in the respiratory tree indicates that 5 to 50% of particles will be deposited, and that 50 to 100% of cadmium deposited in the alveoli will be absorbed (Nordberg *et al.*, 1985). An inhalation relative bioavailability factor of 1.0 was used in this assessment.

5.4.3 Dermal Bioavailability

Health Canada (2003a) recommends a RAF_{dermal} of 0.14. Therefore, a dermal relative bioavailability of 0.14 for cadmium has been adopted in this assessment.

5.5 Conclusion

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

Table 7: Selected Toxicity Reference Values for Cadmium

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	8.0×10^{-4} mg/kg-day	TDI	Health Canada, 2003a
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	$4.29E+01$ $(mg/kg\text{-}day)^{-1}$	Unit Risk	Health Canada, 2003a

NA – Not Applicable

Table 8: Selected Relative Bioavailabilities for Cadmium

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.14	Health Canada, 2003a

5.6 References

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

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

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

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

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

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

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

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

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

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

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

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

6. COPPER

Copper is widely distributed in nature and is an essential element. Copper deficiency is characterized by hypochromic, microcytic anemia which is a result of defect in hemoglobin synthesis. Many oxidative enzymes (e.g., catalase, peroxidase, cytochrome oxides) require copper. The importance of copper in human nutrition has been reviewed in detail (IPCS, 1998; IOM, 2001).

6.1 Assessment of Carcinogenicity

The toxicity of copper has been the subject of several comprehensive reviews (US EPA, 1991; IPCS, 1998; ATSDR, 2002). Copper is classified as Group D – not classifiable as a human carcinogen due to a lack of human data, inadequate animal data from assays of copper compounds, and equivocal mutagenicity data (US EPA, 1991). Health Canada also does not consider copper to be carcinogenic to humans (CCME, 1999).

6.2 Susceptible Populations

Infants and children under 1 year old are unusually susceptible to copper toxicity because they have not developed the homeostatic mechanism to remove copper from the body (ATSDR, 2002). Wilson's Disease is a genetic disorder associated with impaired transport of copper from the liver to the bile, thereby resulting in increased copper concentrations in the liver as they are not able to maintain homeostasis (ATSDR, 2002). Another genetic condition which increases the susceptibility to copper toxicity is a deficiency in the enzyme glucose-6-phosphate dehydrogenase (ATSDR, 2002). Individuals with liver disease are also susceptible to copper toxicity because of the critical role the liver plays in eliminating copper from the body (ATSDR, 2002).

6.3 Toxicity Reference Values

As copper is considered an essential element for humans, there are two types of toxicity values that are considered: (a) the minimal daily intake so that a person will not suffer from copper deficiency and (b) the maximal permissible daily intake so that a person will not suffer from copper toxicity. Major non-carcinogenic effects observed in humans after exposure to excessive amounts of copper include diarrhea, vomiting, hypotension, skin irritation, lung disease, kidney damage and liver damage.

6.3.1 Non-Cancer Oral Toxicity Reference Values

The Recommended Dietary Allowance (RDA) for US adults is 0.900 mg/day or about 0.13 mg/kg-day (IOM, 2001). This RDA is a combination of indicators, including plasma copper and ceruloplasmin concentrations, erythrocyte superoxide dismutase (ESOD) activity and platelet copper concentration in controlled human depletion/repletion studies. The US Reference Daily Intake (RDI) (a term which replaces RDA) for copper is 2.0 mg/day or about 0.030 mg/kg-day for adults (US FDA, 1999).

The tolerable upper intake level for US adults is 10 mg/day or about 0.140 mg/kg-day, and is based on protection from liver damage (IOM, 2001). A reference dose (RfD) for elemental copper has not been developed by the US EPA (1991).

Health Canada has developed lower and upper bound tolerable daily intake (TDI) values for copper of 0.050 mg/kg-day and 0.500 mg/kg-day respectively. The lower limit is comparable to that set by the WHO for a young child. The upper limit set by Health Canada is appreciably higher (more than 3-fold) than the tolerable limit set in the US. Health Canada and Environment Canada have also developed TDIs of 0.100 mg/kg-day and 0.030 mg/kg-day for toddlers and adults, respectively as part of the CCME soil quality guideline development process (CCME, 1999).

ATSDR (2002) has developed a minimal risk level (MRL) for acute duration oral exposure to copper. The MRL of 20 µg/kg-day is based on a no observable adverse effects level (NOAEL) of 27.2 µg/kg-day copper administered as copper sulphate in drinking water (Pizzaro *et al.* 1999). The total copper exposure was estimated at 53.8 µg/kg-day by adding estimated daily dietary intake of copper. An uncertainty factor of 3 was used for human variability. A statistically significant difference was seen between the reported NOAEL and a lowest observable adverse effects level (LOAEL) of 73.1 µg/kg-day (total intake of about 100 µg/kg-day) for gastrointestinal effects in women. The Pizzaro *et al.* study was also reviewed by the Food and Nutrition Board (IOM, 2001).

The Food and Nutrition Board (IOM, 2001) of the US National Academy of Sciences Institute of Medicine, in a joint activity with Health Canada, has published a series of tolerable upper limits of copper for various life stages. The tolerable upper limit is the highest level of daily intake of a nutrient (over a lifetime) likely not to result in an adverse health effect to almost all individuals. The UL for copper were based on a NOAEL of 10 mg/day of copper. A double blind study, conducted over 12 weeks, involved administering seven adults 10 mg of copper gluconate capsules daily. The resulting liver function tests were normal in all cases.

The World Health Organization (WHO, 1996) proposed 12 mg copper/day as a safe upper level of intake for a 65 kg adult.

The Food and Nutrition Board (IOM, 2001) also recommended a "safe range" for oral intake of copper between 10 and 130 µg/kg-day for chronic ingestion by a 76 kg adult. Age specific upper limits (UL) are recommended based on extrapolation by body weight:

- Child 1-3 years, UL of 1,000 µg/day
- Child 4-8 years, UL of 3,000 µg/day
- Child 9-13 years, UL of 5,000 µg/day
- Adolescents 14-18 years, UL of 8,000 µg/day
- Adult 19 years and older, UL of 10,000 µg/day

Tolerable upper intake levels are considered to be the highest level of daily intake of a nutrient likely to not pose an adverse health effect to almost all individuals. These were developed through a risk approach, using a NOAEL for copper of 10 mg/day.

The Health Canada and Environment Canada TDIs for toddlers and adults of 1.0×10^{-1} and 3.0×10^{-2}, respectively have been selected for this assessment.

6.3.2 Cancer Oral Toxicity Reference Values

The carcinogenic potential of copper has not been adequately assessed, therefore an oral slope factor or unit risk is not available.

6.3.3 Non-Cancer Inhalation Toxicity Reference Values

The California Air Resources Board approved a risk assessment health value of 0.0024 mg/m^3 (CARB, 1998, last reviewed 01/1992) for chronic inhalation of copper based on respiratory effects. This value was derived from the ACGIH (1992) threshold limit value (TLV) of 1 mg/m^3 by dividing by a factor 420. This factor is made up of a conversion from a 40 hour work week (4.2), a factor to protect sensitive individuals (10) and a factor to account for the deficiency of using a TLV rather than a NOAEL (10) (CAPCOA, 1993).

Due to insufficient data, a non-cancer TRV for inhalation of copper has not been selected for this assessment.

6.3.4 Cancer Inhalation Toxicity Reference Values

The carcinogenic potential of copper has not been adequately assessed, therefore an inhalation slope factor or unit risk is not available.

6.4 Bioavailability

The following sections describe the oral, inhalation and dermal bioavailabilities of copper.

6.4.1 Oral Bioavailability

Oral bioavailability of copper in humans depends on dietary intake of copper, as this is regulated by homeostasis mechanisms in the body. A range of 25 to 40% bioavailability from the diet was estimated (CCME, 1999). Venugopal and Luckey (1978) report and oral absorption of 30% for dietary intake.

In the gastrointestinal tract, all copper is present as the cupric ion or bound to amino acids and is absorbed as such (ATSDR, 2002). The absorption of ingested dietary copper (bioavailability) in humans is subject to strict homeostatic control and varies widely according to the daily oral intake (IPCS, 1998). It has been reported (IOM, 2001) that the bioavailability of copper is over 50% at daily intakes less than 1 mg/day and less than 20% at daily intakes above 5 mg/day. About 35% of a 2 mg/day intake is absorbed (near the upper range of daily intakes of copper in North America).

The selected toxicity reference value is based on copper gluconate capsules. Insufficient information are available to determine whether the oral bioavailability of copper in this form would be greater than copper from dietary intakes, so no adjustment for this will be made in this assessment.

For this study, the relative oral bioavailability of copper in soil was assumed to be 1.0.

6.4.2 Inhalation Bioavailability

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

6.4.3 Dermal Bioavailability

No information was identified regarding dermal absorption of copper. Health Canada (2003) recommends a relative dermal absorption factor of 0.1 for copper. The Health Canada relative dermal bioavailability has been adopted for this assessment.

6.5 Conclusion

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

Table 9: Selected Toxicity Reference Values for Copper

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion – toddler	1.0×10^{-1} mg/kg-day	RfD	CCME, 1999
Ingestion – adult	3.0×10^{-2} mg/kg-day	RfD	CCME, 1999
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 10: Selected Relative Bioavailabilities for Copper

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.1	Health Canada, 2003

6.6 References

ACGIH (American Conference of Governmental and Industrial Hygienists), 1992. Threshold Limit Values. Cincinnatti, OH.

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

CAPCOA (California Air Pollution Control Officers Association), 1993. *Revised 1992 Risk Assessment Guidelines.* Air Toxics "Hot spots" Program, October.

CARB (California Air Resources Board), 1998. "List of Toxic Air Contaminants – Compound Summary Table." http://www.arb.ca.gov/toxics/tac/tac.htm.

CCME (Canadian Council of Ministers of the Environment), 1999. Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health: Copper. Winnipeg, MN, Canada.

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

IOM (Institute of Medicine), 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Panel on Micronutrients, Institute of Medicine, Food and Nutrition Board. Washington, D.C., National Academy Press.

IPCS (International Programme on Chemical Safety), 1998. Copper. Geneva: International Programme on Chemical Safety. World Health Organization Environmental Health Criteria 200. Available on-line at: http://www.inchem.org/documents/ehc/ehc/ehc200.htm.

Pizzaro F, Olivares M and Uauy R, 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. *Environmental Health Perspectives* 107(2): 117-121. Cited in: ATSDR, 2002.

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

US EPA (United States Environmental Protection Agency), 1991. Integrated Risk Information System (IRIS) Database: Copper. Confirmed current as of December 2004. Available on-line at: http://www.epa.gov/iris/

US FDA (United States Food and Drug Administration), 1999. Center for Food Safety and Applied Nutrition. A Food Labeling Guide. September, 1994 (Editorial revisions June, 1999).

WHO (World Health Organization), 1996. "Copper:" In: *Trace Elements in Human Nutrition and Health.* Geneva, pp. 123-143.

Venugopal B and Luckey TD, 1978. Metal Toxicity in Mammals – 2. Chemical Toxicity of Metals and Metalloids. Plenum Press. pp. 104-112.

7. LEAD

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

7.1 Assessment of Carcinogenicity

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

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

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

7.2 Susceptible Populations

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

7.3 Selection of Toxicity Values

7.3.1 Non-Cancer Oral Toxicity Reference Values

The oral reference dose (RfD) for lead used by Health Canada (1996), is the same as the provisional tolerable weekly intake (PTWI) for children of 25 µg/kg, equivalent to approximately 3.57 µg/kg/day from all sources, established by the World Health Organization (WHO) (1986). The PTWI is considered sufficiently low to protect against effects on the central nervous system and blood (*e.g.* neurobehavioural effects and anemia). This PTWI was based on the results of metabolic studies in infants and was used to establish Canadian drinking water standards for lead (CCME, 1987). WHO (1993) has more recently extended this PTWI to all age groups to protect other sensitive population groups, such as women of child-bearing age. The PTWI of 0.025 mg/kg was maintained at the fifty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (WHO, 1999).

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

An oral RfD of 3.57×10^{-3} mg/kg-day has been adopted in this assessment based on Health Canada's recommended oral RfD.

7.3.2 Cancer Oral Toxicity Reference Values

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

7.3.3 Non-Cancer Inhalation Toxicity Reference Values

Inhalation toxicity values for lead have not been developed by the US EPA or Health Canada and therefore, due to insufficient data, a non-cancer inhalation TRV has not been selected for this assessment.

7.3.4 Cancer Inhalation Toxicity Reference Values

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

7.4 Bioavailability

The following section describes the bioavailabilities of lead.

7.4.1 Oral Bioavailability

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

Oral bioavailability for lead assuming normal feeding habits are 42 to 53% in children (Hrudey *et al.*, 1996) and 4 to 13% in adults (CCME, 1996; Hrudey *et al.*, 1996). Other studies for estimating lead oral bioavailability assuming normal feeding habits are 40 to 50% in children (Alexander *et al.*, 1974; Ziegler *et al.*, 1978) and 4 to 13% in adults (Harrison *et al.*, 1969; Rabinowitz *et al.*, 1980; Blake *et al.*, 1983; Chamberlain, 1985). The oral bioavailability is assumed to be 53% since the RfD is based on oral exposure that is protective of children. The absorption of lead in soil and dust by children has been estimated at 30% (CCME, 1996). For the purpose of this assessment, the relative oral bioavailability from soil exposure was assumed to be 100%.

7.4.2 Inhalation Bioavailability

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

7.4.3 Dermal Bioavailability

The dermal bioavailability factor of 0.01 is recommended by US EPA Region III (1995). Health Canada (2003) recommends a relative dermal absorption factor of 0.006 for lead. Therefore, a relative dermal bioavailability of 0.006 was adopted for this assessment.

7.5 Conclusion

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

Table 11: Selected Toxicity Reference Values for Lead

Route of Exposure	TRV	TRV Type	Source Agency
Non-Cancer Effects			
Ingestion	3.57×10^{-3} mg/kg-day	RfD	Health Canada, 1996
Inhalation	NA	NA	NA
Cancer Effects			
Ingestion	NA	NA	NA
Inhalation	NA	NA	NA

NA – Not Applicable

Table 12: Selected Bioavailabilities for Lead

Route of Exposure	Relative Bioavailability	Reference
Ingestion	1.0	Assumed
Inhalation	1.0	Assumed
Dermal	0.006	Health Canada, 2003

7.6 References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8. PETROLEUM HYDROCARBONS CWS FRACTIONS F2, F3, F4

Petroleum hydrocarbons are mixtures of organic compounds that are derived from naturally occurring geological formations such as coal or oil. Common mixtures include gasoline, diesel and jet fuels. The lighter range petroleum hydrocarbons (C_6-C_{16}) tend to float on water, forming sheens or slicks, and tend to be relatively volatile, mobile and toxic (TPHCWG, 1997). These compounds may evaporate from the water surface, dissolve and disperse, and are readily degraded by natural weathering or microbial processes. Heavier oils have lower volatility and tend to be denser, and may clump or sink, becoming incorporated into sediments. Heavier PHCs ($C_{>16}$-$C_{>34}$) pose problems with their persistence in the environment and are less volatile (TPHCWG, 1997).

Fractionation of petroleum hydrocarbon mixtures is based upon the number of carbon atoms (lighter and heavier molecular weight chains), volatility, as well as aromatic or aliphatic structural comparisons. In general, petroleum hydrocarbons pose aesthetic problems such as unpleasant taste and odour. Some health effects that are associated with PHC exposure include neuropathy and degeneration of neural axons.

The quantification of petroleum hydrocarbon mixtures has historically been accomplished by a variety of methods where the petroleum mixture is extracted using solvents such as hexane or cyclohexane. Fractionation of the total petroleum hydrocarbon (TPH) compounds according to their volatility, number of carbon atoms, and whether they are aromatic or aliphatic compounds, is common. These aliphatic and aromatic sub-fractions play an important role in toxicity to humans and ecological receptors. In general, aromatics are more water soluble and less volatile than aliphatics. Out of these fractions, the aromatic C_5-C_8 fraction contains the indicator compounds benzene, toluene, ethylbenzene and xylenes, collectively referred to as BTEX. Total petroleum hydrocarbons (excluding the BTEX compounds) are generally evaluated as a group due to similar toxicity end points. The BTEX compounds are generally evaluated individually (CCME, 2000).

The toxicity of petroleum hydrocarbon compounds varies widely as a consequence of the variability in the chemical composition of mixtures. The light compounds (particularly aromatics) tend to be most toxic because these compounds are most likely to penetrate and disrupt cell membranes (TPHCWG, 1997). Thus, gasoline and light fuel oils are considerably more toxic than heavy oils, Bunker C, or crude oils. The potency estimates for chemicals of concern are based on the values reported by Health Canada, the U.S. Environmental Protection Agency (US EPA) or the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG).

The TPH model characterizes the toxicity of TPH by dividing these grouped chemicals into separate fractions based upon molecular structure and carbon size, as per TPHCWG (1997) and CCME (2000) methodology. These fractions are treated as threshold toxicants. The toxicity values employed for each of the fractions were chosen from representative indicator compounds in the specific fraction, upon which toxicity data and studies were available. The toxicity data were chosen to representative of that fraction, whether by arbitrary reference dose (RfD) selection, or by RfD weighting, etc. The specific toxicity data employed in the assessment are detailed in the sections that follow.

8.1 Assessment of Carcinogenicity

TPHCWG (1997) and CCME (2000) do not consider these fractions carcinogenic.

8.2 Susceptible Populations

There is no information readily available on susceptible populations.

8.3 Selection of Toxicity Reference Values

Calculations for individual petroleum hydrocarbon sub-fractions are combined to form CWS Fractions F2, F3 and F4 on a weight percent basis. The composition of CWS Fractions F2, F3 and F4 is presented below.

Table 13: Composition of Petroleum Hydrocarbons CWS Fractions F2, F3 and F4

TPH Sub-fraction	Percentage (%)	Reference
Aliphatics $C_{>10}$-C_{12}	36	CCME, 2000
Aliphatics $C_{>12}$-C_{16}	44	CCME, 2000
Aromatics $C_{>10}$-C_{12}	9	CCME, 2000
Aromatics $C_{>12}$-C_{16}	11	CCME, 2000
F2 Total	**100**	
Aliphatics $C_{>16}$-C_{21}	56	CCME, 2000
Aliphatics $C_{>21}$-C_{34}	24	CCME, 2000
Aromatics $C_{>16}$-C_{21}	14	CCME, 2000
Aromatics $C_{>21}$-C_{34}	6	CCME, 2000
F3 Total	**100**	
Aromatics $C_{>34}$-C_{50}	80	CCME, 2000
Aromatics $C_{>34}$-C_{50}	20	CCME, 2000
F4 Total	**100**	

8.3.1 Non-Cancer Oral Toxicity Reference Value

8.3.1.1 Aromatic Fractions >C_{10}-C_{12}, >C_{12}-C_{16}

The TPHCWG (1997) derived an oral reference dose (RfD) for the C_9-C_{16} aromatic hydrocarbon range by looking at toxicity data for Isopropylbenzene (C_9), Naphthalene (C_{10}), Acenaphthene (C_{12}), Biphenyl (C_{12}), Fluorene (C_{13}), Anthracene (C_{14}), Fluoranthene (C_{16}), and Pyrene (C_{16}). The TPHCWG determined that an Oral RfD of 0.04 mg/kg-day would be appropriate for this carbon range. Of the eight identified compounds within this range, four have an Oral RfD of 0.04 mg/kg-day (Isopropylbenzene, Naphthalene, Fluorene and Fluoranthene). The other four compounds had the following Oral RfD's: Acenaphthene 0.06 mg/kg-day, Biphenyl 0.05 mg/kg-day, Anthracene 0.04 mg/kg-day and Pyrene 0.03 mg/kg-day. Since this fraction is a mixture it was felt that the Oral RfD of 0.04 mg/kg-day is appropriate.

8.3.1.2 Aromatic Fractions >C_{16}-C_{21}, >C_{21}-C_{34}, >C_{34}-C_{50}

The TPHCWG (1997) found that there were no previously developed RfDs for aromatic chemicals in the C_{16}-C_{35} range. It was also found that there were insufficient data available to develop a RfD. After reviewing the existing information the TPHCWG adopted the Oral RfD for pyrene (C_{16}) (0.03 mg/kg-d) as a surrogate for this fraction. This was considered to be conservative because it has a lower carbon number than any of the compounds in this fraction.

8.3.1.3 Aliphatic Fraction >C_{10}-C_{12}, >C_{12}-C_{16}

The TPHCWG (1997) found very little information on individual components within the C_9-C_{16} aliphatic range. Studies on JP-8 fuel streams and dearomatized petroleum streams were utilized to produce the RfDs for these fractions. An Oral RfD of 0.1 mg/kg-day was calculated using oral gavage data for dearomatized aliphatics. This RfD appears to be protective of systemic toxicity as well as developmental and reproductive endpoints.

8.3.1.4 Aliphatic Fraction >C_{16}-C_{21}, >C_{21}-C_{34}

The TPHCWG (1997) utilized studies with white mineral oils to derive the RfD values for these fractions. Subchronic oral studies utilizing F/344 rats were employed in the toxicity evaluation. A no observable adverse effects level (NOAEL) of 200 mg/kg-day was observed. A safety factor of 100 was applied to the NOAEL (3 for animal to human extrapolation, 10 for individual

susceptibility, and 3 for subchronic to chronic extrapolation) to calculate the RfD of 2.0 mg/kg-day.

8.3.1.5 Aliphatic Fraction >C_{34}-C_{50}

The TPHCWG (1997) utilized studies with white mineral oils to derive the RfD values for these fractions. Subchronic oral studies utilizing F/344 rats were employed in the toxicity evaluation. A NOAEL of 2000 mg/kg-day was observed. A safety factor of 100 was applied to the NOAEL (3 for animal to human extrapolation, 10 for individual susceptibility, and 3 for subchronic to chronic extrapolation) to calculate the RfD of 20.0 mg/kg-day.

8.3.2 Cancer Oral Toxicity Reference Value

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

8.3.3 Non-Cancer Inhalation Toxicity Reference Value

8.3.3.1 Aromatic Fractions >C_{10}-C_{12}, >C_{12}-C_{16}

The TPHCWG (1997) determined that an aromatic inhalation reference concentration (RfC) of 0.2 mg/m^3 would be appropriate. This was based upon inhalation RfD studies of C_9 aromatic mixtures. The RfC was converted to an inhalation RfD of 0.04 mg/kg-day by multiplying by the breathing rate of 15.8 (m^3/day) and dividing by 70.7 (kg, average weight of receptor).

8.3.3.2 Aromatic Fractions >C_{16}-C_{21}, >C_{21}-C_{34}, >C_{34}-C_{50}

TPHCWG (1997) and CCME (2000) have not established inhalation reference toxicity values for these fractions.

8.3.3.3 Aliphatic Fraction >C_{10}-C_{12}, >C_{12}-C_{16}

The TPHCWG (1997) determined that a RfC of 1.0 mg/m^3 for these fractions was selected based upon on studies of JP-8 (C_9-C_{16}) jet fuel. The RfC was converted to an inhalation RfD of 0.2 mg/kg-day by multiplying by the breathing rate of 15.8 (m^3/day) and dividing by 70.7 (kg, average weight of receptor).

8.3.3.4 Aliphatic Fraction >C_{16}-C_{21}, >C_{21}-C_{34}

TPHCWG (1997) and CCME (2000) have not established inhalation reference toxicity values for these fractions.

8.3.3.5 Aliphatic Fraction >C_{34}-C_{50}

TPHCWG (1997) and CCME (2000) have not established inhalation reference toxicity values for these fractions.

8.3.4 Cancer Inhalation Toxicity Reference Value

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

8.4 Bioavailability

The following section describes the bioavailabilities of Petroleum Hydrocarbon CWS Fractions F2, F3 and F4.

8.4.1 Oral Bioavailability

The Canada Wide Standards for Petroleum Hydrocarbons in Soil: Scientific Rationale (CCME, 2000) employs an Oral Absorption Factor of 1.0.

8.4.2 Inhalation Bioavailability

The Canada Wide Standards for Petroleum Hydrocarbons in Soil: Scientific Rationale (CCME, 2000) employs an Inhalation Absorption Factor of 1.0.

8.4.3 Dermal Bioavailability

The Canada Wide Standards for Petroleum Hydrocarbons in Soil: Scientific Rationale (CCME, 2000) employs a Dermal Absorption Factor of 0.2.

8.5 Conclusion

The following tables present the TRV and bioavailability summaries for Petroleum Hydrocarbon CWS Fractions F2, F3 and F4.

Table 14: Selected Toxicity Reference Values for Petroleum Hydrocarbons CWS Fractions F2, F3 and F4

TPH Sub-fraction	Route of Exposure	Toxicity Reference Value	TRV Type	Source Agency
Non-Cancer Effects				
Aliphatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Ingestion	0.1 mg/kg-day	RfD	CCME, 2000
Aliphatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}	Ingestion	2.0 mg/kg-day	RfD	CCME, 2000
Aliphatic, $C_{>34}$-C_{50}	Ingestion	20.0 mg/kg-day	RfD	CCME, 2000
Aromatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Ingestion	0.04 mg/kg-day	RfD	CCME, 2000
Aromatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}, $C_{>34}$-C_{50}	Ingestion	0.03 mg/kg-day	RfD	CCME, 2000
Aliphatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Inhalation	0.2 mg/kg-day	RfD	CCME, 2000
Aliphatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}	Inhalation	NA	RfD	NA
Aliphatic, $C_{>34}$-C_{50}	Inhalation	NA	RfD	NA
Aromatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Inhalation	0.04 mg/kg-day	RfD	CCME, 2000
Aromatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}, $C_{>34}$-C_{50}	Inhalation	NA	RfD	NA
Cancer Effects				
Aliphatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Ingestion	NA	NA	NA
Aliphatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}	Ingestion	NA	NA	NA
Aliphatic, $C_{>34}$-C_{50}	Ingestion	NA	NA	NA
Aromatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Ingestion	NA	NA	NA
Aromatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}, $C_{>34}$-C_{50}	Ingestion	NA	NA	NA
Aliphatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Inhalation	NA	NA	NA
Aliphatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}	Inhalation	NA	NA	NA
Aliphatic, $C_{>34}$-C_{50}	Inhalation	NA	NA	NA
Aromatic, $C_{>10}$-C_{12}, $C_{>12}$-C_{16}	Inhalation	NA	NA	NA
Aromatic, $C_{>16}$-C_{21}, $C_{>21}$-C_{34}, $C_{>34}$-C_{50}	Inhalation	NA	NA	NA

NA – Not Applicable

Table 15: Selected Bioavailabilities for Petroleum Hydrocarbons CWS Fractions F2, F3 and F4

Route of Exposure	Relative Bioavailability	Reference
Oral	1.0	CCME, 2000
Dermal	0.2	CCME, 2000
Inhalation	1.0	CCME, 2000

8.6 References

CCME, 2000. Canada Wide Standards for Petroleum Hydrocarbons in Soil: Scientific Rationale. Canadian Council for Ministers of the Environment.

TPHCWG. 1997. Total Petroleum Hydrocarbon Criteria Working Group. Development of Fraction Specific Reference Doses (RfDs) and Reference Concentrations (RfCs) for Total Petroleum Hydrocarbons (TPH), Volume 4. Amherst Scientific

9. POLYCHLORINATED BIPHENYLS (PCBS)

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

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

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

9.1 Assessment of Carcinogenicity

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

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