Trichloroethylene

Toxicological overview

Key Points

**Kinetics and metabolism**

- Trichloroethylene is readily absorbed following exposure by inhalation or ingestion and to some extent following skin contact
- Following absorption trichloroethylene is distributed throughout the body
- Trichloroethylene undergoes metabolism via an oxidative pathway
- The main metabolites are trichloroethanol, trichloroethanol-glucuronide and trichloroacetic acid
- Trichloroethylene is excreted unchanged via the lungs and as metabolites in the urine

**Health effects of acute exposure**

- Acute inhalation or ingestion of trichloroethylene can cause systemic effects such as excitement, headache, dizziness, nausea and vomiting followed by loss of coordination and drowsiness. Coma, cardiac arrhythmias and death may occur following substantial exposures
- Local effects following ingestion of trichloroethylene include dyspepsia, gastritis and diarrhoea
- Dermal exposure to trichloroethylene will cause irritation with erythema. Prolonged contact may cause severe irritation with blisters and burns

**Health effects of chronic exposure**

- Chronic inhalation of trichloroethylene can cause neurological, liver and kidney damage
- Chronic dermal exposure may cause dermatitis
- Trichloroethylene is classified as probably carcinogenic to humans
Toxicological Overview

Summary of Health Effects

Acute inhalation causes excitement, dizziness, headache, nausea and vomiting followed by loss of coordination and drowsiness. Exposure to high concentrations may cause respiratory tract irritation, coma, cardiac arrhythmias and death. Chronic inhalation exposure to trichloroethylene may cause neurological effects including fatigue, vertigo, dizziness, headaches and impaired ability to concentrate. Renal and hepatic effects may also occur.

Following acute ingestion of trichloroethylene, systemic effects as seen following inhalation may occur as well as dyspepsia, gastritis and diarrhoea.

Dermal exposure to trichloroethylene causes irritation with erythema. Prolonged contact may cause severe irritation with burns and blisters. Repeated contact with trichloroethylene may cause defatting dermatitis.

Liquid trichloroethylene splashed in the eye may cause superficial damage to the cornea. Ocular exposure to high concentrations of trichloroethylene vapour or the liquid itself can result in burns of the lids, conjunctiva and cornea.

The International Agency for Research on Cancer (IARC) has concluded that there is limited evidence in humans for the carcinogenicity of trichloroethylene, but sufficient evidence in experimental animals for the carcinogenicity of trichloroethylene. It is classified as probably carcinogenic to humans (Group 2A).

There is no evidence to suggest that trichloroethylene causes any significant reproductive or developmental toxicity in humans. There is limited data from experimental animal studies to suggest that maternal exposure to trichloroethylene may cause malformations in the offspring.
Kinetics and Metabolism

Trichloroethylene is extensively absorbed following exposure by inhalation or ingestion and to some extent following dermal contact [1, 2]. Approximately 37 - 64% of inhaled trichloroethylene is absorbed from the lungs [1].

Following absorption, trichloroethylene is distributed to all tissues and it readily crosses the placenta and the blood brain barrier [2, 3]. High concentrations of trichloroethylene accumulate in adipose tissue, due to its high lipid solubility [2].

Trichloroethylene is principally metabolised in the liver and to a much lesser degree, in other tissues including the lungs [4]. The main metabolic pathway is oxidation by cytochrome P-450 and the major metabolites are trichloroethanol, trichloroethanol-glucuronide and trichloroacetic acid [1, 2, 4].

Trichloroethylene is excreted unchanged via the lungs and in the form of metabolites in the urine [1, 2]. The half life for renal elimination of trichloroethanol and trichloroethanol-glucuronide is approximately 10 hours. The renal excretion of trichloroacetic acid is much slower because it binds tightly with plasma proteins, the half life for renal elimination is approximately 52 hours [1].

Alcohol can affect the metabolism of trichloroethylene. Human toxicity studies have reported an increase in trichloroethylene concentration in the blood and breath of male volunteers simultaneously exposed to ethanol and trichloroethylene. A reddening of the skin "degreaser's flush" was noted in the volunteers [1].

Sources and Route of Exposure

The main route of exposure to trichloroethylene is via inhalation. Ingestion and dermal contact are less common routes of exposure to trichloroethylene.

Trichloroethylene is released into the environment as a result of its use. The majority of trichloroethylene emitted enters the atmosphere unchanged [4]. Measured background concentrations of trichloroethylene ranged from 0.002 - 6 µg m⁻³ in rural air and ranged from 0.3 - 30 µg m⁻³ in urban and industrial air [3]. Trichloroethylene is not persistent in the atmosphere; degradation involves a reaction with hydroxyl radicals. The half life for degradation is approximately 7 days [1].

Trichloroethylene may be released into groundwater and surface water in industrial effluents. Groundwater contamination is caused by poor handling and improper disposal of trichloroethylene in landfills. Trichloroethylene surface water levels are generally low (<1 µg L⁻¹), groundwater levels may be higher (≤ 100 µg L⁻¹) due to limited volatilisation and biodegradation [5].

The general public may be exposed to very low levels of trichloroethylene through contaminated air, drinking water or food, which would not be expected to produce any significant health effects [1].

In an occupational setting, workers involved in the manufacture or use of trichloroethylene, particularly the degreasing industry, may be exposed to considerably higher levels than the general population [1, 2].
Health Effects of Acute / Single Exposure

Human Data

General toxicity

Central nervous system toxicity is the main effect following acute exposure to trichloroethylene. There are two main stages of trichloroethylene-induced central nervous system toxicity, the excitation phase and the depression phase. Symptoms of the early excitation phase include euphoria, restlessness, irritability, confusion, headache, nausea, vomiting and dizziness. The subsequent central nervous system depression phase is characterised by loss of co-ordination, drowsiness, coma, respiratory depression and in severe cases death [2].

Exposure to trichloroethylene may cause cardiac effects, including atrial and ventricular extrasystole, tachycardia and ventricular fibrillation. Sudden death due to cardiac arrest has been reported in subjects exposed to high levels of trichloroethylene, in the workplace or medically [2].

Inhalation

Inhalation of trichloroethylene can cause severe acute toxicity, as described in the general toxicity section. Headache, dizziness, nausea and vomiting are common following exposure to 270 - 540 mg m\(^{-3}\) trichloroethylene. Exposure to high concentrations of trichloroethylene vapour (810 - 3510 mg m\(^{-3}\)) can cause irritation to the respiratory tract. Light anaesthesia is induced following inhalation of 27,000 mg m\(^{-3}\), concentrations of up to 108,000 mg m\(^{-3}\) have been used to induce deeper anaesthesia [2].

Other adverse effects that have been reported include bronchial irritation, dyspnoea, pulmonary oedema, renal and hepatic damage [6].

Significant effects on performance in a number of visual-motor function tests have been reported in volunteers exposed to 1000 ppm (5400 mg m\(^{-3}\)) trichloroethylene for two hours. Signs of central nervous system depression (dizziness, light-headedness and lethargy) were also noted. Simultaneous ingestion of ethanol (0.5 ml kg\(^{-1}\)) was found to potentiate the effects of trichloroethylene and greater changes in performance in the visual-motor function tests were noted. When given alone, alcohol (0.5 ml kg\(^{-1}\)) did not have a significant effect [3].

Ingestion

Ingestion of trichloroethylene can cause severe acute toxicity, as described in the general toxicity section. Effects on the digestive system, including dyspepsia, dysphagia, gastritis and diarrhoea may occur following ingestion of trichloroethylene. Other symptoms that may include jaundice, somnolence, hallucinations, partial paralysis and circulatory collapse [2, 6].

In two case studies, men who ingested 350 and 500 ml of trichloroethylene developed ventricular arrhythmias that persisted for 3 days. In another study, a woman who accidentally ingested 20 ml of trichloroethylene suffered a myocardial infarction [1].

The lethal dose of trichloroethylene for adults is approximately 7 g kg\(^{-1}\), however death has been reported following ingestion of 50 ml (75 g) [2].
Dermal / ocular exposure

Dermal contact with trichloroethylene causes skin irritation with erythema and defatting dermatitis. If held in contact with the skin for example, by clothing or footwear, trichloroethylene may cause severe irritation with blisters and burns. Chemical burns have also been reported following exposure to concentrated trichloroethylene vapour [2, 6].

Liquid trichloroethylene splashed in the eye can cause irritation, pain and superficial damage to the cornea, however individuals generally make a complete recovery [2, 7]. In severe cases, exposure to high concentrations of trichloroethylene vapour or liquid can result in solvent-type burns of the lids, conjunctiva and cornea [7].

Animal and In-Vitro Data

General toxicity

Trichloroethylene causes low acute toxicity by inhalation, ingestion or dermal contact. The main signs of acute trichloroethylene toxicity in laboratory animals include central nervous system depression and adverse effects on the liver. Trichloroethylene is also a respiratory, skin and eye irritant [2, 3].

Inhalation

Inhalation LC50 values of approximately 26,000 ppm (140 g m⁻³) for a one-hour exposure and 12,000 ppm (65 g m⁻³) for a four-hour exposure, were reported in the rat. In the mouse, a four hour LC50 of 8450 ppm (45 g m⁻³) was observed [2].

Rats exposed to 54 and 540 mg m⁻³ trichloroethylene for 6 hours showed moderate increases in aspartate aminotransferase levels at 24, 48 and 72 hours following the exposure [2]. A number of studies have reported irritation of the eyes and respiratory tract, stupor, central nervous system depression and respiratory failure in rats following acute inhalation exposure to trichloroethylene. Pulmonary toxicity (vacuolation of Clara cells) was observed in mice exposed to concentrations of 108 mg m⁻³ (20 ppm) and above trichloroethylene for 6 hours. Rats exposed to 5400 mg m⁻³ (1000 ppm) trichloroethylene for 6 hours did not show signs of pulmonary toxicity [3].

Haematological, renal, immunological and neurological effects have also been reported in laboratory animals following acute inhalation exposure to trichloroethylene [1].

Ingestion

Acute oral LD₅₀ values of 2850 and 4920 mg kg⁻¹ body weight were reported in mice and rats, respectively. Minor hepatic effects were observed in rats during the 12 - 24 hour period following administration of 500 mg kg⁻¹ body weight of trichloroethylene [2]. Central nervous system depression and liver lesions were observed in mice following a single oral dose of 700 mg kg⁻¹ and above of trichloroethylene in olive oil. Effects on liver function, including transient increases in aspartate aminotransferase and alanine aminotransferase activity were noted in rabbits administered 1,700mg kg⁻¹ body weight of trichloroethylene [3].
Dermal / ocular exposure

Trichloroethylene (0.5 ml for 24 hours) applied to the shaven skin of rabbits, under an occlusive dressing, caused severe skin irritation. In guinea pigs, degenerative skin changes were noted 15 minutes after clipped skin was exposed to 1.0 ml trichloroethylene [2].

Instillation of 0.1 ml of trichloroethylene into rabbit eyes caused conjunctivitis and keratitis, with complete recovery within 2 weeks [2].
Health Effects of Chronic / Repeated Exposure

**Human Data**

**Inhalation**

Central nervous system toxicity is the main effect following chronic exposure to trichloroethylene. Occupational studies have consistently reported central nervous system effects, including fatigue, vertigo, dizziness, headaches and impaired ability to concentrate [1, 3]. Other neurological effects include mood swings, trigeminal neuropathy, cranial nerve VII damage, impaired acoustic-motor function and psychotic behaviour with impaired cognitive function [1].

Several occupational studies have reported liver effects, including liver enlargement and increases in serum liver enzyme levels in workers exposed to unspecified concentrations of trichloroethylene. Other studies have not reported any adverse effects on the liver [1, 3]. Altered renal function (increased N-acetyl-β-D-glucosaminidase and urinary proteins) has been noted in workers exposed to trichloroethylene and other chemicals in the workplace [1].

Occupational exposure to trichloroethylene at concentrations that caused neurological effects resulted in body weight loss in some workers [1].

**Ingestion**

There are limited data available regarding the health effects of chronic oral exposure to trichloroethylene.

A number of studies have attempted to assess the adverse health effects associated with the consumption of drinking water contaminated with trichloroethylene. Adverse health effects reported include cardiac, gastrointestinal, liver and immunological effects. Limitations of the studies include exposure to other contaminants; therefore the results should be considered inconclusive [1, 3].

**Dermal exposure**

Repeated contact with trichloroethylene may lead to the development of erythematous, exudative, vesicular, eczematous or exfoliative dermatitis, due to a defatting action on the skin [2].

**Genotoxicity**

There are limited data available regarding the genotoxic effects of exposure to trichloroethylene in humans. Data from cytogenetic studies using peripheral lymphocytes of workers exposed to trichloroethylene were inconclusive [1, 3, 8].

**Carcinogenicity**


The International Agency for Research on Cancer (IARC) considered three cohort studies to be particularly relevant for the evaluation of trichloroethylene. Two of the studies conducted in Sweden and Finland involved individuals who had been monitored for exposure to trichloroethylene by measurement of the metabolite trichloroacetic acid in urine. The third study, conducted in the United States, included workers, some of who were exposed to other solvents. The results from the three studies consistently indicated a significant excess relative risk for cancer of the liver and biliary tract combined. There was also a small non-significant excess in cancer of the liver. Results from the three studies indicated a modest excess relative risk for non-Hodgkin's lymphoma [8].

IARC concluded that there is limited evidence in humans for the carcinogenicity of trichloroethylene but that there is sufficient evidence in experimental animals for the carcinogenicity of trichloroethylene. It is classified as probably carcinogenic to humans (Group 2A) [8].

**Reproductive and developmental toxicity**

There are very limited data available regarding the reproductive and developmental toxicity of trichloroethylene in humans. Three Finish reproductive occupational studies did not report an increased incidence of spontaneous abortion or congenital malformations in the children of mothers exposed to trichloroethylene in the workplace. However, it is not possible to draw any definite conclusions from these studies, due to the poor characterisation of exposure levels [3].

**Animal and In-Vitro Data**

**Inhalation**

The effects of long-term and repeated inhalation exposure to trichloroethylene have been extensively investigated in laboratory animals [1-3, 8].

Effects on the liver (including increased liver weight, increased P450 activities, increased serum enzyme markers of liver dysfunction, fatty infiltration, centrilobular cell enlargement) have been reported in rats, mice, rabbits and guinea pigs continuously or repeatedly exposed to trichloroethylene at concentrations of 37 ppm (200 mg m⁻³) and above [3].

Biochemical indications of renal damage were observed in rats continuously exposed to 4320 mg m⁻³ trichloroethylene for 12 weeks [3, 9]. Kidney weights were increased in rats exposed to 400 ppm (2160 mg m⁻³) of trichloroethylene 7 hours day⁻¹, 5 days week⁻¹ for 8 months [3]. In a long term Inhalation study rats and mice were exposed to 0, 540, 1620 or 3240 mg m⁻³ trichloroethylene 7 hours day⁻¹, 5 days week⁻¹ for 104 (rats) or 78 (mice) weeks. Kidney tubule meganucleocytosis was reported in the male rats exposed to 1620 and 3240 mg m⁻³ trichloroethylene, but not in the female rats or mice of either sex [3, 9].

Pulmonary toxicity (vacuolation of Clara cells) was observed in mice exposed to 450 ppm (2430 mg m⁻³) trichloroethylene 6 hours day⁻¹, 5 days week⁻¹ for 2 weeks [1, 3].

Several studies have reported ototoxicity (elevated auditory brainstem response thresholds, hearing loss and a focal loss of hair cells in the cochlea) in rats chronically or repeatedly exposed to very high trichloroethylene concentrations mainly 2500 ppm (13500 mg m⁻³) and above. Neurological effects including EEG abnormalities and behavioural and sleep changes have been observed in trichloroethylene long-term and repeated exposure studies [1, 3].
**Ingestion**

The main toxic effects which have been observed following long-term oral exposure of laboratory animals to trichloroethylene are effects on the liver and kidney.

Toxic nephrosis was reported in F344/N rats and B6C3F1 mice administered trichloroethylene in corn oil by gavage (doses: 500 and 1000 mg kg\(^{-1}\) bw for rats and 1000 mg kg\(^{-1}\) bw for mice) 5 days per week for 103 weeks [2].

In a long term exposure study CD-1 mice were administered trichloroethylene in drinking-water (1.0, 2.5 or 5.0 g L\(^{-1}\)) for 4 - 6 months. A significant reduction in body weight (males and females at 5.0 g L\(^{-1}\)), enlarged liver (males at all doses and females at 5.0 g L\(^{-1}\)) and increased kidney weight (males and females at 5.0 g L\(^{-1}\)) were observed [2].

Increased liver weights were reported in rats administered trichloroethylene by gavage 100 mg kg\(^{-1}\) bw day\(^{-1}\) 5 days week\(^{-1}\), for 6 weeks and 50 mg kg\(^{-1}\) bw day\(^{-1}\) administered by gavage for 14 days. Liver weights were not increased in mice administered trichloroethylene in drinking water (18 mg kg\(^{-1}\) bw day\(^{-1}\) ) for 6 months. Other liver effects noted in laboratory animals exposed to trichloroethylene include increases in serum levels of liver enzymes, necrosis and cell hypertrophy [9].

**Genotoxicity**

The genotoxic potential of trichloroethylene has been tested in several in-vitro systems. However, in several studies no conclusions could be drawn because inadequate information was provided regarding the purity of the test material or the presence of mutagenic stabilisers. Pure trichloroethylene, when tested in the vapour phase, induced gene mutations in *Salmonella typhimurium* in the presence of a metabolic activation system. Trichloroethylene has been reported to bind to DNA in vitro, following metabolic activation [2].

Inconsistent results have been reported in in-vivo bone marrow assays for clastogenicity [8, 9]. Negative results were obtained in liver unscheduled DNA synthesis assays in mice and rats exposed to pure or unspecified purity trichloroethylene. Micronuclei were not induced in mice spermatocytes and trichloroethylene did not induce dominant lethal mutation in mice in vivo [8, 10].

The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) have examined the genotoxicity data on trichloroethylene. The committee concluded that the in-vitro studies indicate that trichloroethylene has some mutagenic potential whereas the majority of the in-vivo studies produced negative results. However, due to the conflicting results in the bone marrow assays the committee requested an in-vivo bone marrow micronucleus test in male CD rats exposed to trichloroethylene by inhalation [10].

The EC Working Group on the Classification and Labelling of Dangerous Substances, on the advice of its specialist experts, considered that trichloroethylene should be regarded as an in-vivo mutagen in somatic cells. It is therefore classified as a category 3 mutagen in the EU [3].
**Carcinogenicity**

The carcinogenicity of trichloroethylene has been investigated in rodents. An increase in incidence of benign and malignant liver tumours was observed in mice orally administered trichloroethylene. Liver tumours were also noted in mice exposed to trichloroethylene by inhalation. Increased incidences of testicular tumours and renal-cell tumours were observed in rats exposed to trichloroethylene by inhalation or ingestion. Inhalation studies reported increased incidences of lymphomas and lung tumours in mice. The IARC has concluded that there is sufficient evidence in experimental animals for the carcinogenicity of trichloroethylene [8].

**Reproductive and developmental toxicity**

An inhalation study reported reductions in testes weight, sperm count and motility and serum testosterone in rats exposed to 2030 mg m\(^{-3}\) 4 hours day\(^{-1}\), for 12 - 24 weeks. Reduced fertility was reported when the males mated with untreated females [9]. In a short-term inhalation study, rats and mice were exposed to trichloroethylene concentrations of 0, 100 or 500 ppm (0, 540 or 2,700 mg m\(^{-3}\)) 7 hours day\(^{-1}\), for 5 days. Significant increases in abnormal sperm were reported in the mice but not in the rats. In a similar study, mice were exposed to 0, 200 or 2,000 (0, 1,080 or 10,800 mg m\(^{-3}\)) of trichloroethylene 4 hours day\(^{-1}\) for 5 days. The percentage of abnormal sperm was significantly greater in the mice exposed to 2,000 ppm [3].

The reproductive effects of long-term oral administration of trichloroethylene have been investigated in rats and mice. Effects on reproduction were only observed at exposure levels that produced general toxicity. Reduced sperm motility and reductions in neonatal bodyweight and survival were reported in mice and, in rats, disrupted copulatory behaviour and reduced pup survival were observed. Slight reductions in the litter size and numbers of litters were also observed in continuously bred rats. The no observed adverse effect levels (NOAELs) for reproductive effect were 350 mg kg\(^{-1}\) bw day\(^{-1}\) in mice and 75 mg kg\(^{-1}\) bw day\(^{-1}\) in rats [3].

A number of rodent inhalation and oral studies have not reported any teratogenic effects on the developing fetus [1, 2]. However, more recent studies have reported cardiovascular and eye malformations in the offspring of rats exposed to trichloroethylene. Eye defects (reduced or absent ocular bulge) were reported in the offspring of rats administered ≥ 475 mg kg\(^{-1}\) bw trichloroethylene by gavage on gestation days 6 - 15. The doses were also maternally toxic. Cardiac abnormalities in the absence of maternal toxicity were observed in the offspring of rats administered trichloroethylene (0.2 and 129 mg kg\(^{-1}\) bw day\(^{-1}\)) in their drinking water, 7 days before and throughout gestation [9, 11]. Trichloroethylene has been reported to disturb heart valve and septal development in chick embryos [11].
References


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