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Tetrachloroethylene

Toxicological Overview

Key Points

Kinetics and metabolism

- tetrachloroethylene is readily absorbed following inhalation, ingestion and dermal exposure
- following absorption, tetrachloroethylene is mainly distributed to adipose tissue
- tetrachloroethylene is primarily excreted unchanged by the lungs, with a small amount excreted in the urine following metabolism

Health effects of acute exposure

- can cause local irritation following ingestion, inhalation, dermal or eye contact
- exposure by inhalation, ingestion or on significant dermal absorption may cause systemic effects, the most pronounced being CNS depression
- respiratory depression, coma and death can occur following substantial exposures

Health effects of chronic exposure

- chronic inhalation of tetrachloroethylene may cause CNS, hepatic and renal toxicity
- tetrachloroethylene is classified as probably carcinogenic to humans (group 2A)

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Summary of Health Effects

Tetrachloroethylene is irritating to the skin and mucous membranes and may cause systemic toxicity following inhalation, ingestion or significant dermal absorption. The effects include excitement, dizziness, drowsiness, ataxia and dysarthria. High exposures may lead to respiratory depression, coma and death.

Inhalation of tetrachloroethylene may cause central nervous system (CNS) depression and irritation of the nose, throat and respiratory tract.

Following acute ingestion of tetrachloroethylene, irritation of the gastrointestinal tract, nausea and vomiting may be seen, together with systemic effects.

Prolonged dermal contact with tetrachloroethylene may cause erythema and blistering. Tetrachloroethylene is irritating to the eye and may cause corneal injury.

Chronic inhalation exposure to tetrachloroethylene may cause CNS, hepatic and renal toxicity.

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

While tetrachloroethylene does not appear to have any significant mutagenic potential, a number of its metabolites are considered genotoxic.

A number of studies have reported an increased incidence of spontaneous abortion in women who work in the dry cleaning industry, where tetrachloroethylene is extensively used. Following an evaluation of a reproductive outcome study commissioned by the Health and Safety Executive (HSE), the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the increased risk of spontaneous abortion could not be specifically linked to tetrachloroethylene exposure.

Kinetics and Metabolism

Tetrachloroethylene is readily absorbed following inhalation exposure [1, 2]. Approximately 90% of inhaled tetrachloroethylene is absorbed; after an 8-hour exposure this value may fall to around 50% [3]. There is limited data regarding the absorption of tetrachloroethylene in humans following oral exposure. One report following accidental ingestion suggests tetrachloroethylene is readily absorbed by the oral route [4]. Animal studies report rapid and near-complete absorption of tetrachloroethylene following oral administration [5].

In humans, dermal absorption of tetrachloroethylene vapours is insignificant (1%) compared with absorption from the respiratory tract [4]. However, absorption following skin contact with tetrachloroethylene liquid may be more significant [4].

Following absorption, tetrachloroethylene is rapidly distributed to tissues [4]. Owing to its lipophilic nature, the highest concentrations of tetrachloroethylene are found in adipose and other fatty tissues [4]. Tetrachloroethylene has been detected in human breast milk with levels reaching up to 43 µg/L [4]. In one case, liver toxicity was reported in a breast-fed infant whose mother's milk was found to contain 10 mg/L tetrachloroethylene 1 hour after visiting a dry cleaning establishment [5].

Studies in humans and experimental animals suggest that metabolism of tetrachloroethylene is limited, especially at high doses [4]. The two major pathways of tetrachloroethylene metabolism are the cytochrome P450 dependent oxidative pathway and the glutathione (GSH) conjugation pathway [4]. The cytochrome P450 pathway is predominant, particularly at environmental exposure levels, owing to the higher affinity of the cytochrome P450 (CYP) enzymes for tetrachloroethylene than the enzymes of the GSH pathway [4]. However, studies suggest that the CYP-dependent oxidation pathway is readily saturable and limited [2]. Conjugation with GSH results in several reactive metabolites, some of which are considered mutagenic [4]. Generally, the rate of tetrachloroethylene metabolism and the concentration of metabolites is notably higher in rodents than in humans [5]. The extent of metabolism in humans appears to be variable and dependent on dose [4]. In one study, less than 2% of the absorbed dose was estimated to be metabolised following exposures of up to 144 ppm, while levels of around 0.001 (peaking at 1 ppm) resulted in an estimated metabolism of 36% in another [4]. The half-life of tetrachloroethylene has been estimated at 144 hours [4].

Regardless of the route of exposure, the majority of absorbed tetrachloroethylene is eliminated unchanged by the lungs; the total excretion by exhaled air has been measured at between 80 and 100% [4]. Between 40 and 70% of tetrachloroethylene is excreted by the lungs in the first 24 hours, while the remainder is lost more slowly [6]. A smaller fraction of tetrachloroethylene is excreted in the urine as metabolites, predominantly trichloroacetic acid (accounting for 1–3% of intake) [4].

Sources and Route of Human Exposure

The main routes of exposure to tetrachloroethylene are by inhalation, ingestion and, to a lesser extent, by dermal exposure [7].

Tetrachloroethylene is released into the environment as a result of its use; the majority enters the atmosphere unchanged [8]. The major uses of tetrachloroethylene are as a solvent in dry cleaning and as a chemical intermediate; other notable uses include metal degreasing and extraction processes [3]. A large proportion of atmospheric releases are due to evaporative loss during dry cleaning. Tetrachloroethylene undergoes degradation in air through reaction with hydroxyl radicals. The main products of degradation are phosgene, trichloroacetyl chloride, hydrogen chloride, carbon dioxide and carbon monoxide. The half-life of tetrachloroethylene in air is approximately 3–5 months [1]. In rural and urban areas ambient air concentrations of tetrachloroethylene are generally less than 1 µg/m^3 and 5 µg/m^3, respectively [8].

Tetrachloroethylene has been detected in surface and ground waters [1]. Concentrations of tetrachloroethylene in drinking water are generally below 3 µg/L; the drinking-water quality guideline for tetrachloroethylene is 0.04 mg/L [9].

It is likely that the general population will only be exposed to low levels of tetrachloroethylene in air, drinking water and food [7]. People living in the vicinity of dry cleaning facilities and industrial plants that emit tetrachloroethylene may be exposed to higher levels [7, 8].

Individuals working in industries that use tetrachloroethylene, particularly the dry cleaning industry and metal degreasers, are exposed to levels that are higher than normal background levels [2, 8]. Workplace exposure limits (WEL) for tetrachloroethylene have been set in the UK to protect workers from the harmful effects of tetrachloroethylene. The long-term WEL is 345 mg/m^3 (8-hour time weighted average exposure (TWA) reference period). The short-term WEL is 689 mg/m^3 (15-minute reference period) [10].

Health Effects of Acute/Single Exposure

Human data

General toxicity

Tetrachloroethylene is irritating to the skin and mucous membranes and may cause systemic toxicity following inhalation or ingestion. The main target organ for tetrachloroethylene toxicity is the CNS [5]. CNS depression following exposure to tetrachloroethylene is characterised by dizziness, drowsiness, ataxia and dysarthria [11]. In severe cases, coma, respiratory depression and death may occur [1, 11].

Inhalation

Irritation on acute inhalation exposure has been reported at a range of concentrations in volunteer studies. Mild nasal irritation has been reported at 1,500 mg/m^3 for 1 hour or 690 mg/m^3 for 7 hours; exposures of 6,400–8,200 mg/m^3 have resulted in immediate and severe respiratory tract irritation [1].

A number of CNS effects have been reported in volunteer studies following acute exposure to tetrachloroethylene. One study reported dizziness and drowsiness, impaired motor coordination and loss of inhibition in some subjects exposed to concentrations above 1,490 mg/m^3 (recovery was complete within an hour). Another study reported subjective CNS effects (including headache, sleepiness, speech difficulties and light headedness) in 25–40% of subjects exposed to 690 mg/m^3 for 7 hours [3].

Hepatic damage has been reported in some individuals accidentally exposed to high levels of tetrachloroethylene (sufficient to cause severe CNS effects) [1, 2].

Ingestion

Following ingestion of tetrachloroethylene, irritation of the mouth, throat, epigastric pain, nausea and vomiting may occur [11]. In the past, doses up to several grams of tetrachloroethylene were used to treat internal parasites. Nausea, vertigo, inebriation, dizziness, sleepiness and loss of consciousness were reported in patients receiving 4.2–6 g of tetrachloroethylene orally [1, 2]. Vertigo, agitation, hallucinations, drowsiness and subsequent coma were reported in a 6-year-old child who ingested 12–16 g of tetrachloroethylene [2].

Dermal/ocular exposure

Concentrated tetrachloroethylene is irritating to human skin. Erythema and blistering have resulted from prolonged skin contact [1]. Significant dermal absorption may lead to systemic toxicity [11].

Tetrachloroethylene vapour causes ocular irritation at concentrations of 500 mg/m^3 and above [7]. Eye contact has caused injury to the corneal epithelium [11].

Animal and in-vitro data

General toxicity

Tetrachloroethylene is of low acute toxicity by inhalation, ingestion or dermal contact. The main target organs are the CNS, liver and kidneys [1].

Inhalation

For rats and mice 6-hour LC_{50} values of 28,000 mg/m^3 and 21,000 mg/m^3, respectively, have been reported [1].

Respiratory tract irritation was observed in dogs exposed to tetrachloroethylene for 10 minutes at 10,000 ppm (67,800 mg/m^3), but not at 5,000 ppm (33,900 mg/m^3) [2].

Neurological effects reported in experimental animals exposed to tetrachloroethylene include anaesthesia, hyperactivity and hypoactivity, hypotonia, loss of reflexes, drowsiness, trembling, ataxia and stupor [1, 2]. In mice exposed to tetrachloroethylene for 4 hours, the no observed effect level for reaction to light stimuli was 462 mg/m^3 [3]. Signs of anaesthesia were observed in rats and mice exposed to 16,000 mg/m^3 tetrachloroethylene and above for 4 hours [1].

Liver toxicity (including changes in serum liver enzyme levels, swelling and hepatocellular vacuolisation) have been reported in rats and mice exposed to tetrachloroethylene by acute inhalation [1, 2, 7]. Kidney effects have been reported in mice exposed to 20,500 mg/m^3 for 6 hours [3]. Cardiac arrhythmias have been reported in rabbits exposed to 35,800 mg/m^3 for 1 hour [3].

Ingestion

Oral LD_{50} values range from 2.4–4.5 and 4.7–9.6 g/kg bw in rats and mice, respectively [1].

CNS depression, depression of heart rate, inflammation of the small intestines and adverse effects on the spleen, liver and kidneys have been reported in experimental animals administered tetrachloroethylene (doses ranging from 100–1,200 mg/kg bw) [1, 2]. Significant liver toxicity, characterised by mild to moderate fatty degeneration and necrosis was observed in rats 24 hours after single doses of 150 mg/kg tetrachloroethylene and above by aqueous gavage [5].

Dermal/ocular exposure

In a dermal exposure study, undiluted tetrachloroethylene (covered 24-hour application) applied to the skin of rabbits at 1.3, 2.5, 5, 10 and 20 g/kg bw resulted in the deaths of 0,1,1,1 and 2 animals, respectively (of 4 in each group) [1]. In another dermal study with rabbits, severe erythema and oedema with necrosis were noted following the application of tetrachloroethylene [7]. Instillation of tetrachloroethylene into the eyes of rabbits resulted in reversible epithelial abrasions and conjunctivitis [7].

Health Effects of Chronic/Repeated Exposure

Human data

Inhalation

Several occupational studies have reported CNS, liver and renal toxicity in workers exposed to tetrachloroethylene [1, 2, 6, 8].

Limited evidence from measurements of urinary excreted renal proteins and the incidence of end-stage renal disease support an association between tetrachloroethylene exposure and chronic kidney disease in workers [5]. Occupational studies suggest that effects on the kidney and liver do not occur at exposure levels below 50 ppm (345 mg/m^3) [3].

CNS effects reported in dry cleaning workers exposed to tetrachloroethylene include fatigue, confusion, dizziness, drunken feeling, floating sensation, heavy feeling in head and facial flushes [1, 2]. Deficits in neuropsychological tests have been reported in dry cleaning workers exposed to tetrachloroethylene at a mean concentration of 83 mg/m^3 and above for prolonged periods. The tests assessed reactions times, attention, visual scanning and memory [1, 2]. Effects on blue-yellow colour vision have been reported in some individuals occupationally exposed to tetrachloroethylene, but the significance of this data is unclear [1, 2, 8].

Limited data in the form of case studies suggests that tetrachloroethylene may have adverse effects on the immune system [5]. Significant differences in immunological (increase in total white cell and lymphocyte counts) and haematological (decreases in red blood cell count and haemoglobin levels) parameters were observed in 40 male dry cleaning workers with a mean exposure of less than 140 ppm (949 mg/m^3) for 7 years compared to age and smoking matched controls [5].

Ingestion

No data could be located regarding the chronic effects of tetrachloroethylene ingestion in humans.

Genotoxicity

There is limited data regarding the genotoxic effects of exposure to trichloroethylene in humans. Studies of individuals occupationally exposed to tetrachloroethylene have not demonstrated statistically significant increases in chromosomal aberrations or sister chromatid exchanges [4].

Carcinogenicity

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) reviewed the human carcinogenicity data on tetrachloroethylene in 1997. COC noted that the cohort studies mainly considered workers who were exposed to a wide range of chemicals and the analysis was based on very few cancer cases. It also

considered that possible confounding factors, including drinking and smoking for oesophageal cancer and virus infection for cervical cancer, had not been adequately addressed. COC concluded that there was “no satisfactory epidemiological evidence to associate tetrachloroethylene exposure to cancer in the available cohort studies” [12].

In 2014 the International Agency for Research on Cancer (IARC) evaluated carcinogenicity data for tetrachloroethylene [4]. In the majority of human studies, exposure to tetrachloroethylene was not directly measured; the studies characterised exposure by employment in the dry cleaning industry [4]. Significant associations with bladder cancer were found in both cohort and case–control studies [4]. Generally, the number of cases was small and evidence of an exposure-response relationship was lacking [4]. Additionally, no studies were identified to explain the mechanistic basis of cancer in the bladder [4]. While some studies showed positive associations for other sites including the oesophagus, cervix and kidney, and for non-Hodgkin’s lymphoma, no clear pattern of association was observed across the studies [4]. IARC concluded that there is limited evidence in humans (noting positive associations with bladder cancer had been seen), but that there is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene [4]. Therefore tetrachloroethylene is classified as probably carcinogenic to humans (group 2A) [4].

Reproductive and developmental toxicity

A number of epidemiological studies have reported an increased risk of spontaneous abortion in women exposed to tetrachloroethylene in the workplace. In 1993 the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) considered the evidence and concluded that “the available epidemiological evidence, although based on studies that were methodologically weak, was consistent with the view that tetrachloroethylene may be a reproductive toxicant in humans” [13].

The Health and Safety Executive (HSE) commissioned a retrospective occupational study of reproductive outcome in women currently or previously employed in dry cleaning shops or laundry units. Within the group of dry cleaning workers, a higher spontaneous abortion rate was seen in women classified as operators (17.1%) when compared with non-operators (11.6%). The adjusted odds ratio for the period 1980–95 showed that the risk of spontaneous abortion was over 50% higher in operators than in non-operators ($p = 0.04$) [14]. COT evaluated the study and agreed that there was an epidemiological association between the job category (dry cleaning machine operators) and spontaneous abortion. However, COT was of the opinion that “there was no evidence for a plausible mechanism by which tetrachloroethylene could cause this effect and that other factors could have contributed to the observed risk”. COT concluded that the increased risk of spontaneous abortion could not be specifically linked to tetrachloroethylene exposure [15].

There is very limited evidence for an association between tetrachloroethylene exposure and disruption of the menstrual cycle [3].

Some studies from a limited number on populations exposed to tetrachloroethylene in drinking water have found associations with effects including low birth weight, eye/ear

abnormalities and oral clefts [5]. However, in these studies exposures were not well defined and included multiple contaminants.

Animal and in-vitro data

General toxicity

The effects of long-term or repeated exposure to tetrachloroethylene have been investigated in experimental animals. The liver, kidneys and CNS are the main target organs. Studies have demonstrated that mice are more sensitive than rats to the liver toxicity of tetrachloroethylene [1, 2, 6, 8].

Inhalation

Decreased activity, reduced response to sound, salivation, breathing irregularities and piloerection were observed in rats exposed to tetrachloroethylene at 1,000 ppm (6,780 mg/m^3) for 6 hours a day, 5 days a week for 11–19 weeks. The reported effects were only observed for the first 2 weeks, which suggests that animals may adapt to some of the neurological effects of tetrachloroethylene [2]. Mice exposed to 2,069 mg/m^3 tetrachloroethylene for 6 hours a day for 5 days exhibited epithelial degeneration of the olfactory mucosa [3].

In a 13-week inhalation study rats and mice were exposed to tetrachloroethylene at 0, 690, 1,400, 2,800, 5,550 or 11,000 mg/m^3 for 6 hours a day, 5 days a week. Renal tubular karyomegaly was observed in all mice at all concentrations except the lowest. No kidney lesions were observed in rats. Minimal mitotic changes were seen in mice exposed to 1,400 mg/m^3; at 2,800 mg/m^3 and above, minimal to mild hepatic leukocytic infiltration, centrilobular necrosis and bile stasis were observed. Rats exposed to 1,400 mg/m^3 and above showed only minimal to mild liver congestion [1].

Studies in mice have shown effects on the liver after continuous, prolonged exposure to tetrachloroethylene. One study gave a lowest observed effect level (LOEL) of 62 mg/m^3 for a significant increase in liver weight, while another showed a doubling of liver weight (with cell hypertrophy and vacuolisation) after exposure to 517 mg/m^3 (both exposures lasting 30 days) [3].

A 3-month study in gerbils identified a LOEL of 414 mg/m^3 for neurotoxicity (which was defined by changes in DNA and astroglial protein S100) on continuous exposure [3].

Ingestion

Liver injury (including hepatocellular hypertrophy, centrilobular necrosis and hepatocellular vacuolisation) was reported in mice administered tetrachloroethylene by gavage at doses of 200–2,000 mg/kg bw/day for 6 weeks. Increased liver weights and triglyceride levels were seen at 100 mg/kg bw/day and no signs of toxicity were reported at 20 mg/kg bw/day [1, 2, 6].

Increases in liver and kidney weights and decreases in body weight of both sexes were reported in rats administered 400 and 1,400 mg/kg bw/day tetrachloroethylene for 90 days. No effects were seen at 14 mg/kg bw/day [6].

In a repeat dose study, mice administered tetrachloroethylene by gavage at 100 mg/kg bw/day for 11 days developed hepatocellular swelling. This effect was not observed in rats administered up to 1,000 mg/kg bw/day [1, 2, 6].

Effects on the kidneys (including degenerative tubule and fatty changes, cloudy swelling and necrosis of the tubular epithelium) have been reported in mice and rats administered tetrachloroethylene in corn oil by gavage for 78 weeks [2, 6].

Genotoxicity

The genotoxic potential of tetrachloroethylene has been extensively tested in several in-vivo and in-vitro assays. Tetrachloroethylene did not induce chromosomal aberrations in the bone marrow of rats exposed by inhalation or mice administered tetrachloroethylene by intraperitoneal injection. Dominant lethal mutations were not reported in rats exposed to tetrachloroethylene by inhalation. Micronuclei induction did not occur in the bone marrow of mice administered tetrachloroethylene by intraperitoneal injection. However, there was a significant increase in micronucleated cells in the liver of mice subjected to a partial hepatectomy [1]. Oral administration of tetrachloroethylene did not induce unscheduled DNA synthesis in the kidneys of rats. Single strand DNA breaks were induced in the liver and kidneys, but not lungs, of male mice administered tetrachloroethylene by intraperitoneal injection. Tetrachloroethylene did not induce DNA strand breaks in the kidneys of rats, following oral administration [1, 4].

In-vitro studies do not show tetrachloroethylene to be directly mutagenic, with or without metabolic activation with S9 from rat liver [4]. However, with the addition of rat liver GSH, GST and kidney microsomal fraction during pre-incubation, a clear dose-response is obtained [4].This supports the theory that tetrachloroethylene metabolites from the glutathione pathway may cause genotoxicity, not the parent compound. IARC considers that it is likely that formation of these metabolites in the kidney contributes to carcinogenesis in the kidney [4].

In other in-vitro assays, tetrachloroethylene did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells, or unscheduled DNA synthesis in human, rat or mouse cells [1, 4].

Carcinogenicity

The carcinogenicity of tetrachloroethylene has been investigated in experimental animals. A significantly increased incidence of hepatocellular carcinomas was observed in mice orally administered tetrachloroethylene [4]. Inhalation carcinogenicity studies reported a significant increase in the incidence of hepatocellular adenomas and carcinomas in mice and a significantly increased incidence of mononuclear-cell leukaemia in rats [4].

IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene [4].

Reproductive and developmental toxicity

Several developmental studies have reported fetotoxic effects in the offspring of rats, mice and rabbits exposed to tetrachloroethylene during pregnancy. However, the effects were only seen at doses that caused maternal toxicity [1, 2, 6].

Experiments in mice have shown that tetrachloroethylene crosses the placenta and may subsequently accumulate in the amniotic fluid and the fetus [3].

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