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HEALTH EFFECTS ASSESSMENT FOR CARBON TETRACHLORIDE

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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 TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. 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. 1980a. Ambient Water Quality Criteria Document for Carbon Tetrachloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-026. NTIS PB81-117376.

U.S. EPA. 1983a. Reportable Quantity Document for Carbon Tetrachloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

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

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

U.S. EPA. 1985a. Assessment of the Mutagenic Potential of Carbon Disulfide, Carbon Tetrachloride, Dichloromethane, Ethylene Dichloride, and Methyl Bromide: A Comparative Analysis in Relation to Ethylene Dibromide. Office of Health and Environmental Assessment, Reproductive Effects Assessment Group, Washington, DC.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Risk estimate for carcinogens: Carbon Tetrachloride. Online. (Verification date: 12/04/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens 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 or risk associated with exposure 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, RfD_S (formerly AIS) or subchronic reference dose, 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 RFD_S 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. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. 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 (1980b) for a discussion of this concept]. The RfD can also be derived for the noncarcinogenic health effects of compounds which are also carcinogenic. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) 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 identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984b).

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

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer 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.

An oral RfD of 7×10^{-4} mg/kg/day for carbon tetrachloride can be derived based on a NOAEL of 1 mg/kg/day, a conversion factor of 5/7, and an uncertainty factor of 1000 (to allow for interspecies and intrahuman variability and extrapolation from subchronic to chronic duration of exposure) in a subchronic gavage study in rats by Bruckner et al. (1986). This value has been verified by the EPA RfD Workgroups (U.S. EPA, 1986b). An oral RfD_S of 7×10^{-3} mg/kg/day can be also be derived from the same study.

Animal oral bioassay data in three species (rats, mice, hamsters) indicate that carbon tetrachloride is a hepatic carcinogen. Human data are limited and equivocal. U.S. EPA (1984a) has used data from the following for quantitative cancer risk estimation purposes: Della Porta et al. (1961); Edwards et al. (1942); NCI (1976) (both rat and mouse). Using these data, the geometric mean of the upper limit unit risk estimates is 3.7×10^{-6} $(\mu g/\ell)^{-1}$ with a corresponding slope factor (q_1^*) of 1.3×10^{-1} $(mg/kg/day)^{-1}$.

U.S. EPA (1986b) estimated a slope factor for inhalation exposure of 5.2×10^{-2} $(mg/kg/day)^{-1}$ using an inhalation absorption factor of 40% and the slope factor of 1.3×10^{-1} $(mg/kg/day)^{-1}$ derived from the oral data.

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ALP	Alkaline phosphatase
BCF	Bioconcentration factor
bw	Body weight
CS	Composite Score
FEL	Frank-effect level
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UDS	Unscheduled DNA synthesis

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.

Carbon tetrachloride is extremely stable and persistent in the lower atmosphere and troposphere. The primary fate process of this compound is diffusion into the stratosphere. Once in the stratosphere, it is photolyzed by shorter wavelength, higher energy ultraviolet light, eventually forming phosgene as the principal degradation product (U.S. EPA, 1984a). Estimates of the atmospheric half-life of carbon tetrachloride range from 18 years to 60-100 years (U.S. EPA, 1984a). It has been estimated that >90% of tropospheric carbon tetrachloride will eventually reach the stratosphere (Callahan et al., 1979). The persistence of carbon tetrachloride in the atmosphere indicates that this compound may be transported long distances from its emission source. Global distribution of carbon tetrachloride in air is reported to be nearly uniform (U.S. EPA, 1984a).

Carbon tetrachloride dissolved in water does not photodegrade or oxidize in any measurable amounts. Volatilization is the primary removal mechanism for carbon tetrachloride from water (U.S. EPA, 1984a). Although carbon tetrachloride is relatively lipophilic, there is little tendency for this compound to bioaccumulate in aquatic or marine organisms (Neeley et al., 1974).

The half-life of carbon tetrachloride in soil was not located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface. This compound is resistant to biodegradation in subsurface soils (Wilson and Wilson, 1985). Based on the

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
Solubility in		
Water:	757 mg/ℓ at 25°C	Banerjee et al., 1980
Organic solvent:	miscible	HSDB, 1988
Octanol/water partition coefficient:	676 (recommended value)	Hansch and Leo, 1985
	537	Banerjee et al., 1980
BCF:	30 in bluegill (Lepomis macrochirus)	U.S. EPA, 1980a
	17 in fathead minnow (Pimephales promelas)	Veith et al., 1979
K_{oc}:	71	Sabljic, 1984
Half-lives in		
Air:	18-100 years	U.S. EPA, 1984a
Water:	0.3-3 days in river 30-300 days in lake	Zoeteman et al., 1980

observed slow biodegradation of chloroform (Wilson et al., 1983), carbon tetrachloride is expected to biodegrade even slower because of the additional chlorine substitution in this compound. Consequently, 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. Upon entering groundwater, carbon tetrachloride will be persistent. The half-life of this compound in groundwater is estimated to range from 30-300 days (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 gastrointestinal tract of humans were located in the available literature. It would be anticipated, however, that carbon tetrachloride is well absorbed from the gastrointestinal tract of humans since it is readily absorbed from the gastrointestinal tract of animals, and there are many accounts of human poisoning resulting from ingestion of carbon tetrachloride. A number of investigators (Seawright and McLean, 1967; Marchand et al., 1970; Reddrop et al., 1981) have studied the extent of absorption of orally administered doses of carbon tetrachloride by measuring the excretion of radiolabeled parent compound and metabolites in the expired air as a function of time following administration of the compound. Typically, the percentage of absorption of an orally administered dose of carbon tetrachloride determined in this fashion is between 65 and 86%. Seawright and Mclean (1967) treated male rats with radiolabeled carbon tetrachloride (4000 mg/kg) by intragastric administration. It was calculated (U.S. EPA, 1985b) from the amount of radioactivity found in the exhaled air over a 24-hour period that $\geq$65% of the administered dose was absorbed from the gastrointestinal tract. Marchand et al. (1970) administered radiolabeled carbon tetrachloride (3200 mg/kg) to male rats by intragastric intubation, and measured exhaled radioactivity for a period of up to 10 hours following dosing. Of the administered radiolabeled carbon, 83% was found in the exhaled air 10 hours after dosing, which led to the conclusion that at least 83% of the dose was absorbed from the gastrointestinal tract over the 10-hour period (U.S. EPA, 1985b). Using a similar method of monitoring radioactivity in the exhaled

air, Reddrop et al. (1981) reported that absorption of carbon tetrachloride from the gastrointestinal tract of male rats given 2000 mg/kg was at least 60% over a 6-hour period following dosing.

In an early study, Robbins (1929) investigated absorption of carbon tetrachloride from the gastrointestinal 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 gastrointestinal tract may vary from species to species. They observed more rapid gastrointestinal absorption in rabbits than in dogs. Nielsen and Larsen (1965) determined that both the rate and the amount of carbon tetrachloride absorbed from the gastrointestinal tract were increased by concurrent ingestion of fat or alcohol.

2.2. INHALATION

Although there are many cases of human overexposure to carbon tetrachloride vapor, there are few quantitative studies of pulmonary absorption of carbon tetrachloride in humans. Lehmann and Schmidt-Kehl (1936) estimated that absorption across the lung was ~60% in humans based on the difference in carbon tetrachloride concentration in inhaled and exhaled air. 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 did not specify the species studied (U.S. EPA, 1980a). 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 carbon tetrachloride in air. Peak blood concentrations of ~35 or ~38 mg/ℓ were attained after ~300 minutes of exposure. McCollister et al. (1951)

studied the absorption of carbon tetrachloride following inhalation in monkeys. Three female monkeys were exposed to radiolabeled carbon tetrachloride (290 mg/m^3) for 139-300 minutes. By determining the difference in concentration of the compound in the inhaled and exhaled air, absorption was calculated to be ~30.4% of the total amount of carbon tetrachloride inhaled at any average absorption rate of 0.022 mg carbon tetrachloride/kg/minute.

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 toxicity from ingestion of the compound in man were located in the available literature. Della Porta et al. (1961) treated groups of 10 male and 10 female Syrian golden hamsters by gavage with 12.26 mg/week carbon tetrachloride in corn oil for 30 weeks (~12.3 mg/kg/day). Before treatment was completed, 50% of the hamsters of each sex died. The survivors all developed hepatocellular carcinoma within the next 13 weeks.

Several recent studies have examined the effects of subchronic oral administration of carbon tetrachloride in rats and mice (Bruckner et al., 1986; Condie et al., 1986; Hayes et al., 1986). Bruckner et al. (1986) dosed groups of ~15 male Sprague-Dawley rats with carbon tetrachloride in corn oil by gavage at levels of 1, 10 or 33 mg/kg, 5 times/week for 12 weeks. The toxicity of carbon tetrachloride was found to be dose-dependent. A dose of 1 mg/kg produced no apparent adverse effects, whereas 10 mg/kg produced a slight but significant increase in sorbitol dehydrogenase activity and 33 mg/kg produced marked hepatotoxicity in the form of cirrhosis. Condie et al. (1986) studied the effects of the vehicle (corn oil versus Tween-60) on the subchronic toxicity of carbon tetrachloride in CD-1 mice. Carbon tetrachloride was administered by gavage at doses of 1.2, 12 or 120 mg/kg once daily, 5 days/week for 90 days. Carbon tetrachloride was more toxic when administered in corn oil. The NOAEL for carbon tetrachloride administered in corn oil was 1.2 mg/kg and the corresponding NOAEL for carbon tetrachloride administered in Tween-60 was 12 mg/kg. A greater

degree of hepatotoxicity, as measured by serum enzyme levels and histopathologic changes, was also observed in mice treated with 12 and 120 mg/kg of carbon tetrachloride when corn oil was the vehicle than when Tween-60 was the vehicle.

Hayes et al. (1986) administered carbon tetrachloride in corn oil by gavage to groups of 20 male and 20 female CD-1 mice. The doses used were 12, 120, 540 and 1200 mg/kg and the mice were dosed for 90 consecutive days. A NOAEL was not observed in this study. A generally dose-related increase in serum enzyme levels (LDH, SGPT, SGOT and ALP) was observed in both sexes at all dose levels. Relative liver and spleen weights were increased at all dosage levels in both sexes and relative thymus weights were increased at $\geq$540 mg/kg/day in both sexes. Liver damage was observed at all doses in both sexes, with the severity and intensity of the lesions increasing in a dose-related fashion.

3.1.2. Inhalation. Prendergast et al. (1967) performed two studies of subchronic inhalation exposure in animals. In the first experiment, 15 Hartley guinea pigs and monkeys were exposed to 80 ppm (503 mg/m^3) carbon tetrachloride 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. All the animals showed a body weight loss. In the second experiment, several species of animals were exposed to either 1 or 10 ppm (6 or 63 mg/m^3) 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 at 10 ppm also experienced depressed growth rates and similar histopathological liver lesions, but no mortality.

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.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic exposure of man to carbon tetrachloride were not located in the available literature. A 2-year study of the toxicity of carbon tetrachloride was performed by Alumot et al. (1976) who administered the compound in the diets of rats at levels of 0, 80 or 200 ppm. Taking into account the amount of food consumed and the loss of carbon tetrachloride from the food before consumption, a dietary level of 200 ppm provided a daily dose of carbon tetrachloride of 10-18 mg/kg bw. At this dose level (10-18 mg/kg/day), the authors found no biochemical abnormalities attributable to carbon tetrachloride exposure, and this dose level was indicated to be a NOAEL over a 2-year period. The study was, however, criticized by U.S. EPA (1985b) because of the high incidence of respiratory infection in the experimental animals.

3.2.2. Inhalation. NIOSH (1975) provided an in-depth discussion of the pathology of chronic inhalation exposure of carbon tetrachloride in man; however, since exposure data are lacking, it is not useful in risk assessment. The U.S. EPA (1983a) summarized human studies that are more relevant to risk assessment (see Section 4.1.). 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 (31-736 mg/m^3), with peak exposures up to a maximum of 1680 ppm (10,570 mg/m^3). 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 an investigation of 27 workers in a plant manufacturing polyfluorohydrocarbons for refrigerators from carbon tetrachloride and hydrofluoric acid. This manufacturing process is virtually an automated and enclosed system, but carbon tetrachloride has to be delivered by road tanker, discharged into the receiving tanks, and the pipes and tanks need periodic maintenance, repairs and cleaning. It is on these occasions that the worker becomes exposed. However, information concerning the age, sex, job history and exposure levels of the workmen was not provided in this reported. Elevated urinary urobilinogen in 6/16 and

elevated urine protein in 3/16 carbon tetrachloride-exposed workers were observed, whereas all 11 unexposed workers were tested negative for both tests. Microscopic and macroscopic examination of the urine for cells and casts were negative although a trace of albumen occurred in two. Therefore, the authors concluded that kidney damage was not observed in this study. Zinc turbidity and average thymol turbidity tests were elevated in exposed workers (5.0 units for zinc turbidity and 4.0 units for thymol turbidity) compared with controls (1.0 units and 0.6 units, respectively). Carbon tetrachloride-exposed workers also experienced elevated serum bilirubin (average 1.36, range 0.45-4.0) and slightly elevated SGOT (average 37.3, range 25-48), compared with controls [0.46 (range 0.20-0.60) for serum bilirubin and 32.7 (range 27-38) for SGOT, respectively]. Therefore, the authors concluded that liver damage was a feature in exposed workmen. 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 (31, 63, 157, 315, 629, 1258 or 2516 mg/m^3) carbon tetrachloride for 7 hours/day, 5 days/week for up to 184 exposures over a period of 258 days. The numbers of animals involved initially 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 >50% died in the 400 ppm group. Survivors had elevated kidney and liver weights,

fatty degeneration and cirrhosis of the liver. Guinea pigs showed hepatomegaly at all concentrations tested, moderate hepatic fatty degeneration at ≥10 ppm and moderate liver cirrhosis at ≥25 ppm. At 400 ppm, ≥50% of the rats died. Hepatomegaly was observed in all exposed rats, but liver cirrhosis was not detected at exposure concentrations <50 ppm.

In another part of the study, two rabbits of each sex were exposed to 10, 25, 50 or 100 ppm carbon tetrachloride 7 hours/day, 5 days/week (Adams et al., 1952). Exposure to 25 ppm, 178 times (248 days) resulted in moderate fatty liver degeneration and cirrhosis. At 50 and 100 ppm, decreased growth rate, increased kidney weights and increased blood clotting time (indicative of liver damage) were observed.

Adams et al. (1952) also exposed groups of two monkeys to 25, 50 or 100 ppm carbon tetrachloride by the same schedule 148-198 times (~30-40 weeks). 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 (0, 315, 629, 1258 or 2516 mg/m^3) carbon tetrachloride 8 hours/day, 4-6 days/week for periods of up to 321 days; however, because all guinea pigs exposed to ≥100 ppm died by 94 days of age, the experiment was redesigned. In the second trial, groups of 15 or 16 guinea pigs were exposed to 25, 50, 100 or 200 ppm carbon tetrachloride for 8 hours/day, 5 days/week for a total of 10.5 months. A group

of 7 unexposed guinea pigs served as controls. All animals in the second trial were provided with a high calcium diet. In the 0, 25, 50, 100 and 200 ppm exposed groups, 0/7, 12/15, 9/16, 11/16 and 11/15 guinea pigs died, 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 Wistar rats were exposed to 0, 50, 100, 200 or 400 ppm carbon tetrachloride for 8 hours/day, 5 days/week for 10.5 months (Smyth and Smyth, 1935; Smyth et al., 1936). No significant increase in mortality was observed. Liver degeneration, regeneration and cirrhosis were observed in rats exposed to $\geq$50 ppm carbon tetrachloride. Degeneration of the myelin sheath of the sciatic nerve and degenerative changes in ocular muscles, as well as unspecified kidney damage, were also observed in rats exposed to $\geq$50 ppm carbon tetrachloride.

Smyth and Smyth (1935) and Smyth et al. (1936) also exposed four monkeys to 50 ppm and three monkeys to 200 ppm carbon tetrachloride 8 hours/day, 5 days/week for 93-231 days. Nerve tissue appeared normal in all 50 ppm exposed monkeys; however, two of the monkeys exposed to 200 ppm showed damage to the sciatic nerve. Cloudy swelling of the kidney and fatty changes in the liver were noted in rats exposed to $\geq$50 ppm. A 28-day recovery period demonstrated the reversible nature of these mild liver and kidney changes.

Carbon tetrachloride has been found to cause effects primarily on the liver, kidney and central nervous system (Smyth and Smyth, 1935; Smyth et al., 1936). Effects on the central nervous system are usually rapid and the most common effects are headache, dizziness, vomiting and nausea (Barnes and

Jones, 1967). In severe cases, stupor or coma can occur. However, these effects are often reversible except in severe cases when permanent damage to nerve cells can occur. The principal clinical signs of liver injury following exposure to carbon tetrachloride are swollen and tender liver, elevated levels of hepatic enzymes in the serum, elevated serum bilirubin levels and decreased serum levels of liver proteins. Repeated or chronic exposure often leads to fibrosis or cirrhosis (Adams et al., 1952; Smyth and Smyth, 1935; Smyth et al., 1936). Nephritis and nephrosis are also common effects following exposure to carbon tetrachloride with oliguria or anuria developed within hours to days after exposure (Smetana, 1939). Both hepatic and renal effects following carbon tetrachloride exposure are generally reversible because both organs can repair damaged cells and replace dead tissue (Adams et al., 1952; Smyth and Smyth, 1935; Smyth et al., 1936).

In experimental animals, guinea pigs have been found to be more sensitive to the toxic effects of carbon tetrachloride than are rats or monkeys (Smyth and Smyth, 1935; Smyth et al., 1936; Adams et al., 1952).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. No reports were located on developmental and reproductive effects in humans following oral exposure to carbon tetrachloride. Twenty-nine pregnant rats were administered, by gavage, 0.6-0.9 cc/day carbon tetrachloride during gestation (Wilson, 1954). Marked maternal toxicity and total resorption of fetuses in some animals were observed, but no teratogenic effects or other adverse effects were apparent in surviving offspring. Administration of carbon tetrachloride in the diet of rats does not appear to affect their reproductive capacity. The reproductive activity of male and female rats fed 80 or 200 ppm in the diet over a 2-year period was generally unaffected by the treatment (Alumot et al., 1976).

3.3.2. Inhalation. No reports were located regarding developmental and reproductive effects in humans following inhalation exposure to carbon tetrachloride. 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. Maternal weight loss and clear maternal hepatotoxicity were observed; however, no effect on conception, number of implants or number of resorptions was apparent. A significant decrease in body weights and crown-rump lengths was found in fetuses from dams exposed to either 300 or 1000 ppm (1887-6291 mg/m^3) 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, although fetal toxicity was observed. Adams et al. (1952) noted moderate to marked degeneration of testicular germinal epithelium in rats exposed repeatedly to $\geq$200 ppm of carbon tetrachloride.

3.4. TOXICANT INTERACTIONS

In the early 1900s, carbon tetrachloride was used as an anthelmintic, particularly against hookworm, in both humans and animals. Smillie and Pessoa (1923) studied severe carbon tetrachloride-induced toxicity in 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. von Oettingen (1964) reported that habitual users or occasional users of alcoholic beverages became more seriously ill when exposed to carbon tetrachloride than those who do not drink alcohol.

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 potentiated the toxicity of carbon tetrachloride, with isopropanol being the most potent. Maximum potentiation was observed when alcohols were administered 18 hours before carbon tetrachloride exposure. Neither carbon tetrachloride nor the alcohols alone elevated SGPT levels. Wei et al. (1971) investigated the potentiation of carbon tetrachloride-induced hepatotoxicity by ethanol and cold. 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. The authors postulated that the ethanol could release norepinephrine which in turn increased the susceptibility of the liver to carbon tetrachloride. Cornish and Adefuin (1966) reported that ethanol ingestion potentiated the toxicity of subsequent exposure to carbon tetrachloride. Sixteen to eighteen hours after pretreatment with a single dose of ethanol (5 g/kg), rats were exposed to carbon tetrachloride vapor (100 or 1000 ppm) for 2 hours. Twenty-four hours after exposure, SGOT activities in the ethanol-pretreated rats were 2.4- and 8.5-fold higher than in control rats (not given ethanol) at the 100 and 1000 ppm exposure levels, respectively.

Alcohol ingestion was suspected to play a significant role in the toxicity of carbon tetrachloride from nonmedicinal exposure (Abbott and Miller, 1948), particularly when renal failure occurred. The ACGIH (1986b) suggested that ethanol and other substances (e.g., barbiturates and polychlorinated biphenyls) increase the toxicity of carbon tetrachloride by inducing the synthesis of one or more microsomal enzymes involved in the metabolic activation of carbon tetrachloride.

Hafeman and Hoekstra (1977) reported that rats given a diet supplemented with vitamin E, selenium and methionine were protected against 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 useful for risk assessment were 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 developed 7 years after a 5-day exposure to carbon tetrachloride, which was used to clean his rug. The man did not ingest alcohol after exposure to carbon tetrachloride, but had ingested it before exposure. Blair et al. (1979) reported 87 cancer deaths in a group of 330 laundry and dry cleaning workers in which 67.9 cancer deaths would have been expected. The malignant neoplasms reported included lung, cervical and liver cancers, and leukemia. The proportionate mortality ratio [PMR = (obsverved death/expected death)x100] for deaths associated with malignant neoplasms was 128 and statistically significant (χ^2=6.423, 1 degree of freedom, significant at $p<0.05$). However, it is difficult to conclude that the elevated PMR is indicative of an excess risk of carcinogenicity in this study. One of the compounding factors of the paper was that the causes of death in workers group was compared with that of U.S. population deaths, instead of another working population to control for the "healthy worker effect." Additionally, concurrent exposure to other workroom chemicals precluded attributing the observed increase in cancer incidence to carbon tetrachloride alone. Therefore, one can only conclude from this study that there is a need for additional work on this occupational group to clarify the issue raised.

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 C_3H 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, followed by cirrhosis and eventually hepatomas in C_3H mice. Hepatomas were found in 126/143 C_3H and all 54 A-strain mice. Della Porta et al. (1961) treated five Syrian golden hamsters of each sex with 30 weekly doses of 6.25-12.5 µℓ (10-20 mg) carbon tetrachloride. Liver cell carcinomas were found in all hamsters (five/sex) that survived ≥10 weeks after the end of treatment.

Edwards et al. (1942) performed a study with inbred L mice, a strain with an extremely low rate of spontaneous hepatomas, 2.5-3.5 months or 3.5-7.5 months of age at the start of the experiment. Mice, 8-39/group, were treated by gavage with 46 doses of carbon tetrachloride (0.1 mℓ of a 40% solution of carbon tetrachloride/dose) over a 4-month period and were killed and necropsied 3-3.5 months after the last treatment. Hepatomas developed in 7/15 younger male mice (47%), 21/39 older male mice (54%), 3/8 younger females (38%) and 3/11 older females (27%), in comparison with 2/152 (1%) in untreated mice. Therefore, strain L male and female mice were highly susceptible to the induction of hepatomas by carbon tetrachloride, and male mice were slightly more susceptible than female mice.

Edwards and Dalton (1942) investigated the induction of cirrhosis of the liver and hepatomas in mice following exposure to high-dose, low-dose and limited treatment with carbon tetrachloride. For high-dose treatment,

strains C3H, A, Y and C (1-5 months of age) were given 0.1 mℓ of a 40% solution of carbon tetrachloride in olive oil by gavage 2 or 3 times/week for a total number of 23-58 treatments. Incidences of hepatoma as well as cirrhosis were significantly increased in all four strains of mice. For low-dose treatment, 58 strain A female mice were given 0.1 mℓ of 5% carbon tetrachloride in olive oil, by gavage, 3 times/week for 2 months. The total dose of carbon tetrachloride administered in the low-dose treatment group (0.125-0.145 mℓ) is comparable to the total dose used in the high-dose treatment group (0.120 mℓ). The incidences of hepatoma, as well as cirrhosis, were significantly increased in the low-dose group. The tumors of the liver observed were morphologically similar in both high- and low-dose treatment groups. Limited treatment involved dosing of strain A mice with 0.04, 0.01 or 0.005 mℓ of carbon tetrachloride (21-62 mice/group, 1-3 treatments/animal). No hepatoma was observed in animals exposed to limited dose.

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, but a majority of tumors at each dose level occurred in groups treated every 3 or 4 days. In a later study, Eschenbrenner and Miller (1946) demonstrated that single gavage doses of 12.5 μℓ/kg, but not 6.25 μℓ/kg 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 $\geq$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 the 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 (1980a) discussed other short-term carcinogenicity studies with carbon tetrachloride, but since they provide no additional information and are not useful for risk assessment, they are not included here.

In an NCI-sponsored bioassay (NCI, 1976; Weisberger, 1977), groups of 50 male and 50 female Osborne-Mendel rats were treated by gavage 5 days/week with carbon tetrachloride in corn oil (47 or 94 mg/kg for males, or 80 or 160 mg/kg for females) for 78 weeks. Vehicle control groups consisting of 100 males and 100 females were maintained. Observations were continued for 33 additional weeks following cessation of treatment. Survival data indicate that excessive mortality occurred in high-dose female rats by 78 weeks and in high-dose male rats at termination. 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 50 female B6C3F1 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/sex. All mice were necropsied. By the end of the 78-week exposure period, most carbon tetrachloride-exposed mice died. Most carbon tetrachloride-treated mice had hepatocellular carcinomas (95-100%). 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. Few hepatocellular tumors were seen in vehicle-treated mice. The incidences of hepatocellular carcinomas are presented in Table 4-1.

4.2.2. Inhalation. Few data concerning carcinogenicity of carbon tetrachloride from inhalation exposure were 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 survived to termination, 12 had adenocirrhosis and 10 had liver nodules measuring up to 1 cm, which were microscopically diagnosed as incipient or established hepatocellular carcinomas. Established carcinomas were found in five livers and incipient carcinomas were found in five others.

4.3. OTHER RELEVANT DATA

Few 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. IARC (1979) also reported a lack of mutagenicity in S. typhimurium strains TA100, TA1535, TA1538 (McCann and Ames, 1976; McCann et al., 1975; Uehleke et al., 1976; Uehleke et al., 1977) and E. coli (Uehleke et al., 1976, 1977). Studies in which the mutagenicity of carbon tetrachloride was tested under conditions that controlled for volatility of the compound were also negative. Simmon et al. (1977) used a desiccator to expose plates of bacteria to carbon tetrachloride vapor, and observed no mutagenic activity. Barber et al. (1981) tested carbon tetrachloride for mutagenic activity in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 using both a standard assay system (in which volatilization was not prevented) and a closed incubation system that prevented the escape of volatilized carbon

TABLE 4-1

Incidence of Liver Tumors in Mice Treated by Gavage with Carbon Tetrachloride in Corn Oil 5 Days/Week for 78 Weeks*

Dose	Carcinomas
Males	
Control	
Matched	2/19 (11%)
Pooled	5/77 (6%)
1250 mg/kg/day	49/49 (100%)
2500 mg/kg/day	47/48 (98%)
Females	
Control	
Matched	1/20 (5%)
Pooled	1/80 (1%)
1250 mg/kg/day	40/40 (100%)
2500 mg/kg/day	43/45 (96%)

*Source: NCI, 1976

NR = Not reported

tetrachloride. Carbon tetrachloride was not mutagenic in either the standard or closed incubation system.

Assays using S. typhimurium and E. coli to assess the mutagenicity of a compound often use an exogenous mammalian liver S-9 activation system to metabolize the compound to its active form. The yeast Saccharomyces cerevisiae strain D7 contains an endogenous cytochrome p-450 dependent mono-oxygenase activation system, and Callen et al. (1980) used this yeast to demonstrate that carbon tetrachloride was mutagenic and caused gene cross-over and mitotic recombination. Callen et al. (1980) suggested that because of the presence of an endogenous activation system this yeast system was more sensitive than some of the other in vitro test systems.

Dean and Hodson-Walker (1979) found that carbon tetrachloride did not induce chromosome damage in cultured rat liver cells. Mirsalis and Butterworth (1980) reported that there was no UDS in hepatocytes isolated from rats following oral exposure to carbon tetrachloride (10 or 100 mg/kg). Craddock and Henderson (1978) also reported that carbon tetrachloride did not cause DNA repair (UDS) in hepatocytes isolated from animals exposed to 4000 mg/kg. In their most recent study, Mirsalis et al. (1982) reported that combinations of carbon tetrachloride doses (up to 400 mg/kg) and exposure times (up to 48 hours) which resulted in liver toxicity were negative with respect to UDS.

4.4. WEIGHT OF EVIDENCE

There is sufficient evidence in mice, rats and hamsters to designate carbon tetrachloride as a hepatic carcinogen in animals. Brief exposures have led to fibroblastic proliferation and histopathological liver abnormalities (Prendergast et al., 1967), while prolonged exposure (NCI, 1976; Weisburger, 1977) results in a very high incidence of hepatocellular carcinoma.

The few case reports associated with carbon tetrachloride provide inadequate 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 guidelines adopted by the U.S. EPA (1986a) for evaluating the overall weight of evidence for carcinogenicity to humans, carbon tetrachloride is classified as a Group B2 -- Probable Human Carcinogen. This is consistent with the earlier analysis by U.S. EPA (1986b).

ACGIH (1986a,b) and U.S. EPA (1980a) have established regulatory standards for carbon tetrachloride (Table 5-1).

IRIS (U.S. EPA, 1986b) lists a verified RfD_0 of 7×10^{-4} mg/kg/day for carbon tetrachloride based on a NOAEL of 1 mg/kg/day in a subchronic gavage study in rats by Bruckner et al. (1986). The IRIS report reflects an analysis by the U.S. EPA (1985b) Office of Drinking Water.

TABLE 5-1

Current Regulatory Standards and Criteria for Carbon Tetrachloride

Criterion	Value		Reference
TLV	5 ppm (30 mg/m^3)		ACGIH, 1986a,b
NIOSH ceiling level to prevent cancer	2 ppm (12.6 mg/m^3)		ACGIH, 1986b
Japan and most European nations	10 ppm		ACGIH, 1986b
Most eastern European nations	3-7.5 ppm		ACGIH, 1986b
Maximum contaminant level in drinking water	0.005 mg/ℓ		U.S. EPA, 1987
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. SUBCHRONIC REFERENCE DOSE (RfD_S)

Bruckner et al. (1986) dosed groups of ~15 male Sprague-Dawley rats with carbon tetrachloride in corn oil by gavage (1, 10 or 33 mg/kg/day, 5 days/week for 12 weeks). Liver lesions, as evidenced by mild centrilobular vacuolization and statistically significant increases in serum sorbitol dehydrogenase activity, were observed at the 10 and 33 mg/kg/day doses. A NOAEL of 1 mg/kg/day was observed in this study. An RfD_S of $7x10^{-3}$ mg/kg/day can be derived based on a NOAEL of 1 mg/kg/day, a conversion factor of 5/7 (to adjust for 5 days/week dosing regimen) and an uncertainty factor of 100 (to allow for interspecies and intrahuman variability).

6.2. REFERENCE DOSE (RfD)

An oral RfD of $7x10^{-4}$ mg/kg/day can be calculated based on a NOAEL of 1 mg/kg/day in a subchronic gavage study by Bruckner et al. (1986). In addition to the conversion factor of 5/7 and an uncertainty factor of 100 as discussed in Section 6.1., another uncertainty factor of 10 was applied to adjust for extrapolation from subchronic to chronic duration of exposure. This RfD value was verified by the U.S. EPA RfD Workgroup on 12/04/86.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Carbon tetrachloride is classified as a Group B2, probable human carcinogen, based on sufficient animal weight of evidence and inadequate human weight of evidence. The Carcinogen Assessment Group, as described in U.S. EPA (1984a), used data from the Della Porta et al. (1961) (hamster), Edwards et al. (1942) (mouse) and NCI (1976) (both rat and mouse) studies for risk assessment purposes. Since the studies used were deficient in some respect for quantitative purposes, precluding the choice of any one study as most appropriate, the geometric mean of the upper limit unit risk

estimates (3.7×10^{-6}) from four data sets has been calculated for unit risk corresponding to drinking water containing 1 µg/ℓ. Assuming human consumption of 2 ℓ of water/day and a human body weight of 70 kg, a slope factor of 1.30×10^{-1} $(mg/kg/day)^{-1}$ can be calculated from the unit risk of 3.7×10^{-6} $(\mu g/\ell)^{-1}$ for the oral route. U.S. EPA (1984a) contains an in-depth explanation of the rationale applied and the calculations employed. This value has been verified and is available on IRIS (U.S. EPA, 1987).

6.3.2. Inhalation. U.S. EPA (1987) adopted the oral slope factor of 1.3×10^{-1} $(mg/kg/day)^{-1}$ and an inhalation absorption factor of 0.4, based on pharmacokinetic data evaluated by U.S. EPA (1984a), to estimate a slope factor for inhalation exposure. Applying the inhalation absorption factor of 0.4 to the oral slope factor of 1.3×10^{-1} $(mg/kg/day)^{-1}$ results in an inhalation slope factor of 5.2×10^{-2} $(mg/kg/day)^{-1}$.

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