Appendix B
Section B

CARBON TETRACHLORIDE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Carbon tetrachloride is a relatively nonpolar haloalkane that is slightly water soluble. It is manufactured by the chlorination of methane, propane, ethane, propylene, or carbon disulfide. Carbon tetrachloride is classified as a probable human carcinogen (U.S.EPA Group B2) and has been shown to induce liver neoplasms in hamsters, mice, and rats. Based on a mouse bioassay, a quantitative estimate of human liver cancer hazard was calculated for exposure to carbon tetrachloride in drinking water. A drinking water level of 0.4 ug carbon tetrachloride per liter of water is associated with a lifetime excess cancer risk of one in a million.

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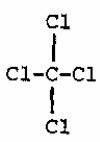
BACKGROUND INFORMATION AND PROPERTIES

Chemical properties

Chemical name	Carbon Tetrachloride
Synonyms	Tetrachloromethane, carbona,
CAS Number	56-23-5
Chemical formula	CCl_4
Chemical structure	
Molecular weight	153.8
Physical state (room temperature)	clear, colorless liquid
Melting point	-22.9 °C
Boiling point	76.5 °C at 760 torr
Vapor pressure, volatility	115.2 torr at 25 °C
Specific gravity, density	1.59 g/ml at 25 °C
Water solubility	785 mg/l at 20 °C
Log octanol/water partition coefficient	2.64
Taste threshold (water)	not available
Odor threshold (water)	not available
Odor threshold (air)	not available
Conversion factors	1 ppm = 6.402 mg/m^3

Production and Use

Carbon tetrachloride is produced by the chlorination of carbon disulfide, ethane, methane, propane, or propylene using industrial processes, and as a byproduct of vinyl chloride and perchlorethylene production. A major

use of carbon tetrachloride is in the manufacture of chlorofluorocarbons which are used as refrigerants, foam-blowing agents, and solvents (U.S.EPA, 1984a).

Guidelines, Regulations, and Standards

The Occupational Safety and Health Administration (OSHA), U.S. Department of Labor, workplace standard for carbon tetrachloride is 65 mg/m^3 for an 8-hour time-weighted-average (TWA) exposure with an acceptable ceiling exposure concentration of 162.5 mg/m^3.

The U.S. Environmental Protection Agency published an Ambient Water Quality Criteria Document for carbon tetrachloride (U.S.EPA, 1980). Assuming consumption of 2 L of water and 6.5 g of fish per day by a 70-kg adult, a carbon tetrachloride level of 0.4 ug/L was estimated to limit excess lifetime cancer risk to one in a million. The corresponding drinking-water- only concentrations was 0.44 ug/L.

Health Advisory drinking water guidance on non-carcinogenic health effects has been developed by the Office of Drinking Water, U.S.EPA (U.S.EPA, 1985b). Assuming that a 10-kg child consumes 1 L per day of water, the one-day, ten-day, and longer-term Health Advisories are 4,000, 160, and 71 ug/L, respectively. The longer-term Health Advisory for a 70-kg adult with a daily consumption of 2 L per day of water is 250 ug/L.

Excess human cancer risk associated with lifetime exposure to carbon tetrachloride has been extrapolated from animal cancer studies (U.S.EPA, 1984a). The carbon tetrachloride drinking-water concentration associated with an one in a million excess cancer risk was 0.27 ug/L.

The U.S.EPA promulgated final recommended maximum contaminant levels (RMCLs), and proposed maximum contamination levels (MCLs) under the Safe Drinking Water Act (U.S.EPA, 1985a). The RMCL and MCL for carbon tetrachloride are 0 and 5 ug/L, respectively.

The World Health Organization recommended a tentative guideline value of 3 ug/L for drinking water (WHO, 1984). A linear multistage extrapolation model was used to derive a level that should give rise to less than one additional cancer per 100,000 population, assuming a daily drinking water consumption of 2 L.

ENVIRONMENTAL EXPOSURE

Fate and Transport

Carbon tetrachloride tends to evaporate quickly from water. Compared with evaporation, hydrolytic decomposition appears to be an insignificant means of removal from water. Although little data exist on

adsorption of carbon tetrachloride onto sediment, estimates of the sorption potential based on the octanol/water partition coefficient suggest that it moves with soil and sediment (U.S.EPA, 1984b).

Ambient Levels

The U.S.EPA used data from the Federal Reporting Data Systems (FRDS) on primary drinking water systems to estimate population level exposure to carbon tetrachloride in the United States. An estimated 26,810,000 individuals are exposed to levels of carbon tetrachloride in drinking water at or above concentrations of 0.5 ug/L (Table I), (U.S.EPA, 1984b).

From 1978 through 1981, the Office of Science and Research of the New Jersey Department of Environmental Protection surveyed water supplies in the state for the presence of over 100 contaminants. Carbon tetrachloride was detected in 4% of the approximately 500 samples at an average concentration of 2 ug/L. Recently, A-280 listed chemicals were monitored by New Jersey potable water purveyors. Carbon tetrachloride was found in 4% of the samples. The concentration levels observed ranged from 0.7 to 7.6 ug/L.

Table I

Estimated Drinking Water Intake of Carbon Tetrachloride

Exposure Level (ug/L)	Population	Intake* (ug/kg/day)
$\geq$ 0.5	26,810,000	$\geq$ 0.014
> 5.0	2,087,000	> 0.14
> 10	698,000	> 0.29
> 20	655,000	> 0.57

*Intake estimates assume 70 kg body weight and 2 L consumption of water per day.

Source: U.S.EPA, 1984b.

METABOLISM AND PHARMACOKINETICS

Absorption

Carbon tetrachloride is readily absorbed through the lungs and more slowly through the gastrointestinal tract (Nielson and Larsen, 1965). Considerable quantities can be absorbed through the small intestine (Robbins, 1929).

Distribution

The distribution of carbon tetrachloride in dogs after oral administration was studied (Robbins, 1929). The amount found in the liver, pancreas, and spleen was one-fifth of the concentration noted in the bone marrow. Inhaled carbon tetrachloride was distributed in a female rhesus monkey to fat, liver, and bone marrow with a particularly high concentration in the fat (McCollister et al., 1951).

Metabolism

In mammals, carbon tetrachloride is metabolized primarily in the liver. The exact mechanism is still under debate. The metabolites include carbon dioxide, chloroform, hexachloroethane, and carbonyl chloride (phosgene) (Reynolds et al., 1984; Shah et al., 1979).

Excretion

Carbon tetrachloride and its volatile metabolities are eliminated primarily in exhaled air and also in urine and feces (U.S.EPA, 1984b). Carbon tetrachloride was administered to rats as a solution in light liquid paraffin by intragastric cannulation. The rats expired unchanged 60% of the dose within 6 hours (Reddrop et al., 1981).

Human Exposure and Body Burden

Based on limited information 80-100% of the carbon tetrachloride ingested is absorbed and approximately 30% of the inhaled dose is absorbed (U.S.EPA, 1984b).

HEALTH EFFECTS

Overview

The principal adverse effect of carbon tetrachloride is liver injury. The numerous adverse effects observed in the liver include inhibition of protein synthesis, accumulation of triglyceride, destruction of normal intracellular morphology, and necrosis. Carbon tetrachloride has induced liver cancer in rats, mice, and hamsters.

Human

The major pathological changes from carbon tetrachloride ingestion occur in the liver and kidney. Ingestion of as little as 0.18 to 0.92 mL (29 to 150 mg/kg) may be fatal in children (U.S.EPA, 1985b). When inhaled, carbon tetrachloride may induce central-nervous-system depression, pulmonary edema, renal failure, and fatal cardiac arrhythmias (IARC, 1978).

Animal

The single oral dose LD_{50} for rats is 2800 mg/kg, and for mice 12,800 mg/kg. The most pronounced effects are liver necrosis and fatty liver degeneration (IARC, 1979).

Behavioral and Central Nervous System

Symptoms of an acute human inhalation are mental confusion, agitation, feeling of suffocation, and loss of consciousness (IARC, 1979).

Reproductive, Embryotoxic, and Teratogenic

Carbon tetrachloride has not been shown to be teratogenic in rats, but may be embryotoxic at doses which are toxic to the dam. Fetal, neonatal, and young rats appear to be more resistant than adults to the hepatotoxic effects of carbon tetrachloride (Barlow and Sullivan, 1982).

Genetic

Carbon tetrachloride has not been found to be mutagenic in the Salmonella revertant system (Table II). Callen et al. (1980) noted an increase in gene conversion in the yeast Saccharomyces cerevisiae. Chromosomal aberrations were not found in an in vitro assay (Dean and Hudson-Walker, 1979). There is not enough information available to classify carbon tetrachloride as a mutagen.

Carcinogenicity

Carbon tetrachloride induced hepatocellular carcinomas in rats, mice, and hamsters (Andervont, 1958; Della Porta et al., 1961; Edwards et al., 1942; NCI, 1976; Weisburger, 1977). The International Agency for Research on Cancer (IARC) concludes that carbon tetrachloride is probably carcinogenic in humans (group 2B). Even though the evidence for carcinogenicity in humans is inadequate, there is sufficient evidence for carcinogenicity in animals (IARC, 1979; IARC, 1982).

Table II

Genetic Toxicology of Carbon Tetrachloride

Process	End Point	Test System	Conclusions	References
Gene Mutation	Base-pair substitution Frameshift	Ames Salmonella battery with and without metabolic activation	Negative	NTP unpublished results
Chromosomal Rearrangement Homologous recombination	Gene conversion	Saccharomyces cerevisiae	Positive	Callen et al., 1980
Chromosomal Rearrangement Non-homologous recombination	Chromosomal aberrations	Rat in vitro	Negative	Dean and Hudson-Walker, 1979

The U.S.EPA also classified carbon tetrachloride as a probable human carcinogen (Group B2) (U.S.EPA, 1985 a,b).

Carbon tetrachloride was used as a positive control in animal bioassays for several other compounds sponsored by the NCI (NCI, 1976; Weisburger, 1977). Carbon tetrachloride was administered to Osborne-Mendel rats and $B6C3F_1$ mice. Animals were distributed so that there were 50 animals of each species and sex in each treatment group. Colony controls (animals of the same strain and source as test animals) consisted of 99 male and 98 female rats, and 77 male and 80 female mice.

Carbon tetrachloride doses were administered by gavage 5 times per week in a corn oil vehicle for 78 weeks. Rats were started on the test at the age of 6 weeks and mice at the age of 5 weeks. Food and water were provided ad libitum. Male rats received a time-weighted-average (TWA) dose of 47 mg/kg body weight (25 mg/kg for 10 weeks, and 100 mg/kg for 68 weeks). The TWA doses for female rats were 80 mg/kg (100 mg/kg for 14 weeks, and 75 mg/kg for 64 weeks), or 160 mg/kg (200 mg/kg for 14 weeks, and 150 mg/kg for 64 weeks). Male and female mice received either 1250 or 2500 mg/kg body weight for 78 weeks.

Dosing periods were followed by observation periods of 32 weeks for rats and 12 weeks for mice. All animals dying during the experiment, as well as those sacrificed at the termination of the experiment, were necropsied. Comparison of hepatocellular carcinoma incidence in treated male rats revealed no statistically significant increase over the incidence in controls. Female rats in the low-dose group did show a significantly ($p < 0.05$) increased incidence of hepatocellular carcinomas. Practically all mice treated with carbon tetrachloride had hepatocellular carcinoma (Table III).

In a study conducted by Edwards et al. (1942) 73 inbred strain L mice received 46 0.1 mL doses of a 40% carbon tetrachloride solution in olive oil through stomach tube over a 4 month period. The mice were fed Purina dog chow pellets, and tap water was provided ad libitum. All surviving animals were sacrificed 3 to 3.5 months after the last treatment. At autopsy mouse age varied from 8.5 to 14 months. The mice developed a high incidence of liver hepatomas (28/54 for males and 6/19 for females). Liver hepatoma incidence for historical controls was reported as 2/69 for males and 0/83 for females (Table III). This experiment failed to use concurrent controls.

Carbon tetrachloride was administered to male and female C3H mice that were 3.5-7.5 and 3.5-6.5 months of age, respectively (Andervont, 1958). Treatment groups consisted of 77 males and 37 females, while concurrent controls consisted of 45 males and 30 females. Carbon tetrachloride was provided once weekly in an olive oil vehicle for 19 weeks. The first two doses consisted of 0.1 mL of a 2% solution (4 mg carbon tetrachloride), and the remaining 17 doses were each of 0.2 mL of a 3% solution (6 mg carbon tetrachloride). Food and water were provided ad libitum, except on the night before dosing when food was removed from the

Table III
Incidence of Liver Tumors in Mice
and Rats Induced by Carbon Tetrachloride[a]

Dose Levels[b] Experimental mg/kg	Adjusted mg/kg/day	Male	Female	Combined
	NCI - Mouse Hepatocellular Carcinoma			
0	0	5/77	1/80	6/157
1250	547	49/49	40/40	89/89
2500	1094	47/48	43/45	90/93
	NCI - Rat Hepatocellular Adenoma			
0	0	1/99		
47	16.37	2/50		
94	32.75	2/50		
0	0		0/98	
80	27.87		4/49	
160	55.74		1/49	
mg	Edwards - Mice Liver Hepatoma			
0	0	2/69	0/83	
40	4.072	28/54	6/19	
	Andervont - Mice Liver Hepatoma			
0	0	22/45		
5.789[c]	0.6178	61/77		
0	0		1/30	
5.789[c]	0.6848		17/37	

[a] Data are taken from the National Cancer Institute (NCI) gavage studies (1976), Edwards et al. (1942), and Andervont (1958).

[b] Dose levels are converted from milligram per kilogram to milligram per kilogram per day by multiplying by a factor of 5/7 to account for the fact that carbon tetrachloride was administered 5 days per week for NCI study. A factor of $(92/104)^4$ for mice and $(111/130)^4$ for rats are further applied for NCI study, because the experiment was terminated before the animals lived out their full life spans. In addition, a factor of 78/85 is applied to the NCI rat study to account for the fact that dosing was stopped at 1/5 of normal life span prior to the final sacrifice. Conversion factor for the Edwards study is $[46/(4 \times 30 \times 0.03)][7.25 \times 30/(107 \times 7)]^4$ and for the Andervont study is $(1/7[19/(30y/7 - 20.8)] \times [30y/(7 \times 107)]^4$, where y = 9.5 for males and y = 10 for females.

[c] These are time-weighted-average doses and are computed by

$$\frac{\text{(dose in mg/kg x number of days at that dose)}}{\text{(number of days receiving any dose)}}$$

animals. Surviving animals were sacrificed at the age of 15 months (approximately 41 weeks on test). The livers of the mice were histologically examined.

Liver hepatoma incidence in treated male mice was 61/77. Control male mice had a hepatoma incidence of 22/45. The incidence of hepatomas in female mice was 17/37 in the treated group and 1/30 in the controls (Table 3).

Ten male and ten female Syrian golden hamsters received a 5% carbon tetrachloride solution in corn oil by gavage on a weekly basis for 30 weeks (Della Porta et al., 1961). During the first 7 weeks, 0.25 mL of the solution containing 12.5 uL of carbon tetrachloride was given. For the remaining 23 weeks, 0.125 mL of the solution containing 6.25 uL of carbon tetrachloride was administered. All surviving animals were killed after 55 weeks on the study. Detailed histopathological examinations were conducted on all hamsters, except for one female lost through cannibalism at the 28th week. The hamsters developed liver-cell carcinomas (5/10 for males and 5/9 for females). Liver tumor incidence reported for historical controls was 0/30 for the males and 0/50 for the females. This study failed to use concurrent controls.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

The evidence to classify carbon tetrachloride as a probable human carcinogen was obtained from animal laboratory bioassays (Andervont, 1958; Della Port et al., 1961; Edwards et al., 1942; NCI, 1976). An evaluation of these bioassays has been conducted based on the guidelines of Crump and Howe (1980). The Edwards et al. (1942) and Della Porta et al. (1961) studies did not use concurrent controls and are not suitable for quantitative risk assessment. The Andervont (1958), Della Porta et al. (1961), and Edwards et al. (1942) studies did not dose the animals throughout the experiment. The NCI (1976) study is, therefore, the most appropriate for making quantitative risk estimates. The mice in the NCI (1976) study displayed a maximum response to the effects of carbon tetrachloride. The time-to-death with tumor data set for combined male and female hepatocellular carcinoma was modeled. The multistage-Weibull model adjusts for the premature mortality found in the NCI (1976) study.

Calculation of the Health-Based Maximum Contaminant Level

The dose-response relationships obtained from the NCI (1976) mouse study were modeled by using regression techniques. The multistage Weibull model was used in this analysis for low dose extrapolation with time-to-tumor data. This multistage Weibull model is given by:

$$P(d,t) = 1 - \exp\left[(-q_0 - q_1 d - \ldots - q_k d^k)\,(t-\delta)^{\beta}\right],\ q_i \geq 0,\ i = 0, 1, \ldots, k,$$

where $P(d,t)$ is the lifetime probability of cancer at dose d and time t. In practice, k is set equal to the number of

dose groups less one. The multistage-Weibull model was implemented by using the computer program WEIBULL82. All calculations were provided by K.S. Crump and Company (Crump, 1985).

Risk has been defined as "extra risk", i.e.,

$$[P(d,t) - P(0,t)]/[1-P(0,t)]$$

where P(d) is the lifetime probability of dying of liver cancer when exposed to carbon tetrachloride dose d and P(0) is the lifetime probability of dying of liver cancer when not exposed to carbon tetrachloride. A risk level of one in a million was selected for a lifetime exposure scenario. The 95% upper confidence limit on risk is linear at low doses and will be considered a plausible upper bound on risk.

Animal-to-human extrapolation is based on the assumption that both animals and humans are equally susceptible (in terms of extra risk) to the carcinogen when dose is measured in the same unit for both species (Crump and Howe, 1980). The units of mg/m^2 body surface area per day will be used for animal-to-human extrapolation. If D_A represents animal dose in milligrams per kilogram per day, then the human dose (D_H) is given by:

$$D_H = D_A \, (W_A/W_H)^{1/3},$$

where W_A and W_H are the weights of animals and humans, respectively. The standard assumption is that a 70 kg adult consumes 2 L of water per day.

The multistage Weibull model fitted to the NCI (1976) mouse time-to-death with hepatocellular carcinoma information provided an animal dose of 1.46×10^{-4} mg/kg per day.

$$\begin{aligned}
&= \text{human dose (mg/kg/day)} \times (1000 \text{ ug/mg}) \times (70 \text{ kg})/(2 \text{ L/day}),\\
&= \text{animal dose (mg/kg/day)} \times (W_A/W_H)^{1/3} \times 35000,\\
&= \text{animal dose (mg/kg/day)} \times (0.03 \text{kg}/70 \text{ kg})^{1/3} \times 35000,\\
&= \text{animal dose (mg/kg/day)} \times 35000/13,\\
&= (1.46 \times 10^{-4})(35000)/13,\\
&= 0.39 \text{ ug/L}.
\end{aligned}$$

A drinking water level of 0.4 ug carbon tetrachloride per liter is associated with a lifetime excess cancer risk of one in a million.

Assumptions and Uncertainty

The extrapolation of liver cancer risk from bioassay data to human liver cancer risk was carried out by assuming that animals and humans were equally sensitive relative to a particular measure of dose. The interspecies conversion factor used was mg/m^2 surface area/day. This is equivalent to (rat weight/human weight)$^{1/3}$. Rat and human weights used are 0.03 and 70 kg, respectively.

A 70 kg adult was assumed to consume two L of drinking water per day for life. The 95% upper confidence level on risk was considered a plausible upper bound on risk. The risk level applied was one in a million excess cancer risk.

Conclusions

Carbon tetrachloride was classified as a probable human carcinogen (IARC Category 2B; EPA Group B2). Carbon tetrachloride induced liver neoplasms in hamsters, mice, and rats. The quantitative estimation of liver cancer hazard was based on the NCI (1976) mice bioassay. A drinking water level of 0.4 ug carbon tetrachloride per liter was associated with a lifetime excess cancer risk of one in a million.

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