



Carbon Tetrachloride

Toxicological Overview

Key Points

Kinetics and metabolism

- Carbon tetrachloride is readily absorbed after ingestion and inhalation, but more slowly through the skin
- Carbon tetrachloride is metabolised by cytochrome P450 enzymes which results in the formation of reactive potentially toxic metabolites
- A substantial proportion of absorbed carbon tetrachloride is eliminated unchanged in exhaled air

Health effects of acute exposure

- Acute inhalation or ingestion may cause nausea, vomiting, headache, dizziness, abdominal pain, diarrhoea, and difficulty breathing
- Acute inhalation or ingestion can also cause liver and kidney damage which in severe cases may lead to coma and death
- Dermal exposure may cause irritation and contact with undiluted carbon tetrachloride may cause a burning sensation and redness
- Ocular exposure may cause irritation

Health effects of chronic exposure

- Chronic inhalation or ingestion may cause similar effects to acute exposure
- Carbon tetrachloride is considered to be a possible human carcinogen

Toxicological Overview

Summary of Health Effects

Carbon tetrachloride is readily absorbed after ingestion and inhalation, but more slowly through the skin [1, 2].

Acute exposure to carbon tetrachloride can also cause central nervous system (CNS) depression as well as gastrointestinal and neurological effects such as nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, in-coordination, impairment of speech, confusion, anaesthesia, fatigue and dyspnoea [2, 3].

The liver and kidney are the major target organs for toxicity following acute inhalation or ingestion exposure to carbon tetrachloride [2, 3]. Liver damage can occur after 24 hours and in serious cases this can result in painful swollen liver, ascites, haemorrhages, hepatic coma and death [1, 2]. Kidney damage with an 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 [1]

Acute ocular exposure or skin contact can cause irritation of the eyes and skin [4]. Direct skin contact with undiluted carbon tetrachloride 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 [1].

Chronic inhalation may result in liver and kidney toxicity and neurological effects from depression of the central nervous system [1]. 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 [1].

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of carbon tetrachloride in humans. However, based on evidence in animal studies, IARC has concluded overall that carbon tetrachloride is possibly carcinogenic to humans (Group 2B) [6]. 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 [2, 5].

Carbon tetrachloride does not have any significant mutagenic properties [2, 5].

Data from animal studies indicate that carbon tetrachloride does not have any adverse effects on development at dose levels below those producing toxicity to the maternal animals [2, 5]. There are no adequate reproductive toxicity studies on carbon tetrachloride [5], but limited data has suggested that exposure to relatively high concentrations of carbon tetrachloride may impair fertility [1].

Kinetics and Metabolism

Carbon tetrachloride is readily absorbed after ingestion and inhalation, but more slowly through the skin [1, 2].

Following systemic absorption in animals, carbon tetrachloride is distributed to the major organs with highest concentrations measured in the fat, liver, brain, spinal cord, blood, bone marrow, adrenals and kidney. No studies on distribution were identified in humans [1].

Absorbed carbon tetrachloride can be metabolised by cytochrome P450 enzymes leading to the formation of the reactive trichloromethyl radical. This undergoes oxidative biotransformation to form the highly reactive trichloromethylperoxy radical which may decompose to form phosgene. Phosgene may be detoxified by reacting with water, to form carbon dioxide, or with glutathione or cysteine [1, 2].

Few data on the elimination of carbon tetrachloride in humans were identified [1]. Animal studies have shown that around 34-75% of absorbed carbon tetrachloride leaves the body in expired air, 20-60% leaves the body in faeces and relatively low amounts in the urine [1]. Animal studies have also suggested that it may take weeks for the remainder of the chemical to be eliminated, especially the fraction that has entered body fat [1].

Sources and Route of Human Exposure

People can be exposed to carbon tetrachloride from the air, drinking water, foodstuffs and from soil due to very low background levels [1, 2]. Exposures higher than background levels can occur near certain industrial sites where carbon tetrachloride is still used or there has been previous industrial contamination [1].

The main route of exposure to carbon tetrachloride is by inhalation or ingestion [2].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Acute exposure to carbon tetrachloride via any route of exposure can cause gastrointestinal and neurological effects in the first 24 hours, such as nausea, vomiting, diarrhoea, headache, dizziness, depression of conscious level and dyspnoea.

The liver and kidney are the major target organs for toxicity following acute inhalation or ingestion exposure to carbon tetrachloride [2, 3]. Liver damage can occur after 24 hours and in serious cases this can result in painful swollen liver, haemorrhage, hepatic coma and death [1, 2]. Kidney damage with an 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 [1].

Adverse effects on the liver can be markedly increased by the co-ingestion of alcohol [4], due to hepatic enzyme induction which results in increased production of toxic metabolites [1].

Inhalation

Inhalation of carbon tetrachloride may cause rapid depression of the central nervous system, leading to headache, giddiness, weakness, lethargy and stupor. No effects were reported in healthy volunteers following exposure to 50 ppm for 70 minutes or 10 ppm for 3 hours. A review of a number of reports of carbon tetrachloride intoxication led to the conclusion that no effects were noted up to 80 ppm for 3-4 hours. At higher concentrations nausea, vomiting, headache, and more severe CNS effects have been noted [2]. Headache and dizziness was also reported following exposure to 250 ppm for 15 minutes [1, 2, 7].

Carbon tetrachloride is hepatotoxic, the principle features include swollen and tender liver, elevated serum enzyme levels and jaundice as well as marked liver necrosis with steatosis. It is also nephrotoxic and nephritis and nephrosis may occur. Few quantitative data are available regarding the hepatotoxicity and nephrotoxicity of carbon tetrachloride. Exposure to 200 ppm for up to 3 hours has been reported to result in changes in clinical chemistry, suggestive of hepatotoxicity and also renal toxicity (proteinuria). Exposure to 250 ppm for 15 minutes resulted in death of an alcoholic, but other men exposed to the same level for 4 hours showed no clinical effects apart from a slight headache [1].

The acute toxic effects following inhalation of carbon tetrachloride are summarised in table 1.

Table 1. Toxic effects following acute exposure to carbon tetrachloride by inhalation.

Dose (ppm)	Signs and symptoms
10-80	No adverse effects after 3-4 hours
100	Nausea, gastrointestinal irritation, headache, dizziness and depression and dyspnoea
>200	Drowsiness, nausea, vomiting, tachycardia, tachypnoea, liver and kidney toxicity

Pulmonary oedema commonly occurs in humans exposed to lethal concentrations of carbon tetrachloride, but this appears to be secondary to the renal toxicity [1].

Ingestion

Ingestion of carbon tetrachloride can lead to hepatotoxicity. Single doses of approximately 90-180 mg kg⁻¹ bw caused mild hepatotoxicity (fatty liver) and ingestion of 670 mg/kg resulted in marked hepatotoxicity (severe necrosis) and also nephrotoxicity [1, 4].

Ingestion of carbon tetrachloride can also result in CNS effects, with drowsiness being noted after ingestion of 300 mg kg⁻¹. No CNS effects were seen at lower concentrations, with only nausea being reported following ingestion of 100 mg kg⁻¹ [1, 2, 4].

There is considerable variation in the doses found to cause death, with alcohol ingestion leading to markedly increased rates. In most cases, lethality has been due to estimated doses of 50-150 ml, but death has occurred after ingestion of 2-15 ml or 40 mg kg⁻¹ [1].

Dermal / ocular exposure

Carbon tetrachloride can cause irritation of the eyes and skin [4]. Direct skin contact with undiluted carbon tetrachloride has been reported to produce a mild burning sensation with mild redness [1]. Some individuals may be hypersensitive and develop marked swelling, itching and blisters following skin contact [1].

Acute toxicity of carbon tetrachloride is reported to be independent of the route of exposure [2-4], therefore dermal exposure to relatively high concentrations may cause similar effects as for oral and inhalation exposure.

Delayed effects following an acute exposure

Acute exposure to carbon tetrachloride via any route can cause liver damage after 24 hours or more, renal dysfunction may occur in 1-6 days but may, in many cases, only be apparent two to three weeks after exposure [1, 3].

Animal and In-Vitro Data

General toxicity

The liver is the most sensitive target organ following inhalation or ingestion of carbon tetrachloride in animals [1]. Adverse effects on the kidney, central nervous system and lungs also occur [2, 7].

Inhalation

In animals, the hepatic effects of inhalation exposure to carbon tetrachloride are much the same as in humans, such as elevated serum enzyme levels, steatosis, and centrilobular necrosis progressing to fibrosis [1].

Changes in serum enzyme levels indicative of liver damage were seen in rats following 4-hour exposure to 530 ppm or above. Liver necrosis has been reported following exposure to 4800 ppm (species unknown). Signs of central nervous system depression, such as lack of coordination, breathing difficulties and unconsciousness have also been observed in animals exposed to approximately 7000 to 10500 ppm. In another study, rats exposed to <4600 ppm

for up to 8 hours showed signs of drowsiness; 7300 ppm caused uncoordination and unconsciousness occurred at 12000 and 19000 ppm [7].

Ingestion

Adverse effects on the liver have been reported to be the major effect in rats following acute ingestion of carbon tetrachloride. Rats given 20 mg kg⁻¹ bw showed histopathological evidence of liver toxicity and centrilobular vacuolisation. An increase in liver fat and liver weight was observed after administration of 39.9 mg kg⁻¹ and liver cell necrosis was reported after ingestion of 80 mg kg⁻¹ bw [1, 2]. In mice, a single oral dose of 32 mg kg⁻¹ caused liver necrosis [2].

Morphological changes and necrosis of Clara cells in the lungs of both mice and rats have been reported after an acute oral dose of approximately 4000 mg kg⁻¹ [2].

Dermal / ocular exposure

The irritant effects on carbon tetrachloride on skin have been investigated in guinea-pigs. Carbon tetrachloride (513 mg cm⁻²) was applied under an occlusive dressing for 15 minutes to 16 hours. Degenerative damage to the epidermal cells and oedema was reported within 15 minutes, which increased in severity over the following few hours. Liver necrosis was seen approximately 16 hours after the initial contact [1, 2].

Application of 0.1 ml into the eyes of rabbits in a Draize test produced mild irritation. The response was evident at 24, 48 and 72 hours after exposure and recovery was complete after 14 days [2, 7].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

The main adverse health effects associated with chronic inhalation of carbon tetrachloride are liver and kidney damage and depression of the central nervous system [1].

Occupational exposure to carbon tetrachloride at concentrations of 20-80 ppm for 2-3 months caused effects such as drowsiness, headache, dizziness, nausea, vomiting, loss of appetite and diarrhoea,. Some studies have also reported CNS effects at concentrations as low as 10 ppm [5, 7]. Early indications of liver injury, such as jaundice, liver tenderness and altered blood chemistry have been seen in employees exposed to 10-200 ppm for several months to many years [7].

Ingestion

No studies were identified regarding the toxicity of carbon tetrachloride in humans following chronic ingestion.

Dermal / ocular exposure

Few studies were identified regarding the toxicity of carbon tetrachloride in humans following chronic dermal or ocular exposure. No increase in skin fold thickness or erythema was detected when carbon tetrachloride was applied daily for 10 days to the volar surface of the skin on the forearms of a healthy individual. However, as no occlusion was used it is likely that the carbon tetrachloride evaporated [2].

Genotoxicity

No studies were identified regarding genotoxic effects of carbon tetrachloride in humans.

Carcinogenicity

IARC noted that the risk of cancer from carbon tetrachloride has been examined in occupational studies and that associations with non-Hodgkin lymphoma have been suggested. However the studies had limitations in determining whether the exposure was specifically to carbon tetrachloride and the associations were not statistically significant. IARC concluded that there is inadequate evidence for the carcinogenicity of carbon tetrachloride in humans. However, based on evidence in animal studies, IARC has concluded overall that carbon tetrachloride is possibly carcinogenic to humans (Group 2B) [6].

A number of epidemiological studies have investigated the potential association between carbon tetrachloride exposure and the incidence of cancer. However, due to the co-exposure to other chemicals and a lack of data on the exposure to carbon tetrachloride any carcinogenic effects arising from exposure to this chemical cannot be reliably identified [2].

Reproductive and developmental toxicity

No human reproductive toxicity studies were identified. A few epidemiological studies conducted in New Jersey have suggested associations between very low levels of carbon tetrachloride in drinking water and low birth weight. However, the studies had methodological

limitations [1]. A questionnaire-based study conducted in West Germany with 3,418 pregnant women found no association between a probable occupational exposure to carbon tetrachloride and the birth of infants who were small for their gestational age [1].

Animal and In-Vitro Data

Inhalation

The liver and the kidneys are the principle target organs following chronic inhalation to carbon tetrachloride in animals. The predominant signs of hepatotoxicity include steatosis, elevated serum enzyme levels and centrilobular necrosis [1, 2].

In a subchronic (13 week) study rats and mice were exposed to up to 800 ppm (5192 mg m³) for 6 hours per day, 5 days per week. In both species microscopic changes were seen in the liver at autopsy at the lowest dose level (10 ppm; 64 mg/m³). In rats, effects on the blood were seen at 30 ppm (192 mg m³) and kidney damage at 270 ppm (1731 mg m³) and above. In mice haematological effects were only seen at the top dose [8].

A 2-year inhalation study with rats exposed to approximately 0, 5, 25 or 125 ppm for 6 hours per day, 5 days per week reported decreases in body weight, changes in haematology and blood biochemistry including markers of hepatotoxicity and nephrotoxicity at 25 ppm and a significant decrease in survival at 125 ppm, predominantly due to liver tumours and/or chronic nephropathy. In a parallel study, mice exposed to the same concentrations had a significantly decreased survival rate, mainly due to liver tumours, when exposed to 25 or 125 ppm. A decrease in body weight gain, changes in haematology and blood biochemistry were also observed at 25 ppm [2].

Ingestion

The liver and kidneys are also target organs for chronic oral exposure to carbon tetrachloride in animal studies [1, 2].

Rats given carbon tetrachloride via gavage 5 days per week for 12 weeks had an increase in serum liver enzymes and mild liver damage (vacuolation) at 10 mg kg⁻¹ bw day⁻¹ and cirrhosis was observed at 33 mg kg⁻¹ bw day⁻¹. No effects were seen at 1 mg kg⁻¹ bw day⁻¹ [7, 8].

In mice given carbon tetrachloride in corn oil 5 days a week for 90 days, changes in serum levels of liver enzymes were seen at 12 mg kg⁻¹ bw day⁻¹ and above, together with histopathological evidence of liver damage (fatty infiltration and necrosis). Similar to the previous study, no effects were seen at 1.2 mg kg⁻¹ bw day⁻¹ [8].

Oral exposure has also been associated with suppression of the immune system [1, 2]. One study with mice given 50 mg kg⁻¹ bw day⁻¹ of carbon tetrachloride for 14 days (sufficient for liver toxicity) showed a reduced T-cell response to sheep red blood cells, and at 500 mg kg⁻¹ bw day⁻¹ a reduction in the absolute numbers of CD4⁺ and CD8⁻ T-cells per spleen was reported [1, 2].

Genotoxicity

Carbon tetrachloride was not mutagenic in, but did induce DNA damage and mutations in *Escherichia coli* [2]. The results of *in-vivo* genotoxicity tests suggest that genotoxic effects only occur at doses that produce cytotoxicity [1]. Although carbon tetrachloride has produced

some effects on genetic material, such as in mammalian cells, the effects are considered to be secondary to carbon tetrachloride toxicity and not from direct interaction with DNA [2, 5]. Thus, overall carbon tetrachloride is not regarded as genotoxic [2, 5].

Carbon tetrachloride has been extensively investigated in the *Salmonella typhimurium in-vitro* assay for gene mutation and negative results have been consistently obtained. Negative results have also been obtained in assays for chromosome damage in hamster ovary cells, rat liver cells and human lymphocytes. DNA damage has been reported in *E. Coli* and it has been shown to induce intrachromosomal and mitotic recombination in yeast.

When investigated *in-vivo*, carbon tetrachloride did not induce chromosome aberrations in bone marrow of mice or liver of rats. Nor did it induce micronuclei or unscheduled DNA synthesis in the liver of rats and mice. DNA binding has been reported in the liver of rats, mice and hamsters [2, 8].

It has been suggested that the positive effects on carbon tetrachloride in a few assays are explicable in terms of damage to nuclear protein or to DNA damage induced as a secondary effect to general toxicity [2, 8].

The weight of evidence indicates that carbon tetrachloride does not have any significant genotoxic potential.

Carcinogenicity

Liver tumours have been produced in rats, mice and hamsters following carbon tetrachloride exposure via oral, inhalation and subcutaneous administration [2, 5]. The doses inducing liver tumours were higher than those causing liver cell toxicity, and therefore are considered to arise secondary to toxic effects on the liver [2, 5]. IARC also noted one inhalation study in mice that reported an increased incidence of a rare tumour in the adrenal glands [6]. Overall, IARC concluded that there is sufficient evidence for the carcinogenicity of carbon tetrachloride in experimental animals [6].

Reproductive and developmental toxicity

There are a number of studies that have investigated the developmental toxicity of carbon tetrachloride in pregnant rats, using the oral or inhalation route. There is also one study in mice using the oral route. In all cases adverse effects (limited to fetotoxicity rather than gross malformations) were seen only at dose levels associated with maternal toxicity. It was concluded that the available data suggest that the fetus is not preferentially sensitive to carbon tetrachloride and the effects on fetal development and post-natal survival are likely to be secondary to maternal toxicity [2, 8].

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