International Journal of Applied and Natural Sciences (IJANS)
ISSN(P): 2319-4014; ISSN(E): 2319-4022
Vol. 6, Issue 4, Jun – Jul 2017; 79-90

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

TOXIOLOGICAL PROFILE OF TETRACHLOROMETHANE

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ABSTRACT

Tetra chloromethane is an unmistakable fluid that vanishes effectively. Most Tetrachloromethane that escapes to nature is found as a gas. Tetrachloromethane does not effectively blaze. Tetrachloromethane has a sweet scent, and the vast majority can start to notice it in the air, when the focus achieves 10 sections of Tetrachloromethane for every million sections of air (ppm). It is not known whether individuals can taste it. Tetrachloromethane has been created in extensive amounts to make refrigeration liquid and charges for vaporized jars. Since numerous refrigerants and airborne forces have been found to influence the world's ozone layer, the generation of these chemicals is being eliminated. Hence, the production and utilization of Tetrachloromethane have declined.

KEYWORD: Tetra Chloromethane

INTRODUCTION

Before, Tetrachloromethane was generally utilized as a cleaning liquid (in industry and cleaning foundations and in family units as a spot remover for garments, furniture, and covering). Tetrachloromethane was likewise utilized as a part of flame quenchers and as a fumigant to slaughter bugs in grain. The greater part of these uses was ceased in the mid-1960s. Up to this point, Tetrachloromethane was utilized as a pesticide, however, this was halted in 1986. Tetrachloromethane (CCl4) is a haloalkane with an extensive variety of modern and substance applications. Around 423,000 metric tons (932.7 million pounds) are created every year at 11 plant destinations in the U.S. Tetrachloromethane has an atomic weight of 153.82, a dissolving purpose of - 22.99°C, and a breaking point of 76.54°C. It is a substantial (thickness of 1.594 g/ml), vapid fluid at room temperature. The compound is generally nonpolar and miscible with liquor, CH3) 2CO, and most other natural solvents. Its dissolvability in water at 25°C is 800, 000 µg/l, and its vapor weight at 10ºC is 55.65 mm Hg. It has an octanol/water allotment coefficient of 2.73. The greater part of this synthetic is utilized as a part of the assembling of fluorocarbons which were once utilized basically as vaporized forces.

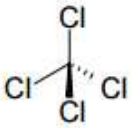
Tetrachloromethane is utilized as a segment of flame quencher arrangements and as a modern and concoction dissolvable. Its utilization in grain fumigation is by and large generally supplanted by other enlisted pesticide items. Its utilization as a degreaser in the dry-cleaning industry has been generally supplanted by perchloroethy. Tetrachloromethane may be entirely steady under certain ecological conditions. An expected 70,000 years are required for half of a given amount of CCl4 to break down in the water. This deterioration rate is impressively quickened in the vicinity of metals, for example, iron (Pearson and McConnell, 1975). Hydrolytic deterioration as a method of expulsion of water gives off an impression of being irrelevant when contrasted with vanishing. Dilling, et al. (1975) discovered that CCl4 has an evaporative half-existence of 29 minutes in water at surrounding temperatures. Volatilization is the real transport process for expulsion of tetrachloromethane from amphibian frameworks. Once in the troposphere, tetrachloromethane stays stable;

it displays an amazingly moderate rate of response with hydroxyl radicals present in the troposphere. Tetrachloromethane in the end diffuses into the stratosphere or is conveyed back to the earth amid the precipitation process. Once in the stratosphere, tetrachloromethane is corrupted on introduction to shorter wavelength, higher vitality, bright light to inevitably shape phosgene as the main introductory item.

Chemical and Physical Information

Information regarding the chemical identity and physical and chemical properties of Tetrachloromethane is located in Table 1 and Table 2.

Table 1: Chemical Identity of Tetrachloromethane

Characteristic	Information	Reference
Chemical name	Carbon tetrachloride	IARC 1979
Synonym(s)	Carbona; carbon chloride; carbon tet; methane tetrachloride; perchloromethane; tetrachloromethane; benzinoform	HSDB 2004
Registered trade name(s)	Benzinoform; Fasciolin; Flukoids; Freon 10; Halon 104; Tetraform; Tetrasol	IARC 1979
Chemical formula	CCl_4	IARC 1979
Chemical structure		IARC 1979
Identification numbers:		
CAS registry	56-23-5	NLM 1988
NIOSH RTECS	FG4900000	HSDB 2004
EPA hazardous waste	U211; D019	HSDB 2004
OHM/TADS	7216634	HSDB 2004
DOT/UN/NA/IMCO shipping	UN1846; IMCO 6.1	HSDB 2004
HSDB	53	HSDB 2004
NCI	No data	

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency;

HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health;

OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 2: Physical and Chemical Properties of Tetrachloromethane

Property	Information	Reference
Molecular weight	153.82	Lide 1993
Color	Colorless	Verschueren 1983
Physical state	Liquid	Verschueren 1983
Melting point	-23 °C	Lide 1992
Boiling point	76.5 °C	Lide 1992
Density	1.594 g/mL	Lide 1992
Odor	Aromatic, sweet	HSDB 2004
Odor threshold:		
Water	0.52 mg/L	IRIS 2004
Air	10–71,000 mg/m^3	Verschueren 1983
	96 ppm (600 mg/m^3)	Amoore and Hautala 1983
	60–1,500 mg/m^3	Ruth 1986
Solubility:		
Water at 20 °C	800 mg/L	Verschueren 1983
Organic solvent(s)	Miscible	HSDB 2004
Partition coefficients:		
Log K_{ow}	2.64	EPA 1984
Log K_{oc}	2.04	Kenaga 1980
Vapor pressure at 20 °C	90 mmHg	Verschueren 1983
Henry's law constant:		
at 25 °C	$2.94x10^{-2}$ atm-m^3/mol	Yaws et al. 1991
at 24.8 °C	$3.04x10^{-2}$ atm-m^3/mol	HSDB 2004
at 20 °C	$2.04x10^{-2}$ atm-m^3/mol	Tse et al. 1992
at 30 °C	$3.37x10^{-2}$ atm-m^3/mol	Tse et al. 1992
Autoignition temperature	Nonflammable	HSDB 2004
Flashpoint	Nonflammable	HSDB 2004
Flammability limits	Nonflammable	HSDB 2004
Conversion factors		
ppm (v/v) to mg/m^3 in air (25 °C)	1 ppm=6.39 mg/m^3	HSDB 2004
mg/m^3 to ppm (v/v) in air (25 °C)	1 mg/m^3=0.16 ppm	Verschueren 1983
Explosive limits	No data	

PRODUCTION

Tetrachloromethane is delivered by thorough chlorination of an assortment of low atomic weight hydrocarbons, for example, carbon disulfide, methane, ethane, propane, and ethylene dichloride. It is likewise delivered by warm chlorination of methyl chloride. Tetrachloromethane is a feedstock for chlorofluorocarbon gases, for example, dichlorodifluoromethane (F-12) and trichlorofluoromethane (F-11), which were utilized as vaporized charges as a part of the 1950s and 1960s. Taking over this, the development rate for the generation of Tetrachloromethane arrived at the midpoint of 10.7% every year from 1960 to 1970. This rate eased back to 7.2% every year from 1970 to 1974, when the creation of this substance was at its top, as different types of fuels turned out to be industrially accessible. The FDA banned the offer of Tetrachloromethane in any item utilized as a part in the home and the EPA managed the utilization of chlorofluorocarbon gases as pressurized canned products or charges. From that point forward, generation of Tetrachloromethane has declined by around 8% a year from 1974 to 1994. Tetrachloromethane is as of now fabricated in the United States by Vulcan Materials Company at two plants: Geismar, Louisiana and Wichita, Kansas, with a consolidated 130 million pound limit. It ought to be noted, nonetheless, that these limits are adaptable, since other chlorinated solvents are made utilizing the same hardware this late decrease underlay is because of the selection of a worldwide understanding (the Montreal Protocol) to diminish natural centralizations of ozone-exhausting chemicals (counting Tetrachloromethane), and to the procurements of Title VI of the Clean Air Act Amendments of 1990 tending to these chemicals. The regulation called for lessening to 15% of 1989 creation levels by 1995 and a complete eliminate of Tetrachloromethane generation for nonfeedstock utilizes by 2000. The EPA distributed a standard creation recompense of

around 138 million pounds (63,000 metric tons) of Tetrachloromethane, allocated among the eight U.S. organizations delivering the compound in 1989.

TOXICITY OF TETRACHLOROMETHANE

Tetrachloromethane is quickly consumed by any course of introduction in people and creatures. Once ingested, it is broadly disseminated among tissues, particularly those with high lipid substance, coming to crest focuses in under 1–6 hours, contingent upon introduction fixation or measurements. It is metabolized by the liver, lung, and different tissues. Tetrachloromethane is quickly discharged, basically in, breathing out breath.

ABSORPTION

Oral Exposure

Tetrachloromethane is promptly assimilated through the gastrointestinal tract in people and creatures. There is proof of gastrointestinal ingestion in people in light of reports of a poisonous quality after harming occurrences. Complete assimilation was diminished by 37–56% when the same dosages were directed by mixture over a 2-hour period. An oral measurement of around 3200 mg/kg accomplished a crest blood focus in around 2 hours in rats. After radiolabeled Tetrachloromethane was infused into the duodenum of rats, no less than 82% was ingested in light of recuperations of name in breathing out air.

Inhalation Exposure

Data from humans and animals suggest that Tetrachloromethane is rapidly absorbed through the lungs, which is inferred from the rapid onset of symptoms of toxicity or detection of Tetrachloromethane in blood or in exhaled air. In volunteers exposed to 10 ppm for 180 minutes, Tetrachloromethane was detectable in exhaled air within 15 minutes (Stewart et al., 1961). Human subjects exposed to 60 mg/L (9600 ppm) or higher reported symptoms of toxicity within the first minute of exposure; symptoms appeared after 3 minutes in subjects exposed to 30 mg/L (4800 ppm). After male Sprague-Dawley rats were exposed at 100 or 1000 ppm, Tetrachloromethane was detected in arterial blood in the initial 5 minute samples blood levels rose during the 2-hour exposure period to a near steady-state level. In dogs exposed to 5000 ppm of Tetrachloromethane, blood levels reached a near steady-state level within 2 hours.

Health Effects

Tetrachloromethane is readily absorbed after ingestion and inhalation, but more slowly through the skin. Acute exposure to Tetrachloromethane can also cause central nervous system (CNS) depression as well as gastrointestinal and neurological effects such as nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, and in-coordination, impairment of speech, confusion, anaesthesia, fatigue and dyspnoea.

The liver and kidney are the major target organs for toxicity following acute inhalation or ingestion exposure to Tetrachloromethane [2, 3]. Liver damage can occur after 24 hours and in serious cases this can result in painful, swollen liver, ascites, haemorrages, hepatic coma and death [1, 2]. Kidney damage with impairment in function normally occurs 2-3 weeks after exposure [2], but in severe cases this can occur within 1-6 days in association with liver failure.

Acute ocular exposure or skin contact can cause irritation of the eyes and skin [4]. Direct skin contact with undiluted Tetrachloromethane has been reported to cause a mild burning sensation with mild redness. Some individuals may be hypersensitive and develop marked swelling, itching and blisters following skin contact.

Chronic inhalation may result in liver and kidney toxicity and neurological effects from depression of the central nervous system. Neurological and gastrointestinal symptoms are similar to those for acute exposure, such as depression, nausea and other gastrointestinal effects [5]. In long term repeated dose studies in animals the liver has been shown to be the most sensitive organ regarding toxicity.

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of Tetrachloromethane in humans. However, based on evidence in animal studies, IARC has concluded overall that Tetrachloromethane is possibly carcinogenic to humans (Group 2B). The doses inducing liver tumours in animal studies are higher than those causing liver cell toxicity, and therefore are considered to arise secondary to toxic effects on the liver. Tetrachloromethane does not have any significant mutagenic properties.

METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to Tetrachloromethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to Tetrachloromethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to Tetrachloromethane:

Reducing Peak Absorption Following Exposure

Human exposure to Tetrachloromethane may occur by inhalation, ingestion, or dermal contact. Inhalation or oral exposure to Tetrachloromethane may cause hepatic, renal, and neurological effects. There is evidence, though limited, that dermal contact causes a similar pattern of effects.

If Tetrachloromethane has been inhaled, movement of fresh air is recommended. Humidified supplemental oxygen (100%) may be administered as required.

Ingestion of Tetrachloromethane should be considered a toxic emergency in which treatment should begin immediately. Treatment currently involves gastric emptying, either by gastric lavage (with a small bore nasogastric tube) or by induction of vomiting, preferably within minutes of exposure. The patient needs to have a gag reflex and should not show signs of seizure, lethargy, or coma because of the risk of pneumonitis of pulmonary aspiration. In infants and young children, the induction of vomiting may induce severe fluid loss. Supportive therapy should be followed in all instances of treatment. A cathartic may be administered to speed fecal excretion. Administration of activated charcoal is unlikely to be effective. Animal studies revealed peak blood levels of Tetrachloromethane within 3–6 minutes after oral exposure when Tetrachloromethane was ingested undiluted or in aqueous vehicles by fasted rats. Chemicals that induce P-450, such as ethanol and phenobarbital, should not be given. The administration of epinephrine is avoided, due to the possibility of inducing ventricular arrhythmias. In order to minimize absorption through the skin, all contaminated clothing should be removed and the skin should be washed with soap and water. In cases where the compound has been splashed into the eyes, irrigation with copious amounts of tepid water for 15 minutes has been recommended. Medical treatment is required if irritation, pain, swelling, lacrimation, or photophobia persist.

Reducing Body Burden

Hemodialysis may be employed in order to lower plasma Tetrachloromethane at the onset of renal failure. Although this method is not very effective in removing lipophilic compounds from the blood, it is effective in controlling the extracellular fluid composition if renal failure occurs. Because a substantial portion of absorbed Tetrachloromethane is exhaled within the first hour, maintenance of a good tidal volume is recommended; hyperventilation may also be of value. Administration of hyperbaric oxygen is an experimental treatment that is also available. Hyperbaric oxygen has been used in treating overdoses of Tetrachloromethane in humans. Administration of hyperbaric oxygen following exposure to Tetrachloromethane improved survival from 31 to 96% in rats. Hyperbaric oxygen has also been used in treating overdoses of Tetrachloromethane in humans and may correct regional tissue hypoxia and damage, as well as inhibit the P-450- dependent reductive dehalogenation of Tetrachloromethane to the metabolically active trichloromethyl radical in the liver. However, the effectiveness of this method has not been established in humans.

Interfering with the Mechanism of Action for Toxic Effects

Information is limited in humans regarding compounds that interfere with the mechanism of action of Tetrachloromethane. However, there is evidence that liver toxicity associated with exposure to Tetrachloromethane is mediated by reactive metabolites that bind to hepatocytes and initiate lipid peroxidation, thus resulting in loss of cell function. N-acetylcysteine has been suggested to bind the toxic metabolite phosgene and to serve as a precursor for the formation of glutathione and was protective against hepatotoxicity in Tetrachloromethane-exposed rats. Glutathione, a cellular antioxidant, tends to decrease lipid peroxidation due to Tetrachloromethane ingestion in rats. Prior oral treatment with glutathione protected against hepatic necrosis, but did not modify lipid peroxidation or prevent covalent binding of Tetrachloromethane metabolites to hepatic microsomes in rats exposed intraperitoneally. Agents that foster the maintenance of hepatic reduced glutathione levels have a similar protective effect against Tetrachloromethane: cysteine, a precursor to glutathione taurine constituents of garlic oil such as diallyltrisulfid gamma-glutamylcysteinylethyl ester metformin, a dimethyl biguanide anti-hypoglycemic agen and clofibrate. Administration of 1616-dimethyl prostaglandin E2 to block the accumulation of intracellular lipids has also been suggested. Administration of fructose 1,6-diphosphate to rats has been shown to decrease Tetrachloromethane liver toxicity by increasing hepatocyte levels of ATP. The ATP, thus generated is thought to promote hepatocellular regeneration and tissue repair. Shertzer and Sainsbury (1991) reported that indole antioxidants 4b,5,9b,10-tetrahydroindeno [1,2-b] indole (THII) and 5,10-dihydroindeno [1,2-b] indole (DHII) inhibited Tetrachloromethane initiation of lipid peroxidation in rat liver microsomes, and protected against hepatotoxicity in rats when administered prior to Tetrachloromethane treatment. The authors suggested that these compounds may be suitable candidates for further development as potential chemoprotective and therapeutic agents for use in human disorders that involve free-radicals. Colchicine and trimethylcolchicinic acid, an analog that does not bind tubulin, prevented decreases in Ca2+-ATP-ase activity, and reduced increases in gamma-glutamyltranspeptidase, alanine aminotransferase, and alkaline phosphatase in hepatocyte plasma membranes in rats treated with Tetrachloromethane.

Oxygen supplementation improved ratios of ATP/ADP, inorganic phosphate/ATP, and lactate/pyruvate that had been altered in cirrhotic livers of rats previously treated with Tetrachloromethane. These results were consistent with the hypothesis that hepatocyte damage in cirrhotic livers is exacerbated by a reduced oxygen supply and may partly explain the efficacy of hyperbaric oxygen therapy.

Compounds that suppress the activity or expression of CYP2E1 have been shown to reduce the hepatic necrosis caused by the bioactivation of Tetrachloromethane. Pretreatment with 100–400 μmol/kg (subcutaneous) oleanolic acid,

a triterpenoid compound, reduced heptatoxicity in rats and mice injected with Tetrachloromethane, the protective effect occurred 12–72 hours after pretreatment and was found to be unrelated to metallothionein levels. In mice, the protective effect of oleanolic acid was associated with inhibition of expression and activity of CYP2E1 (Jeong 1999). Another triterpenoid, alpha-hederin similarly reduced expression of CYP2E1 and hepatic injury in mice treated with Tetrachloromethane (Jeong and Park 1998). Methylenedioxybenzenes such as isosafrole, dihydrosafrole, and benzodioxole, administered 1 hour before Tetrachloromethane, prevented increases in plasma AST and ALT in mice (Zhao and O'Brien 1996). Isosafrole co-treatment also prevented the development of liver necrosis. Safrole was partially hepatoprotective, whereas piperonylbutoxide, eugenol, isoeugenol, sesamol, and curcumin were ineffective. Other similar compounds that prevented increases in plasma AST and ALT in rats included tetrahydro-5-methyl bis[1,3]benzdioxide [4,5-C: 5', 6]-azecin-13 (5*H*)-one (protopine) and 2-methylaminoethyl-4,4'-dimethoxy-5,6,5',6' dimethylenedioxybiphenyl- 2-carboxylic acid-2' -carboxylate monohydrochloride (DBB-S). A synthetic agent, 2-(allylthio) pyrazine, suppressed constitutive and inducible CYP2E1 expression and also blocked Tetrachloromethane-induced hepatotoxicity in mice; the compound also elevated hepatic GSH levels.

Tumor necrosis factor alpha (TNF-alpha) has been implicated in the process of hepatocellular injury following exposure to Tetrachloromethane. Co-treatment of rats with the soluble receptor to TNF-alpha reduced hepatocellular necrosis and the elevation in serum enzyme levels caused by Tetrachloromethane. Mortality was 16% in the rats co-treated with the soluble receptor and 60% in rats cotreated with IgG.

A number of agents have been shown to reduce the severity of fibrosis induced in animals following intermediate-duration exposure to Tetrachloromethane. A weak but significant reduction in the area of Tetrachloromethane-induced hepatic fibrosis was measured by image analysis in rats co-treated with interferon alpha2a over a period of 9 weeks. There were concomitant reductions in several biochemical markers of fibrosis (hyaluronate, hydroxyproline, and the mRNAs for procollagen and fibronectin). In mice transgenic for the alpha (2) (I) collagen gene (COL1A2) promoter sequence and receiving a single intraperitoneal injection of Tetrachloromethane, interferon-alpha antagonized the transcription of COL1A2 that is stimulated by transforming growth factor-beta and the coactivator Smad3; the progression of hepatic fibrosis was also prevented in interferon-treated mice.

Administration of interferon-alpha2b also reduced the severity of fibrosis in the kidneys of rats subcutaneously injected with Tetrachloromethane over 7 weeks. Histopathology analysis revealed reductions in necrosis, dilatation and atrophy of renal tubules, hypercellularity of glomeruli, and obliteration of renal capillaries in rats co-treated with interferon compared to placebo-cotreated rats; the level of interstitial fibrosis was also reduced by interferon, although the difference was not statistically significant from the placebo co-treatment group. The kidneys of rats co-treated with interferon had more interstitial inflammation than the rats in the control group or in the placebo-cotreatment group. Pirfenidone (5 methyl-1-phenyl-2-(1H) -pyridone), an anti-fibrotic drug approved by the U.S. FDA for Phase II trials against pulmonary and renal fibrosis, reduced both the number of activated hepatic stellate cells and the severity of hepatic fibrosis when administered to rats with Tetrachloromethane-induced hepatic cirrhosis (Garcia et al. 2002); according to the authors, the anti-fibrotic effect of pirfenidone involves suppression of collagen gene transcription and possibly an inhibition of proline hydroxylase levels that would be expected to reduce the availability of hydroxyproline required for collagen synthesis.

Administration of liver growth factor in rats with hepatic cirrhosis following intraperitoneal injections of

Tetrachloromethane for 10 weeks significantly improved the structure and function of the liver. Significant decreases were observed in the levels of serum enzymes, the hepatic collagen content, and microscopic findings of fibrosis, necrosis, and inflammatory infiltration of the liver. In addition, hepatic hemodynamic measures were improved in rats treated with liver growth factor compared to cirrhotic rats: reduced portal pressure and portosystemic shunting, reduced ascites, and increased mean arterial pressure and systemic vascular resistance. Implantation of rat fibroblasts genetically modified to express hepatic growth factor into the spleens of syngeneic rats significantly reduced hepatic injury (serum enzymes, histopathology) resulting from an intraperitoneal injection of Tetrachloromethane. Gene therapy using an adenoviral vector bearing cDNA for a nonsecreted form of human urokinase plasminogen activator (Ad-ΔhuPA) reduced hepatic fibrosis in rats that became cirrhotic following treatment with Tetrachloromethane for 6–8 weeks. The beneficial effect of enhanced uPA expression was partly attributed to its induction of hepatocyte growth factor.

Treatment of insulin-like growth factor-I (IGF-I) to rats during the last 3 weeks of exposure to Tetrachloromethane/phenobarbitol partially normalized the expression of 8 of 16 genes that were either up- or down-regulated in the cirrhotic liver. Three of the genes affected by IGF-I are for protease inhibitors; restoration of the expression of these genes would be expected to protect against necrosis. IGF-I treatment also partially restored the expression of growth hormone receptor and the levels of global genomic DNA methylation, which are reduced during the development of cirrhosis. Evaluation of hepatic effects following IGF-I administration to cirrhotic rats on the same protocol resulted in reductions in lipid peroxidation, fibrosis, and plasma AST and ALT, and increases in mitochondrial transmembrane potential.

Several agents have been shown to ameliorate the effect of Tetrachloromethane on hepatic membranes. When co-administered with Tetrachloromethane, betaine, a mitochondrial metabolite of choline, reduced the extent of centrilobular steatosis and minimized the loss of hepatocyte organelle membranes (rough endoplasmic reticulum) in treating rats; the effect was attributed to the enhancement, which have a 34-dihydroxycinnamoyl structure and inhibit lipoxygenases and cyclooxygenases, were potent inhibitors of lipid peroxidation in cultured rat hepatocytes. Polyenylphosphatidyl choline also reduced hepatic fibrosis induced by Tetrachloromethane in rats and accelerated the regression of existing fibrosis.

One effect of lipid injury following exposure to Tetrachloromethane is the release of hydrolytic enzymes such as calpain from lysosomes into the extracellular space where activation by calcium occurs. As a result, cell necrosis progresses to neighboring cells, extending the hepatic lesion. Administration of the calpain inhibitor *N*-CBZ-Val-Phe -methyl ester (CBZ) or the cell-impermeable inhibitor E64 1 hour after a toxic, nonlethal intraperitoneal dose of Tetrachloromethane protected against calpain-specific breakdown of alpha-fodrin, a cytoskeletal protein, and reduced the increase in serum ALT. Administration of CBZ 1 hour after a lethal dose (3 g/kg) increased survival from 25 to 75%. The calpain inhibitors have no effect on the metabolism of Tetrachloromethane by CYP2E1 or the generation of metabolites that bind to liver tissue.

As vitamin A (retinol) shows species-specific variations on Tetrachloromethane-related hepatotoxicity, it is not possible to predict whether it would be useful as a therapeutic agent in exposed humans. Pretreatment of male mice with vitamin A for 7 days prior to a single exposure to Tetrachloromethane reduced the elevations in plasma ALT levels as well as the extent of hepatic degeneration. Some strain variations were evident in the protective effect of vitamin A, with no hepatocyte damage visible in C3H/He or athymic nude mice and only minimal hepatocyte damage visible near the central

vein in Swiss-Webster or Balb/C mice. Conversely, pretreatment with vitamin A increased the hepatotoxicity (plasma ALT levels) of Tetrachloromethane 10-fold in male and female Sprague-Dawley rats, and male nude and Fischer-344 rats. The underlying basis for the species and strain differences is not known, but the possible involvement of Kupffer cells or polymorphonuclear neutrophils is under investigation. It determined that the effect of vitamin A in Swiss-Webster mice do not involve alteration of the constitutive or inducible expression of CYP2E1.

Avid retention of Na+ is a feature of liver cirrhosis. Icatibant (HOE 140), an antagonist of the bradykinin B2 receptor, normalized Na+ retention and reduced the hyperactivity of the renin-angiotensin-aldosterone system in rats that had become cirrhotic following treatment with Tetrachloromethane.

Malnutrition is a common result of cirrhosis. Survival was improved in rats with Tetrachloromethaneinduced cirrhosis by the dietary administration of branched-chain amino acids in addition to a casein diet. Supplementation with branched-chain amino acids significantly preserved plasma albumin concentration and inhibited the occurrence of ascites and hyperammonemia without altering liver histopathology. The authors hypothesize that administration of branched-chain amino acids may suppress muscular protein catabolism and aid in detoxifying excess serum ammonia levels, which are characteristic of cirrhotic patients.

The protective effects of gadolinium a rare earth metal (lanthanide) and glycine against Tetrachloromethane injury operate via inactivation of Kupffer cells, which are hepatic macrophages. When either compound was administered to rats with Tetrachloromethane-induced cirrhosis, the livers showed reductions in fibrosis, collagen protein, and transforming growth factor-beta-1 caused by Tetrachloromethane. The inactivation of Kuppfer cells by glycine is suspected to be related to the inhibition of calcium signaling via glycine-gated chloride channels. Gadolinium chloride also prevented liver injury and increased hepatocyte proliferation (as measured by immunostaining for the hepatocyte proliferating cell nuclear antigen) in rats when administered prior to treatment with Tetrachloromethane. Gadolinium chloride inhibited CYP2E1 activity in cultured hepatocytes, reducing the loss of plasma membrane integrity caused by Tetrachloromethane.

CONCLUSIONS

Other substances that have been demonstrated to be protective against the toxic effects of Tetrachloromethane in animals include disulfiram enprostil, an analog of prostaglandin E2 bosentan, and TAK-044, antagonists to the endothelin receptor the xanthine oxidase inhibitor allopurinol the prolyl 4-hydroxylase inhibitors S 0885 and HOE 077 pyridoxol L, 2-pyrrolidon- 5 carboxylate (metadoxine) cyclosporine the calcium antagonist nifedipine alpha-tocopherol and derivatives polyamines adenosine various phenolic compounds (mostly flavinoids) and chromium III (but not chromium IV). Supplementation with sodium tungstate for 7 weeks significantly reduced lipid peroxidation and necrosis produced by Tetrachloromethane in rats. A combination treatment with hyaluronic acid and chondroitin-4-sulfate (but not either agent alone) partly reduced the effects of Tetrachloromethane treatment; the therapy reduced hepatic necrosis and the increases in hepatic malondialdehyde, plasma TNF-alpha, and neutrophil-mediated myeloperoxidase and reversed the reduction in glutathione. Exercise has been shown to protect subsequently isolated rat hepatocyte from Tetrachloromethane cytotoxicity, probably by affecting cytochrome P-450-2E1 activity, and perhaps also by stimulating intracellular levels of free radical scavengers and antioxidants. Food restriction (25 or 50% lower caloric than control intake) for 30 days prior to administration of Tetrachloromethane reduced the magnitude of blood lipid peroxidation and of increases in serum enzymes in carbon-tetrachloride treated rats.

REFERENCES

1. Haselmann KF, Laturnus F, Svensmark B, Gron C (2000) Formation of Trichloromethane in spruce forest soil — results from laboratory incubation studies. *Chemosphere*, 41 (11): 1769–1774.
2. Health Canada (1994) *Canadian Environmental Protection Act. Human health risk assessment for Priority Substances*. Ottawa, Ontario, Minister of Supply and Services Canada, 36 pp. (Catalogue No. En40-215/41E; ISBN 0-662-22126-5).
3. Health Canada (1999) *Canadian Environmental Protection Act. Priority Substances List. Supporting documentation for Trichloromethane: exposure assessment.* Ottawa, Ontario, Health Canada, Environmental Health Directorate, Priority Substances Section, November.
4. Heavner DL, Morgan WT, Ogden MW (1996) Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. *Environment International*, 22 (2): 159–183.
5. Heikes DL (1987) Purge and trap method for determination of volatile halocarbons and carbon disulfide in table-ready foods. *Journal of the Association of Official Analytical Chemists*, 70 (2): 215–226.
6. Heikes DL, Hopper ML (1986) Purge and trap method for determination of fumigants in whole grains, milled grain products, and intermediate grain-based foods. *Journal of the Association of Official Analytical Chemists*, 69 (6): 990–998.
7. Heikes DL, Jensen SR, Fleming-Jones ME (1995) Purge and trap extraction with GC-MS determination of volatile organic compounds in the table-ready foods. *Journal of Agricultural and Food Chemistry*, 43:2869–2875.
8. Henderson CJ, Scott AR, Yang CS, Wolf RC (1989) Testosterone-mediated regulation of mouse renal cytochrome P-450 isoenzymes. *Biochemical Journal*, 278:499–503.
9. Hermens J, Broekhuyzen E, Canton H, Wegman R (1985) Quantitative structure activity relationships and mixture toxicity studies of alcohols and chlorohydrocarbons: Effects on growth of *Daphnia magna*. *Aquatic Toxicology*, 6 (3): 209–217.
10. Smith MT, Loveridge N, Wills ED, Chayen J (1979) The distribution of glutathione in the rat liver lobule. *BiochemistryJournal*, 182:103–108.
11. Snell TW, Moffat BD, Janssen C, Persoone G (2002) Acute toxicity tests using rotifers. III. Effects of temperature, strain, and exposure time on the sensitivity of *Brachionusplicatilis*. *Environmental Toxicology and Water Quality*, 6 (1): 63–75.
12. Solomon K, Bergman H, Huggett R, Mackay D, McKague B (2005) *A review and assessment of the ecological risks associated with the use of chlorine dioxide for the bleaching of pulp*. Erin, Ontario, Alliance for Environmental Technology.

13. Stewart ME, Blogoslawski WJ, Hsu RY, Helz GR (2006) Byproducts of oxidative biocides: toxicity to oyster larvae. *MarinePollution Bulletin*, 10:166–169.

14. Tancrède M, Yanagisawa Y, Wilson R (2008) Volatilization of volatile organic compounds from showers — 1. Analytical method and quantitative assessment. *Atmospheric Environment*, 26A:1103–1111.

15. Taylor DC, Brown DM, Kebble R, Langley PF (1974) Metabolism of Trichloromethane: II. A sex difference in the metabolism of [14C] -Trichloromethane in mice. *Xenobiotica*, 4 (3): 165–174.

16. Templin MV, Jamison KC, Wolf DC, Morgan KY, Butterworth BE (2014) Comparison of Trichloromethane-induced toxicity in the kidneys, liver, and nasal passages of male Osborne-Mendel and F- 344 rats. *Cancer Letters*, 104:71–78.

17. Templin MV, Larson JL, Butterworth BE, Jamison KC, Leininger JR, Mery S, Morgan KT, Wong BA, Wolf DC (2013) A 90-day Trichloromethane inhalation study in F-344 rats: profile of toxicity and relevance to cancer studies. *Fundamental and Applied Toxicology*, 32:109–125.

18. Templin MV, Jamison KC, Sprankle CS, Wolf DC, Wong BA, Butterworth BE (2012) Trichloromethane-induced cytotoxicity and regenerative cell proliferation in the kidneys and liver of BDF1 mice. *Cancer Letters*, 108:225–231.

19. Templin MV, Constan AA, Wolf DC, Wong BA, Butterworth BE (2016) Patterns of Trichloromethane-induced regenerative cell proliferation in BDF1 mice correlate with organ specificity and dose– response of tumor formation. *Carcinogenesis*, 19 (1): 187–193.

20. Testai E, Vittozzi L (2014) Biochemical alterations elicited in rat liver microsomes by oxidation and reduction products of Trichloromethane metabolism. *Chemico-Biological Interactions*, 59:157 171.