March 31, 1987

CARBON TETRACHLORIDE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

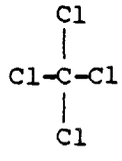
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for carbon tetrachloride (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #85-118155/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 56-23-5

Structural Formula



Synonyms

- Methane tetrachloride, tetrachloromethane, CCl_4, perchloroethane.

Uses

- The major use of CCl_4 is in the production of chlorofluorocarbons, which are used as refrigerants, foam-blowing agents and solvents. Carbon tetrachloride also is used in fumigants, as a solvent in metal cleaning and in manufacture of paints and plastics (Rams, et al., 1979). It is being replaced in grain fumigation by other registered pesticides (U.S. EPA, 1980a).

Properties (U.S. EPA, 1985a)

Chemical Formula	CCl_4
Molecular Weight	153.8
Physical State	Colorless liquid
Boiling Point	76.5°C
Melting Point	-23°C
Density	d_4^{20} 1.594
Vapor Pressure	115.2 mm Hg at 25°C
Water Solubility	800 mg/L
Taste Threshold	not available
Odor Threshold	0.52 mg/L (Amoore and Hautala, 1983)
Conversion Factor	6.4 mg/m^3 = 1 ppm

Occurrence

- Carbon tetrachloride (CCl_4) is a synthetic chemical with no natural sources (U.S. EPA, 1983).

- Production of CCl_4 was approximately 600 million lbs in 1983 (U.S.ITC, 1983). Carbon tetrachloride also is produced as a by-product of the manufacture of a number of other chlorinated materials.

- Current major sources of CCl_4 released to the environment are from accidental releases from production and uses. Previously, large amounts of CCl_4 were released from its use as a solvent. Most of the releases of CCl_4 occur to the atmosphere by evaporation because of its high volatility. Some CCl_4 may be released to the environment during the disposal of wastes in landfills or surface waters. The majority of releases will occur in the areas near its production and use (U.S. EPA, 1983).

- Carbon tetrachloride released to: (1) the environment is fairly stable; (2) the air, degrades slowly; (3) surface waters, migrates to the atmosphere in a few days or weeks; and (4) the land, does not sorb onto soil and migrates readily to ground water. Carbon tetrachloride is expected to remain in ground water for months to years. Unlike more highly chlorinated compounds, CCl_4 does not bioaccumulate in individual animals or food chains (U.S. EPA, 1979).

- Carbon tetrachloride occurs ubiquitously in the air but at concentrations of less than 10 ppt. Carbon tetrachloride is a fairly rare contaminant in ground and surface waters, with higher levels found in ground water. The Agency estimates that less than 1% of all ground waters derived drinking water systems have levels of CCl_4 greater than 0.5 ug/L and less than 0.2 % greater than 5 mg/L (U.S. EPA, 1983).

- Very limited information is available on the occurrence of carbon tetrachloride in food. In the past, CCl_4 has been used as a grain fumigant and low levels have been reported to occur in some foods from this use (U.S. EPA, 1983).

- The major source of exposure to CCl_4 is from contaminated air. Water and food are only a minor sources.

III. PHARMACOKINETICS

Absorption

- Carbon tetrachloride is absorbed readily from the gastrointestinal tract, the respiratory tract and the skin. About 60% of an oral dose (1600 mg/kg) was absorbed by rats within six hours (Reddrop et al., 1981), and 65 to 86% of oral doses of 2,000-4,000 mg/kg were absorbed by rats within 24 hours (Paul and Rubinstein, 1963; Seawright and McLean, 1967; Marchand et al., 1970).

Absorption from the lung has been reported as about 30% in monkeys exposed to 290 mg CCl_4/m^3 for 139, 344 or 300 minutes (McCollister et al., 1952).

° Bruckner et al. (1986a) assessed potential effects of different vehicles on the pharmacokinetics of CCl_4. Fasted 200 g male Sprague-Dawley rats with indwelling arterial cannulas received 25 mg/kg CCl_4 by gavage: in corn oil; as an aqueous emulsion; in water; and as pure undiluted chemical. A 25 mg/kg dose was given intravenously for calculation of bioavailability. Serial blood samples were taken and analyzed for CCl_4. Peak concentrations of CCl_4 in the blood were reached within 8 minutes after dosing in the emulsion and saturated water groups. These peak levels were slightly higher than in the pure CCl_4 group and substantially higher than in the corn oil group. There was evidence of later secondary peaks of lesser magnitude in the corn oil group. The absolute bioavailability for the emulsion and saturated water groups was higher than for the corn oil and pure chemical groups, and comparable to the intravenous group.

Distribution

° Carbon tetrachloride appears to be distributed to all major organs following absorption (U.S. EPA, 1985a). Carbon tetrachloride has been found in fat, liver, blood, brain, kidney and muscle, with particularly high concentrations in fat. Carbon tetrachloride reaches maximal concentrations in most tissues at approximately two to four hours following intragastric administration (Marchand et al., 1970).

Metabolism

° Carbon tetrachloride metabolism occurs primarily in the liver. The first step is thought to be formation of a trichloromethyl radical in the cytochrome heme moiety. This trichloromethyl radical undergoes a variety of reactions, including hydrogen abstraction to form chloroform, dimerization to form hexachloroethane and addition to cellular molecules. Further metabolism of the heme-bound trichloromethyl radical is postulated to result in the eventual formation of carbonyl chloride (phosgene) (Shah et al., 1979 with an in vitro study with rat liver).

° After a single oral dose of CCl_4 in Wistar rats, Bini et al. (1975) proposed that the trichloromethyl free radical was the main metabolite of CCl_4 after they found chloroform and hexachloroethane as metabolites in the rats. Fowler (1969) found these metabolites in rabbits given CCl_4 orally. McCollister et al. (1951) detected labeled carbon dioxide exhaled by monkeys exposed to ^{14}C-CCl_4 by inhalation.

Excretion

° Carbon tetrachloride and its volatile metabolites are excreted primarily in exhaled air and also in the urine and feces (U.S. EPA, 1985a). Elimination of orally ingested CCl_4 occurs with an estimated half-time of four to six hours, and most of an oral dose is excreted

within one to two days. No reports were located regarding the tissue accumulation and retention of CCl_4 during chronic exposure.

IV. HEALTH EFFECTS

Humans

- The effects of CCl_4 exposure in humans are similar to effects seen in animals, with the liver, kidney and lungs being most sensitive.

- Single oral doses of 2.5 to 15 mL (57 to 343 mg/kg) are usually without effect, although changes may occur in liver and kidney (U.S. EPA, 1985a). Some individual adults suffer adverse effects (including death) from ingestion of as little as 1.5 mL (34 mg/kg), and 0.18 to 0.92 mL may be fatal in children (29 to 150 mg/kg) (U.S. EPA, 1985a).

- Inhalation exposure also results in central nervous system depression and renal and hepatic damage (U.S. EPA, 1985a). No ill effects result from three hours of exposure to 63 mg/m^3, but 70 minutes of exposure to 2,309 mg/m^3 may produce liver effects. High levels (1,500 mg/m^3) may produce severe poisoning and death.

Animals

Short-term Exposure

- Carbon tetrachloride is toxic to animals, with oral LD_{50} values ranging from 1,000 to 12,800 mg/kg (U.S. EPA, 1985a).

- The tissue most affected by CCl_4 is the liver. Using release of liver enzymes into serum and histological examination as end-points, single oral doses (in corn oil) of 40 mg CCl_4/kg did not produce adverse effects, while doses of 80 mg/kg or higher did in male Sprague-Dawley rats (Bruckner et al., 1986b). Numerous studies have found that oral doses ranging from about 100 to 4,000 mg/kg produce fatty infiltration, loss of cytochrome P-450 and other enzymes, inhibition of protein synthesis and histological alterations in the liver. When damage is severe, hepatocellular necrosis may result, but the effects observed following lower doses are largely reversible (U.S. EPA, 1985a).

- Kidney and lung also are affected following oral exposure to CCl_4 (U.S. EPA, 1985a). Single doses of about 4,000 mg/kg result in lesions of the renal proximal tubule in rats and pulmonary Clara cells and endothelial cells in rats and/or mice. These changes also appear to be reversible when damage is not too severe.

- Bruckner et al. (1986b) found hepatotoxic effects (increased serum enzymes, pathology) in rats given CCl_4 in corn oil at daily doses of 20 mg/kg and higher by gavage for 9 days in an 11-day study.

- Hayes et al. (1986) observed hepatotoxicity (increased serum enzymes, increased organ weight) in male and female CD-1 mice given CCl_4 in corn oil by gavage at doses of 625, 1,250 or 2,500 mg/kg for 14 consecutive days.

- The objective of a study by Kim et al. (1986) was to assess the influence of dosing vehicles on the acute hepatotoxicity of CCl_4. Fasted 200 g male Sprague-Dawley rats were given 0, 10, 25, 50, 100, 250, 500, 1,000 or 2,000 mg CCl_4/kg by gavage in: corn oil; as an aqueous emulsion; as the undiluted chemical; and in the 10 and 25 mg/kg doses only in water. Blood and liver samples were taken 24 hrs after dosing for measurement of serum and microsomal enzymes. Pathological examination of liver samples was also conducted. Dose-dependent increases in serum enzyme levels and pathological changes, and dose-dependent decreases in microsomal P-450 and glucose-6-phosphatase activity were observed in each vehicle group. CCl_4 was less hepatotoxic at each dosage level when given in corn oil than when given as an emulsion or as the pure chemical. CCl_4 in corn oil was also less toxic than CCl_4 in water at the 10 and 25 mg/kg doses.

Long-term Exposure

- The effects of longer-term exposure to CCl_4 are similar to the effects of short-term exposure: the liver is the most sensitive tissue, showing fatty infiltration, release of liver enzymes, inhibition of cellular enzyme activities, inflammation and, ultimately, cellular necrosis (U.S. EPA, 1985a).

- Rats exposed by gavage to CCl_4 in corn oil at doses of 1 mg/kg 5 days/week for 12 weeks did not show measurable adverse effects, while doses of 10 or 33 mg/kg resulted in enzyme release, centrilobular vacuolization and necrosis in liver (Bruckner et al., 1986b).

- Condie et al. (1985) investigated the effects of a corn oil vehicle as well as Tween-60 on the subchronic hepatotoxicity of carbon tetrachloride (CCl_4). Male and female CD-1 mice were given 0, 1.2, 12 and 120 mg/kg CCl_4 by gavage in either corn oil as a solution or 1% Tween-60 as a suspension once daily for five consecutive days per week for 90 days. Hepatotoxicity was greater in the corn oil vehicle groups of mice than in the Tween-60 groups. Significant increases in serum enzyme activities were detected in the 12 mg/kg CCl_4 corn oil male and female groups but not in the corresponding Tween-60 groups. When comparing the serum enzyme activities in the high dose groups, there were dramatic increases in both the male and female corn oil groups as compared to the corresponding Tween-60 groups. Liver and liver/body weights were significantly greater in each high dose group. Histopathological findings indicated that hepatocellular changes occurring during the administration of CCl_4 at the 12 mg/kg (hepatocellular cytomegaly, fat and necrosis) and 120 mg/kg (necrosis and fat) dose levels were more frequently observed when CCl_4 was given in corn oil than when it was administered in Tween-60. The experimental findings indicate that the corn oil vehicle lowered the no-observed-adverse-effect level (NOAEL) from CCl_4 exposure by an

order of magnitude (from 12 mg/kg to 1.2 mg/kg) compared to the Tween-60 vehicle and also enhanced the hepatotoxicity of CCl_4 in the high dose treatment groups.

- Hayes et al. (1986) reported hepatotoxic effects (increased serum enzymes, increased organ weight, pathological lesions) in male and female CD-1 mice given CCl_4 in corn oil by gavage at doses of 12, 120, 540 or 1,200 mg/kg for 90 consecutive days.

- Alumot et al. (1976) fed 18 male and 18 female rats (strain not given) 0, 80 or 200 ppm CCl_4 in the diet until final sacrifice at two years. The authors equated 200 ppm to 10-18 mg/kg body weight/day. No adverse effects from exposure to CCl_4 were observed. However, tissues were not examined microscopically, liver weights were not taken, and survival was below 50% at 21 months. In an earlier 6-week study, Alumot et al. (1976) found no effect with 22 mg/kg and increased lipid and triglyceride in liver with 40 and 76 mg/kg. Only body weight was additionally measured.

- Prendergast et al. (1967) found hepatotoxicity in guinea pigs, rats, monkeys, rabbits and dogs exposed to 515 mg CCl_4/m^3 air eight hours/day, five days/week for six weeks. Liver effects were also found in these species after continuous exposure to 61 mg/m^3 for 90 days but not to 6.1 mg/m^3. After inhalation exposure of Wistar rats to CCl_4 eight hours/day, five days/week for ten months, Smyth et al. (1936) found liver toxicity with levels above 315 mg/m^3 and kidney changes with at least 315 mg/m^3 (lowest level tested). Adams et al. (1952) noted liver damage in Wistar rats, guinea pigs, and rabbits at some inhalation exposures ranging from 32.5 to 2,600 mg/m^3, seven hours/day, five days/week for 258 days and no observable effect in a Rhesus monkey similarly exposed to 25 mg/m^3 for 212 days, but the study cannot be adequately assessed from the limited details reported.

Reproductive Effects

- No reproductive evvects were noted in rats fed diets containing CCl_4 at 80 and 200 ppm for up to two years (Alumot et al., 1976)

Developmental Effects

- No evidence was located to demonstrate that CCl_4 is teratogenic (U.S. EPA, 1985a). Newborn rats appear to be less sensitive to liver damage by CCl_4 than 7-day-old rats (Dawkins, 1963). An intraperitoneal dose of 2,400 mg/kg has resulted in adverse effects on testicular function in rats (Chatterjee, 1966).

Mutagenicity

- No evidence of mutagenic activity for CCl_4 has been found in bacterial test systems or in cultured liver cells (U.S. EPA, 1985a), except that Sina et al. (1983) found CCl_4 weakly positive at cytotoxic levels in an alkaline elution/rat hepatocyte assay to measure DNA single-strand breaks. Increased gene crossover and mitotic recombination were

observed in yeast cells exposed to CCl_4 at 3,300 to 5,400 mg/L buffer (Callen et al., 1980). Amacher and Zelljadt (1983) concluded CCl_4 as positive for cell transformation in Syrian hamster embryo cells.

- In an in vivo-in vitro hepatocyte DNA repair assay by Mirsalis, et al. (1985), CCl_4 failed to induce unscheduled DNA synthesis in male and female $B_6C_3F_1$ mice but did significantly elevate hepatic cell proliferation. The latter effect was also induced by CCl_4 in male Fischer 344 rats but at higher doses.

Carcinogenicity

- Carbon tetrachloride is carcinogenic in animals, producing mainly hepatic neoplasms. Doses of about 30 mg/kg/day or higher for six months or longer have been found to produce an increased frequency of hepatocellular tumors in mice, rats and hamsters (U.S. EPA, 1985a).

- In an exploratory study of a large number of solvents and cancers in rubber industry workers, Wilcosky et al. (1984) associated exposure to carbon tetrachloride with lymphosarcoma and lymphatic leukemia, but they stressed cautious interpretation because of the modest number of cases and biases.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The acute animal study by Bruckner et al. (1986b) has been selected to serve as the basis for the One-day Health Advisory in the 10-kg child because this study clearly defined a one-day NOAEL (40 mg/kg) and LOAEL (80 mg/kg)

for CCl_4 based on changes in BUN, GPT, SDH and OCT and histopathological changes in the liver and kidneys of rats sacrificed 24 hours after dosing. The abstract report of the study by Kim et al. (1986) does not provide sufficient details for assessment as a basis for the One-day HA.

The One-day HA for a 10-kg child is calculated as follows:

$$\text{One-day HA} = \frac{(40 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 4.0 \text{ mg/L } (4{,}000 \text{ ug/L})$$

where:

40 mg/kg day = NOAEL based on absence of liver toxicity following one-day exposure in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with ODW/NAS guidelines for use with a NOAEL from an animal study.

1 L/day = assumed water consumption of a child.

Ten-day Health Advisory

The short-term study by Bruckner et al. (1986b) has been selected to serve as the basis for the Ten-day HA for the 10-kg child. This study identified a LOAEL of 20 mg/kg/day in rats given 9 doses over 11 days, based on significant increases in serum enzyme levels and hepatic midzonal vacuolization by 11 days. Higher doses of CCl_4 caused even more extensive liver damage. The 14-day study by Hayes et al. (1986) is not selected because all doses used were effect levels above those in the Bruckner et al. (1986b) study.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(20 \text{ mg/kg/day})\ (10 \text{ kg})\ (9)}{(1{,}000)\ (1 \text{ L/day})\ (11)} = 0.16 \text{ mg/L } (160 \text{ ug/L})$$

where:

20 mg/kg/day = LOAEL based on liver toxicity in rats.

9/11 = factor accounting for 9 doses given over 11 days.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed water consumption of a child.

Longer-term Health Advisory

The 12-week study by Bruckner et al. (1986b) has been selected to serve as the basis for calculation of the Longer-term HA. Bruckner and co-workers dosed rats with CCl_4 in corn oil by gavage five times weekly for 12 weeks with doses of 1, 10 or 33 mg/kg. This study identified a NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg day for hepatotoxicity. Condie et al. (1985) obtained similar results with a NOAEL of 1.2 mg/kg/day and a LOAEL of 12 mg/kg/day in CD-mice given CCl_4 in corn oil by gavage five times weekly for 90 days. In the same study, Condie et al. (1985) found a NOAEL of 12 mg/kg/day with CCl_4 suspended in Tween-60, but these data are not selected for the Longer-Term HA calculation because of use of a rather insoluble form of CCl_4 (suspension) as the method of dosing. The 90-day study by Hayes et al. (1986) is not selected because a NOAEL was not found, although the LOAEL of 12 mg/kg/day approximates the 10 mg/kg/day LOAEL in the Bruckner et al. (1985) study.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1\ \text{mg/kg/day})\ (10\ \text{kg})\ (5)}{(100)\ (1\ \text{L/day})\ \ (7)} = 0.071\ \text{mg/L}\ (71\ \text{ug/L})$$

where:

1 mg/kg/day = NOAEL based on absence of liver toxicity in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5/7 = factor to account for dosing five days per week.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1\ \text{mg/kg/day})\ (70\ \text{kg})\ (5)}{(100)\ (2\ \text{L/day})\ \ (7)} = 0.25\ \text{mg/L}\ (250\ \text{ug/L})$$

where:

1 mg/kg/day = NOAEL based on absence of liver toxicity in rats.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5/7 = factor to account for dosing five days per week.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 12-week study by Bruckner et al. (1986b) described under Longer-term Health Advisory is the most appropriate from which to derive the DWEL in that the available animal toxicity studies with chronic exposure to CCl_4 are concluded to be insufficient for use in the DWEL calculation. From these results, a NOAEL of 1 mg/kg was identified.

The two-year study in rats by Alumot et al. (1976) was not chosen because the assessment of CCl_4 toxicity was deficient with respect to tissue examination. The inhalation studies by Prendergast et al. (1967), Smyth et al. (1936), and Adams et al. (1952) were not used since inhalation data are less desirable for HA development.

Using the NOAEL of 1 mg/kg, the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(1\ mg/kg/day)\ (5)}{(1{,}000)\quad (7)} = 0.0007\ mg/kg/day$$

where:

1 mg/kg/day = NOAEL based on absence of liver toxicity in rats orally given CCl_4 for 90 days.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

5/7 = factor to account for dosing 5 days per week.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0007 \text{ ug/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.025 \text{ mg/L } (25 \text{ ug/L})$$

where:

0.0007 ug/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Carbon tetrachloride may be classified in Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing carbon tetrachloride at 25 ug/L is approximately 8×10^{-5}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- The IARC (1979) classified carbon tetrachloride as a 2B carcinogen with sufficient animal evidence and inadequate human evidence.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), carbon tetrachloride may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- U.S. EPA calculated a unit risk estimate (the 95% upper limit by the linearized multistage model) of 0.37×10^{-5} for a human continuously exposed to 1 ug CCl_4 per liter of water (U.S. EPA, 1984). The corresponding 10^{-6}, 10^{-5} and 10^{-4} risks are associated with 0.3, 2.7 and 27 ug/L, respectively.

- It should be noted that this approach, which involved using the geometric mean of risk estimates based on four studies, for calculating unit risk estimates for CCl_4 is from U.S. EPA (1984) which was reviewed by the U.S. EPA's Science Advisory Board.

- There was an attempt to compare risk estimates derived with the multistage model with other models in U.S. EPA, 1984. Of the studies used (Della Porta et al., 1961; Edwards et al., 1942; NCI rat and mouse, 1976), risk estimates could not be calculated with the Weibull and log probit models, and a time-to-tumor model was successful only with the NCI (1976) data which gave 95% upper confidence limits similar to those obtained with the multistage model. Unit (ingestion of 1 ug CCl_4/L water/lifetime) risk estimates (95% upper confidence limits) with individual studies and the multistage model were 3.4×10^{-5}

(Della Porta et al., 1961), 9.4×10^{-6} (Edwards et al., 1942), 1.8×10^{-6} (NCI mouse, 1976) and 3.1×10^{-7} (NCI rat, 1976). Unit risk estimates (maximum likelihood estimates) with individual studies and the multistage model were 2.1×10^{-5} (Della Porta et al., 1961), 7.1×10^{-6} (Edwards et al., 1942), 1.4×10^{-6} (NCI mouse, 1976) and 1.9×10^{-7} (NCI rat, 1976). While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Data from the animal studies have been used by NAS (1977) and U.S. EPA (1980b, 1984) to calculate the upper 95% bound on the number of additional cancer cases that may occur when CCl_4 is consumed in drinking water over a 70-year lifetime. By these methods, a 10^{-6} lifetime excess cancer risk was associated with CCl_4 in drinking water at levels of 4.5 ug/L by the NAS (1977), 0.4 ug/L by the U.S. EPA (1980a) and 0.3 ug/L by the U.S. EPA (1984).

- The criteria for the U.S. EPA, OHEA and NAS risk calculations differ in two respects: (1) NAS used the multistage model, while U.S. EPA used an "improved" multistage model; and (2) NAS used the data set from the National Cancer Institute (NCI) study in male rats while U.S. EPA initially used the data set from the NCI study in male mice (U.S. EPA, 1980b) and subsequently used a geometric mean of four studies (NCI, 1976 - mice; NCI, 1976 - rats; Edwards et al., 1942 - mice; and Della Porta et al., 1961 - hamsters) (U.S. EPA, 1984).

- Ambient water quality criteria for CCl_4 calculated by the EPA (U.S. EPA 1980b) were based on increased lifetime cancer risk estimates of 10^{-5} (4.0 ug/L), 10^{-6} (0.40 ug/L), and 10^{-7} (0.04 ug/L). It is noteworthy that these estimates were derived by assuming a lifetime consumption of both drinking water (2 L/day) and aquatic species (6.5 g fish and shellfish/day) taken from waters containing the corresponding CCl_4 levels. Specifically, daily CCl_4 exposure assumptions were as follows: 94% from ingesting drinking water and 6% from consuming seafood "fish factor." The corresponding "drinking water only" concentrations were 4.41, 0.44, and 0.04 ug/L, respectively.

- Using the carcinogenicity data set and a linear multistage model, WHO (1984) derived a recommended tentative limit for CCl_4 of 3 ug/L as a level which should result in less than one additional cancer per 100,000 population (10^{-5}) for a lifetime of exposure assuming daily consumption of two liters of drinking water.

- The U.S. EPA (1981) and NAS (1980) previously calculated SNARLS (Suggested No-Adverse-Response Levels) for CCl_4 in drinking water. These guidelines are summarized in Table 1.

TABLE 1

Summary of Existing Guidelines for CCl_4

	USEPA[a]	NAS[b]
One-day	0.2 mg/L	14 mg/L
Seven-day[c]	-	2 mg/L
Ten-day[c]	0.02 mg/L	-
Long-term	None[d]	None[e]

[a]U.S. EPA (1981) used a LOAEL of 20 mg/kg (Korsrud et al., 1972) as the basis for their calculations.
[b]NAS (1980) used a LOAEL of 400 mg/kg (Murphy and Malley, 1969) as the basis for their calculations.
[c]In the absence of subacute oral data, the NAS (1980) and U.S. EPA (1981) calculated 7- and 10-day SNARLS by dividing their one-day values by 7 and 10, respectively.
[d]The U.S. EPA (1981) did not calculate a long-term SNARL due to a lack of acceptable chronic oral exposure data at that time.
[e]The NAS (1980) did not determine a long-term SNARL because of NAS policy at that time not to calculate such values for animal carcinogens.

- The final RMCL by the U.S. EPA Office of Drinking Water is 0, the proposed MCL is 5 ug/L, and the practical quantitation level is 5 ug/L (U.S. EPA, 1985e).
- The U.S. EPA Office of Pesticide Programs has published a notice of intent to cancel registrations of grain fumigation products containing CCl_4 (U.S. EPA, 1986b).
- The OSHA standard in 10 ppm (TWA), and the ACGIH (1983) has recommended a TLV of 5 ppm and an STEL of 20 ppm.
- The U.S. EPA (1985d) has published a notice of intent to list CCl_4 under Section 112 of the Clean Air Act.

VII. ANALYTICAL METHODS

- Analysis of CCl_4 is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping CCl_4 on an adsorbent material. The adsorbent material is heated to drive off the CCl_4 onto a gas chromatographic column. This method is applicable to the measurement of CCl_4 over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for carbon tetrachloride is by mass spectrometry (U.S. EPA,

1985c). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Treatment techniques which will remove carbon tetrachloride from drinking water include granular activated carbon adsorption, boiling, and aeration (Combs, 1980).

- Pilot plant studies by EPA's Drinking Water Research Division have shown consistently that conventional treatment processes (coagulation, sedimentation, filtration), even when augmented by the addition of powdered activated carbon, provide little removal of carbon tetrachloride.

- The use of powdered activated carbon was only partially effective at doses as high as 30 ug/L (Love et al., 1983; Symons et al., 1979; Lykins et al., 1980).

- Carbon tetrachloride at a raw water concentration of 12 ug/L treated using Filtrasorb® 400 granular activated carbon exhibited breakthrough after three weeks. The empty bed contact time reported was 5 minutes. When the empty bed contact time was increased to 10 minutes, breakthrough occurred at 14 to 16 weeks (Symons, 1978).

- A full-scale installation investigation conducted by Calgon using twin granular activated carbon beds in series (EBCT of 130 minutes) reported that, along with other chemicals, carbon tetrachloride was removed to below detection from an influent concentration of 73 ug/L (O'Brien et al., 1981).

- A study demonstrated that the synthetic resin (Ambersorb XE-340) removed carbon tetrachloride from treated drinking water with an effectiveness similar to Filtrasorb® 400 (Symons et al., 1979). It should be noted that these resins are not commercially available.

- Boiling also is effective in eliminating carbon tetrachloride from a solution. Studies have shown that five minutes of vigorous boiling will remove upwards of 99% of the carbon tetrachloride originally present (Combs, 1980; Love and Eilers, 1981).

- Finally, aeration may be used to remove carbon tetrachloride from water. Laboratory studies conducted by Love et al. (1983) showed that a diffused air aerator could remove 91% of the carbon tetrachloride in the water using a 4:1 air to water ratio.

- Air stripping is an effective, simple, and relatively inexpensive process for removing carbon tetrachloride and volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure, and various hazards associated with the chemical.

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