



Carbon tetrachloride

General Information

Key Points

Fire

- Non flammable
- Reacts with some metals such as aluminium, magnesium and zinc causing fire and explosion hazard
- Emits irritating or toxic fumes including chlorine, hydrogen chloride and phosgene, when heated to decomposition
- In the event of a fire involving carbon tetrachloride, use fine water spray and normal fire kit with breathing apparatus

Health

- Toxic by inhalation, ingestion and dermal exposure
- Inhalation and ingestion may cause a reduced conscious level, sickness, headache, dizziness, vomiting, stomach pain, diarrhoea and difficulties with breathing
- Ingestion and inhalation may also cause liver and kidney damage, which in severe cases can lead to coma and death
- Skin or eye contact can cause irritation
- Carbon tetrachloride possibly causes cancer in humans

Environment

- Dangerous for the environment
- Inform Environment Agency of substantial incident

Background

Carbon tetrachloride is a clear, colourless, volatile liquid with a sweet odour.

Carbon tetrachloride is a manufactured chemical and is not expected to occur naturally in the environment. It can be present in low amounts in the air, drinking water, soil, ground water and the sea.

In the past, carbon tetrachloride was produced in large quantities to make refrigerant fluid and propellants for aerosol cans. It was also used in the past as a cleaning fluid, metal degreasing agent and solvent in industry, in dry cleaning facilities as well as a fumigant to kill insects in grain. However, since 2002 the supply and use of carbon tetrachloride in consumer products or as a fumigant has been banned due to it depleting the ozone layer. At present, only industrial uses remain.



The general population may be exposed to small amounts of carbon tetrachloride in the air, drinking water, food and soil, due to releases to the environment.

Occupational exposure may occur during the production and use of carbon tetrachloride.

Breathing vapours or drinking water contaminated with carbon tetrachloride for a short period of time can cause stomach pain, diarrhoea, sickness and difficulty in breathing. Other effects include headache, dizziness, difficulties with coordination,

confusion and tiredness. Liver and kidney damage can also occur, which, in severe cases, can lead to coma and death. Liver damage may occur 24 hours or more after exposure, but kidney damage may only be apparent a few weeks later.

Skin contact with carbon tetrachloride may cause irritation, a burning sensation and redness. Eye contact may also cause irritation.



Breathing or drinking carbon tetrachloride over longer periods of time may cause similar effects to a single exposure.

Children exposed to carbon tetrachloride are expected to show similar effects to those seen in adults, although the effects may be more severe. Exposure during pregnancy is not expected to cause damage to the unborn child at doses that do not affect the mother.

The International Agency for Research on Cancer (IARC) has classified carbon tetrachloride as being possibly carcinogenic to humans. Carbon tetrachloride is not considered to be mutagenic.

Frequently Asked Questions

What is carbon tetrachloride?

Carbon tetrachloride is a clear, colourless non-flammable liquid with a sweet odour. The main use of carbon tetrachloride has been in the production of chlorofluorocarbons, which were mainly used as refrigerants, aerosol propellants, and foam blowing agents, solvents and for dry cleaning. Under EC regulations aimed at preventing damage to the ozone layer the supply and use of carbon tetrachloride was banned from 2002.

How does carbon tetrachloride get into the environment?

Carbon tetrachloride may be released into the environment due to its use by industry.

How will I be exposed to carbon tetrachloride?

People may be exposed to carbon tetrachloride by breathing contaminated air, drinking contaminated water or by eating food contaminated with carbon tetrachloride.

If there is carbon tetrachloride in the environment will I have any adverse health effects?

The presence of carbon tetrachloride in the environment does not always lead to exposure. Clearly, in order for it to cause any adverse health effects you must come into contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact. Following exposure to any chemical, the adverse health effects you may encounter depend on several factors, including the amount to which you are exposed (dose), the way you are exposed, the duration of exposure, the form of the chemical and if you were exposed to any other chemicals.

Breathing carbon tetrachloride vapours or drinking material containing may cause sickness, headache, dizziness, and difficulties in breathing. Liver and kidney damage can also occur. Severe exposures can result in coma and death. Skin or eye contact may cause irritation.

Can carbon tetrachloride cause cancer?

Carbon tetrachloride has been classified by the International Agency for Research on Cancer as possibly causing cancer in humans. Prolonged exposure to high levels such as those sufficient to cause liver damage is believed to be necessary to cause cancer.

Does carbon tetrachloride affect children or damage the unborn child?

Children will be affected by carbon tetrachloride in the same way as adults, although children may be more sensitive to the effects due to their smaller size. There is no evidence to suggest that carbon tetrachloride can affect the health of the unborn child at amounts that do not affect the mother.

What should I do if I am exposed to carbon tetrachloride?

It is very unlikely that the general population will be exposed to a level of carbon tetrachloride high enough to cause adverse health effects.

This document has been created by the PHE Centre for Radiation, Chemical and Environmental Hazards. The information contained in this document is correct at the time of its publication. .



Carbon Tetrachloride

Incident management

Key Points

Fire

- Non flammable
- Reacts with some metals such as aluminium, magnesium and zinc causing fire and explosion hazard
- Emits irritating or toxic fumes including chlorine, hydrogen chloride and phosgene, when heated to decomposition
- In the event of a fire involving carbon tetrachloride, use fine water spray and normal fire kit with breathing apparatus

Health

- Toxic via all routes of exposure Ingestion, inhalation or prolonged skin contact can cause systemic effects including headache, dizziness, ataxia, confusion, drowsiness, convulsions and coma. Liver and kidney effects, cardiovascular arrhythmias, hypotension and pulmonary oedema may also occur.
- Central nervous system depression will be increased by alcohol and sedative drugs
- Dermal contact can result in pain, redness and swelling
- Ocular exposure may cause pain and minimal injury to the conjunctiva

Environment

- Chronic hazard to the aquatic environment
- Inform Environment Agency of substantial incidents

Prepared by the Toxicology Department
CRCE, PHE
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Hazard Identification

Standard (UK) Dangerous Goods Emergency Action Codes^(a)

UN		1846	Carbon tetrachloride	
EAC		2Z	Use fine water spray. Wear normal fire kit in combination with breathing apparatus.* Spillages and decontamination run-off should be prevented from entering drains and watercourses.	
APP		-		
Hazards	Class	6.1	Toxic substances	
	Sub risks	-		
HIN		60	Toxic or slightly toxic substance	

UN – United Nations number; EAC – Emergency Action Code; APP – Additional Personal Protection; HIN - Hazard Identification Number

*Normal fire fighting clothing i.e. fire kit (BS EN 469), gloves (BS EN 659) and boots (HO specification A29 and A30) in combination with self-contained open circuit positive pressure compressed air breathing apparatus (BS EN 137).

^a Dangerous Goods Emergency Action Code List 2011. National Chemical Emergency Centre (NCEC). The Stationary Office, London.

Chemical Hazard Information and Packaging for Supply Classification^(a)

Classification	Carc. Cat 3	Category 3 carcinogen	
	T	Toxic	
	N	Dangerous for the environment	
Risk phrases	R23/24/25	Toxic by inhalation, in contact with skin and if swallowed	
	R40	Limited evidence of a carcinogenic effect	
	R48/23	Toxic: danger of serious damage to health by prolonged exposure through inhalation	
	R59	Dangerous for the ozone layer	
	R52/53	Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment	
Safety phrases	S1/2	Keep locked up and out the reach of children	
	S23	Do not breathe fumes/vapour/spray	
	S36/37	Wear suitable protective clothing and gloves	
	S45	In case of accident, or if you feel unwell seek medical advice immediately (show the label where possible)	
	S59	Refer to manufactures/supplier for information on recovery/recycling	
	S61	Avoid release to the environment. Refer to special instructions/safety data sheet	

Specific Concentration Limits

Concentration	Classification
C ≥ 1%	T; R23/24/25
0.2% ≤ C < 1%	Xn; R20/21/22
C ≥ 1%	T; R48/23
0.2% ≤ C < 1%	Xn; R48/20

^a Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures- Table 3.2.

<http://esis.jrc.ec.europa.eu/index.php?PGM=cla> (accessed 02/2013)

Globally Harmonised System of Classification and Labelling of Chemicals (GHS)^(a)*

Hazard Class and Category	Carc. 2	Carcinogen, category 2	
	Acute Tox. 3	Acute toxicity (oral, dermal, inhalation), category 3	
	STOT RE 1	Specific target organ systemic toxicity following repeated exposure, category 1	
	Aquatic Chronic 3	Chronic hazard to the aquatic environment, category 3	
	Ozone 1	Hazardous to the ozone layer	
Hazard Statement	H351	Suspected of causing cancer	
	H331	Toxic if inhaled	
	H311	Toxic in contact with skin	
	H301	Toxic if swallowed	
	H372	Causes damage to organs through prolonged or repeated exposure	
	H412	Harmful to aquatic life with long lasting effects.	
	H420	Harms public health and the environment by destroying ozone in the upper atmosphere	

^a Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures- Table 3.1.
<http://esis.jrc.ec.europa.eu/index.php?PGM=cla> (accessed 02/2013)

CARBON TETRACHLORIDE – INCIDENT MANAGEMENT

Suppl. Hazard Statement	EUH059	Hazardous to the ozone layer
Signal Words	DANGER	

Specific concentration limits

Concentration	Hazard Class and Category	Hazard Statement	
$C \geq 1 \%$	STOT RE 1	H372	Causes damage to organs through prolonged or repeated exposure
$0.2 \% \leq C < 1 \%$	STOT RE 2	H373	May cause damage to organs through prolonged or repeated exposure

* Implemented in the EU on 20 January 2009.

Physicochemical Properties

CAS number	56-23-5
Molecular weight	153.8
Empirical formula	CCl ₄
Common synonyms	Tetrachloromethane; Perchloromethane; Necatorina; Benzinoform; Tetrachlorocarbon
State at room temperature	Colourless liquid
Volatility	Vapour pressure 12.2 KPa (91.3 mm Hg) at 20°C
Specific gravity	1.59 at 20°C (water = 1)
Flammability	Non combustible
Lower explosive limit	Data not available
Upper explosive limit	Data not available
Water solubility	Poor solubility in water, 0.1g 100 ml ⁻¹ at 20°C
Reactivity	Reacts with some metals such as aluminium, magnesium, zinc causing fire and explosion hazard
Reaction or degradation products	Gives off irritating or toxic fumes including chlorine, hydrogen chloride and phosgene, on contact with hot surfaces or flames
Odour	Characteristic odour
Structure	$ \begin{array}{c} \text{Cl} \\ \\ \text{Cl} - \text{C} - \text{Cl} \\ \\ \text{Cl} \end{array} $

References^(a,b,c)

^a International Programme on Chemical Safety (IPCS): Carbon tetrachloride. International Chemical Safety Card: 0024. 2000, WHO: Geneva.

^b The Merck Index (14th Edition). Entry 1816: Carbon tetrachloride, 2006

^c The Dictionary of Substances and their Effects. Ed. S Gangolli. Second Edition, Volume 7, 1999.

Threshold Toxicity Values

EXPOSURE VIA INHALATION			
ppm	mg m⁻³	SIGNS AND SYMPTOMS	REFERENCES
10 - 80	64 – 513	No adverse effects observed following exposure for 3 – 4 hours	a
> 80	> 472	Nausea, vomiting, headache, tachycardia, tachypnoea, drowsiness, dizziness, unconsciousness, kidney and liver injury and death (10 to 30 minute exposure)	a

^a International Programme on Chemical Safety (IPCS). Carbon tetrachloride. Environmental Health Criteria 208. 1999, WHO: Geneva.

Published Emergency Response Guidelines

Emergency Response Planning Guideline (ERPG) Values^(a)

	Listed value (ppm)	Calculated value (mg m ⁻³)
ERPG-1*	20	125.81
ERPG-2**	100	629.04
ERPG-3***	750	4717.79

* Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odour.

** Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action.

*** Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing life-threatening health effects.

Acute Exposure Guideline Levels (AEGLs)^(b)**Interim values**

	ppm				
	10 min	30 min	60 min	4 hr	8 hr
AEGL-1[†]	58	58	44	25	19
AEGL-2^{††}	380	250	190	100	81
AEGL-3^{†††}	1100	680	520	300	220

[†] The level of the chemical in air at or above which the general population could experience notable discomfort.

^{††} The level of the chemical in air at or above which there may be irreversible or other serious long-lasting effects or impaired ability to escape.

^{†††} The level of the chemical in air at or above which the general population could experience life-threatening health effects or death.

^a American Industrial Hygiene Association (AIHA). 2011 Emergency Response Planning Guideline Values.

http://www.aiha.org/insideaiha/GuidelineDevelopment/ERPG/Documents/2011erpgweelhandbook_table-only.pdf (accessed 01/2013).

^b U.S. Environmental Protection Agency. Acute Exposure Guideline Levels, <http://www.epa.gov/oppt/aegl/pubs/chemlist.htm> (accessed 01/2013).

Exposure Standards, Guidelines or Regulations

Occupational Standards

WEL ^(a)	LTEL(8 hour reference period): 2 ppm (13 mg m ⁻³)
	STEL(15 min reference period): No guideline value specified

Public Health Guidelines

DRINKING WATER QUALITY GUIDELINE ^(b)	4 µg L ⁻¹
AIR QUALITY GUIDELINE	No guideline value specified
SOIL GUIDELINE VALUE AND HEALTH CRITERIA VALUES	Data not available
HEALTH CRITERIA VALUES ^(c)	Tolerable Daily Intake _{oral} 1.42 µg kg ⁻¹ bw day ⁻¹
	Mean Daily Intake _{oral} 0.2 µg day ⁻¹
	Tolerable Daily Soil Intake _{oral} Adult: 1.4 µg kg ⁻¹ bw day ⁻¹ Child: 1.4 µg kg ⁻¹ bw day ⁻¹
	Tolerable Daily Intake _{inhalation} 3.26 µg kg ⁻¹ bw day ⁻¹
	Mean Daily Intake _{inhalation} 50 µg day ⁻¹
	Tolerable Daily Soil Intake _{inhalation} Adult: 2.5 µg kg ⁻¹ bw day ⁻¹ Child: 2.0 µg kg ⁻¹ bw day ⁻¹

WEL – Workplace exposure limit; LTEL - Long-term exposure limit; STEL – Short-term exposure limit

^a EH40/2005 Workplace Exposure Limits (second edition, published 2011).
<http://www.hse.gov.uk/pubns/priced/eh40.pdf> (accessed 01/2013)

^b Guidelines for Drinking-Water Quality, Fourth Edition. WHO, Geneva. 2011.

^c Department for Environment, food and Rural Affairs and the Environment Agency. Contaminants in soil: collection of toxicological data and intake values for humans. Carbon tetrachloride.2005

Health Effects

Major Route of Exposure^(a)

- Toxic by all routes of exposure

Immediate Signs or Symptoms of Acute Exposure^(a,b)

- Ingestion may cause nausea, vomiting, abdominal pain and diarrhoea.
- Systemic effects are possible following ingestion, inhalation and prolonged skin contact. Initial features reflect effects on the central nervous system and include headache, dizziness, ataxia, confusion and drowsiness or, in more severe cases, respiratory depression, convulsions and coma. Fever, hypotension and subconjunctival haemorrhage may be present. Cardiac arrhythmias, including ventricular fibrillation may cause sudden death and is due in part to carbon tetrachloride-induced sensitisation of the myocardium to catecholamines.
- Evidence of hepatic injury usually occurs some 2-4 days after exposure but may be observed as early as 24 hours. Jaundice, increased liver enzyme activity, prolonged INR, metabolic acidosis and liver failure may occur. Haemolysis may be present. Renal failure usually begins a few days after hepatic damage becomes manifest and reaches its peak in the second week. Oliguria may progress to anuria due to renal tubular necrosis. Pulmonary oedema may be related to renal failure or direct cardiotoxicity.
- CNS depression will be increased by alcohol and sedative drugs.
- Skin contact can result in pain, redness and swelling as well as contact dermatitis.
- Eye contact may cause pain and minimal injury to the conjunctiva...

TOXBASE - <http://www.toxbase.org> (accessed 02/2013)

^a TOXBASE: Carbon tetrachloride, 2009.

^b TOXBASE: Carbon tetrachloride, features and management 2009.

Decontamination and First Aid

Important Notes

- Ambulance staff, paramedics and emergency department staff treating chemically-contaminated casualties should be equipped with Department of Health approved, gas-tight (Respirex) decontamination suits based on EN466:1995, EN12941:1998 and prEN943-1:2001, where appropriate.
- Decontamination should be performed using local protocols in designated areas such as a decontamination cubicle with adequate ventilation.

Dermal Exposure^(a)

- Contaminated clothing should be removed, double bagged, sealed and stored safely.
- Decontaminate open wounds first and avoid contamination of unexposed skin.
- Any particulate matter adherent to skin should be removed and the patient washed with copious amounts of water under low pressure for at least 10 – 15 minutes or until pH of the skin is normal (pH of the skin is 4.5 – 6 although it may be closer to 7 in children, or after irrigation).
- **The earlier the irrigation begins, the greater the benefit.**
- Pay particular attention to mucous membranes, moist areas such as skin folds, fingernails and ears.
- For management of systemic effects see ingestion.

Ocular Exposure^(b)

- Remove patient from exposure.
- Remove contact lenses if present and immediately irrigate the affected eye thoroughly with water or 0.9% saline for at least 10 – 15 minutes. Continue until the conjunctival sac pH is normal (7.5 – 8.0). Retest after 20 minutes and use further irrigation if necessary.
- Any particles lodged in the conjunctival recesses should be removed.
- Patients with corneal damage and those whose symptoms do not resolve rapidly should be referred for **urgent** ophthalmological assessment.

Inhalation^(a)

- Maintain a clear airway and ensure adequate ventilation
- Good neurological outcome after cardiac arrest due to poisoning may occur following prolonged resuscitation.
- If appropriate remove the patient from the source of exposure and decontaminate patient (see dermal exposure).
- Administer 100% oxygen via high-flow mask, or endotracheal tube if needed.
- Monitor pulse, blood pressure, respiratory rate, oxygen saturation and cardiac rhythm for a minimum of 2 hours after exposure.
- Other measures as indicated by the patient's clinical condition.

Ingestion^(a)

- Maintain a clear airway and ensure adequate ventilation.

^a TOXBASE: Carbon tetrachloride, features and management, 2009.

^b TOXBASE: Chemicals Splashed or Sprayed into the Eyes, 2012.

- Good neurological outcome after cardiac arrest due to poisoning may occur following prolonged resuscitation.
- If appropriate remove the patient from the source of exposure and decontaminate patient (see dermal exposure).
- Administer oxygen if altered mental status or dyspnoea occurs.
- Monitor pulse, blood pressure, respiratory rate, oxygen saturation, conscious level and cardiac rhythm for a minimum of 6 hours.
- Other measures as indicated by the patient's clinical condition.

This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.



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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This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.