

Vinyl chloride

Toxicological overview

Key Points

Kinetics and metabolism

- Vinyl chloride is readily and rapidly absorbed via inhalation, ingestion and through the skin
- At room temperature vinyl chloride is a gas, so inhalation is the major route exposure
- Following absorption, it is distributed through the body, with the highest concentrations found in the liver and kidneys, followed by the lungs and spleen
- Vinyl chloride is mainly metabolised in the liver into reactive metabolites
- Vinyl chloride is mainly excreted in the urine as thiodiglycolic acid

Health effects of acute exposure

- Acute inhalation of vinyl chloride may cause nausea, headache, dizziness and drowsiness; central nervous system depression and cardiac arrhythmias
- Vinyl chloride can cause irritation to the eyes, mucous membranes and respiratory tract
- Compressed gas or liquid can cause frostbite or irritation of the skin and eyes

Health effects of chronic exposure

- Repeated exposure to vinyl chloride may cause liver toxicity, neurological and behavioural symptoms
- Vinyl chloride is considered to be a human carcinogen

Toxicological Overview

Summary of Health Effects

Vinyl chloride is rapidly and well absorbed after inhalation or following oral exposure (as a solution in an organic solvent). The primary route of exposure to vinyl chloride is inhalation, approximately 40% of inspired vinyl chloride is absorbed after exposure by inhalation. Although no there are no human studies, animal studies showed absorption of more than 95% after oral exposure. Dermal absorption of vinyl chloride in the gaseous state is not significant [1-3].

Acute exposure to vinyl chloride can cause dizziness, drowsiness, unconsciousness, and at extremely high levels can cause death. Vinyl chloride is a respiratory irritant producing coughing, wheezing and breathlessness. Other effects include headache, ataxia and coma [3, 4].

Dermal exposure to vinyl chloride may cause irritation, pain and burns. Rapid evaporation may produce local frostbite. Contact dermatitis has been reported. Vinyl chloride is not readily absorbed dermally. Ocular exposure may cause irritation, pain and possible frostbite and corneal injury [5].

In the past, long term occupational exposure to concentrations of 1000 ppm or more produced a distinctive syndrome ('vinyl chloride illness'). This includes peripheral circulatory changes typical of Raynaud's Disease (numbness, tingling and blanching of the fingers on exposure to cold), and sclerosis-like changes in the fingers with subsequent bony changes in the tips of the fingers (acro-osteolysis), chronic exposure can also cause liver damage [1-4]. Currently all manufacturing processes using vinyl chloride use completely enclosed systems hence any exposure of workers is unlikely [3].

According to the International Agency for Research on Cancer (IARC), vinyl chloride is a recognised human carcinogen. There is much data to substantiate a causal association between exposure to vinyl chloride and a distinctive form of liver cancer (angiosarcoma). Several studies also confirm that exposure to vinyl chloride causes other forms of cancer i.e. hepatocellular cancer, brain tumours, lung tumours and malignancies of the lymphatic and haematopoietic system [2].

Kinetics and metabolism

Vinyl chloride is readily and rapidly absorbed via inhalation, ingestion, and minimally through the skin. It is a gas at room temperature, and thus inhalation is the major route of exposure.

In various studies of human volunteers exposed to vinyl chloride by inhalation, retention (the difference between the inhaled and exhaled concentrations) in the lung was estimated to be 27 to 42% [4, 6]. Concentrations reached a maximum within 15 minutes, declined rapidly after 30 minutes and increased to a constant value [6].

Uptake of vinyl chloride when given as a solution in organic solvent via the oral route is more than 95%. Any vinyl chloride not metabolised during first pass through the liver will be expired. Thus the net dose may be less than the uptake, especially at high doses resulting in saturation of metabolising enzymes [3]. After an acute oral exposure in rats, peak levels of vinyl chloride in brain, liver, kidney and lung were measured 5 minutes after dosing, indicating rapid absorption from gastrointestinal tract [3].

No data were available regarding skin absorption in humans. Animal studies in which rhesus monkeys were exposed to vinyl chloride vapour showed that very little was absorbed through the skin [3, 6].

Vinyl chloride is rapidly distributed through the body, with the highest concentrations found in the liver and kidneys, followed by the lungs and spleen [4, 7]. Placental transfer of vinyl chloride has been shown to occur rapidly in rats.

The main route of metabolism of vinyl chloride is in the liver by cytochrome P450 enzymes. It is first metabolised to chloroethylene oxide, a highly reactive, short-lived epoxide that rapidly rearranges to form chloroacetaldehyde. These reactive metabolites are detoxified via conjugation with glutathione [3, 4]. The rapid metabolism and excretion limits the accumulation of vinyl chloride in the body [6].

In humans, at low doses vinyl chloride is largely excreted in the urine as thiodiglycolic acid, its excretion increasing with exposure to the parent compound [4]. At higher doses when metabolism is saturated, the major route of excretion is exhalation of unchanged vinyl chloride. Excretion via faeces is only a minor route [3].

Sources and route of exposure

The major source of exposure to vinyl chloride is from occupational exposure, since its principal use is in industrial processes, such as during the production of PVC [4, 6]. However, currently all manufacturing processes using vinyl chloride use completely enclosed systems hence any exposure of workers is unlikely [3].

Vinyl chloride is unlikely to be present in significant quantities in domestic situations and does not occur naturally, although it has been found in landfill gas and groundwater as a degradation product of chlorinated hydrocarbons deposited [3].

There is very little exposure of the generally population to vinyl chloride. WHO estimated that the majority of the population would inhale 2 – 10 $\mu\text{g day}^{-1}$ vinyl chloride, assuming a daily inhalation rate of 20 m^3 . Vinyl chloride may be present in the environment close to industrial locations where it is manufactured or used, or near waste disposal sites. Calculation of daily inhalation rates for populations living in the immediate vicinity of some vinyl chloride plants

indicates the population could inhale 4 - 100 $\mu\text{g day}^{-1}$ [4]. However, concentrations present at such locations would be expected to be many times lower than those observed during occupational exposure [3, 8]. Exposure to vinyl chloride may also be higher in situations where large amounts of vinyl chloride are accidentally released to the environment, such as during a spillage during transportation.

There is little information regarding vinyl chloride in drinking water. Due to its volatility and reactivity, it would not be expected to remain in drinking water in significant quantities [8]

Vinyl chloride is found in cigarette (1.3-1.6 ng cigarette⁻¹) and cigar (14-27 ng) smoke. Heavy smokers may therefore inhale up to 0.5 $\mu\text{g day}^{-1}$ [8].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

The acute toxic effects following inhalation of vinyl chloride are summarised in table 1. The main effect of acute exposure to vinyl chloride is on the central nervous system causing headache, vertigo, drowsiness, disorientation, nausea, burning of extremities, dizziness, ataxia and narcotic effects at higher concentrations [4, 6, 9-11].

Acute inhalation of vinyl chloride may cause respiratory tract irritation, wheezing, chemical bronchitis and respiratory depression. Such effects are usually transient and resolve when exposure is removed. Exposure to vinyl chloride may also lead to Reactive Airway Dysfunction Syndrome (RADS), a chemical-induced type of asthma [4, 6, 9-11].

Exposure to higher concentrations for longer periods may result in death due to central nervous system and respiratory depression [11].

Exposure to vinyl chloride may predispose the person to cardiac arrhythmias [11].

Table 1. Summary of toxic effects following acute exposure to vinyl chloride by inhalation [4, 6, 9-11].

Dose (ppm)	Duration of exposure (min)	Signs and symptoms
8000 - 20000		Dizziness, nausea, headache
70000 – 100000		Narcotic, coma
120000		Cardiac arrhythmias, death
4000	5	Threshold of effect
8000	5	Dizziness
12000	5	Dizziness, headache, nausea and dulling of vision
1000	60	Drowsiness, faltering gait, visual disturbances and numbness and tingling in the extremities

There have been two fatalities reported from acute vinyl chloride exposure to airborne levels estimated to be greater than 100,000 ppm; deaths were from respiratory failure [4].

Ingestion

Ingestion of vinyl chloride is unlikely as it is a gas at room temperature. No data could be retrieved [4].

Dermal / ocular exposure

Vinyl chloride is stored under pressure as a liquid. Exposure to escaping vinyl chloride may cause frostbite to the exposed skin, with redness, blistering and scaling. A man whose hands were accidentally sprayed with vinyl chloride developed erythema and some second-degree burns which healed without complication [3, 11].

Ocular contact with vinyl chloride vapours is moderately irritating to the eye. Contact with escaping compressed gas may cause mechanical injury and frostbite [4, 11].

Delayed effects following an acute exposure

Individuals who are exposed to vinyl chloride may not experience immediate symptoms as there may be a latent period of 24 to 48 hours between exposure and CNS and respiratory depression and liver or kidney toxicity [11].

Animal and In-Vitro Data

Inhalation

Vinyl chloride appears to be of low toxicity when administered to various species by inhalation; the two hour LC50 value being 293000 – 595000 mg kg⁻¹ for a range of species [4]. At these high exposures congestion was seen in internal organs particularly the lung, liver and kidney as well as pulmonary oedema [3].

Following exposure of mice and rats to 10000 – 30000 ppm vinyl chloride for 30 minutes, narcosis was reported, as well as, pulmonary oedema, congestion of the lungs, liver and kidneys and pulmonary haemorrhage [3, 7]. In rats, mice and hamsters, exposed to high levels by inhalation, death was preceded by increased motor activity, twitching of extremities, tremor, ataxia, tonic-clonic convulsions and accelerated respiration [3].

Cardiovascular effects were also reported in-vivo. In dogs, severe cardiac arrhythmias (intermittent tachycardia, ventricular fibrillation, atrioventricular block) occurred under narcosis after inhalation of 260,000 mg m⁻³ of vinyl chloride, although the statistical significance of these were not reported [3, 7].

Studies have reported the effect of vinyl chloride on blood clotting. Guinea pigs exposed to 400000 ppm vinyl chloride for 30 minutes had a decrease in blood clotting [7].

Hepatic damage was observed in animals exposed to high concentrations of vinyl chloride. Acute exposure of guinea pigs and mice to 200000 - 300000 ppm had liver congestion, fatty degeneration and fatty infiltration, as well as centrilobular vacuolisation, although rats exposed to 60000 ppm for 6 hours showed no observable effects [4, 7].

Hepatic changes increase by ethanol or phenobarbitone pre-treatment have been observed following massive exposure in animals [4].

Ingestion

No studies reporting adverse effects following acute ingestion of vinyl chloride in animals were identified.

Dermal / ocular exposure

Few studies reporting toxicity following acute dermal or ocular exposure to vinyl chloride were identified. Guinea pigs exposed to up to 400000 ppm vinyl chloride for 30 minutes in an inhalation chamber did not show any adverse effects on skin or eyes [7]

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Prior to 1974, it was not uncommon for workers to be exposed to concentrations of vinyl chloride in the region of 2590 mg m⁻³ (1000 ppm) for periods ranging from 1 month to several years. Such exposure has been reported to cause a specific pathological syndrome called the “vinyl chloride illness” characterised by scleroderma-like changes in the fingers with subsequent bony changes in the tips of the fingers, acro-osteolysis and Raynaud’s phenomenon [3, 4]. Other symptoms described were earache and headache, dizziness, unclear vision, fatigue and lack of appetite, nausea, sleeplessness, breathlessness, stomach ache, pain in the liver/spleen area, pain and tingling sensation in the arms/legs, cold sensation at the extremities, loss of libido and weight loss [3]. Peripheral circulatory changes may also occur which correlate with length of exposure [10].

Chronic exposure to vinyl chloride may also result in liver toxicity, initially hepatomegaly, with hepatic fibrosis and portal hypertension occurring after several years [4].

Chronic inhalation of vinyl chloride may also cause respiratory effects, such as emphysema, decreased respiratory volume, decreased oxygen and carbon dioxide transfer, pulmonary fibrosis and dyspnoea, although cohort studies have reported an overall deficit in mortality from respiratory disease [10].

Ingestion

There are currently no data on the effects of chronic vinyl chloride ingestion in humans.

Dermal / ocular exposure

Occupational exposure to vinyl chloride has produced scleroderma-like skin changes on the hands of a small percentage of exposed workers in the past. The skin changes were characterized by a thickening of the skin, decreased elasticity and oedema, and were almost exclusively observed in exposed individuals who also suffered from Raynaud’s phenomenon. Skin biopsies revealed increased collagen bundles in the sub-epidermal layer of the skin [7].

Genotoxicity

Vinyl chloride has been demonstrated to be clastogenic in humans and is hence a mutagen. Frequencies of chromosomal aberrations, micronuclei and sister chromatid exchanges in the peripheral blood lymphocytes of workers exposed to high levels of vinyl chloride have been shown to be increased compared to controls [3, 7]. Although in many studies the exposure concentrations and duration of exposure were only estimated, a dose-response relationship and a normalisation of genotoxic effects with time after reduction of exposure can be seen [3].

Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified vinyl chloride as being carcinogenic to humans (Group 1) [2].

A large number of epidemiological studies and case reports have substantiated the causal association between vinyl chloride and angiosarcoma of the liver as well as hepatocellular carcinoma, brain tumours, lung tumours and malignancies of the lymphatic and haematopoietic system. Slightly elevated risks for gastric and gastrointestinal cancer (other than liver cancer) were reported in some studies, but these were not confirmed in others [2].

Reproductive and developmental toxicity

Several epidemiological studies have reported an association between vinyl chloride exposure in pregnant women and an increased incidence of birth defects, while other studies have not reported similar findings [3, 4, 7]. However, those studies that reported an increased rate of birth defects among the children of parents residing nearby vinyl chloride production facilities failed to show a significant correlation between development toxicity and proximity to the facility or parental occupation [3, 4, 7].

Increased incidence and severity of preeclampsia during pregnancy was reported in exposed women compared to non-exposed women [7].

Several case reports suggest that male sexual performance such as impotence, loss of libido and decreased androgen secretion, may be affected by vinyl chloride. However, these studies are limited by lack of quantitative exposure information and possible co-exposure to other chemicals [3, 4, 7].

Epidemiological studies have suggested an association between paternal exposure to vinyl chloride and spontaneous abortion and/or birth defects although other studies have not supported these findings [3, 4, 7, 10].

In summary, epidemiological studies on the potential developmental toxicity of vinyl chloride or of effects on libido and potency have not produced conclusive results [6].

Animal and In-Vitro Data

Inhalation

Rats, mice and hamsters exposed to 260 mg m⁻³, 130 mg m⁻³ and 520 mg m⁻³ vinyl chloride, respectively for up to 24 months (rats) or 18 months (mice and hamsters) showed increased mortality. In most species the main target organ for vinyl chloride is the liver. A dose-related increase in liver weight has been reported in rats exposed to 26 – 7800 mg m⁻³, and degenerative effects on liver parenchyma occurred in rabbits (520 mg m⁻³), rats (1300 mg m⁻³) and mice (2600 mg m⁻³). Adverse effects on the testes in rats were also noted (26 – 7000 mg m⁻³), as well as kidney and lung in rats and mice at higher doses. Rats, mice and rabbits appear to be more sensitive than guinea pigs and dogs [3].

Other studies reported that rats exposed to 130 mg m⁻³ showed reduced body weight and increased relative spleen weight, as well as hepatocellular lipid accumulation, mitochondrial swellings and proliferation of cells lining the liver sinusoids, rats exposed to 1300 mg m⁻³ showed reduced body weight, increased weight of heart, spleen, liver and kidney,

degeneration of the testis and myocardium and tubular necrosis and those exposed to 52000 mg m⁻³ showed reduced body weight, elevated weight of heart and spleen, liver, kidney and testis. Hepatotoxicity was observed at all doses [3].

Increases in relative heart weight was also reported in rats exposed to 10 ppm vinyl chloride for 6 months and 100 ppm for 3 months, whereas rats chronically exposed to 5000 ppm vinyl chloride for one year showed increases in areas of myodegeneration and arterial wall thickening, although statistical significance was not reported. Exposure of rats to 30000 ppm vinyl chloride for one year also caused thickening of arterial walls and consequently blockage of the lumen due to proliferation of the endothelium [7].

Exposure to 5000 ppm vinyl chloride for one year caused increased splenic haematopoiesis and decreased blood clotting time in rats, although statistical significance was not reported [7].

Following exposure to 20000 ppm vinyl chloride for 10 months no bone alterations in rats was reported, but 30000 ppm for 12 months cause osteochondrome, although again statistical significance was unreported [7].

Ingestion

The primary target organ of vinyl chloride in rats after long-term oral exposure is the liver. Female rats appeared to be more sensitive than males to the hepatotoxicity of vinyl chloride, with increased mortality in females at doses of 1.3 mg kg⁻¹ body weight⁻¹ day⁻¹ and above and in males at 5.0 mg kg⁻¹ body weight⁻¹ day⁻¹ and above. Increased relative liver weights were found at 14.1 mg kg⁻¹ body weight⁻¹ day⁻¹ after feeding periods of 6 or 12 months and blood clotting time was decreased [3]. Morphological alterations of the liver included extensive hepatocellular necrosis at doses of ≥5 mg kg⁻¹ body weight⁻¹ day⁻¹, foci of haematopoiesis at 14.1 mg kg⁻¹ body weight⁻¹ day⁻¹, and cysts and liver cell polymorphism at doses ≥ 1.3 mg kg⁻¹ body weight⁻¹ day⁻¹ [3, 7].

Dermal effects may also occur following ingestion of vinyl chloride. Exposure to 30 mg kg⁻¹ body weight⁻¹ day⁻¹ for two years caused skin fibrosis [7].

Genotoxicity

Vinyl chloride has been extensively studied in the Ames test. Positive results were consistently obtained in the presence of metabolic activation. Activity was seen against *Salmonella typhimurium* strains TA100, TA1530 and TA1535 but not in TA98, TA1537 and TA1538 indicating that the mutations are the result of base-pair substitutions (transversion and transition) rather than frameshift mutations [3]. Vinyl chloride has also been shown to give positive results in *in-vitro* tests for gene mutation in yeasts and for chromosome aberrations in mammalian cells in culture. *In-vitro* studies indicate it has mutagenic potential [7].

Vinyl chloride has also been extensively studied for mutagenic effects *in-vivo* in rodents. Studies to investigate clastogenicity following exposure by inhalation using either metaphase analysis or the micronucleus test have consistently given positive results [4].

Carcinogenicity

Various carcinogenicity studies in different animal species indicate that there is sufficient evidence that vinyl chloride is carcinogenic to animals [2].

Following oral and inhalation exposure, vinyl chloride was carcinogenic in rats, mice and hamsters, producing tumours in the mammary gland, lung, Zymbal gland, skin and angiosarcomas of the liver [2]. A combination of oral administration of ethanol and inhalation of vinyl chloride resulted in more liver tumours (including angiosarcomas) than after treatment with vinyl chloride alone [2].

Vinyl chloride was carcinogenic in rats following prenatal exposure. A dose-response effect has been demonstrated [1].

Reproductive and developmental toxicity

Inhalation studies in which rats or mice were exposed to vinyl chloride throughout pregnancy indicated developmental toxicity only occurred at doses above those causing maternal toxicity. Potential fetal toxicity was observed at 1300 mg m⁻³ in mice and 3900 mg m⁻³ in rats with no evidence of teratogenicity in either species [6].

In a 2-generation reproductive toxicity study in rats exposed to concentrations up to 2860 mg m⁻³ by inhalation, no adverse effects on embryo-fetal development or reproductive capacity at any dose level [7].

In a 12 month repeated dose inhalation toxicity study, signs of testicular toxicity (damage to seminiferous tubules) was observed at 260 mg m⁻³ and above, with a no observable adverse effect level (NOAEL) of 260 mg m⁻³ [6].

References

- [1] International Agency for the Research on Cancer (IARC) (1979). Vinyl chloride, polyvinyl chloride and vinyl chloride-vinyl acetate copolymers. Vol 19. IARC. Lyon.
- [2] International Agency for the Research on Cancer (IARC) (1987). Vinyl chloride. Supplement 7. IARC. Lyon.
- [3] International Programme on Chemical Safety (IPCS) (1999). Vinyl chloride. Environmental Health Criteria 215. WHO. Geneva.
- [4] International Programme on Chemical Safety (IPCS) (1997). Vinyl chloride. Poisons Information Monograph. PIM 558. WHO. Geneva.
- [5] National Poisons Information Service (NPIS) (2004). Vinyl chloride. TOXBASE®.
- [6] Department for Environment Food and Rural Affairs (DEFRA) and Environment Agency (EA) (2004). Contaminants in soil: Collation of toxicological data and intake values for humans. Vinyl chloride. Environment Agency. Bristol.
- [7] Agency for Toxic Substances and Disease Registry (ATSDR) (2006). Toxicological Profile for vinyl chloride. US department of Health and Human Services. Atlanta, US.
- [8] World Health Organisation (WHO) (2000). Air quality guidelines for Europe. WHO Regional Publications, European Series, No. 91. 2nd edition. WHO Regional Office for Europe. Copenhagen.
- [9] Hathaway G.J. and Proctor N.H. (2004). Chemical Hazards of the Workplace. 5th edition. Inc. John Wiley & Sons, New Jersey.
- [10] Risk Assessment Information System (RAIS) (1993). Toxicity summary for vinyl chloride. Chemical Hazard Evaluation and Communication Group, Biomedical and Environmental Information Analysis Section, Health and Safety Research Division.
- [11] Agency for Toxic Substances and Disease Registry (ATSDR) (2007). Vinyl chloride. US Department of Health and Human Services. Atlanta, US.

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.