDR, 1999).

A5-1.4 Biomonitoring

Human blood, hair, breast milk, and urine are used as indicators of mercury exposure (ATSDR, 1999). Reference values for total mercury in human tissue have been estimated in surveys from several countries, where average levels are: 8 µg/L in blood; 4 µg/L in urine; 8 µg/L in breast milk; 2 µg/g (ppm) in hair, and 10 µg/g in placenta (WHO, 1990). Due to the short half-life (3 days) of mercury in blood, blood samples are most useful for short-term exposures (WHO, 2003). However, long-term consumption of fish containing elevated methylmercury levels can be determined through blood analysis, as discussed below. In general, methylmercury concentrations in umbilical cord blood (cord blood) are greater than maternal blood. For hair to blood, a ratio of 250:1 has been approximated for methylmercury, although slight deviations from this exist due to inter-individual variation (ATSDR, 1999). Hair is regarded as a good indicator of methylmercury in the diet and in blood. When bound to hair, methylmercury is stable, and concentrations remain unchanged (WHO, 1990). Mercury vapours also accumulate in hair; however, this has not been regarded as a suitable indicator for inorganic mercury exposure (WHO, 1991). Urine samples are most appropriately used to indicate long-term exposure to inorganic forms of mercury (ATSDR, 1999; WHO, 2003). Inorganic mercury levels in urine are more strongly correlated with exposure than blood in cases of long-term, low level exposure (Yoshida, 1985). It must be taken into consideration that mercury content in blood or urine may not reflect concentrations in different organs in the body (WHO, 1991).

The relationship between body burden and toxicological effects have been used to derive toxic reference values for humans. In several studies documenting central nervous system effects in

workers chronically exposed to metallic mercury vapour, mean blood levels ranged from 9.8 to 12 µg/L, and mean urine levels ranged from 19.3 to 25 µg/L (Piikivi and Tolonen 1989; Piikivi 1989; Ngim *et al.,* 1992; Liang *et al.,* 1993). In many cases, exposure levels were extrapolated using measured blood mercury levels based on conversion factors derived by Roels *et al.* (1987). This study correlated metallic mercury exposure in air with levels in the blood and urine of battery manufacturing workers, and reported a conversion factor of 1:0.045 for mercury in air: blood, and 1:1.11 in air: urine (as creatinine: urinary Hg concentrations were corrected for urine dilution by adjusting to a urinary creatinine concentration of 1 g/L) (WHO, 1991; U.S. EPA IRIS, 1995a). For example, 40 µg/m^3 mercury in air corresponds to 50 µg Hg/g of creatinine in urine and 15 to 20 µg Hg/L in blood. Air to urine mercury ratios reported are approximately 4:5 which are lower than previously reported by WHO (WHO, 1991).

Long-term fish consumption is related to elevated levels of mercury in human blood. In these populations levels have been found to contain methylmercury blood levels of up to 200 µg/L compared to studies which show non-exposed individuals to contain blood mercury levels averaging 8 µg/L (WHO, 1990). Although the 200 µg/L value is elevated it is only associated with approximately 5% neurological damage risk in adults (WHO, 1990). In several epidemiological studies, neurological effects in children associated with *in utero* exposure to methylmercury have been associated with mean concentrations of 22.8 µg/L in cord blood, 11.68 ppm in children's hair, and 13 ppm in maternal hair (Kjellstrom *et al.,* 1989; Grandjean *et al.,* 1997). From the blood concentrations reported in these studies, acceptable dietary intake levels have been estimated (U.S. EPA IRIS, 2001). Effects to the cardiovascular system in children have been associated with increases in cord-blood mercury from 1 to 10 µg/L (Sorensen *et al.,* 1999), and similar effects in adults have been attributed to >2 ppm mercury in hair (Salonen *et al.,* 1995).

A5-1.5 Chemical and Physical Properties

Table A5-2 Chemical and Physical Properties of Elemental/Metallic Mercury

Chemical/Physical Property	***Value***	***Reference***
Colour/Form	Silver-white (liquid metal); tin-white (solid mercury)	Merck, 1989 in ATSDR, 1999
Dissociation Constant (pKa)	None reported	ATSDR, 1999
Henry's Law constant	No data (at 24.8 ºC)	ATSDR, 1999
Log K_{ow}	5.95	Stein *et al*., 1996 in ATSDR, 1999
Molecular Weight	200.59	Merck, 1989 in ATSDR, 1999
Vapour Pressure	2E-03 mm Hg at 25ºC	Merck, 1989 in ATSDR, 1999
Water Solubility	0.28 µmoles/L at 25ºC	Merck, 1989 in ATSDR, 1999
Odour	Odourless	HSDB, 1997 in ATSDR, 1999

Forms of inorganic mercury include mercuric chloride, mercuric sulphide, and mercurous chloride, *etc*. Organic mercury forms include mercuric acetate, methyl mercuric chloride, dimethylmercury and phenyl mercuric acetate, *etc.* (ATSDR, 1999).

A5-2.0 TOXICOLOGICAL SUMMARY: HUMAN HEALTH EFFECT

A5-2.1 Elemental/Metallic Mercury

Inhalation

Acute Effects

Respiratory effects have been reported in numerous studies as a result of acute inhalation of metallic mercury vapours (ATSDR, 1999, Cal EPA, 1999). McFarland and Reigel (1978) reported chest pains, dyspnea, hemoptysis, and impairment of pulmonary function in six workers exposed to an estimated concentration of 44,000 µg/m^3 for 4 to 8 hours. Death due to respiratory failure has been reported following accidental exposure to high (unquantified) concentrations of mercury vapour (Kanluen and Gottlieb, 1991).

Effects on the central nervous system resulting from acute exposure to mercury vapours include cognitive, sensory, personality, and motor disturbances (ATSDR, 1999; Cal EPA, 1999). Musculoskeletal effects (*e.g.,* muscle tremors) are thought to be neutrally mediated (ATSDR, 1999). After years of exposure at an estimated concentration of 44,000 µg/m^3 for 4 to 8 hours, workers reported irritability, and lack of ambition and loss of sexual desire (McFarland and Reigel, 1978).

Dermal effects such as erythematous and pruritic (itchy) skin rashes have been reported in numerous studies following acute inhalation of mercury vapours (ATSDR, 1999). Nakayama *et al.* (1983) found accidental exposure to mercury vapours from broken thermometers resulted in skin eruptions in 15 individuals.

Various studies have reported gastrointestinal (stomatitis, abdominal pains), cardiovascular (increased blood pressure, heart palpitations), haematological (elevated leukocyte count), hepatic (hepatomegaly), renal (proteinuria), and endocrine (thyroid enlargement, elevated triiodothyronine, low thyroid-stimulating hormone levels) effects resulting following acute exposure to mercury vapours (ATSDR, 1999). Exposure levels were not reported.

Chronic Effects

The central nervous system is the most sensitive target organ of metallic mercury vapour. Increased frequency of hand tremors compared to controls occurred in a cross-section of 26 workers employed at a chloralkali plant, a fluorescent tube, or an acetaldehyde manufacturing facility. Workers were exposed to a mean concentration of 26 µg/m^3 Hg for an average duration of 15 years (Fawer *et al.,* 1983). Ngim *et al.* (1992) reported impaired performance on several neurobehavioral tests (measures of motor speed, visual scanning and memory, visuomotor coordination and concentration) in 98 dentists exposed to a mean air concentration of 14 µg/m^3 for an average of 5.5 years. Piikivi and Tolonen (1989) detected changes in brain activity using the electroencephalogram (EEG) in 41 chloralkali workers exposed to an average air concentration of 25 µg/m^3 for a mean of 15.6 years. Exposure concentrations in air were extrapolated from blood mercury levels measured in the study. Piikivi and Hanninen (1989) documented sleep and memory disturbance in 60 chloralkali workers who experienced exposure to air concentrations of mercury similar to those reported in the latter study (Piikivi and Tolonen, 1989) over an average of 13.7 years. Piikivi (1989) reported symptoms of autonomic dysfunction (palpitations, pulse rate variations) in workers exposed to mercury vapours estimated at 30 µg/m^3 for 15.6 years. Liang *et al.* (1993) reported reduced performance on neurobehavioral tests (finger tapping, mental arithmetic, visual reaction time, or switching

attention) in 88 fluorescent lamp factory workers exposed to an average concentration of 30 µg/m^3 for an approximate duration of 15.8 years. These studies were used as the basis for identifying the safe chronic exposure levels of various agencies (U.S. EPA IRIS, 1995a; ATSDR, 1999; Cal EPA, 2005).

The kidney has also been identified as a sensitive target organ of metallic mercury toxicity. Cardenas *et al.* (1993) calculated estimated air concentrations from mercury urine concentrations. They documented renal tubular effects and changes in plasma enzymes (glycoaminoglycans, prostaglandin E2, thromboxane B2) in workers chronically exposed to an average air concentration of 15 µg/m^3. Proteinuria, proximal tubular and glomular changes, albuminuria, glomerulosclerosis, and increased urinary N-acetyl-ß-glucosaminidase occurred as a result of chronic occupational exposure at mercury vapour concentrations ranging from 25 to 60 µg/m^3 (Kazantzis *et al.,* 1962; Bernard *et al.,* 1987; Barregard *et al.,* 1988; Piikivi and Ruokonen, 1989). Several of these studies correlated renal toxicity endpoints with urinary mercury.

Cardiovascular effects (increased incidence of palpitations, reduced cardiovascular reflex responses) occurred in workers exposed to mercury vapours at an estimated air concentration of 30 µg/m^3 for approximately 5 years (Piikivi, 1989). Siblerud (1990) documented increased diastolic and systolic blood pressure in volunteers with mercury-containing dental amalgams. However, exposure duration was not specified and the comparisons with the control group were questionable. Other studies have documented increased heart and blood pressure (Tubbs *et al.,* 1982; Barregard *et al.,* 1990; Fagala and Wigg, 1992; Taueg *et al.,* 1992).

Limited information was available with respect to other toxic effects of metallic mercury. Autoimmune responses have been reported in association with renal effects in several studies (Tubbs *et al.,* 1982; Cardenas *et al.,* 1993). The stimulation of T-lymphocytes occurred in workers exposed to mercury vapour at concentrations ranging from 14 to 90 µg/m^3 for periods of <10 to 31 years (Moszczynski *et al.,* 1995). Bencko *et al.* (1990) observed immunological disturbances as measured by increases in IgA and IgM in workers in a metallic mercury plant. This study lacked information in regards to exposure duration, levels, and did not make adjustment for important confounding factors.

Gastrointestinal effects (stomatitis, ulcerations of oral mucosa, oropharyngeal symptoms) have been observed in workers chronically exposed to metallic mercury vapours (Smith *et al.,* 1970; Vroom and Greer, 1972; Buckell *et al.,* 1993). Endocrine effects (elevated T3, T4) have been reported in chronically exposed workers (Barregard *et al.,* 1994)

Musculoskeletal effects such as muscle fasciculation and tremors have been reported in numerous studies resulting from chronic exposure (ATSDR, 1999). Some of these muscular effects are also associated with neurological toxicity.

Studies of chronic exposure to mercury vapour provide weak evidence for reproductive toxicity. An increase in the rate of spontaneous abortions was associated with increased metallic mercury concentrations in the urine of expectant fathers who had experienced ≥4 month occupational exposure to mercury when compared to unexposed controls (Cordier *et al.,* 1991). No effect of chronic mercury exposure was reported on male fertility in this population. Sikorski *et al.* (1987) reported increased reproductive failures in women occupationally-exposed to mercury in the dental industry; however, results of this study were uncertain (Larsson, 1995).

Conflicting evidence for developmental effects of chronic exposure to mercury vapour has been reported. Studies have reported healthy births after chronic occupational exposure to mercury

vapours (Melkonian and Baker, 1988; Thorp *et al.,* 1992). No studies investigating developmental effects in children exposed *in utero* were located (ATSDR, 1999; RIVM, 2001; Cal EPA, 2005).

A5-2.2 Inorganic Mercury

Limited information is available pertaining to the chronic effects inorganic mercury in humans (WHO, 1991; ATSDR, 1999; OEHHA, 1999; RIVM, 2001). The kidney is a major target organ of chronic inorganic mercury exposure, and autoimmune glomerulonephritis has been documented in humans (U.S. EPA, 1992; OEHHA, 1999). Renal failure, dementia, and irritability occurred in two women from chronic ingestion of laxatives containing mercurous chloride (120 mg mercurous chloride, or 720 µg/kg-day) (Davis *et al.,* 1974). The first subject ingested 2 tablets/day for 25 years, and the second, 2 tablets/day for 6 years. Both women died from mercury poisoning. Non-fatal poisoning has resulted from chronic use of the medicine calomel (mercury [1] chloride), causing stomatitis and salivation (Skerfving and Vostal, 1972). Dermal effects have been reported in children from subchronic exposure to mercurous chloride in medications (tablets, powders) (Warkany and Hubbard, 1953). Acrodynia (pink disease) occurred in some of the subjects. This condition is characterized by rash, swelling, itching, excessive perspiration and thirst. Warkany and Hubbard (1953) also reported increased blood pressure and tachycardia in exposed children.

A5-2.3 Organic Mercury

Oral

Chronic Effects

Several epidemiological studies of neurotoxicity caused by chronic foetal exposure provide the basis for chronic oral exposure levels for methylmercury for agencies such as ATSDR (1999), U.S. EPA IRIS (2001), RIVM (2001), WHO (2004), and Health Canada (2007a).

Once ingested, methylmercury is rapidly absorbed in the gastrointestinal tract. Approximately 95% of the methylmercury ingested is absorbed, and peak methylmercury levels in the blood are reached within 6 hours. In comparison to inorganic mercury compounds, methylmercury is readily able to cross plasma membranes as well as the blood-brain barrier and the placenta as animal studies have shown since the blood-brain barrier in the foetus is not fully developed. Once in the brain, methylmercury accumulates and is slowly converted to inorganic mercury (Maycock and Benford, 2007). Developmental neurotoxicity is considered to be the most sensitive chronic endpoint of methylmercury (ATSDR, 1999). There is clear evidence from the concentrations of mercury in human milk and in the blood of infants that, compared with exposure *in utero*, postnatal exposure to methylmercury is considerably lower in infants who are breastfed (JECFA, 2007). Postnatally, both neuronal myelination and remodelling of the cortex of the brain occur and have a protracted time course, continuing through adolescence until about 17 years of age (Rice and Barone, 2000; JECFA, 2007).

Davidson *et al.* (1998) tested neurodevelopmental capabilities in children (5.5 years old) that were exposed *in utero* (maternal fish ingestion) and through breast milk in 779 mother-infant pairs in fish-eating populations in the Republic of Seychelles. Mercury exposure was determined from maternal and child hair for which determinations of mean concentrations were 6.9 and 6.5 ppm, respectively. Fish in the maternal diet were contaminated with methylmercury and fish consumption was comparable to that in the U.S. In addition, the location of the Seychelles was considered pristine, suggesting the health of the population was not influenced

by other contaminants. A NOAEL (1.3 µg/kg-day) was established for developmental effects in this study. Similar epidemiological studies by Myers *et al.* (1997) and Crump *et al.* (1998) reported NOAELs (0.5 and 0.62 µg/kg-day, respectively) that indicated effects were observed at lower levels of contamination. Grandjean *et al.* (1997) reported neurotoxicity associated with *in utero* exposure in children at 7 years of age in a study of 900 mother-infant pairs in the Faroe Islands. Tests showed mercury-related abnormalities with neuropsychological indicators such as language, attention, and memory. The mean cord blood concentration of mercury was 22.8 µg/L, and the average concentration of methylmercury found in children's hair was 11.68 ppm. In Northern New Zealand, dose-related effects for psychological endpoints occurred in 6 year olds resulting from pre-natal exposure (Kjellstrom *et al.,* 1989). Maternal hair mercury levels of 13 ppm (during pregnancy) were associated with the effects in this study population. Data from these studies were used to derive benchmarks for chronic oral exposure limits (U.S. EPA IRIS, 2001; WHO, 2004). No studies in regards to reproductive effects of chronic exposure to mercury in humans were located (ATSDR, 1999; Cal EPA, 2005).

In adults over 40, Weil *et al.* (2005) and Auger *et al.* (2005) have attempted to show associations of mercury exposure and altered neurobehavioural scores and abnormalities. Weil *et al.* (2005) studied the association of mercury blood levels and altered neurobehavioural scores in 474 participants aged 50 to 70 years and found no evidence to suggest that blood mercury levels were adversely associated with scores on neurobehavioural tests in aging adults. Auger *et al.* (2005) reanalyzed data collected from an indigenous population (Quebec Cree in 1977) also investigated the possibility that to investigate low level methylmercury exposure as a risk factor for neurologic abnormalities. Elevated levels of mercury in hair samples (<50,000 µg/kg) were associated with tremors in younger members of the band. Specifically, a 6,000 µg/kg increase in mercury in the past month's average scalp hair resulted in a 2.1 x increased chance for tremors in adults under 40. There was no additional evidence to suggest sensory disturbance, lack of coordination, auditory defects, motor abnormalities, reflexes, systemic symptoms or cognitive impairment.

In terms of cardiotoxicity, conclusive evidence resulting from chronic exposure to methylmercury is not available. There is inconclusive evidence to support a causal relationship between cardiovascular effects and chronic methylmercury exposure. However, this area has been targeted for continued research, due to recent studies with evidence of cardiovascular effects. A recent study by Sorensen *et al.* (1999) reported a link between a decrease in heart rate variability and blood-cord mercury in children that were exposed *in utero*. In a 7 year study, Salonen *et al.* (1995) found that men with higher levels of methylmercury in hair were at greater risk of myocardial infarction than the general population. An epidemiological study by Virtanen *et al.* (2005) concluded that high mercury content in hair may be a risk factor for cardiovascular disease and coronary heart disease.

A5-2.4 Carcinogenicity

OSHA and NTP have not classified mercury and its compounds as to their carcinogenicity. ACGIH (1996) and EPA (U.S. EPA IRIS, 1995a) determined that metallic mercury is not classifiable as human carcinogens (Groups A4 and D, respectively). IARC (2007) stated that mercury and inorganic mercury compounds are not classifiable as to its carcinogenicity to humans (Group 3).

Cal EPA (2006) classified methylmercury compounds as known to cause cancer; however, mercury and compounds were not classified as to their carcinogenicity. The U.S. EPA IRIS (2001) classified methylmercury and one inorganic form of mercury (mercuric chloride) as possible human carcinogens (Group C), and deemed elemental mercury as not classifiable as

to human carcinogenicity (Group D). In the absence of human carcinogenicity data, this was based on carcinogenicity in mice and rats (NTP, 1993).

IARC (2007) classified methylmercury compounds as being possibly carcinogenic to humans (Group 2B), and deemed metallic mercury and inorganic mercury compounds as not classifiable as to their carcinogenicity to humans (Group 3).

A5-3.0 TOXICOLOGICAL REFERENCE VALUES (TRVS)

Carcinogenic TRVs

In accordance with carcinogenic classifications outlined above, mercury was evaluated as a non-carcinogen within the current assessment. Therefore, carcinogenic TRVs were not required.

Non-Carcinogenic TRVs

Elemental/Metallic Mercury

For the purposes of the current assessment, elemental mercury was assessed *via* the inhalation pathway only. RIVM has stated that absorption of metallic mercury in the body after oral consumption is quite minimal compared to inhaled metallic vapour whereby, 70 to 80% is absorbed into the body. Therefore, since absorption into the body is minimal after oral consumption, this pathway will not be assessed in the HHRA. Additionally, mercury is most common found in rocks and soil as mercuric sulphide (an inorganic form).

U.S. EPA IRIS (1995a) derived a chronic inhalation RfC of 0.3 µg/m^3 for elemental mercury vapour based on neurobehavioral effects (hand tremors, increases in memory disturbance, and slight subjective and objective evidence of autonomic dysfunction) in occupationally-exposed subjects (Fawer *et al.,* 1983; Piikivi and Tolonen, 1989; Piikivi and Hanninen, 1989; Piikivi, 1989; Ngim *et al.,* 1992; Liang *et al.,* 1993). A LOAEL of 9 µg/m^3 was derived from measured air concentrations reported by Fawer *et al.* (1983), Ngim *et al.* (1992), and Liang *et al.* (1993), and mercury blood levels reported by Piikivi and Tolonen (1989), Piikivi and Hanninen, (1989), and Piikivi (1989). These blood levels were converted to air concentrations using a conversion factor (air:blood;1:4.5) derived by Roels *et al.* (1987). Air concentrations associated with neurobehavioral effects in these studies converged at a LOAEL of 25 µg/m^3, which was corrected for occupational ventilation rates (0.5 m^3/d) and the length of a work week (5/7days), resulting in an adjusted LOAEL of 9 µg/m^3. An uncertainty factor of 10 was applied for the protection of sensitive human subpopulations, and an uncertainty factor of 3 was applied to account for the lack of reproductive and developmental studies. U.S. EPA IRIS (1995a) assigned a medium level of confidence in the RfC (0.3 µg/m^3). This value was adopted as the inhalation chronic exposure limit for elemental mercury in the current assessment (Table A5-3). The studies used for the derivation of the RfC (U.S. EPA IRIS, 1995a) were also employed for the derivation of the chronic REL by Cal EPA (1999), and one study (Fawer *et al.,* 1983) was used as the basis of the chronic MRL and TCA developed by ATSDR (1999) and RIVM (2001), respectively.

Health Canada (2008) has selected a provisional tolerable concentration (TC) value of 0.06 µg/m^3 for chronic inhalation of elemental mercury vapour. This value is based on an epidemiology study by Ngim *et al*. (1992) of an occupational cohort who was exposed to mercury vapours over an average duration of 5.5 years. Neurobehavioral effects were noted and a corresponding LOAEL of 14 µg/m^3 was derived and the adjusted LOAEL to a time

weighted average at a continuous air concentration was calculated to be 6 µg/m^3. An uncertainty factor of 100 was chosen; 10 for inter-individual variation and 10 for the extrapolation from a LOAEL to a NOAEL. This value was chosen as the chronic inhalation exposure limit for elemental mercury in the current assessment (Table A5-3).

Inorganic Mercury

For the current risk assessment, inorganic mercury was evaluated for both the oral and inhalation pathways.

Cal EPA (1999) derived an acute inhalation REL of 1.8 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.,* 1993). A cumulative uncertainty factor of 1,000 was applied: 10 for the use of a LOAEL, 10 for intraspecies uncertainty, and 10 for the extrapolation from rats to humans. This REL is considered to be an overestimate for inorganic mercury (Cal EPA, 1999). This value was adopted as the 1 hour acute exposure limit for the current assessment (Table A5-3).

MOE (2008) lists an AAQC (24 hour average) of 2 µg/m^3 for elemental mercury. This value was adopted as the 24 hour acute exposure limit for the current assessment; however, the basis of this value is unknown (Table A5-3).

An annual average guideline of 1 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.,* 1993). 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. This value was adopted as the chronic inhalation exposure limit for inorganic mercury for the current assessment (Table A5-3).

Mercury was retained for evaluation in the multi-pathway exposure model due to its persistence; therefore, an oral RfD was required. Acute and intermediate oral MRLs were derived by ATSDR (1999) for inorganic mercury. Seven µg/kg-day was selected as the acute oral MRL in this current assessment (Table A5-3) and was calculated using the NOAEL of 930 µg/kg-day for renal effects noted in rats that were exposed to gavage doses of mercuric chloride over a 14 day period (NTP, 1993). The intermediate oral MRL was calculated as 2 µg/kg-day and is based on renal effects seen in rats whereby a NOAEL of 230 µg/kg-day was derived (Dieter *et al*., 1992; NTP, 1993).

A TDI of 0.3 µg/kg-day for the chronic oral intake of inorganic (ionic) mercury has been derived by Health Canada (2004a). This value was back-calculated from a drinking water equivalent level (DWEL) of 10 µg/L and adjusted for daily water consumption and body weight (RfD = 10 µg/L x 2L/day/kg bw). The U.S. EPA (1987) recommended the DWEL based on three studies documenting kidney effects in Brown Norway rats exposed to inorganic mercury (Druet *et al*., 1978; Bernaudin *et al*., 1981; Andres, 1984). Rats injected with mercuric chloride doses ranging from zero to 2,000 µg/kg 3 times per week for a period of 8 to 12 weeks developed renal tubular lesions at high doses, and proteinuria was reported at doses ≥100 µg/kg. In exposed rats, antibody formation was detected by the fixation of IgG antiserum in kidney cryostat sections (Druet *et al*., 1978). Bernaudin *et al*. (1981) exposed rats to mercurials *via* ingestion (0 and

3,000 µg/kg-week) and by inhalation for 60 days. IgG deposition in glomeruli was observed in 80% of exposed rats in the early stages of the study (15 days). This effect was observed in 100% of exposed rats but not controls after 60 days. Andres (1984) reported deposits of IgG in renal glomeruli of rats injected twice a week with mercuric chloride (3,000 µg/kg in 1 ml water) for a period of 60 days. Additional effects on exposed rats included lesions on the colon, and abnormal deposits (IgG) on the intestinal glands and mucous membranes. LOAELs ranging from 226 to 633 µg/kg-day were derived from the studies, with the application of dose conversions in all of the studies (factor 0.739 for $HgCl_2$ to Hg^2+; 10% for subcutaneous to oral exposure; and time-weighted average for dosing).

The U.S. EPA also identified an oral RfD for mercuric chloride of 0.3 µg/kg-day (U.S. EPA, IRIS, 1995b). An uncertainty factor of 1,000 was applied to an adjusted LOAEL ranging from 226 to 633 µg/kg-day to account for the use of sub-chronic studies (10), the extrapolation from a LOAEL to a NOAEL (10), and for variation of sensitivity within the human population and for the extrapolation of from animal to humans (10) (U.S. EPA IRIS, 1995b). The Health Canada (2004a) TDI was adopted as the chronic oral exposure limit for inorganic mercury for the current assessment (Table A5-3).

Organic Mercury

For the purposes of the current assessment, methylmercury was only assessed *via* oral exposure. Methylmercury is primarily produced by microorganisms, which can convert inorganic mercury to an organic form. In the past, organic forms of mercury were used as fungicides, but these uses are presently banned in North America and Europe due to evidence of adverse human health effects. WHO has indicated that methyl mercury does not largely occur in the atmosphere; therefore, inhalation exposure will contribute minimally to the overall intake of methyl mercury. The inhalation pathway for methyl mercury is not commonly assessed in HHRA.

WHO (2004) derived a pTWI of 1.6 µg/kg-week for methylmercury based on the association between maternal exposure and developmental effects in children (Grandjean *et al*., 1997; Davidson *et al.,* 1998; Budtz-Jorgensen *et al.*, 1999). A steady state of 1.5 µg/kg-day was estimated to represent the level of exposure not expected to have any appreciable adverse effects on children. An uncertainty factor of 2 was applied to the TDI to account for interindividual variation of the maternal hair:blood. In addition, a combined uncertainty factor of 3.2 (WHO, 1990) was applied to account for total human interindividual variation for dose reconstruction in converting maternal blood concentration to a steady-state TDI. Therefore, an uncertainty factor of 6.4 (2x3.2) was applied to the calculated TDI of 1.5 µg/kg-day to result in a TDI of 0.23 µg/kg-day, which equates to a pTWI of 1.6 µg/kg-week (1.5 µg/kg-day x 7 days). The calculated pTWI is for the protection of developing fetuses, which are the most sensitive subpopulation. This revised pTWI was considered protective of all effects, including neurodevelopmental effects (Maycock and Benford, 2007). In the UK and the Scientific Advisory Committee on Nutrition and Committee on Toxicity of Chemicals in Food (COT) found no evidence to suggest that the previous JECFA pTWI of 3.3 µg/kg-week was insufficiently protective for effects of methylmercury other than developmental adverse effects. Therefore, the guideline of 3.3 µg/kg bw/week could be used for all groups with the exception of women of child bearing age. Taking into account the half-life of methylmercury, the COT considered that the JECFA pTWI of 1.6 µg/kg-week should be used in assessing dietary exposure to methylmercury of women who were pregnant or likely to become pregnant.

The pTWI of 1.6 µg/kg-week is similar to the value adopted by Health Canada (2007a). This value was adopted as the oral chronic exposure limit for methylmercury in the current

assessment (Table A5-3). JECFA (2007) and Health Canada (2007a) could not identify a level of intake higher than the existing pTWI that would not pose a risk of developmental neurotoxicity for infants and children. Health Canada (2007a) took a similar approach and calculated a TDI of 1 µg/kg-day for a 60 kg woman. An uncertainty factor of 5 for pregnant women, women of childbearing age, and young children and has resulted in the establishment of a pTDI of 0.2 µg/kg-day. This correlates approximately with the values determined in the UK by the Scientific Advisory Committee on Nutrition and COT for weekly intake (Health Canada: 0.02 µg/kg-day x 7 days=1.4 µg/kg). For the general population, Health Canada has stated a pTDI value of 0.47 µg/kg-day (Health Canada, 2007a) (Table A5-3).

A5-4.0 RELATIVE DERMAL BIOAVAILABILITY

The relative dermal bioavailability for mercury in soil is 0.05 (Health Canada, 2004b). The dermal permeability co-efficient in water is 0.003 cm/hr (U.S. EPA, 2004).

Table A5-3 Non-Carcinogenic Toxicological Exposure Limits for Mercury

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
Elemental Mercury									
Inhalation (µg/m^3)									
REL (intended for use in assessing mercury salts as well as elemental mercury)	Chronic	0.09	Neurotoxicity as measured by: intention tremor; memory and sleep disturbances; decreased performance on neurobehavioral tests	Human inhalation of workplace air	Fawer *et al*., 1983; Piikivi and Hanninen 1989; Piikivi and Tolonen 1989; Piikivi 1989; Ngim *et al*., 1992; supported by Liang *et al*., 1993.	LOAEL: 25 µg/m^3	100	Cal EPA, 1999	1993
MRL (metallic)	Chronic	0.2	Significant increase in the average velocity of naturally occurring tremors	Human occupational study (average exposure of 15.3-years)	Fawer *et al.*, 1983	LOAEL (HEC): 6 µg/m^3	30	ATSDR, 1999	1999
TCA (metallic vapours)	Chronic	0.2	Increased frequency of mild tremors and cognitive skills associated with elevated blood and creatinine levels	Human study	Fawer *et al.,* 1983	LOAEC (ADJ): 6 µg/m^3	30	RIVM, 2001	1999/2000
RfC (metallic)	Chronic	0.3	Hand tremor; increases in memory disturbances; slight subjective and objective evidence of autonomic dysfunction	Human occupational studies	Fawer *et al.,* 1983; Piikivi and Tolonen, 1989; Piikivi and Hanninen, 1989; Piikivi, 1989; Ngim *et al.,* 1992; Liang *et al.,* 1993	LOAEL (AJ): 9 µg/m^3	30	U.S. EPA IRIS, 1995a	1995
TC (provisional) (mercury vapour)	**Chronic**	**0.06**	**Neurobehavioral effects**	**Occupationally exposed cohort (inhalation) (Duration of 5.5 years (average))**	**Ngim *et al*., 1992**	**LOAEL: 14 µg/m^3 (6 µg/m^3 adjusted to a time weighted average continuous air concentration)**	**100**	**Health Canada, 2008**	**Not provided**

Table A5-3 Non-Carcinogenic Toxicological Exposure Limits for Mercury

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
Inorganic Mercury									
Inhalation (µg/m^3)									
REL; 1 hour exposure time	**Acute**	**1.8**	**Behavioural deficits after *in utero* exposure to metallic mercury vapour (CNS disturbances in offspring)**	**Maternal rats Exposed during gestation**	**Danielsson *et al*., 1993**	**1 hour LOAEL: 1800 µg/m^3**	**1,000**	**Cal EPA, 1999**	**1999**
AAQC; 24 hours averaging time (metallic)	**Acute**	**2.0**	**Health effects**	**Not provided**	**Not provided**	**Not provided**	**Not provided**	**MOE, 2005; 2008**	**Not provided**
Annual average guideline (inorganic vapour)	**Chronic**	**1.0**	**Objective tremor, renal tubular effects (changes is plasma enzymes) and non-specific symptoms**	**Workers subjected to long term exposure of Hg vapour**	**WHO, 1991; Cardenas *et al.,* 1993**	**LOAEL: 10 to 30 µg/m^3**	**20**	**WHO, 2000**	**1999**
Oral (µg/kg-day)									
MRL (inorganic)	**Acute**	**7.0**	**Renal effects (increased absolute and relative kidney weights, increased incidence and severity of tubular necrosis)**	**Rats exposed to gavage doses of mercuric chloride for 10 days**	**NTP, 1993**	**NOAEL: 930 µg/kg-day**	**100**	**ATSDR, 1999**	**1999**
MRL (inorganic)	Intermediate	2.0	Renal effects (Increased absolute and relative kidney weights, increased incidence of nephropathy)	Rats exposed to gavage doses of mercuric chloride 5 days a week for 6 months	Dieter *et al*., 1992; NTP 1993	NOAEL: 230 µg/kg-day	100	ATSDR, 1999	1999
TDI (inorganic, ionic)	**Chronic**	**0.3[a]**	**Kidney effects**	**Rat gavage and subcutaneous injection studies**	**Druet *et al*., 1978; Bernaudin *et al*., 1981; Andres, 1984**	**LOAEL (ADJ): 226 to 633 µg/kg-day**	**1,000**	**Health Canada, 2004a; 2008**	**Not provided**

Table A5-3 Non-Carcinogenic Toxicological Exposure Limits for Mercury

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
RfD (mercuric chloride)	Chronic	0.3[b]	Autoimmune effects	Rat gavage and subcutaneous injection studies	Druet *et al*.,1978; Bernaudin *et al*., 1981; Andres, 1984; U.S. EPA, 1987	LOAEL (ADJ): 226 to 633 µg/kg/day	1,000	U.S. EPA IRIS, 1995b	1995
$_{P}$TWI (total mercury)[d] (µg/kg-wk)	Chronic	5.0	Poisoning	Not provided	Not provided	Not provided	Not provided	JECFA, 1972; WHO, 1978	1972
TDI (inorganic)	Chronic	2.0	Renal toxicity (kidney weight)	Experimental animal studies	NTP, 1993	NOAEL: 230 µg/kg-day	100	RIVM, 2001	1999/2000

Table A5-3 Non-Carcinogenic Toxicological Exposure Limits for Mercury									
Reported Exposure Limit	***Duration***	***Exposure Limit***	***Critical Effect***	***Description of Study***	***References***	***Endpoint***	***Uncertainty Factor***	***Source***	***Derivation Date***
Methylmercury									
Inhalation (µg/m^3)									
AAQC; 24 hours averaging time (Hg as alkyl compounds)	Acute	0.5	Health effects	Not provided	Not provided	Not provided	Not provided	MOE, 2005, 2008	Not provided
Oral (µg/kg-day)									
RfD	Chronic	0.1	Developmental neuropsychological impairment	Human epidemiological studies of mother-infant pairs	Kjellstrom *et al.,* 1989; Grandjean *et al.,* 1997; Davidson *et al.,* 1998; Budtz-Jorgensen *et al.*, 1999	$BMDL_{05}$: 0.857 - 1.472 µg/kg-day	10	U.S. EPA IRIS, 2001	2001
TDI (organic)	Chronic	0.1	Developmental effects	Children exposed *in utero* to methylmercury from maternal fish ingestion	Davidson *et al.,* 1998.	NOAEL: 1.3 µg/kg-day	10	RIVM, 2001	1999/2000
pTDI (total mercury)[c]	**Chronic**	**0.47 (general adult population) and 0.2 (women of childbearing age, children (<12 yrs)**	**Neurotoxicity and neurodevelopmental toxicity**	**General population: epidemic accidental poisoning and chronic low-level exposure in populations with high consumption of fish & Women of child-bearing age and young children: epidemiological prospective studies of neurodevelopmental effects**	**Grandjean *et al*., 1997; Feeley and Lo, 1998**	**10 ppm maternal hair methylmercury level as the approximate threshold (for women of child-bearing age and young children TDI value) (equivalent to 1 µg/kg-day)**	**5 (for women of child-bearing age and young children TDI value)**	**Health Canada, 2007a; 2008**	**1997**

Table A5-3 Non-Carcinogenic Toxicological Exposure Limits for Mercury

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
$_{P}$TWI (µg/kg-wk)	Chronic	1.6	Association between maternal exposure and developmental effects in children	Not provided	Grandjean *et al*., 1997; Davidson *et al.*, 1998; Budtz-Jørgensen *et al.*, 1999	NOAEL: 1.5 µg/kg-day	6.4	WHO, 2004	2003
MRL	Chronic	0.3	Neurodevelopmental effects	Children exposed *in utero* to methylmercury from maternal fish ingestion	Davidson *et al.*, 1998.	NOAEL: 1.3 µg/kg-day	4.5	ATSDR, 1999	1999

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment
MRL Minimal risk level
TDI Tolerable Daily Intake
TI Tolerable Intake
TC Tolerable Concentration
$_{P}$TWI Provisional Tolerable Daily Intake
AAQC Ambient Air Quality Criteria
REL Reference Exposure Levels
RfD Reference Dose
RfC Reference Concentration
TCA Tolerable Concentration in Air
[a] All oral exposure limits are in mg/kg/day, while all inhalation exposure limits are in mg/m^3
[b] Back calculated from a drinking water equivalent level of 0.10 mg/L. Until 1997 this value was adopted by the U.S. EPA IRIS as the oral RfD for inorganic mercury.
[c] Health Canada (2007) makes the assumption that 100% of total mercury is present as methylmercury.
[d] No more than 2/3 of the total mercury is present as methylmercury

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APPENDIX A:

TOXICOLOGICAL PROFILES

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A6-1.0 SELENIUM

Selenium has been reviewed by U.S. EPA IRIS (1991); Health Canada (1992; 2008); IOM (2000); Cal EPA (2001); ATSDR (2003); and, MOE (2005; 2008). The following profile represents a short summary of the relevant background information and human toxicity data for selenium. A summary of the toxicity reference values selected for the HHRA is provided in Table A6-1.

Table A6-1 Summary Table of Toxicity Reference Values Selected for the HHRA

Route of Exposure	*Exposure Limit*	*Type of Limit*	*Toxicological Basis*	*Reference*	
				Study	*Regulatory*
Acute Effects					
Inhalation (24 hour)	10 µg/m^3	AAQC	Health Effects	Not provided	MOE, 2008
Chronic-Cancer (Non-threshold) Effects					
Oral	NA		NA	NA	NA
Inhalation	NA		NA	NA	NA
Dermal	NA		NA	NA	NA
Chronic-Non-cancer (Threshold) Effects					
Oral	<6mo: 5.5; 7mo-4yrs: 6.2; 5-11yrs: 6.3; 12-19yrs: 6.2; 20+(70.7kg): 5.7 g/kg/day	UL	Selenosis	Shearer and Hadjimarkos, 1975; Yang and Zhou, 1994	Health Canada, 2008
Inhalation	20 µg/m^3	REL	Clinical selenosis	Yang *et al*., 1989a	Cal EPA, 2001
Dermal	NA		NA	NA	NA

NA Not applicable
REL Reference exposure level (derived from oral RfD)
AAQC Ambient Air Quality Criteria
UL Tolerable Upper Intake Level

A6-1.1 Background Information

Selenium is a naturally occurring element which is widely but unevenly distributed within the earth's crust (ATSDR, 2003). Selenium has four valence states (I, II, IV, VI) and can exist in a variety of chemical forms in the environment including various salts, oxides, hydrides, sulphides, and metal selenides. The soluble oxyanions selenate [Se(VI)] and selenite [Se(IV)] are the primary forms of selenium in the ambient environment. In air, the most common selenium compounds are selenium dioxide, dimethyl selenide, dimethyl diselenide and hydrogen selenide. Hydrogen selenide is highly reactive, and is rapidly oxidized to elemental selenium and water (NAS, 1976); thus, it does not persist. Selenium compounds are used in the glass industry as decolourizing agents and in the rubber industry as vulcanizing agents (Cal EPA, 2001). Selenium-containing compounds can also be found in photographic toning baths, insecticides and photoelectric cells (Cal EPA, 2001). The most widely used selenium compound in industry is selenium dioxide which catalyzes reactions of organic compounds (Cal EPA, 2001). The greatest anthropogenic sources of selenium in the ambient environment are from the combustion of fossil fuels and the production and refinement of copper (Cal EPA, 2001).

Selenium is an essential nutrient required by humans. Exposure to low levels of selenium occurs on a daily basis *via* food, water, and air (ATSDR, 2003). However, typically, the greatest percentage of exposure to selenium comes from the dietary ingestion of organic (selenomethionine and selencysteine) and inorganic (selenate and selenite) forms of selenium, although, the organic forms are more readily absorbed as compared to the inorganic forms (ATSDR, 2003). In the U.S., dietary intake of selenium is approximately 1 to 2 µg/kg/day but can be greater depending on the area. In foods, meat products have the highest levels of selenium, whereas fruits and vegetables have the lowest levels (ATSDR, 2003). Brazil nuts have elevated selenium levels since they are grown in soils containing high levels of selenium (Secor and Lisk, 1989). Worldwide, selenium concentrations in the soil are on average between 0.05 to 0.09 mg/kg and in the U.S. most soils have concentrations are between 0.01 to 0.2 mg/kg (Sindeeva, 1964). In seleniferous soils, concentrations in the U.S. range from <2 to <100 mg/kg (Rosenfeld and Beath, 1964). Atmospheric depositions of selenium from mining and smelting operations will also contribute to these levels (Glooschenko and Arafat, 1988). Normally, humans are not exposed to large amounts of selenium in the air, unless selenium dust or volatile selenium compounds are formed in the workplace (ATSDR, 2003).

A6-1.2 Fate and Transport

Selenium in air exists mainly in its more volatile states such as the inorganic compounds selenium dioxide and hydrogen selenide, as well as the organic compounds dimethyl selenide and dimethyl diselenide. Elemental selenium can also be formed by the rapid oxidation of hydrogen selenide and the reduction of selenium dioxide released to the air from fossil fuel combustion (ATSDR, 2003). These airborne compounds may be removed by wet or dry deposition to soil or surface water. However, dimethyl selenide and methyl selenide can persist in the atmosphere due to their high volatility (ATSDR, 2003). In surface water and soil pore water, the predominant selenium species are the salts of selenic (selenates) and selenious (selenites) acids (CCME, 2007). Because of its high solubility and inability to adsorb to soil particles, sodium selenate is one of the more mobile selenium compounds, which are more available for uptake by biological systems (ATSDR, 2003). Under alkaline and well-oxidized conditions, selenates and selenites predominate in aqueous environments; between pH 3.5 and 9, selenates and selenites in the form of the diselenite ion predominate. Insoluble elemental selenium is formed under reducing conditions, but its bioavailability is low due to its low solubility (CCME, 2007). Selenium is also bioaccumulated by aquatic organisms such as algae, insect larvae, molluscs, and crustaceans (ATSDR, 2003).

Natural levels of selenium in soils are mostly the product of weathering and leaching, with some input from wet and dry deposition from the atmosphere (CCME, 2007). The pH and pE in soils are important factors in the transport of selenium. In soils of low pH and strong reducing conditions (high organic content), metal selenides, selenium sulfides and selenites predominate (CCME, 2007). In neutral conditions, selenites are the more common species (ATSDR, 2003), but can form insoluble complexes with iron oxides/hydroxides and clays (CCME, 2007). As in fully aqueous environments, in strong oxidizing and alkaline conditions, the predominating species are selenates, which are more available for uptake by biological systems due to their high mobility and their relative inability to be adsorbed by soil particles (ATSDR, 2003).

Terrestrial plants that take up soluble selenates and selenites convert these species into organic selenium compounds, which are then released to the soil when the plants die (ATSDR, 2003). In reducing soil conditions, elemental selenium is formed, which (along with inorganic selenium compounds) can be methylated by microorganisms and then volatilized into the atmosphere (CCME, 2007). Selenium is also known to bioaccumulate in both aquatic and terrestrial food webs (earthworms, insects) (CCME, 2007).

A6-1.3 Toxicokinetics

Absorption of selenium *via* inhalation has shown inconclusive results in occupational studies (Sanchez-Ocampo *et al*., 1996; Glover, 1970). When ingested orally, selenium is readily absorbed from the gastrointestinal tract. Both sodium selenite and selenomethionine exceeded 80% absorption after consumption of both small and large doses (Thomson, 1974; Thomson and Stewart, 1974; Griffiths *et al*., 1976; Thomson *et al*., 1977). Other studies demonstrated that the extent of adsorption is dependent on the chemical form of selenium; particularly selenomethionine was absorbed more efficiently in the body than sodium selenite (Robinson *et al*., 1978; Swanson *et al*., 1991; Moser-Veillon *et al*., 1992). Those with selenium deficient diets did not show evidence of increased absorption (Martin *et al*., 1989). No evidence could be found correlating selenium absorption due to dermal exposure (Cummins and Kimura, 1971; Burke *et al*., 1992; Kalivas, 1993).

After oral absorption of selenium, it is distributed into plasma proteins including selenoprotein-P, gluthathione peroxidases and albumin (Ducros *et al*., 2000). Since 3% of the plasma selenium is bound to lipoproteins, then selenomethionine can replace methionine during protein synthesis and/or be bound to cysteine residues by Se-S bonds (ATSDR, 2003). As well, selenoprotein-P is an extracellular protein in the plasma, therefore it is involved in the transport of selenium and as an antioxidant (Hill and Burk, 1989; Yang *et al*., 1989a; Burk and Hill, 2000). Generally, selenium from selenomethionine is in greater concentrations in tissues and for a greater period of time as compared to inorganic selenium because of slower elimination rates as a result of its incorporation into body proteins (Stadtman, 1983; 1987; 1990; Ip and Hayes, 1989; Butler *et al*., 1990; Salbe and Levander, 1990; Gronbaek and Thorlacius-Ussig, 1992).

In brief, inorganic selenium is reduced to hydrogen selenide which is incorporated into selenoproteins in the form of covalent carbon-selenium bonds after transformation to selenophosphate and selenocysteinyl tRNA or excreted from the body after transformation to the methylated metabolites of selenide (Holmgren and Kumar, 1989; Lobinski *et al*., 2000). Selenomethionine, is also metabolized, but if not immediately, it can be stored in the skeletal system, muscle, liver, stomach, gastrointestinal muscosa and erythrocytes until it is metabolized (Schrauzer, 2000). Excretion and elimination of selenium from the body may be dose dependent and occurs mainly *via* the urine, feces and expired air; minor amounts may also be excreted *via* released sweat (McConnell and Roth, 1966; Lathrop *et al*., 1972; Thomson and Stewart, 1974; Griffiths *et al*., 1976; Levander *et al*., 1987; Hawkes *et al*., 1992; 1994; ATSDR, 2003). The proportion of selenium released by each is dependent on the level and time since exposure and the level of exercise by the individual (Olson *et al*., 1963; McConnell and Roth, 1966; ATSDR, 2003).

A6-1.4 Biomonitoring

Human blood, urine, toenails, fingernails, breast milk, semen, and various body tissues are commonly analyzed for selenium levels as indicators of selenium exposure (Yang *et al.*, 1989b; Roy, 1990; Longnecker *et al.*, 1991; Brätter *et al*., 1996). As mentioned, the primary route of exposure for humans is through the ingestion of food; the most common cause of selenosis is through the ingestion of food derived from seleniferous soils (ASTDR, 2003).

Selenium is an important component of human dietary intake, but excess levels can have a negative impact on human health. Clinical signs of selenosis include the characteristic garlic odour in breath and urine, as well as brittle nails and hair, mottled teeth, skin lesions, and lowered haemoglobin levels (U.S. EPA IRIS, 1991). Additional traits in humans include fatigue, anorexia, gastroentitis, enlarged spleen and high concentrations of selenium in hair and nails

(U.S. EPA IRIS, 1991). In a Chinese study, blood concentrations in selenosis-affected citizens ranged from 1.05 to 1.85 mg/L (Yang *et al.*, 1989b). A Wyoming study measured selenium concentrations in blood, urine, toenails and food from the highly seleniferous region (Longnecker *et al*., 1991). Other research includes measurements of selenium in umbilical blood, fetal tissues and post-mortem analysis of livers, lungs, and spleens of infants (ATSDR, 2003).

A6-1.5 Chemical and Physical Properties

Table A6-2 Chemical and Physical Properties

Chemical/Physical Property	*Value*	*Reference*
Colour/Form	red, grey, or black	Budavari *et al.*, 1996
Dissociation Constant (pKa)	Not provided	ATSDR, 2003
Henry's Law constant	Not applicable	Budavari *et al.*, 1996
Log K_{ow}	No data	Budavari *et al.*, 1996
Molecular Weight	78.96	Budavari *et al.*, 1996
Vapour Pressure	1mm Hg at 356°C	Budavari *et al.*, 1996
Water Solubility	Insoluble	Budavari *et al.*, 1996
Odour	Unknown; upon combustion, smells like horseradish	Budavari *et al.*, 1996

A6-2.0 TOXICOLOGICAL SUMMARY: HUMAN HEALTH EFFECTS

Inhalation

Acute Effects

The main organ affected by high-level acute inhalation exposures to selenium dusts or fumes is the lung (ATSDR, 2003). Cardiovascular, hepatic, nervous, and renal effects can also be observed upon acute selenium exposure *via* the inhalation route (ATSDR, 2003). Lesser effects can be observed in other organs and organ systems (ATSDR, 2003). Workers exposed to high concentrations of elemental selenium dust have reported stomach pain and headaches, whereas workers briefly exposed to high levels of selenium dioxide dust experienced a variety of respiratory symptoms including pulmonary oedema, bronchial spasms, symptoms of asphyxiation and persistent bronchitis. Other symptoms of acute inhalation exposure were elevated pulse rates, lowered blood pressure, vomiting, nausea, and irritability (ATSDR, 2003).

Chronic Effects

Irritation of the nose, respiratory tract, and lungs resulting in bronchial spasms, and coughing followed chronic exposure to selenium dioxide or elemental selenium as dust in several occupational studies (ATSDR, 2003). No information was reported regarding haematological, musculoskeletal, dermal, reproductive, developmental or ocular effects in humans exposed to selenium or selenium compounds through the inhalation route (ATSDR, 2003).

Oral

Chronic Effects

No human mortalities have been reported due to chronic oral exposures to selenium or selenium compounds in the U.S (ATSDR, 2003). In areas of endemic selenosis, such as the Hubei Province of China, one woman was reported to have died from hemiplegia. It was

reported that the death may have been caused by chronic selenosis induced by eating locally grown foods that contained high levels of organic selenium compounds (Yang *et al*., 1983). No studies were located regarding adverse effects on human reproduction following oral exposure to elemental selenium or to selenium compounds. Furthermore, no studies have demonstrated that selenium or its compounds are teratogenic in humans (ATSDR, 2003).

Signs of toxicity in humans orally exposed to elevated levels of selenium in foods and soils include: loss of hair, thickened or brittle nails, skin lesions, tooth decay, irregularities of the nervous system, garlicky breath, reduced haemoglobin, and altered thyroid hormone levels in blood (Yang *et al*., 1983; Yang *et al*., 1989a,b; Contempre *et al*.,1991; Longnecker *et al*., 1991; Brätter *et al*., 1996; Hagmar *et al*., 1998; Duffield *et al*., 1999). Dietary levels (high, unspecified) of selenium compounds have been reported to cause gastrointestinal disturbances in chronically exposed humans as well (Smith *et al*., 1936). Dilation of the stomach, small intestine (Carter, 1966) and erosive changes in the gastrointestinal track are some of the effects that have been documented after ingestion of selenium compounds (Koppel *et al*., 1986). The reported gastrointestinal disturbances may not to be specific to selenium intoxication (ATSDR, 2003). Chronic selenium intake also causes haematological effects such as decreased blood clotting as determined by increased prothrombin time (Yang *et al*., 1989a).

Selenium intake or use over a long period also contributes to enhanced immune functions (Baum *et al*., 1997; Kiremidjian-Schumacher *et al*., 1992; Peretz *et al*., 1991). Reports have described enhanced lymphocyte response (as measured by the T-lymphocyte proliferative response to pokeweed mitogen) in the elderly after taking a selenium-enriched yeast supplement (0.0014 mg/kg/day for 6 months) (ATSDR, 2003). Significant changes were also observed in phagocytosis, chemotactic factor generation, and antibody or leukocyte migration inhibitory factor production by lymphocytes. Low levels of selenium intake were also observed to enhance proliferative responses to the T-cell mitogens phytohemagglutinin or concanavalin A (ATSDR, 2003). Adverse neurological effects can also be caused by chronic selenosis (ATSDR, 2003). Chronic oral selenium intake at 4.99 mg/day was reported to cause peripheral anesthesia, pain of the limbs, exaggerated tendon reflexes, convulsions, paralysis and hemiplegia (Yang *et al*., 1983).

A6-2.1 Carcinogenicity

The U.S. EPA IRIS (1991) and IARC (1987) have currently evaluated the carcinogenicity of selenium compounds as not classifiable as to human carcinogenicity. An exception is selenium sulphide, which the U.S. EPA IRIS (1991) has classified as a probable human carcinogen. Selenium sulphide is typically not present in soils, foods or other environmental media to any significant extent; therefore, human environmental exposure to selenium sulphide would likely be negligible. The Eleventh Annual Report on Carcinogens (ROC) classed selenium sulphide as reasonably anticipated to be a human carcinogen (NTP, 2005). For the purposes of this risk assessment selenium was assessed as a non-carcinogen.

A6-3.0 TOXICOLOGICAL REFERENCE VALUES (TRVS)

Carcinogenic TRVS

Carcinogenic TRVs were not required as selenium was evaluated as a non-carcinogen within the current assessment.

Non-Carcinogenic TRVs

The MOE (2008) derived an AAQC (24 hour averaging time) of 10 µg/m^3 for selenium which was selected as the 24 hour acute exposure limit for selenium. The basis of this value was not provided (Table A6-3).

The Cal EPA (2001) utilized the U.S. EPA IRIS (1991) RfD to derive a chronic REL of 20 µg/m^3 for selenium using a body weight of 70 kg and an inhalation rate of 20 m^3/day. The specific study used to derive the RfD is described below. This value was selected to evaluate human health effects of long-term selenium exposure *via* inhalation (Table A6-3).

Selenium was retained for evaluation in the multi-pathway exposure model due to its persistence; therefore, an oral RfD was required. An oral RfD of 5.0 µg/kg-day was established by the U.S. EPA IRIS (1991) based on clinical selenosis in human epidemiological studies (Yang *et al*., 1989a,b). An uncertainty factor of 3 for intraspecies variation was applied to the study NOAEL of 15 µg/kg-day. A full uncertainty factor of 10 for intraspecies variation was not considered necessary as similar NOAELs were identified in two additional moderately-sized human populations exposed to selenium levels in excess of the RDA throughout a lifetime without apparent clinical signs of selenosis (Yang and Zhou, 1994). A chronic oral exposure limit of 50 µg/kg-day was also derived by Cal EPA (2001) and ATSDR (2003) using similar epidemiological studies.

IOM (2000) derived a set of tolerable upper intake levels (UL) for adults based on the study by Yang and Zhou (1994) which was based on a human epidemiological diet study. A NOAEL of 800 µg/day was calculated for adults and this value was divided by the uncertainty factor to calculate upper intake levels. Similarly, IOM calculated UL for infants and children based on a diet study by Shearer and Hadjimarkos (1975) and calculated a NOAEL of 7 µg/kg-day for infants and children. The UL values adopted by Health Canada are equal to those of IOM but have been adjusted for the duration of the life stage and body weight. These values were selected as the chronic exposure limit for the current assessment (Table A6-3).

A6-4.0 RELATIVE DERMAL BIOAVAILABILITY

The relative dermal bioavailability for selenium in soil is 0.002 (Health Canada, 2004). The permeability co-efficient in water is 0.001cm/hr (U.S. EPA, 2004).

Table A6-3 Non-Carcinogenic Toxicological Exposure Limits for Selenium

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
Inhalation (µg/m^3)									
AAQC; 24 hour averaging time	**Acute**	**10**	**Health effects**	**Not provided**	**Not provided**	**Not provided**	**Not provided**	**MOE, 2008**	**Not provided**
REL	**Chronic**	**20[a]**	**Clinical selenosis**	**Derived from the U.S. EPA IRIS (1991) oral chronic REL which is the same the oral RfD. (route to route extrapolation of the RfD)**	**Yang *et al.*, 1989b**	**NOAEL: 0.015 mg/kg-day; LOAEL: 0.023 mg/kg-day**	**3**	**Cal EPA, 2001**	**2001**
Oral (µg/kg-day)									
RfD	Chronic	5.0	Clinical selenosis	Human epidemiological study (low, medium and high environmental levels of Se)	Yang *et al.*, 1989a	NOAEL: 0.015 mg/kg-day; LOAEL: 0.023 mg/kg-day	3	U.S. EPA IRIS, 1991	1991
UL (µg/day)	Chronic	0-6 mo: 4.5E+01; 7mo-1 yr: 6E+01; 1-3 yrs: 9E+01; 4-8 yrs: 1.5E+02; 14 yrs+: 4E+02	Selenosis	Human epidemiological diet study Infant epidemiological diet study	Shearer and Hadjimarkos, 1975; Yang and Zhou, 1994	NOAEL: 0.8 mg/day (adults); NOAEL: 7 µg/kg-day (infants and children)	2;1	IOM, 2000	Not provided
UL (µg/kg-day)	**Chronic**	**0-6 mo: 5.5; 7 mo-4 yrs: 6.2; 5-11 yrs: 6.3; 12-19 yrs: 6.2; 20+(70.7 kg): 5.7**	**Selenosis**	**UL HC = UL IOM adjusted for life stage duration and body weight**	**Yang and Zhou, 1994; Shearer and Hadjimarkos, 1975**	**NOAEL: 0.8 mg/day (adults); NOAEL: 7 µg/kg-day (infants and children)**	**2;1**	**Health Canada, 2008**	**Not provided**
REL	Chronic	5.0	Clinical selenosis	Adopted U.S. EPA IRIS (1991) RfD	Yang *et al.*, 1989b	NOAEL: 0.015 mg/kg-day; LOAEL: 0.023 mg/kg-day	3	Cal EPA, 2001	2001

Table A6-3 Non-Carcinogenic Toxicological Exposure Limits for Selenium

Reported Exposure Limit	*Duration*	*Exposure Limit*	*Critical Effect*	*Description of Study*	*References*	*Endpoint*	*Uncertainty Factor*	*Source*	*Derivation Date*
MRL	Chronic	5.0	Disappearance of selenosis symptoms	Human study, subjects recovering from selenosis	Yang and Zhou, 1994	NOAEL: 0.015 mg/kg-day	3	ATSDR, 2003	Not provided
MAC (µg/L)	Chronic	10	Health effects (humans); decreased liver function (rabbits); toxic effects (rats)	Drinking water study in rabbits and rats	Pletnikova, 1970; Schroeder and Mitchener, 1971;Palmer and Olson, 1974	Not provided	Not provided	Health Canada, 1992	Not provided

Bold Bold exposure limits were selected as toxicological reference values for the current risk assessment
MRL Minimal risk level
MAC Maximum acceptable concentration
AAQC Ambient Air Quality Criteria
REL Reference Exposure Levels
RfD Reference Dose
RfC Reference Concentration
UL Tolerable Upper Intake Level
[a] The REL was derived from an oral RfD using a body weight of 70 kg and an inhalation rate of 20 m^3/day

A6-5.0 REFERENCES

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