excessive exposure, since 0.2 ppm was tolerable although disagreeable to a small series of test subjects.

3 UNSATURATED HALOGENATED HYDROCARBONS

3.1 **Vinyl Chloride,** Monochloroethylene, chloroethene, CAS 75-01-4

$$CH_2{=}CHCl$$

3.1.1 Uses and Industrial Exposures

Vinyl chloride is used as a chemical intermediate primarily as a monomer in plastic manufacture. The fire and explosion hazards were generally considered to be the dominant problem in handling vinyl chloride until 1974, when it was reported that three cases of angiosarcoma of the liver had occurred in workmen grossly exposed to vinyl chloride. Subsequently many diseases have been alleged to have been caused by exposure to vinyl chloride. Because many of these alleged effects are poorly documented it is difficult to draw solid conclusions at this time and the reader is cautioned to evaluate the literature carefully. One thing is certain, vinyl chloride is significantly more toxic than was generally accepted prior to 1974. It is hepatotoxic, carcinogenic, and possibly mutagenic. Acroosteolysis has been associated with vinyl chloride and polyvinyl chloride production. It will be possible to discuss only a few of the rapidly growing number of references. Numerous bibliographies and literature surveys are available, including those by von Oettingen (33); Warren et al. (287); NCI (288); and IARC (289).

3.1.2 Physical and Chemical Properties

Physical state	Gas
Molecular weight	62.5
Specific gravity	0.9121 (20/4°C)
Melting point	−153.71°C
Boiling point	−13.8°C
Vapor pressure	2580 torr (20°C)
Solubility	0.25 g/100 ml at 25°C; soluble in ethanol, ethyl ether
Stability	May produce peroxides
Flash point	−78°C (open cup)
Autoignition temperature	472.22°C
Explosive limits	4 to 22 percent by volume in air

1 mg/liter ≈ 391 ppm and 1 ppm ≈ 2.56 mg/m^3 at 25°C 760 torr

3.1.3 Physiologic Response

Summary. Because vinyl chloride is a gas the only significant route of toxic exposure is inhalation. If it is confined on the skin in a liquid, some might be expected to be absorbed, but the relative amount is small. The likelihood of acute effects is not nearly as significant as are liver injury, angiosarcoma, and probably acroosteolysis which may occur following excessive repeated exposures.

It appears that metabolism of vinyl chloride is necessary before many of its toxic effects occur.

Single or Short-Term Exposure. The primary acute physiological effect of vinyl chloride is depression of the central nervous system, which begins to occur at concentrations of 8000 to 10,000 ppm (290). Early studies as a surgical anesthetic were discouraged by its high flammability and by cardiac and circulatory disturbances noted in animals and patients at the 10 to 20 percent concentration necessary to produce surgical anesthesia (291–293).

Acute liver toxicity even at these concentrations appeared to be low, but there have been suggestions of a delayed carcinogenic response following massive subacute exposures (294).

Repeated or Prolonged Exposure. Essentially no investigations were published on the response to chronic vapor exposure prior to 1961. Schaumann exposed mice and rats and found that they tolerated a level sufficient for "light narcosis" for periods of 4 hr/day for 5 to 8 consecutive days or for 1 hr/day for 4 weeks without showing kidney or liver injury [as cited by Lehmann and Flury (102)]

Torkelson et al. (295) report on repeated exposures of animals for 7 hr/day, 5 days/week. At 500 ppm, rats showed increased liver weight and histopathology. At 200 and 100 ppm, rats showed increased liver weight, but no changes could be observed in dogs or guinea pigs. All species tolerated 50 ppm for 6 months with no adverse effect. Repeated exposures for 1 hr/day at 200 or 100 ppm were tolerated without observable effect. The effects on the liver were mild and apparently reversible, since they were not observed in rats kept 6 to 8 weeks after the 6 months exposures ceased. This was the longest period any animals were observed in this study.

Noncarcinogenic effects in the liver have been reported in the oncological studies reported later.

Teratogenesis, Mutagenesis, and Carcinogenesis. ***Teratogenesis.*** At least two studies have shown no teratological response in laboratory animals inhaling vinyl chloride during pregnancy; however, fetotoxic effects were observed particularly when ethanol was administered simultaneously in the drinking water.

John et al. (296) evaluated the effects on mice, rats, and rabbits. Groups of pregnant CF-1 mice, Sprague-Dawley rats, and New Zealand white rabbits were exposed to 500 ppm vinyl chloride 7 hr daily during organogenesis. Mice were also exposed to 50 ppm and rats and rabbits to 2500 ppm. Maternal toxicity was observed, most prominently in the mice, but the exposures did not cause significant embryonal or fetal toxicity or teratological effect. Simultaneous administration of 15 percent ethanol in the drinking water produced toxic effects greater than those of vinyl chloride alone. Maternal toxicity was increased more than embryotoxicity.

Ungvary et al. (297) have shown that vinyl chloride crosses the placenta and is found in the amniotic fluid and fetal blood as well as the maternal blood of rats. Pregnant rats were exposed continuously to 1500 ppm (4000 mg/m^3) during the first, second, or third trimester of pregnancy with no teratological effects. No embryotoxicity was noted when vinyl chloride was administered during the second or third trimester, but during the first trimester it increased fetal mortality and caused other fetotoxic effects. Fetal losses and induction of CNS malformation due to trypan blue administration were not potentiated by a combined exposure of pregnant rats to vinyl chloride and the dye.

Mutagenesis. Numerous references attest to the mutagenic effect of vinyl chloride or its metabolites in in vitro systems using bacteria, yeast, and hamster cells. Drosophila males treated with 1 to 20 percent vinyl chloride vapors had an increased frequency of complete and mosaic recessive lethals. Muratov and Guskova (298) reported that continuous exposures of rats to 0.15, 0.4, or 10 mg/m^3 (60, 160, or 3900 ppm) for 3.5 months increased the incidence of chromosomal fragmentation, agglutination, and bridging. The incidence was reportedly increased when the rats were housed at 35°C rather than at 22°C. No mutagenic effects were observed at 0.07 mg/m^3 (28 ppm).

Inhalation of 2500 or 5000 ppm 4 hr/day for 5 days or intraperitoneal injection of 300 or 600 mg vinyl chloride/kg/day resulted in chromosomal changes in the marrow cells of Chinese hamsters (299). However, Anderson et al. (300) reported the lack of dominant lethal effect in a study in which mice were exposed to 3000, 10,000, or 30,000 ppm for 5 days. Similarly Short et al. (301) found no evidence of pre- or post-implantation loss in female rats mated with males which had been exposed for 11 weeks to 0, 250, or 1000 ppm. Exposures were 6 hr/day, 5 days/week.

Carcinogenesis. Since Viola et al. in 1970 (302) reported the production of tumors in rats by exposing them to 30,000 ppm vinyl chloride, numerous other studies have confirmed the carcinogenicity to rats as well as mice and hamsters. Maltoni (303) in 1973 first reported angiosarcomas of the liver, which in 1974 were also observed in man (304).

Maltoni's group has exposed laboratory animals 4 hr/day for 1 year to vapor

concentrations ranging from 30,000 to 1 ppm and has fed olive oil solutions by gavage (305). The animals were kept for their lifetimes following treatment. These studies and those of many other investigators have produced a wide range of tumors, particulary at high concentrations.

In a summary paper of his massive studies, Maltoni states that liver angiosarcoma, carcinoma of the Zymbal glands, nephroblastoma, neuroblastoma, mammary adenocarcinoma, forestomach papilloma and acanthoma, extrahepatic angiosarcoma, and hepatoma in the rat were correlated to exposure to vinyl chloride (305). Table 48.12 from Maltoni's summary paper describes those tumors that occurred at the lowest dosages.

None of the previously cited tumors were observed at 5 ppm by inhalation and 0.03 mg/kg by ingestion. There appear to be marked differences between strains of animals and between species, with mice more susceptible than rats, which are more susceptible than hamsters (306). Based on angiosarcoma of the liver, all species appear considerably more susceptible than man. The discussion by Gehring et al. (307) of the relationship between species as it relates to production of reactive metabolites is presented in the following section.

Metabolism and Biologic Monitoring. Numerous studies indicate that probably a reactive metabolite, not vinyl chloride per se, is responsible for its toxicity. Although some inhaled vinyl chloride is excreted unchanged (308), depending on the dose, a varying amount is metabolized. The metabolism of vinyl chloride has been the subject of numerous recent studies which need confirmation and interpretation. Currently it is thought that vinyl chloride is metabolized by epoxidation with subsequent production of chloroacetaldehyde. Further oxi-

Table 48.12. Onset of Tumors Considered as Vinyl Chloride Correlated, at the Lowest Dose (305)

Dose	No. of Animals	Results
25 ppm	120	5 liver angiosarcomas
		4 Zymbal gland carcinomas
		1 nephroblastoma
10 ppm	120	1 liver angiosarcoma
		2 extrahepatic angiosarcomas
		2 Zymbal gland carcinomas
1 mg/kg	150	3 liver angiosarcomas
		1 extrahepatic angiosarcoma
		1 hepatoma
		5 Zymbal gland carcinomas
0.3 mg/kg	150	1 liver angiosarcoma
		1 hepatoma

dation and conjugation with glutathione are responsible for the metabolites found in urine.

Gehring et al. (307, 309) analyzed the metabolic and carcinogenic data from man and laboratory animals. Using several models to predict the incidence in man from animal data, they found that all models overpredicted unless corrections were made for rates of metabolism and for surface area of the different species.

Observations in Man. Tamburro (310) has concluded that current clinical, biochemical, and hematologic tests are of limited value in predicting angiosarcoma but may be of value in other hepatotoxic effects.

Laboratory Studies. Limited human studies by Mastromatteo et al. (290) have shown that concentrations must approach 1 percent (10,000 ppm) before humans notice the anesthetic effects of vinyl chloride gas. Surgical anesthesia requires concentrations greater than 10 percent. Baretta et al. (308) studied expired air of subjects exposed to 50, 250, or 500 ppm for 7.5 hr with a half-hour lunch break. Although they concluded that expired air sampling might have utility in monitoring exposure at the occupational standards then in use, expired air can be expected to be of little value at currently accepted levels of exposure.

Industrial Experience. The early industrial history of vinyl chloride is remarkably free of adverse reports except for problems of fire and explosion. The earliest reports of adverse effect on industrial workers related to vinyl chloride were to anesthesia and anesthetic deaths. Danziger (311) reported two fatal cases, only one of which was definitely ascribed to a massive exposure to vinyl chloride. Other reports indicate exposures were poorly controlled, and probably were to thousands of parts per millions in many situations prior to 1974.

Cutaneous lesions (scleroderma), collagen disease, and Raynaud's syndrome were reported by Suciu et al. (312) to have been observed in a polyvinyl chloride (PVC) plant, but contrary to some reports these authors did not ascribe the effects to vinyl chloride per se; rather they considered them to be related to other materials used in the factory. Subsequently numerous authors reported acroosteolysis in PVC workers in Europe and the United States. This was accompanied by scleroderma and Raynaud's syndrome. Recently a vast number of alleged effects on the liver and other organs have been reported. Although it is possible that some of these effects associated with PVC production may be related to vinyl chloride, most reports have failed to eliminate other chemicals as possible causes of injury. Furthermore, there is rarely an indication of the concentrations inhaled.

There appears to be no question that angiosarcoma of the liver has been caused by exposures to vinyl chloride primarily while cleaning reactor vessels,

As of May 1980, approximately 85 cases have been found worldwide, with five to six others probable (313). Angiosarcomas are certainly consistent with the results of animal studies in which these tumors have been produced in several studies; however, the epidemiologic evidence is not consistent from one study to the next, in regard to other cancers or toxic effects. Some of the most careful studies on populations in which several angiosarcomas have occurred do not confirm liver injury, splenomegaly, blood changes, respiratory injury, or other effects alleged to have been seen in other studies. Acroosteolysis, scleroderma, Raynaud's syndrome, angiosarcoma of the liver, and mutagenic changes appear to have been most conclusively shown to occur as a result of exposure of workmen to vinyl chloride. It appears probable that other effects such as other tumors, hepatic injury, and splenomegaly may also be related, but other causative agents have not been eliminated. Other effects are not well established and must at this time be considered as associated with the PVC/VCM production process but not necessarily with the monomer itself. Continued insistence by some that vinyl chloride per se is the causative agent of all those effects is probably retarding our acquisition of knowledge of the true cause of injury.

3.1.4 Hygienic Standards

The ACGIH in 1980 recommended 5 ppm (10 mg/m^3) as threshold limit value for vinyl chloride. The U.S. Department of Labor (OSHA) standard is 1 ppm, and the standards in other countries vary, but generally require that exposures be limited to 5 to 10 ppm or less. It appears reasonable to assume that these levels established to protect against angiosarcoma of the liver will prevent other adverse effects as well.

3.1.5 Odor and Warning Properties

Although vinyl chloride has an odor at high concentrations, it is of no value in preventing excessive exposure. The actual vapor concentration that can be detected has never been adequately determined and varies from one individual to another, from impurities in the sample and probably from duration of exposure.

3.2 **Vinyl Bromide,** Monobromoethylene, Bromoethene, CAS 593-60-2

$$CH_2{=}CHBr$$

3.2.1 Uses and Industrial Exposure

Vinyl bromide is used as a copolymer in the production of flame resistant acrylic polymers and to a limited extent as a chemical intermediate. A toxicology review is available (289).