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Carbon Tetrachloride

Guideline

The maximum acceptable concentration (MAC) for carbon tetrachloride in drinking water is 0.005 mg/L (5 μg/L).

Identity, Use and Sources in the Environment

Carbon tetrachloride (tetrachloromethane) is a volatile organic alkyl halogen that is present in the environment largely because of release from man-made sources. It is a clear, colourless and non-flammable heavy liquid with a characteristic odour.[1] One millilitre of carbon tetrachloride dissolves in 2 L of water; carbon tetrachloride is miscible with many organic solvents.[1] Its vapour pressure is 13 kPa at 25°C.

In Canada, over 25 million kilograms (80% of which are manufactured in this country) are produced annually for use as intermediates in the manufacture of other chlorinated hydrocarbons, principally chlorofluorocarbons or freons. Carbon tetrachloride is also used to a limited extent as an industrial solvent and metal degreasing agent.[2] Use in Canada as a pesticide in the fumigation of grains was suspended in February 1984; under the Hazardous Products Act, carbon tetrachloride may not be contained in any consumer product.

Sources of exposure of Canadians to carbon tetrachloride include fugitive emissions to the air during manufacturing and use, effluents released to water during these processes, effluents leached from hazardous waste sites and residues in foods (primarily imported) from its use as a pesticide.

Exposure

An average concentration of carbon tetrachloride of less than 0.1 μg/L was reported in surface waters from nine locations in the lower Great Lakes region;[3] there were, however, detectable concentrations (usually less than 10 μg/L) in 60% of surface water samples from the St. Clair River near Sarnia, Ontario, in the vicinity of a number of chemical manufacturing industries.[4]

In a national survey of 29 Canadian municipal drinking water supplies conducted in 1979, concentrations of carbon tetrachloride did not exceed the detection limit of 5 μg/L.[5] No concentrations above 1 μg/L were detected in a more recent survey of 10 municipal drinking water supplies in Ontario, including the water supply in the city in which the majority of carbon tetrachloride is manufactured.[6] A maximum concentration of 3 μg/L was detected in the water supply of a southern Ontario municipality after a chemical spill.[7] There is potential for exposure in the home to airborne carbon tetrachloride released from tap water and for dermal exposure during bathing;[8,9] however, available data are insufficient to allow estimation of exposure by these routes.

Although no recent data are available, intake of carbon tetrachloride in food is probably low in Canada. The U.S. Environmental Protection Agency has estimated a daily dietary intake of carbon tetrachloride for an adult to be between 0 and 1.3 μg/d, based on data collected in 1981 to 1982 when carbon tetrachloride was still used, to a limited extent, as a grain fumigating agent.[10]

Intake of carbon tetrachloride from air is much greater than that from food or drinking water. Concentrations of airborne carbon tetrachloride in two Canadian cities averaged 1.1 μg/m^3 over a one-year period, with a range of 0.4 to 1.9 μg/m^3.[11] This is less than the average concentration of 1.5 μg/m^3 reported for 10 U.S. cities[12,13] and is comparable with reported background concentrations of 0.7 to 0.8 μg/m^3 reported in different areas.[13] Concentrations of carbon tetrachloride in indoor air are usually slightly less than concentrations in ambient air.[14,15]

Analytical Methods and Treatment Technology

The U.S. Environmental Protection Agency has determined that the practical quantitation limit (PQL) (based on the ability of laboratories to measure carbon tetrachloride within reasonable limits of precision and

accuracy) is 5 µg/L.[16] This conclusion is supported by work carried out by the Department of National Health and Welfare.[17,18]

Carbon tetrachloride does not appear to be formed in drinking water during the chlorination process,[19] and concentrations are not significantly reduced during conventional drinking water treatment processes.[20] Removal of volatile organic compounds by packed tower aeration and granular activated carbon adsorption has been estimated to be 90 to 99%, and concentrations of carbon tetrachloride below 1 µg/L are commonly achieved in drinking water using these methods.[16,20]

Health Effects

Carbon tetrachloride is readily absorbed from the gastrointestinal tract (86% in 24 hours in the rat)[21] and the lungs (30 to 50% in monkeys exposed for up to six hours).[22] Dermal absorption, determined by alveolar air sampling, was significant in three human volunteers who immersed their thumbs in carbon tetrachloride for 30 minutes.[23] Carbon tetrachloride is distributed preferentially to fatty tissue and is found in highest concentrations in bone marrow, brain, liver, kidney and blood. Elimination of unchanged carbon tetrachloride in exhaled air and of metabolites in urine is relatively rapid; peak concentrations occur within four hours, and elimination is essentially complete within 24 to 48 hours. Small amounts may be retained in the tissues for up to 20 days.[22] Carbon tetrachloride is metabolized in cell microsomal membranes to a highly toxic trichloromethyl radical that initiates lipid peroxidation, and it binds to and destroys cell enzymes (cytochrome P-450), lipids and proteins in various cell membranes, especially the hepatic endoplasmic reticulum.[24–26] Other metabolic reactions of the free radical include formation of chloroform, carbonyl chloride (phosgene) and carbon dioxide.[27]

In humans, acute effects of ingestion of high doses (5 to 40 mL; 8 to 64 g) of carbon tetrachloride include anorexia, nausea and vomiting, liver and kidney damage, pulmonary oedema, central nervous system depression and cardiac arrhythmias.[28,29] The most serious effects are manifested in the liver; hepatic damage (indicated by enlargement and tenderness, as well as elevated levels of circulating hepatic enzymes, such as serum glutamic–oxaloacetic transaminase) may lead to death within several days to two weeks after ingestion.[28] Chronic exposure to lower doses also causes damage to the liver (liver enlargement, changes in serum enzyme levels, fatty infiltration and centrilobular necrosis) and kidney (necrosis of the renal tubular epithelium).[29] The acute and chronic effects of exposure to carbon tetrachloride are potentiated by ingestion of ethanol and by exposure to acetone, to other alcohols, such as isopropyl or isobutyl alcohol, and to such solvents as n-hexane, n-pentane and n-heptane.[26,30,31]

Liver cancer has been reported in three humans several years after carbon tetrachloride poisoning; however, it is not possible to draw any conclusions on the basis of these data concerning the possible association between carbon tetrachloride and human liver cancer.[10,32] There are few epidemiological studies of populations exposed to carbon tetrachloride for extended periods. Studies that have been conducted have several limitations, including poor statistical power,[33] lack of data on levels and length of exposure[34] and concomitant exposure to other known hepatotoxic agents.[35]

Carbon tetrachloride has caused hepatic tumours (both neoplasms and carcinomas) in rats, mice and hamsters by three different routes of exposure — oral, subcutaneous and inhalation.[36–39] In addition, increased incidence of hemangiosarcomas, carcinomas of the thyroid, multicystic kidneys and mammary tumours in rats[36,37,40] and adrenal tumours in mice[36] has been noted in some experiments. Pronounced differences in the sensitivity of various strains of rats to tumour induction have been observed,[37] and the time to first tumour has generally been short, within 12 to 16 weeks in some experiments.[36,41] The tumour incidence in mice in one study was dose-related.[36]

The most comprehensive carcinogenesis bioassay relevant to the assessment of risk associated with the ingestion of carbon tetrachloride in drinking water is that of the National Cancer Institute (NCI).[36] In this study, doses of 47 and 94 mg/kg bw (males) and 80 and 159 mg/kg bw (females) were administered daily by gavage in corn oil five days per week for 78 weeks to groups of 50 male and 50 female Osborne-Mendel rats (20 animals in control groups; animals sacrificed at 110 weeks). In a similarly conducted bioassay, doses of 1250 and 2500 mg/kg bw were administered daily by gavage in corn oil five days per week to groups of 50 male and 50 female B6C3F_1 mice for 78 weeks (20 animals in control groups; animals sacrificed at 90 weeks). In rats, there was a statistically significant increase in the incidence of both hepatocellular carcinomas and hepatic neoplastic nodules; in mice, hepatocellular carcinomas developed in nearly all treated animals.

Carbon tetrachloride has not been found to be mutagenic in bacterial tests either with or without metabolic activation.[42–44] It has caused point mutations and gene recombination in a eukaryotic (yeast) test system;[45] effects on chromosomes or unscheduled DNA synthesis in mammalian cells in *in vitro* or *in vivo* studies have not been demonstrated.[46–48]

Reproduction is adversely affected by high doses of carbon tetrachloride in males and in offspring, with atrophy of the testis, abnormal spermatogenesis and decreases in viability and in weight of offspring at maternally toxic doses. Teratogenic effects have not been observed.[37,49–51]

Classification and Assessment

The carcinogenicity of carbon tetrachloride in animal species is well documented. It has, therefore, been classified in Group II — probably carcinogenic to man (sufficient evidence in animals, inadequate evidence in man) on the basis that it has been shown to be carcinogenic in both sexes of two animal species.[36] Incorporating a surface area correction and using the robust linear extrapolation model, one can calculate that the unit lifetime risk associated with the ingestion of 1 μg/L carbon tetrachloride in drinking water ranges from 3.30×10^{-7} (based on hepatocellular carcinomas in male mice) to 1.04×10^{-6} (based on hepatic neoplastic nodules and hepatocellular carcinomas in male rats)*. The estimated ranges of concentrations in drinking water corresponding to lifetime risks of 10^{-5}, 10^{-6} and 10^{-7} for these same tumour types based on the model described above are as follows:**

Lifetime risk	Concentrations in drinking water (μg/L)
10^{-5}	9.6 – 30
10^{-6}	0.96 – 3.0
10^{-7}	0.096 – 0.30

Rationale

Because carbon tetrachloride is classified as a probable human carcinogen in Group II, the maximum acceptable concentration (MAC) is derived based on consideration of available practicable treatment technology and estimated lifetime cancer risks. Because the MAC must also be measurable by available analytical methods, the PQL is also taken into consideration in its derivation.

An MAC of 0.005 mg/L (5 μg/L) for carbon tetrachloride was established, therefore, on the basis of the following considerations:

(1) The estimated unit lifetime risks associated with the ingestion of 1 μg/L carbon tetrachloride in drinking water range from 3.30×10^{-7} (based on hepatocellular carcinomas in male mice) to 1.04×10^{-6} (based on hepatic neoplastic nodules and hepatocellular carcinomas in male rats). Therefore, the estimated lifetime risk associated with the ingestion of drinking water containing 5 μg/L carbon tetrachloride (i.e., 1.65×10^{-6} to 5.2×10^{-6}) is within a range that is considered to be "essentially negligible."

(2) Available data indicate that concentrations of carbon tetrachloride are not reduced significantly during conventional drinking water treatment processes. However, concentrations of carbon tetrachloride below 1 μg/L can be achieved by packed tower aeration and granular activated carbon adsorption.

(3) The PQL (based on the ability of laboratories to measure carbon tetrachloride within reasonable limits of precision and accuracy) is 5 μg/L.

* May be an underestimate because of poor survival in mice.

** Average adult body weight = 70 kg; average daily intake of drinking water = 1.5 L.

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