ACUTE TOXICITY SUMMARY

VINYL CHLORIDE

(chloroethene; chloroethylene; vinyl chloride monomer; VC; VCM)

CAS Registry Number: 75-01-4

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**180,000 µg/m³**
Critical effect(s)	mild headache and dryness of eyes and nose in healthy human volunteers
Hazard Index target(s)	Eyes; Nervous System; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless gas
Molecular formula	C_2H_3Cl
Molecular weight	62.5
Density	2.56 g/L @ 25°C
Boiling point	-13°C
Melting point	-153.8°C
Vapor pressure	2,660 mm Hg @ 25°C
Flashpoint	-77.8°C (open cup) (ACGIH, 1991)
Explosive limits	4 to 22% by volume in air (ACGIH, 1991)
Solubility	soluble in alcohol, ethyl ether, carbon tetrachloride, benzene
Odor threshold	3,000 ppm (Amoore and Hautala, 1983)
Odor description	sweet (AIHA, 1989)
Metabolites	chloroethylene oxide, chloroacetic acid (Antweiler, 1976)
Conversion factor	1 ppm = 2.56 mg/m³ @ 25°C

III. Major Uses or Sources

The chief use of vinyl chloride (VC) is in the production of polyvinyl chloride (PVC) resins used for plastic piping and conduit (IARC, 1979). It is also used in the manufacture of methyl chloroform. Vinyl chloride was used as a propellant until 1974 when this use was banned due to its demonstrated carcinogenicity. The main toxicological concern for vinyl chloride is from exposure to the monomer rather than the polymerized forms (i.e., PVC). Thermal decomposition of VC produces hydrogen chloride, carbon monoxide, and traces of phosgene (ACGIH, 1991).

IV. Acute Toxicity to Humans

The primary acute physiological effect of VC inhalation is CNS depression (Holmberg, 1984). Anesthesia may occur at high concentrations (7,000 - 10,000 ppm) for short durations in both animals and humans (Purchase *et al*., 1987).

In two accidental human poisonings, workers became incapacitated when exposed to high concentrations of VC gas (Anon., 1953). Following removal from exposure, one of the workers experienced tightness of the chest, nausea, abdominal pain, and headache. Before VC's relationship with certain forms of cancer was established, workers in at least one polyvinyl chloride manufacturing facility reportedly inhaled VC fumes for its euphoric effect, sometimes to the point of unconsciousness (Klein, 1976). Danziger (1960) reported a worker death associated with exposure to high concentrations of VC. Autopsy revealed cyanosis, local burns of the conjunctiva and cornea, congestion of internal organs (especially lung and kidneys), and failure of blood to clot.

Suciu *et al*. (1975) reported that factory workers exposed to high concentrations of VC experienced euphoria, giddiness, somnolence and, in some cases, narcosis. Yearly average concentrations reported at this factory were between 98 and 2,298 mg/m³ (38 to 898 ppm).

Two male volunteers exposed to 25,000 ppm (64,000 mg/m³) VC for 3 minutes reported the odor as pleasant, but became dizzy and disoriented to the space and size of surrounding objects. The men also reported a burning sensation on the soles of their feet (Patty *et al*., 1930).

In a controlled exposure, 6 adult volunteers (3 male, 3 female) were exposed to varying concentrations up to 20,000 ppm (51,200 mg/m³) of VC via an oral-nasal mask (Lester *et al*., 1963). The 5 minute exposures took place twice each day and were separated by 6-hour periods for 3 successive days. No CNS effects were reported at 4,000 ppm (10,240 mg/m³). Exposure to 12,000 ppm (30,720 mg/m³) resulted in complaints of dizziness and reeling in 2 subjects. A clear dose-response was observed in this study, but statistical comparisons were not made by the authors.

In a chamber exposure, human volunteers were exposed to 59, 261, 491, or 493 ppm VC for up to 7.5 hours (excluding a 0.5-hour lunch period) (Baretta *et al*., 1969). The subjects exposed to either 59 or 261 ppm VC reported no untoward effects. However, 2 of 7 subjects exposed to 491 ppm for 3.5 hours and 2 of 4 subjects exposed to 493 ppm for 7.5 hours reported mild headache and dryness of eyes and nose.

Vinyl chloride is known to cause "vinyl chloride disease" upon repeated exposures in workers. This multisystem disorder consists of Raynaud's phenomenon, acro-osteolysis, thrombocytopenia, splenomegaly, portal fibrosis, and hepatic and pulmonary dysfunction (IARC, 1979). This disease is likely an immune complex disorder from the adsorption of VC or a metabolite onto tissue proteins and is unlikely to occur following single acute exposure (Ward *et al*., 1976).

Differences in genetic susceptibility to hepatotoxicity of vinyl chloride have been described (Huang *et al*., 1997). Vinyl chloride is metabolized by cytochrome P450 2E1 (CYP2E1) to form the toxic electrophilic metabolites, chloroethylene oxide and chloroacetaldehyde. These metabolites are detoxified by glutathione S-transferases (GSTs). A total of 251 workers from polyvinyl chloride plants were categorized into high or low exposure groups based on air exposure monitoring. Serum alanine aminotransferase (ALT) was used as an indicator of liver function. CYP2E1, GST theta, and GST mu were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) on peripheral white blood cell DNA. For the low vinyl chloride exposure group, positive GST theta (odds ratio = 3.8, 95% CI 1.2-14.5) but not CYP2E1 was associated with abnormal ALT levels in serum. For the high exposure group, a c2c2 CYP2E1 genotype was associated with an increased risk of abnormal ALT (odds ratio = 5.4, 95% CI 0.7-35.1), while a positive GST theta was associated with significantly reduced risk of abnormal ALT (odds ratio = 0.3, 95% CI 0.1-0.9).

Predisposing Conditions for Vinyl Chloride Toxicity

Medical: Inherited cytochrome P450 and glutathione S-transferase alleles may affect individual susceptibility (Huang *et al*., 1997).

Chemical: Inducers of hepatic cytochrome-P450 enzymes, such as phenobarbital, potentiate the hepatotoxic effects of inhaled VC in rats (IARC, 1979; Jaeger *et al*., 1974; Kappus *et al*., 1975). Liver damage was measured by the release of alanine alpha-ketoglutarate, SGOT, and SGPT enzymes.

Ethanol co-administration with VC resulted in greater toxicity to pregnant mice, rats, or rabbits than exposure to VC alone (John *et al*., 1981).

V. Acute Toxicity to Laboratory Animals

A lethality study was carried out by Prodan *et al*. (1975) in which mice, rats, guinea pigs, and rabbits were exposed to VC for 2 hours. Deaths were due to respiratory failure. Animals that were still alive at the end of exposure recovered quickly following removal from the gas. However, no post-exposure observation period was included in the study to investigate possible delayed mortality. Table 1 below shows the LC_{50}, MLE_{05} (maximum likelihood estimate expected to produce a response rate of 5%), BC_{05} and BC_{01} (benchmark concentration at the 95% lower confidence interval of the 5% and 1% lethality level, respectively) as determined by log normal probit analysis (Crump, 1984; Crump and Howe, 1983).

Table 1. Animal lethality benchmark concentration estimates from Prodan *et al*. (1975) for 2-hour vinyl chloride exposure

Species	LC_{50} (mg/m³ x 10^3)	MLE_{05} (mg/m³ x 10^3)	BC_{05} (mg/m³ x 10^3)	BC_{01} (mg/m³ x 10^3)
mouse	299	253	246	227
rat[1]	(394)	(329)	(292)	(260)
guinea pig	591	527	453	410
rabbit	600	545	466	424

[1] Log normal probit analysis indicates the data points for rats resulted in an unacceptable fit.

Exposure of rats, mice and guinea pigs to 100,000 ppm VC (5 animals/species) resulted in increased motor activity at 10 minutes but progressed to muscular incoordination, unsteady gait and pronounced tremor in all species 15 minutes into the exposure (Mastromatteo *et al*., 1960). Rats and mice became unconscious at 25 minutes while guinea pigs remained conscious during the entire 30 minute exposure period. At 200,000 and 300,000 ppm VC, rats and mice exhibited muscular incoordination at 2 and 1 minutes, respectively, following initiation of exposure. Guinea pigs were slightly more tolerant of the CNS depressant effects at these concentrations. Deaths in mice, rats and guinea pigs occurred at 200,000 ppm and above, 300,000 ppm and 400,000 ppm, respectively.

Exposure to 5,000 and 10,000 ppm vinyl chloride for 8 hours did not produce signs of CNS depression in guinea pigs (Patty *et al*., 1930). Inhalation of 25,000 ppm (64,000 mg/m³) (sample size unspecified) resulted in motor ataxia and unsteadiness by 5 minutes, deep narcosis without convulsions or twitching by 90 minutes, and death by respiratory paralysis by 6 hours. Gross pathological changes included congestion and edema in the lungs, and hyperemia in the liver and kidneys. Guinea pigs exposed to 100,000 ppm developed complete loss of coordination and incomplete narcosis 2 minutes into exposure.

Lester *et al*. (1963) showed that rats exposed to 50,000 ppm (128,000 mg/m³) VC for 2 hours exhibited moderate intoxication with loss of the righting reflex. Loss of the corneal reflex was apparent following a 2-hour exposure to 100,000 ppm (256,000 mg/m³). Exposure of these rats to 100,000 ppm (256,000 mg/m³) for two 8-hour periods resulted in mortality from a “pneumonic process.”

Tatrai and Ungvary (1981) exposed mice, rats and rabbits to 1,500 ppm VC for up to 24 hours. Rats and rabbits were unaffected, but 90% of mice died following 12 hours of exposure and 100% of mice died following 24 hours of exposure. Pathological examination of mice revealed hemorrhages and vasodilatation in the lungs, suggestive of pulmonary edema.

Dermal exposure of monkeys to gaseous VC indicated that absorption of VC across the intact skin is very limited (Hefner *et al*., 1975).

Rhesus monkeys eliminate VC at approximately half the rate of mice and rats (Buchter *et al*., 1980). Rodents may therefore be less sensitive than primates to systemic VC toxicity.

VI. Reproductive or Developmental Toxicity

In a review of the epidemiological data, Hemminki and Vineis (1985) concluded that there was inadequate evidence of increased teratogenesis in humans exposed to VC.

Animal studies have also failed to show significant association between VC exposure and teratogenesis. In rats, exposure to VC at a concentration of 1,500 ppm (3,840 mg/m³) for 24 hours/day during all three trimesters of pregnancy did not result in an increased incidence of birth defects (13-28 rats per group) (Ungvary *et al*., 1978). Pharmacokinetic studies showed that VC crossed the placental barrier of these rats, and was present in fetal blood.

John *et al*. (1981) showed that exposure of pregnant mice, rats or rabbits to 500 ppm (1,280 mg/m³) VC for 7 hours/day during organogenesis did not result in teratogenicity or embryotoxicity. Inhalation of 2,500 ppm (6,400 mg/m³) caused slight ossification changes in the offspring and maternal mortality in the mice. Co-administration of 15% ethanol in drinking water resulted in maternal toxicity, but no elevation in fetal effects above that seen for ethanol exposure alone.

Male mice exposed to 30,000 ppm (76,800 mg/m³) VC 6 hours/day for 5 days were mated to control females, with no resultant increase in spontaneous abortions (Purchase, 1975). However, Bi *et al*. (1985) showed that inhalation exposure of male rats to 100 ppm VC for 6 hours/day, 6 days/week for 3 months resulted in significant damage to seminiferous tubules compared to controls ($p < 0.05$).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 180,000 µg/m³

Study	Baretta *et al*., 1969
Study population	4-8 healthy human volunteers
Exposure method	(1) 7.5 hour exposures to 261 ppm VC (2) 3.5 hour exposures to 491 ppm VC (3) 7.5 hour exposures to 493 ppm VC
Critical effects	subjective reports of mild headaches and dryness of eyes and nose (groups 2 and 3); no effects reported by group 1
LOAEL	3.5 to 7.5 hour exposure to 491 or 493 ppm
NOAEL	7.5 hour exposure to 261 ppm
Exposure duration	7.5 hours
Equivalent 1 hour concentration	715 ppm (C^2 * 1 hr = [261 ppm]^2* 7.5 hrs)

LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	72 ppm (180 mg/m³, 180,000 µg/m³)

Level Protective Against Severe Adverse Effects

Exposure of guinea pigs to 10,000 ppm VC for 8 hours did not produce signs of CNS depression (Patty *et al*., 1930). Exposure to 25,000 ppm produced motor ataxia and unsteadiness within 5 minutes and unconsciousness in 90 minutes. Exposure to 100,000 ppm produced motor ataxia within 2 minutes in guinea pigs (Patty *et al*., 1930) and motor ataxia with a pronounced tremor within 15 minutes in rats and mice (Mastromatteo *et al*., 1960). Higher concentrations of VC (200,000 and 300,000 ppm) reduced the onset of CNS depression to 1 to 2 minutes following initiation of exposure (Mastromatteo *et al*., 1960).

Based on the results of Patty *et al*. (1930), the NOAEL for motor ataxia, or muscular incoordination, in guinea pigs was 10,000 ppm for 8-hour exposure. The LOAEL was 25,000 ppm, which resulted in motor ataxia within 5 minutes and unconsciousness in 90 minutes. The NOAEL was adjusted to a 1-hour exposure by the formula C^n x T = K (where "n" = 2), which resulted in a concentration of 28,282 ppm VC. Applying uncertainty factors of 10 each to account for interspecies differences and increased susceptibility of sensitive human individuals results in a final value of 280 ppm (720 mg/m³) VC for a level protective against serious adverse effects.

Level Protective Against Life-threatening Effects

Log-normal analysis of lethality data for mice, guinea pigs, and rabbits (Prodan *et al*., 1975) yielded BC_{05} estimates of 246,000, 453,000, and 466,000 mg/m³, respectively. Mastromatteo *et al*. (1960) reported 30-minute no-observed-lethality levels of 100,000, 300,000, and 400,000 ppm, respectively, for mice, rats and guinea pigs.

The study by Prodan *et al*. (1975) provides data from which to derive an estimate for VC using the benchmark concentration approach. The BC_{05} of the most sensitive species, the mouse, was adjusted to a 1-hour equivalent exposure using the equation C^n x T = K, where "n" = 2. Uncertainty factors of 3 and 10 were applied to the adjusted BC_{05} of 348,000 mg/m³ (136,000 ppm) to account for interspecies differences and increased susceptibility of sensitive human individuals, respectively. The resultant level protective against life-threatening effects is thus 4,500 ppm (12,000 mg/m³).

VIII. References

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