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Advisory Opinion for Carbon Tetrachloride
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460

AN OFFICE OF DRINKING WATER HEALTH EFFECTS ADVISORY

The Office of Drinking Water provides advice on health effects upon request, concerning unregulated contaminants found in drinking water supplies. This information suggests the level of a contaminant in drinking water at which adverse health effects would not be anticipated. A margin of safety is factored in so as to protect the most sensitive members of the general population. The advisories are called Suggested No Adverse Response Levels (SNARLs). SNARLs have been calculated by EPA and by the National Academy of Sciences (NAS) for selected contaminants in drinking water. An EPA-SNARL and a NAS-SNARL may well differ due to the possible selection of different experimental studies for use as the basis for the calculations. Furthermore, NAS-SNARLs are calculated for adults while the EPA-SNARLs are established for a 10 kg body weight child. Normally EPA-SNARLs are provided for one-day, ten-day and longer-term exposure periods where available data exist. A SNARL does not condone the presence of a contaminant in drinking water, but rather provides useful information to assist in the setting of control priorities in cases where contamination occurs. EPA-SNARLs are provided on a case-by-case basis in emergency situations such as spills and accidents.

In the absence of a formal drinking water standard for carbon tetrachloride the Office of Drinking Water has developed EPA-SNARLs following the state-of-the-art concepts in toxicology for non-carcinogenic risk for short and longer term exposures. For carcinogenic risk, a range of risk estimates is provided for life-time exposures discussed by the NAS (1977) and the EPA Cancer Assessment Group (EPA, 1980b). The EPA-SNARL calculations for short-term and chronic exposures ignore the possible carcinogenic risk that may result for those exposures. In addition, EPA-SNARLs usually do not consider the health risk resulting from possible synergistic effects of other chemicals in drinking water, food, and air.

EPA-SNARLs are not legally enforceable standards; they are not issued as an official regulation, and they may or may not lead ultimately to the issuance of national standards or Maximum Contaminant Levels (MCLs). The latter must take

into account occurrence, relative source contribution factors, treatment technology, monitoring capability, and costs, in addition to health effects. It is quite conceivable that the concentration set for EPA-SNARL purposes might differ from an eventual MCL. The EPA-SNARLs may also change as additional information becomes available. In short, EPA-SNARLs are offered as advice to assist those to protect public health when dealing with specific contamination situations.

General Information:

Carbon tetrachloride, also known as tetrachloromethane (CCl_4) is a colorless liquid at room temperature with a characteristic, non-irritant odor. Its boiling point is 76.7°C and its specific gravity is 1.59 (20/4°C) (Kirk-Othmer, 1979). Carbon tetrachloride is partly soluble in water (0.8 g/liter at 25°C) (Kirk-Othmer, 1979), but more soluble in other media, as determined by partition coefficient studies: oil>blood>air>water (Morgan et al., 1972, Sato and Nakajima, 1979). A concentration of 1 part per million in air is equivalent to 6.3 mg/m^3. It is noteworthy that the American Conference of Government Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA) recommended threshold limit values (TLV) for carbon tetrachloride as follows: 64.1 mg/m^3 (10 ppm), 12.8 mg/m^3 (2 ppm), and 64.1 mg/m^3 (10 ppm), respectively.

The principal use of carbon tetrachloride (95%) is as an intermediate in the production of chlorofluoromethanes, which are used as propellants and refrigerants. Carbon tetrachloride is also used in grain fumigation and as an industrial solvent (Kirk-Othmer, 1979).

Sources of Exposure:

Carbon tetrachloride concentrations in the atmosphere are relatively constant in most regions of the world (0.0008-0.0009 mg/m^3) (EPA, 1980a). However, extremely high concentrations of carbon tetrachloride have been detected in urban atmospheres. The highest reported concentration (0.113 mg/m^3) was found in a sample from Bayonne, New Jersey (Lillian, et al., 1975).

Carbon tetrachloride concentrations in U.S. drinking water have generally ranged up to 6.4 ug/liter (EPA, 1980a). In rare instances, industrial accidents have resulted in dramatic increases in the concentration of carbon tetrachloride in drinking water. Following an alleged spill of 70 tons of carbon tetrachloride into the Kanawha River, levels of carbon

tetrachloride in drinking water reached 100 ug/liter (Landen, 1979). The inadvertant use of chlorine contaminated with carbon tetrachloride for the chlorination of drinking water in Philadelphia and other Northeast locations also resulted in high concentrations of carbon tetrachloride in drinking water (up to 46 ug/liter) (EPA, 1977).

Pharmacokinetics:

In order to ascertain the absorption, distribution, and elimination of radioactive carbon tetrachloride in animals, McCollister, et al. (1951) designed experiments in which rhesus monkeys inhaled a vapor concentration of 0.290 mg/l (46 ppm) ^{14}C-labeled carbon tetrachloride for periods of 139, 344, and 300 minutes. The authors made the following observations: (a) of the total amount of carbon tetrachloride inhaled, an average of 30% was absorbed; (b) the highest concentration of radioactive material deposited in tissues was found in the fat which had a distribution ratio of 7.94 (blood = 1); (c) ^{14}C was found in the blood carbonate, exhaled carbon dioxide and in urinary urea and carbonate; and (d) the equivalent of at least 51% of the carbon tetrachloride absorbed during an inhalation period was estimated to have been eliminated in the expired air within 75 days following the end of the exposure. The remainder evidently was excreted to a large extent in the urine and feces.

Among reported metabolic reactions in liver are conversion to carbon dioxide (Rubinstein and Kanics, 1964), chloroform (Butler, 1961), hexachloroethane (Fowler, 1969), carbonyl chloride (phosgene) (Shah et al., 1979), and binding to lipids and proteins (Glende, et al., 1976, Uehleke and Werner, 1975).

Health Effects:

Exposure to carbon tetrachloride is reported to produce fatty liver, with centrilobular necrosis developing if exposure is continued. In humans, this condition may be followed by kidney failure. The histologic changes may be accompanied by biochemical abnormalities including alterations in the activity of the microsomal enzyme system, an increase in triglycerides in the liver, and a decrease in protein synthesis.

Short-Term Exposure:

Lamson et al. (1928) studied the effects of carbon tetrachloride in patients receiving carbon tetrachloride and magnesium sulfate orally as a treatment for hookworms. The authors report the treatment of thousands of patients with a single dose of 2.5-15 ml of carbon tetrachloride without any adverse

effects. One man was reported to have safely ingested 40 ml of carbon tetrachloride. However, an "extremely small" population of adults died after receiving 1.5 ml of carbon tetrachloride; doses of 0.18-0.92 ml were reported to be fatal to children. Alcohol consumption enhanced carbon tetrachloride-induced toxicity in adults.

Stewart, et al. (1961) reported the toxic effects of experimental exposure of human volunteers to carbon tetrachloride vapor. Health males, 30-59 years of age, were exposed to concentrations of 63, 69, and 309 mg/m^3 of carbon tetrachloride (99% pure) in an exposure chamber for 180 minutes at the two lower doses or 70 minutes at the highest dose. All subjects had undergone periodic physical examinations; some participated in more than one of the exposure experiments, which were conducted 4 weeks apart. Six subjects exposed to the highest concentration experienced no nausea or lightheadedness, and carbon tetrachloride was not detected in blood and urine during or after exposure (the detection limit was 5 ppm). One of these six subjects had an increased level of urinary urobilinogen 7 days after exposure. In addition, two of four subjects exposed to the highest concentration and monitored for serum iron showed a decrease within 48 hours after exposure. Carbon tetrachloride was also not detected in the blood or urine of volunteers exposed at 63 or 69 mg/m^3, and the volunteers reported no physiologic effects. No changes in blood pressure, serum transaminase levels, or urinary urobilinogen levels were noted.

Effects of acute exposure to low levels of carbon tetrachloride in rats were reported by Korsrud et al. (1972). Male Wistar rats (260-400 g; 8-10 animals per treatment group) were administered single oral doses of carbon tetrachloride (0 to 4000 mg/kg bw) in corn oil (5 ml/kg bw). The rats were fasted for 6 hours before dosing and for 18 hours afterward, and then killed. Assays included liver weight and fat content, serum urea and arginine levels, and levels of nine serum enzymes, produced mainly in the liver. At 20 mg/kg bw there was histopathologic evidence of toxic effects on the liver. At 40 mg/kg bw, liver fat, liver weight, serum urea, serum arginine, and levels of six of the nine liver enzymes were increased. At higher doses the remaining three enzyme levels were also elevated. The histologic changes seen at the minimum effect level, 20 mg/kg bw, included a loss of basophilic stippling, a few swollen cells, and minimal cytoplasmic vacuolation.

Murphy and Malley (1969) investigated the effects of single oral doses of carbon tetrachloride on the corticosterone-inducible liver enzymes, tyrosine-α-ketoglutarate transaminase, alkaline phosphatase, and tryptophan pyrrolase in rats.

Specifically, groups of 4-7 male rats were administered by gavage 400, 800, 1600, 2400, or 3200 mg/kg undiluted carbon tetrachloride. Single doses of 400 mg/kg or greater of carbon tetrachloride increased liver tyrosine-α-ketoglutarate transaminase and alkaline phosphatase, but not tryptophan pyrrolase activity within 5 hours.

Carcinogenicity

Oral administration of carbon tetrachloride has been shown to be carcinogenic in rats, mice, and hamsters. In all three species, liver neoplasms developed although hamsters appeared to be the most sensitive.

Weekly administration of carbon tetrachloride (20 mg/kg bw) by gavage to 10 male and 10 female Syrian hamsters for 7 weeks, followed by 10 mg/kg bw weekly for an additional 23 weeks, produced liver cell carcinomas in 5 male and 5 female hamsters that survived 13-25 weeks after cessation of treatment. No data on control animals were provided (Della Porta, et al., 1961).

Two groups of 50 Osborne-Mendel rats of each sex were administered carbon tetrachloride in corn oil by gavage five times weekly for 78 weeks. Two doses were given to each sex: 47 or 94 mg/kg for males and 80 or 160 mg/kg for females. Both sexes exhibited statistically significant ($P < .05$) numbers of hepatocellular carcinomas at the low and high doses (males, 2/49, 2/50; females, 4/50, 2/49, respectively) as compared to the pooled controls (males, 1/99; females, 0/98) (NCI, 1976).

In another study, 50 hybird B6C3F1 mice of each sex were dosed by gavage five times weekly for 78 weeks with 1,250 or 2,500 mg/kg bw of carbon tetrachloride in corn oil. After 90-92 weeks, hepatocellular carcinomas developed in all males (49) and females (40) in the low-dose group and in 47 of 48 males and 43 of 45 females in the high-dose group. The incidences in the control group were 3 of 18 males and 1 of 18 females. In this experiment, carbon tetrachloride was used as a positive control (NCI, 1976).

Mutagenicity:

S. cerevisiae, strain D7, incubated with three concentrations of carbon tetrachloride (21, 41, or 54 mM) showed significantly increased frequencies of mitotic gene conversion and recombination at the highest dose compared to the control (Callen et al. 1980). Incubation of S. typhimurium strain G46 and E. coli strain K12 with carbon tetrachloride in the presence

of a metabolic activation system containing mouse liver microsomes produced no mutagenic effects. No data on dose levels, cytotoxicity, or controls were reported, however (Kraemer et al. 1974). Carbon tetrachloride also proved negative as a mutagen in S. typhimurium strain TA 1535 (McCann et al. 1975) at a maximum dose of 10^4 nM, at which less than 70 revertants per plate were produced. The compound was tested with a metabolic activation system, but additional experimental details were not reported.

Teratogenicity/Reproductive Effects:

Exposure of pregnant Sprague-Dawley rats to 1,890 or 6,300 mg/m^3 of 99.9% carbon tetrachloride for 7 hours/day on days 6-15 of gestation were reported to produce both fetotoxic and teratogenic effects (Schwetz et al. 1974). At the low and high concentrations, 22 and 23 litters, respectively, were examined. Fetal body weight and crown-rump length were significantly reduced from control values at both concentrations. At the higher dose the incidence of sternebral abnormalities, including bipartite and delayed ossification, was significantly increased over those in controls. Total skeletal abnormalities were significantly increased in the 1,890 mg/m^3 group, but not at the higher dose (Schwetz et al. 1974). In contrast, another study reported no significant teratogenic effects following exposure of 25 pregnant Sprague-Dawley rats to pure carbon tetrachloride at 1,575 mg/m^3, 8 hours per day for 5 consecutive days between 10 and 15 of gestation (Gilman, 1971). No convincing explanation is available to explain this discrepancy at this juncture.

When three groups of rats were given carbon tetrachloride (2,400 mg/kg bw) intraperitoneally for 10, 15, or 20 days, testicular and seminal vesicle weights were decreased in all rats. The number of animals per group was not specified. In addition, histologic examination of the testes revealed no damage in animals treated for 10 days; an increase in lumen size and a decrease in spermatogenic cells at 15 days; and atrophy of the tubules and an increase in lumen size at 20 days (Kalla and Bansal, 1975).

EPA-SNARL Development:

The available data suggest that the EPA-SNARL for carbon tetrachloride should be based on the potential of this compound to cause liver damage. This decision is justified by the following factors:

1. The liver appears to be the most sensitive indicator of carbon tetrachloride toxicity.

2. Carbon tetrachloride-induced hepatic liver damage has been reported after a single low-level exposure by ingestion.

One-Day EPA-SNARL:

The lowest acute oral dose of carbon tetrachloride reported to cause an adverse effect was 20 mg/kg bw in rats (Korsrud et al. 1972). This dose produced minimal damage to the liver as indicated by histologic examination (i.e., a loss of basophilic strippling, a few swollen cells, and minimal cytoplasmic vacuolation). Several higher and lower doses (0 to 4000 mg/kg) were also tested in that study, so a dose-response relationship could be developed. For these reasons, 20 mg/kg bw carbon tetrachloride will be used in the development of the EPA-SNARL. Because the data are for animals rather than humans and only one species (rat) was considered, a safety factor of 1000 will be used.

In calculating the EPA-SNARL, children are assumed to be the exposure subjects, since research in animals has indicated that young animals may be more sensitive than adults to the toxic effects of carbon tetrachloride (Cagen and Klassen, 1979). Furthermore, due to the lipophilic nature of this chemical, it is assumed that 100% of carbon tetrachloride is absorbed through the gastrointestinal tract.

Accepting 20 mg/kg as the minimal toxic effect dose, calculations of an EPA-SNARL for a 10 kg child, consuming one liter of water, are given below:

Calculations:

$$\frac{20 \text{ mg/kg} \times 100\% \times 10 \text{ kg}}{1 \text{ liter/day} \times 1000} = 0.2 \text{ mg/liter}$$

20 mg/kg = minimal toxic effect dose
100% = assumed absorption rate
10 kg = weight of child
1 liter/day = assumed water consumption by a 10 kg child
1000 = safety factor

Ten-Day SNARL:

In the absence of long-term (10-day) ingestion studies, the 10-day SNARL is thus calculated by dividing the 1-day SNARL of 0.2 mg/liter by 10:

$$\frac{0.2 \text{ mg/liter}}{10} = 0.02 \text{ mg/liter}$$

It should be noted that NAS used a similar approach for the calculation of their 7-day NAS-SNARLs. However, additional pharmacokinetics data are needed to calculate scientifically valid 10-day SNARLs.

The National Academy of Sciences has calculated SNARLs for carbon tetrachloride of 14 mg/liter for 1-day exposure and 2 mg/liter for 7-day exposure (NAS, 1980), in contrast to the EPA-SNARLs developed in this report of 0.2 mg liter for 1-day exposure and 0.02 mg/liter for a 10-day exposure. The reasons for this discrepency are threefold: different data bases were used, the NAS-SNARL was calculated for a 70 kg adult rather than a 10 kg child, and the adult was assumed to consume 2 liters of water per day as compared to 1 liter per day for a child. The NAS-SNARLs are based on the data of Murphy and Malley (1969), who reported liver effects in rats 5 hours after a single oral dose of carbon tetrachloride of 400 mg/kg bw. The study used in the EPA-SNARL reported toxic liver effects at the lower dose of 20 mg/kg bw (Korsrud et al. 1972). This difference, coupled with EPA's choice of a child rather than an adult as representative of the population most sensitive to exposure to carbon tetrachloride in water, accounts for the difference in SNARL values.

Long-Term EPA-SNARL:

Insufficient data on chronic exposure to carbon tetrachloride are available to develop a long-term EPA-SNARL for this compound.

Quantification of Carcinogenic Risk:

Because of positive results in animal carcinogenicity studies, carbon tetrachloride can be considered a suspect human carcinogen. Data from these animal studies have been used by NAS and the EPA Carcinogen Assessment Group (CAG) to calculate the number of additional cancer cases that may occur when carbon tetrachloride is consumed in drinking water over a 70-year lifetime. As shown in Table I, using the NAS and CAG data, estimates of additional carcinogenic risk following the exposure of humans to carbon tetrachloride may be derived.

The criteria for the CAG and NAS risk calculations differ in several respects: (1) NAS used the multistage model, while CAG used an "improved" multistage model, (2) NAS used the data set from the National Cancer Institute (NCI) study in male rats while CAG used the data set from NCI's study in male mice. The levels estimated by CAG thus resulted in a carbon tetrachloride concentration 1/11th that was estimated by NAS for identical cancer risks (EPA, 1980b).

Table I. Estimates of Additional Carcinogenic Risk Following Exposure of Humans to Carbon Tetrachloride in Drinking Water*

	Carbon Tetrachloride Concentrations (ug/liter)	
Excess cancer risk/lifetime	CAG (95% confidence limit)	NAS (95% confidence limit)
10^{-4}	40	450
10^{-5}	4	45
10^{-6}	0.4	4.5

* An average daily drinking water consumption of 2 liters per day was assumed.

EPA's Ambient Water Quality Criteria for carbon tetrachloride (EPA, 1980a) based on increased lifetime cancer risk estimates of 10^{-5}, 10^{-6}, and 10^{-7}, are as follows: 4.0, 0.40, and 0.04 ug/liter, respectively. It is noteworthy that these concentration levels were derived by assuming a lifetime consumption of both drinking water (2 liters/day) and aquatic life (6.5 g fish and shellfish/day) grown in waters containing the corresponding carbon tetrachloride concentrations. Thus, these criteria do not apply to drinking water per se.

Analysis:

Carbon tetrachloride (and 47 other halogenated organics) in water can be analyzed by a purge and trap method (Method 502.1) described by the EPA Environmental Monitoring and Support Laboratory (EPA, 1980c). This method can be used to measure purgeable organics at low concentrations. Using a sample size of 5 ml, purgeable organic compounds are trapped on a Tenax GC-containing trap at 22°C using a purge gas rate of 40 ml/min for 11 minutes. The trapped material is then heated rapidly to 180°C and backflushed with helium at a flow rate of 20-60 ml/min for 4 minutes into the gas chromatographic analytical column. The programmable gas chromatograph

used is capable of operating at 40° ± 1° C. The primary analytical column is stainless steel packed with 1% SP-1000 on Carbopack B (60/80) mesh (8 ft. x 0.1 in. I.D.) and is run at a flow rate of 40 ml/min. The temperature program sequence begins at 45°C for 3 minutes, increases 8°C/min to 220°C, and is then held constant for 15 minutes or until all compounds have eluted. A halogen-specific detector with a sensitivity to 0.10 mg/liter and a relative standard deviation of 10% must be used. The optional use of GC/MS techniques of comparable accuracy and precision is acceptable.

Treatment:

The information available on the removal of carbon tetrachloride from drinking water is limited. However, based upon data obtained from industrial waste treatment, conventional treatment processes are not very effective in the removal of this compound. An isotherm study of carbon tetrachloride on Filtration 400 activated carbon (GAC) showed that at an equilibrium concentration range of 3×10^{-9} to 2.6×10^{-7} mol/l a maximum surface concentration of 2.6×10^{-5} mol/g was obtained (NAS, 1979). Studies have also been conducted to evaluate aeration and adsorption processes in the removal of this compound. It was found that powdered activated carbon (PAC) at 2 to 4 mg/l is not effective in treating contaminated river water containing 16.3 mg/l of carbon tetrachloride. After PAC, coagulation, settling and filtration, the finished water still contains 16.0 mg/l (EPA, 1980d). Aeration by diffused air aerator in a laboratory study was found to be more successful. At 4:1 air-to-water ratio, a 91 percent removal efficiency of the carbon tetrachloride was achieved (EPA, 1980d). Adsorption by GAC in a pilot scale study revealed that carbon tetrachloride at an average concentration of 12 mg/l (Cincinnati tap water) was reduced to less than 0.1 ug/l for 3 weeks with a 5-min. empty bed contact time (EBCT) and between 14 and 16 weeks with a 10-min. EBCT.

Conclusions and Recommendations:

From data on the lowest acute dose of carbon tetrachloride producing health effects in rats (20 mg/kg bw), a 1-day EPA-SNARL of 0.2 mg/liter and a 10-day EPA-SNARL of 0.02 mg/liter have been calculated. Insufficient data on chronic exposure to carbon tetrachloride are available to calculate a long-term SNARL for this compound. Carcinogenic effects of carbon tetrachloride were not considered in the preparation of these SNARLs. Possible risks associated with carcinogenicity as derived from the data calculated by the National Academy of Sciences and EPA Carcinogen Assessment Group are discussed.