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Office of Emergency and
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Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
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Cincinnati OH 45268

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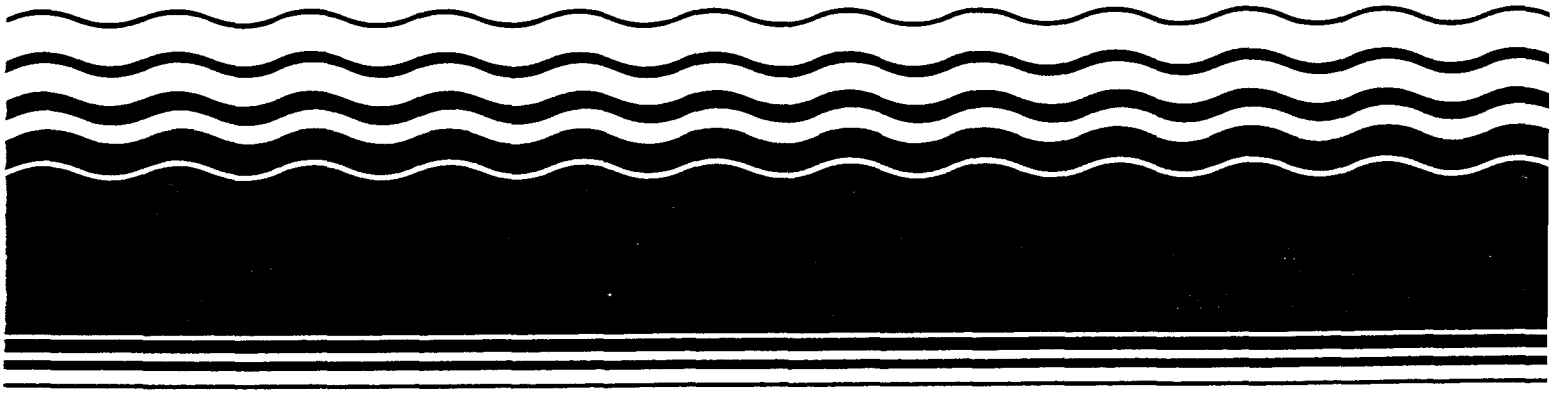
HEALTH EFFECTS ASSESSMENT FOR CARBON TETRACHLORIDE



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U.S. Environmental Protection Agency
Office of Research and Development
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DISCLAIMER

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with carbon tetrachloride. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Carbon Tetrachloride. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA-440/5-80-026. NTIS PB 81-117376.

U.S. EPA. 1983b. Reportable Quantity Document for Carbon Tetrachloride. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983c. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of: Carbon Tetrachloride. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Health Assessment Document for Carbon Tetrachloride. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-82-001F. NTIS PB 85-124196.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is

assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context the reader is referred to the Preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Animal bioassay data in three species (rats, mice, hamsters) indicate that carbon tetrachloride is a hepatic carcinogen. Human data are limited and equivocal. The Cancer Assessment Group, as explained in U.S. EPA (1984), has used data from the following for risk assessment purposes: Della Porta et al. (1961); Edwards et al. (1942); NCI (1976) (both rat and mouse). Since none of these studies were deemed adequate individually, the geometric mean of the upper limit unit risk estimates (3.7×10^{-6}) has been employed. The corresponding slope estimate (q_1^*) is 1.30×10^{-1} $(mg/kg/day)^{-1}$.

A note of caution is provided by U.S. EPA (1984). Some evidence indicates that carbon tetrachloride may act via a nongenotoxic mechanism. If this should be the case, then low-dose risk extrapolation using techniques developed for agents which presumably act through genotoxicity could substantially overestimate risk. The reader is referred to U.S. EPA (1984) for a thorough discussion of this question. More experimental data are needed to resolve this issue.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
FEL	Frank-effect level
GI	Gastrointetinal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
ppm	Parts per million
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of carbon tetrachloride (CAS No. 56-23-5), also known as tetrachloromethane, are shown in Table 1-1.

The value for the retardation factor for carbon tetrachloride is estimated on the basis of a comparison of the octanol/water partition coefficient and water solubility of this compound with chloroform and the estimated retardation factor of 1.2 for chloroform (Wilson et al., 1981).

The half-life of carbon tetrachloride in soil could not be located in the literature searched; however, evaporation is expected to be the predominant loss mechanism from the soil surface. In subsurface soil, biodegradation of carbon tetrachloride will probably be a very slow process, as is true of chloroform (Wilson et al., 1983). Therefore, carbon tetrachloride is expected to leach into groundwater. This has been confirmed by Page (1981), who detected carbon tetrachloride with a 64% frequency in groundwater.

TABLE 1-1

Selected Physical and Chemical Properties and Half-lives for Carbon Tetrachloride

Properties	Values	Reference
Chemical class:	halogenated aliphatic hydrocarbon	
Molecular weight:	153.82	
Vapor pressure:	90 mm Hg at 20°C	Callahan et al., 1979
Water solubility:	757 mg/ℓ at 25°C	Banerjee et al., 1980
Octanol/water partition coefficient:	437	Callahan et al., 1979
	537	Banerjee et al., 1980
Soil mobility: (predicted as retardation factor for a soil depth of 140 cm and organic carbon content of 0.087%)	>1.2 (estimated)	Wilson et al., 1981
BCF:	30 in bluegill (Lepomis macroschirus)	U.S. EPA, 1980b
	17 in fathead minnow (Pimephales promelas)	Veith et al., 1979
Half-lives in Air:	22 years	Singh et al., 1981
	~50 years	U.S. EPA, 1984
Water:	0.3-3 days in river 30-300 days in lake	Zoeteman et al., 1980

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

No pertinent studies of absorption of carbon tetrachloride from the GI tract of humans were located in the available literature. Little information on absorption from the GI tract of experimental animals was available. In an early study, Robbins (1929) investigated absorption of carbon tetrachloride from the GI tract of dogs. He reported that "considerable quantities" were absorbed from the small intestine, lesser quantities from the colon and still lesser quantities from the stomach. Lamson et al. (1923) suggested that the dynamics and kinetics of absorption from the GI tract may vary from species to species. They observed more rapid GI absorption in rabbits than in dogs. Nielsen and Larsen (1965) determined that both the rate and the amount of carbon tetrachloride absorption from the GI tract were increased by concurrent ingestion of fat or alcohol.

2.2. INHALATION

Pertinent studies of pulmonary absorption of carbon tetrachloride in humans were not located in the available literature. Few studies on pulmonary absorption in experimental animals were found. Nielsen and Larsen (1965) stated that carbon tetrachloride is "readily absorbed" through the lungs but the species studied was not reported (U.S. EPA, 1980b). Lehmann and Hasegawa (1910) showed that the rate of absorption decreased with duration of exposure. von Oettingen et al. (1949, 1950) studied blood concentrations in dogs following exposure to 15 or 20 g/ℓ in air. Peak blood concentrations of ~35 or ~38 mg/ℓ were attained after ~300 minutes of exposure to 15 or 20 g/ℓ in air, respectively.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Reports of acute toxicity from accidental, medicinal or suicidal ingestion of carbon tetrachloride are available, but no reports of subchronic ingestion in man were located in the available literature. One study of subchronic oral exposure described the toxicity of carbon tetrachloride in Syrian golden hamsters. U.S. EPA (1983c) discussed the study by Della Porta et al. (1961) in which groups of 10 male and 10 female Syrian golden hamsters were treated with 12.26 mg/week carbon tetrachloride by gavage for 30 weeks (~12.3 mg/kg/day). Mortality claimed 50% of the animals of each sex before treatment was completed. The survivors all developed hepatocellular carcinoma within the next 13 weeks.

3.1.2. Inhalation. Prendergast et al. (1967) performed two studies of subchronic inhalation exposure in animals. In the first experiment, guinea pigs and monkeys were exposed to 80 ppm carbon tetrachloride for 8 hours/day, 5 days/week for 6 weeks (30 exposures). Increased mortality (3/15 guinea pigs, 1/3 monkeys) and severe liver damage were reported. In the second experiment, animals were exposed to either 1 or 10 ppm carbon tetrachloride continuously for 90 days. At 10 ppm, guinea pigs showed increased mortality (3/15 treated vs. 2/314 colony controls), growth depression and liver enlargement with fatty infiltration, hepatocytic degeneration, fibroblastic proliferation and collagen deposition. Rats, monkeys and rabbits also experienced depressed growth rates and similar histopathological liver lesions, but no mortality occurred in these species. No mortality or gross signs of toxicity occurred in guinea pigs, rats, monkeys or rabbits exposed to 1 ppm carbon tetrachloride continuously for 90 days. A depression of body weight gain was observed only in rats. No changes were noted in

hematologic or histologic parameters in any of the species tested; continuous exposure to 1 ppm carbon tetrachloride (6.3 mg/m^3) was designated a LOAEL associated with depression of body weight gain.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic exposure of man to carbon tetrachloride were not located in the available literature. Studies of chronic exposure of animals to carbon tetrachloride were designed to be carcinogenicity bioassays and, as such, used doses >12.26 mg/week, which produced 50% mortality in Syrian golden hamsters. These studies are, therefore, not useful in deriving ADIs, and are reviewed in Chapter 4.

3.2.2. Inhalation. NIOSH (1975) provides an in-depth discussion of the pathology of chronic inhalation exposure of carbon tetrachloride in man. These reports are arranged by effects on organ systems and, since exposure data are lacking, are not useful in risk assessment. The U.S. EPA (1983b) summarized human studies that are more relevant to risk assessment. Smyth et al. (1936) and Smyth and Smyth (1935) studied the hematology, kidney and liver function (parameters not clearly specified) and vision of carbon tetrachloride-exposed workers. TWA exposures were estimated to range from 5-117 ppm, with peak exposures up to a maximum of 1680 ppm. Of 77 workers examined, 9 showed severely restricted visual fields and 26 showed slightly restricted visual fields. Of 67 men tested, 13 had elevated icterus indices. Hematology, kidney function and other parameters of liver function showed no significant alteration associated with exposure to carbon tetrachloride.

Moeller (1973) evaluated the effects of chronic occupational exposure to carbon tetrachloride on several ophthalmologic indices. A cohort of 46

workers was exposed from 1 hour/week to 1 hour/day to an unspecified concentration of carbon tetrachloride for an average of 7.7 years. Of these workers, 28 were found to have reduced corneal sensitivity. A group of 62 locksmiths exposed to 6.4-9.5 ppm carbon tetrachloride for a minimum of 1-3 hours/day and a control group of 82 unexposed persons were evaluated for corneal sensitivity and other visual parameters. Of the 62 exposed locksmiths, 43 had reduced corneal sensitivity, 4 had subnormal dark adaptation corneas, 4 had restricted outer limits of white visual fields, 15 had color limits of the visual field and 7 had instrument-detectable changes in color perception. Further information comparing the control groups and the exposed groups was not presented in the available review.

Barnes and Jones (1967) reported elevated urinary urobilinogen in 6/16 and elevated urine protein in 3/16 carbon tetrachloride-exposed workers compared with 11 unexposed controls. Zinc turbidity and average thymol turbidity tests were elevated in exposed workers compared with controls. Carbon tetrachloride-exposed workers also experienced elevated serum bilirubin and slightly elevated SGOT, compared with controls. Rabes (1972) associated significant elevations in serum iron and glutamic dehydrogenase with occupational exposure for $\geq$5 years to unspecified concentrations of carbon tetrachloride.

Adams et al. (1952) exposed guinea pigs and rats to 5, 10, 25, 50, 100, 200 or 400 ppm carbon tetrachloride for 7 hours/day, 5 days/week for up to 184 exposures over a period of 258 days. The numbers initially involved and surviving were not specified, but apparently 8-9 guinea pigs of each sex were tested at each concentration and ~15 rats of each sex/group were tested at dosages $\geq$25 ppm, 20 rats of each sex were tested at 10 ppm, and 23 females and 26 males were exposed to 5 ppm carbon tetrachloride.

Mortality among guinea pigs was high in the 200 ppm group and claimed >50% of the 400 ppm group. Survivors evidenced elevated kidney and liver weights, fatty degeneration and cirrhosis of the liver. Guinea pigs showed hepatomegaly at all concentrations tested, moderately hepatic fatty degeneration at $\geq$10 ppm and moderate liver cirrhosis at $\geq$25 ppm. Mortality also claimed $\geq$50% of the rats exposed to 400 ppm carbon tetrachloride. Hepatomegaly was observed in all exposed rats but liver cirrhosis was not detected at exposure concentrations <50 ppm.

Concurrently, two rabbits of each sex were exposed to 10, 25, 50 or 100 ppm carbon tetrachloride by the same exposure schedule (Adams et al., 1952). Exposure to 25 ppm, 178 times (248 days) resulted in moderate fatty liver degeneration and cirrhosis. Additionally, at 50 and 100 ppm, decreased growth rate, increased kidney weights and increased blood clotting time (indicative of liver damage) were observed.

Groups of two monkeys were exposed to 25, 50 or 100 ppm carbon tetrachloride by the same schedule for 148-198 times (~30-40 weeks) (Adams et al., 1952). No abnormal findings were reported in monkeys exposed to 25 ppm. Exposure to 50 ppm resulted in weight loss and exposure to 100 ppm resulted in "some indications of microscopic liver change." In this study, guinea pigs appeared to be the most sensitive species. Moderate (presumably reversible) hepatomegaly occurred at all exposures tested, but evidence of fatty degeneration was not noted until concentrations reached 10 ppm. For this study, 5 ppm carbon tetrachloride in guinea pigs constituted a LOAEL.

Smyth and Smyth (1935) and Smyth et al. (1936) exposed groups of 22-24 guinea pigs to 0, 50, 100, 200 or 400 ppm carbon tetrachloride 8 hours/day, 4-6 days/week for periods of up to 321 days. All guinea pigs exposed to

≥100 ppm died by 94 days of age, necessitating restructuring of the experiment. In the second trial, groups of 15 or 16 guinea pigs were exposed to 25, 50, 100 or 200 ppm carbon tetrachloride. A group of 7 unexposed guinea pigs served as controls. Mortality claimed 0/7, 12/15, 9/16, 11/16 and 11/15 of the 0, 25, 50, 100 and 200 ppm-exposed groups, respectively. In addition to the usual hepatic pathology, optic nerve degeneration was noted in 1 or 2 guinea pigs in each exposure group. Fatty degeneration of the ocular muscles was observed in 3-6 guinea pigs in each exposed group.

Groups of 24 rats were exposed to 0, 50, 100, 200 or 400 ppm carbon tetrachloride using the same dosage schedule described above for guinea pigs (Smyth and Smyth, 1935; Smyth et al., 1936). Liver degeneration, regeneration and cirrhosis were observed in rats exposed to ≥50 ppm carbon tetrachloride. Degeneration of the myelin sheath of the sciatic nerve and degenerative changes in ocular muscles, as well as some evidence of kidney damage, were observed sporadically in 50 ppm-exposed rats.

Finally, these investigators (Smyth and Smyth, 1935; Smyth et al., 1936) exposed four monkeys to 50 ppm and three monkeys to 200 ppm carbon tetrachloride by the same exposure schedule for 93-231 days. Nerve tissue appeared normal in all 50 ppm-exposed monkeys. Cloudy swelling of the kidney and fatty changes in the liver were noted at the 50 ppm level. A 28-day recovery period demonstrated the reversible nature of these mild liver and kidney changes.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. No reports of teratogenicity in humans or animals orally exposed to carbon tetrachloride have been found in the available literature.

3.3.2. Inhalation. No reports of fetotoxicity in humans associated with inhalation of carbon tetrachloride have been found in the available literature. Only one investigation of fetotoxicity caused by inhalation exposure of animals to carbon tetrachloride has been found. Schwetz et al. (1974) exposed groups of Sprague-Dawley rats to 300 or 1000 ppm carbon tetrachloride for 7 hours/day on days 6-15 of gestation. A significant decrease in body weights and crown-rump lengths was found in fetuses from dams exposed to either 300 or 1000 ppm carbon tetrachloride, as compared with controls. Gross examination revealed no anatomical or developmental anomalies; microscopic examination revealed delayed ossification of the sternebrae. The authors concluded that carbon tetrachloride was not teratogenic to rats at these exposures. Assuming that rats weigh 0.35 kg and inhale 0.26 m^3 of air/day, exposure to 300 ppm carbon tetrachloride for 7 hours/day results in an intake of 406.7 mg/kg/day.

3.4. TOXICANT INTERACTIONS

Alcohol ingestion has been clearly shown to potentiate the toxicity of carbon tetrachloride. Traiger and Plaa (1971) investigated the potentiation of carbon tetrachloride toxicity by methanol, ethanol and isopropanol in rats. The activity of SGPT was monitored to evaluate hepatotoxicity. All three alcohols tested potentiated the toxicity of carbon tetrachloride, with isopropanol being the most potent. Neither carbon tetrachloride nor the alcohols alone elevated SGPT levels. Wei et al. (1971) investigated the ability of ethanol and exposure to cold to potentiate hepatotoxicity of carbon tetrachloride in rats. Rats were pretreated with ethanol and subjected for 18 hours to a temperature of 4°C. Elevated SGPT indicated that ethanol and exposure to cold potentiated carbon tetrachloride-induced

toxicity. von Oettingen (1964) reported that persons who were habitual users or occasional users of alcoholic beverages became more seriously ill than abstainers when exposed to carbon tetrachloride.

In the early 1900's, carbon tetrachloride was used as an antihelmintic, particularly against hookworm, in both humans and animals. Smillie and Pessoa (1923) reported on severe carbon tetrachloride-induced toxicity among two alcoholics in a group of 34 persons treated with carbon tetrachloride for ancylostomiasis. Since then, other investigators (Guild et al., 1958; McGuire, 1932; Smetana, 1939; Gray, 1947) have observed that chronic alcohol ingestion exacerbates carbon tetrachloride-induced toxicity resulting from single medicinal doses.

Alcohol ingestion was suspected to play a significant role in the toxicity of carbon tetrachloride from nonmedicinal exposure (Abbott and Miller, 1948), particularly where renal failure was a major part of the clinical picture. The ACGIH (1980) suggested that ethanol and other substances (e.g., barbiturates and polychlorinated biphenyls) that induce hepatic microsomal enzymes enhance the toxicity of carbon tetrachloride.

Hafeman and Hoekstra (1977) claimed that vitamin E, selenium and methionine offer partial protection from carbon tetrachloride-induced toxicity. By monitoring the evolution of ethane, a peroxidation product of certain unsaturated fatty acids, these authors concluded that methionine, vitamin E and selenium protected against carbon tetrachloride-induced lipid peroxidation, probably by maintaining intracellular glutathione and glutathione peroxidase.

4. CARCINOGENICITY

4.1. HUMAN DATA

A few cases of liver cancer associated with exposure to carbon tetrachloride have been reported, but no epidemiological studies from which risk figures can be derived have been located in the available literature. Simler et al. (1964) reported the case of a fireman who developed epithelioma of the liver 4 years after being acutely poisoned by carbon tetrachloride. Tracey and Sherlock (1968) suggested that hepatocellular carcinoma in a 59-year-old man was caused by a 5-day exposure to carbon tetrachloride used to clean his rug. The patient denied ingesting alcohol since being exposed to carbon tetrachloride, but admitted to having used it before the exposure to carbon tetrachloride. Blair et al. (1979) reported 87 cancer deaths in a group of 330 exposed workers in which 67.9 cancer deaths would have been expected. Concurrent exposure to other workroom chemicals precluded attributing the observed increase in cancer incidence to carbon tetrachloride alone.

4.2. BIOASSAYS

4.2.1. Oral. Sufficient evidence for the carcinogenicity of carbon tetrachloride in laboratory animals exists in the available literature. Many early studies, although too short in duration to be useful for risk assessment, demonstrated the hepatocarcinogenicity of carbon tetrachloride. Edwards (1941) administered by gavage 0.1 mℓ of a 40% carbon tetrachloride solution in olive oil to C3H and A-strain mice 2-3 times/week for 23-58 doses. Necropsies performed 2-147 days after the last administration revealed a progression of events beginning with liver necrosis and followed by cirrhosis and eventually hepatomas in C3H mice. Hepatomas were found in 126/143 C3H and all 54 A-strain mice. Della Porta et al. (1961) reported

administrating 30 weekly doses of 6.25-12.5 μl (10-20 mg) carbon tetrachloride to five Syrian golden hamsters of each sex. Liver cell carcinomas were discovered in all animals (5 of each sex) that survived ≥10 weeks after the end of treatment.

Subsequently, C3H and strains A, Y, C and L mice were exposed to carbon tetrachloride to further elucidate the process of carcinogenesis (Edwards and Dalton, 1942; Edwards et al., 1942). Small numbers of mice were killed and necropsied after one or more doses. Liver necrosis and regenerative processes were observed throughout the study. Atypical mitotic forms such as triple mitoses were frequent findings. In mice treated for ≥1 month, enlarged hepatocytes with small nuclei were concentrated along strands of fibrous tissue. Hepatic tumors were usually multiple; neither invasion of blood vessels nor metastases were seen. These authors reported finding no evidence of tumors in other organs.

Eschenbrenner and Miller (1944) administered 30 doses of 0.16, 0.32, 0.64, 1.27 or 2.54 g carbon tetrachloride/kg bw by gavage to groups of 60 strain A mice. The interval between doses varied from 1-5 days; thus, the treatment period varied from 30-150 days. The incidence of hepatomas was 23/60, 23/60, 25/59, 32/60 and 33/60 in the five groups, respectively. In a later study, Eschenbrenner and Miller (1946) demonstrated that single doses of 12.5 μl/kg, but not 6.25 μl/kg, by gavage would cause liver cell necrosis in both male and female strain A mice. Administration of 6.25, 12.5, 25 or 50 μl/kg/day for 120 days resulted in hepatoma formation in mice exposed to ≥12.5 μl/day. Other mice were given 30 doses of 25, 50 or 100 μl/kg at 4-day intervals. Microscopic examination revealed small hepatomas in 2/10 mice given 25 μl/kg. Grossly visible tumors were

present in the higher-dosed groups. These investigators theorized that a necrotizing action of carbon tetrachloride on the liver was an important factor in the development of a carcinogenic response.

NIOSH (1975) and U.S. EPA (1980b) discussed short-term carcinogenicity bioassays involving carbon tetrachloride.

In an NCI-sponsored bioassay (NCI, 1976; Weisberger, 1977), Osborne-Mendel rats were exposed to 47 or 94 mg/kg (males) or 80 or 160 mg/kg (females) carbon tetrachloride by gavage for 78 weeks. Observations were continued for 33 additional weeks. Survival data, summarized in Table 4-1, indicate that excessive mortality had occurred in high dose rats of either sex. Although a slight increase in the incidence of hepatocellular carcinomas was noted in both males and females, a clear dose-related response could not be demonstrated.

Mice were also included in the NCI (1976) bioassay. Groups of 50 male and female 35-day-old mice were treated by gavage with 1250 or 2500 mg carbon tetrachloride in corn oil/kg bw/day, 5 days/week for 78 weeks. Observations continued for an additional 13 weeks. Vehicle control groups consisted of 20 mice of each sex. All mice were subjected to necropsy. Survival data are presented in Table 4-2. Mortality claimed most carbon tetrachloride-exposed mice by the end of the 78-week exposure period. Most carbon tetrachloride-treated mice were discovered to have hepatocellular carcinomas. The first carcinomas in female mice were found at 16 weeks and 19 weeks in low and high dose groups, respectively. Among male mice, the first carcinomas were found at 48 and 26 weeks in the low and high dose groups, respectively. The incidences of hyperplastic nodules and hepatocellular carcinomas are presented in Table 4-3.

TABLE 4-1

Survival of Rats Treated with Carbon Tetrachloride*

Dose	Initial	78 Weeks	110 Weeks
Males			
Control	100	67 (67%)	26 (26%)
Low	50	34 (68%)	14 (28%)
High	50	34 (68%)	7 (14%)
Females			
Control	100	75 (75%)	51 (51%)
Low	50	38 (76%)	20 (40%)
High	50	21 (42%)	14 (28%)

*Source: NCI, 1976

TABLE 4-2

Survival of Mice Treated with Carbon Tetrachloride*

Dose	Initial	78 Weeks	91-92 Weeks
Males			
Control			
Matched	20	13 (65%)	7 (35%)
Pooled	77	53 (69%)	38 (49%)
Low	50	11 (22%)	0 (0%)
High	50	2 (4%)	0 (0%)
Females			
Control			
Matched	20	18 (90%)	17 (85%)
Pooled	80	71 (89%)	65 (81%)
Low	50	10 (20%)	0 (0%)
High	50	4 (8%)	1 (2%)

*Source: NCI, 1976

TABLE 4-3

Liver Tumors in Mice*

Dose	Carcinomas
Males	
Control	
Matched	2/19 (11%)
Pooled	5/77 (6%)
Low	49/49 (100%)
High	47/48 (98%)
Females	
Control	
Matched	1/20 (5%)
Pooled	1/80 (1%)
Low	40/40 (100%)
High	43/45 (96%)

*Source: NCI, 1976

NR = Not reported

4.2.2. Inhalation. Little data concerning carcinogenicity of carbon tetrachloride from inhalation exposure have been located in the available literature. Costa et al. (1963) exposed albino rats to unspecified concentrations of atmospheric carbon tetrachloride for up to 7 months. Rats were killed serially from 2-10 months after the beginning of exposure. Of the 30 rats that completed the experiment, 12 had adenocirrhosis and 10 had liver nodules measuring up to 1 cm, which were microscopically diagnosed as incipient hepatocellular carcinoma.

4.3. OTHER RELEVANT DATA

Scarce pertinent data regarding the mutagenicity of carbon tetrachloride were located in the available literature. Kraemer et al. (1974) found no mutagenicity in either the Salmonella typhimurium or Escherichia coli reversion tests. Details of the experimental protocol were not available. Likewise, IARC (1979) reported a lack of mutagenicity in S. typhimurium strains TA100, TA1535, TA1538 (McCann and Ames, 1976; McCann et al., 1975; Uehleke et al., 1976) and E. coli (Uehleke et al., 1976).

4.4. WEIGHT OF EVIDENCE

There is sufficient evidence in mice, rats and hamsters to designate carbon tetrachloride a potent hepatic carcinogen in animals. Prolonged exposure (NCI, 1976; Weisburger, 1977) results in a very high incidence of hepatocellular carcinoma.

The few case reports associated with carbon tetrachloride provide limited, but not sufficient, evidence to confirm human carcinogenicity. Only one epidemiologic study (Blair et al., 1979) was found in the available literature. Blair et al. (1979) observed 87 cancer deaths in a cohort of 330 exposed workers in which 67.9 cancer deaths would have been expected.

Concurrent exposure to other chemicals precluded ascribing the observed increase in cancer incidence to carbon tetrachloride alone. On the basis of the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity to humans (Federal Register, 1984), carbon tetrachloride is most appropriately classified as a Group B2 - Probable Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The American Conference of Governmental Industrial Hygienists (ACGIH, 1980, 1983) and the U.S. EPA (1980b) have established regulating standards for carbon tetrachloride as cited in Table 5-1.

TABLE 5-1

Current Regulatory Standards and Criteria for Carbon Tetrachloride

Criterion	Value		Reference
TLV	5 ppm, 30 mg/m³		ACGIH, 1983
STEL	20 ppm, 125 mg/m³		ACGIH, 1983
NIOSH ceiling level to prevent cancer	2 ppm		ACGIH, 1980
Japan and most European nations	10 ppm		ACGIH, 1980
Most eastern European nations	3-7.5 ppm		ACGIH, 1980
Tolerance in food	exempt		Code of Federal Regulations, 1982
Ambient water criteria associated with cancer risk:	consumption of 6.5 g fish only	2 ℓ water + 6.5 g fish	U.S. EPA, 1980b
10^{-7}	0.69 µg/ℓ	0.04 µg/ℓ	
10^{-6}	6.94 µg/ℓ	0.40 µg/ℓ	
10^{-5}	69.4 µg/ℓ	4.0 µg/ℓ	

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Carbon tetrachloride is amply demonstrated to be carcinogenic in animals and data are sufficient for derivation of a q_1^*. It is inappropriate, therefore, to calculate an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Carbon tetrachloride is amply demonstrated to be carcinogenic in animals and data are sufficient for derivation of a q_1^*. It is inappropriate, therefore, to calculate an AIC for this chemical.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The Carcinogen Assessment Group, as described in U.S. EPA (1984), used data from the following for risk assessment purposes: Della Porta et al. (1961); Edwards et al. (1942); NCI (1976) (both rat and mouse). Since none of these studies was deemed adequate individually and no study could be selected as "best" or "most appropriate", the geometric mean of the upper limit unit risk estimates (3.7×10^{-6}) has been calculated for drinking water containing 1 µg/ℓ. Assuming human consumption of 2 ℓ of water/day, a cancer risk of 3.7×10^{-6} is associated with a dose of 2 µg carbon tetrachloride/day. For a 70 kg human, a q_1^* of 1.30×10^{-1} $(mg/kg/day)^{-1}$ can be calculated from the following formula:

$$q_1^* = 70 \text{ kg} \times 3.7 \times 10^{-6} \div (2 \times 10^{-3})$$

where 3.7×10^{-6} is the risk associated with a daily dose of 2 µg or 2×10^{-3}mg/day. U.S. EPA (1984) contains an in-depth explanation of the rationale applied and the calculations employed.

6.3.2. Inhalation. Sufficient data regarding the carcinogenicity of carbon tetrachloride in laboratory animals exposed by inhalation, from which to calculate a q_1^*, were not located in the available literature.

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APPENDIX

Summary Table for Carbon Tetrachloride

Carcinogenic Potency	Species	Experimental Dose/Exposure (mg/kg/day)	Effect	q_1*	Reference
Inhalation				ND	
Oral	mice	1250-2500	liver tumors	1.3×10^{-1} $(mg/kg/day)^{-1}$	Della Porta et al., 1961; Edwards et al., 1942; NCI, 1976; U.S. EPA, 1984

ND = Not derived