Patty's Industrial Hygiene and Toxicology

THIRD REVISED EDITION

Volume 2B
TOXICOLOGY

1981

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A WILEY-INTERSCIENCE PUBLICATION
JOHN WILEY & SONS, New York • Chichester • Brisbane • Toronto

Calingaert and Shapiro (182) have observed that ethylene dibromide can penetrate through several types of protective clothing, particularly neoprene rubber and several types of plastic gloves. Nylon was found to be the most resistant material but lacking in good physical characteristics. These authors proposed a combination of neoprene and nylon.

Human experience during manufacture of ethylene dibromide has been summarized (183). The mortality of two populations of employees was compared to that expected in an industrial population. In neither study was there evidence of increased deaths due to cancer. However, the populations were small; hence the statistical confidence ranges are very broad. Nevertheless, it is obvious that a one-hit statistical model based on animal data severely overestimates the number of tumors predicted in human populations exposed during the production of ethylene dibromide (184).

The reproductive history of 297 male employees manufacturing ethylene dibromide was also summarized (185). In this limited study, reproduction generally appeared to be unaffected by exposure to ethylene dibromide, although one of four plants had fewer children than predicted.

2.17.4 Hygienic Standards

No threshold limit value for ethylene dibromide was recommended by the ACGIH in 1980 although it was included in their list of animal carcinogens. It would appear prudent to limit exposure to a maximum time-weighted average of 5 ppm or less with careful control to minimize dermal contact.

2.17.5 Odor and Warning Properties

The odor of ethylene dibromide is not unpleasant and has been termed "chloroformlike." The odor is not detectable at a low enough concentration to be considered a good warning of excessive exposure.

2.18 Methyl Chloroform, 1,1,1-Trichloroethane, CAS 71-55-6

CH_3CCl_3

2.18.1 Uses and Industrial Exposures

Methyl chloroform is used almost exclusively as a solvent. Worldwide consumption is about 1 billion lb/year. Increasing consumption is due to a favorable combination of chemical, flammability, physical, and toxicologic properties, compared to many other common solvents. Most commercial methyl chloroform, which is sold under several trade names, contains inhibitors to prevent reaction of the solvent with aluminum and aluminum alloys. This reaction produces

hydrogen chloride and in confined vessels may produce high pressures. Extensive testing and human experience indicate 1,1,1-trichloroethane is probably the least toxic of the chlorinated solvents, but its high volatility and careless use and abuse have resulted in anesthetic deaths from gross exposure, usually in confined spaces.

2.18.2 Physical and Chemical Properties

Physical state	Colorless liquid
Molecular weight	133.42
Specific gravity	1.3249 (26/4°C)
Boiling point	74.1°C
Vapor pressure	127 torr (25°C)
Refractive index	1.43765 (21°C)
Percent in "saturated" air	16.7 (25°C)
Solubility	0.09 g/100 ml water at 20°C; soluble in ethanol, ethyl ether
Flammability	(see note below)

1 mg/liter ≈ 183 ppm and 1 ppm ≈ 5.46 mg/cm^3 at 25°C, 760 torr

Note: The flammable characteristics of methyl chloroform are similar to those of trichloroethylene. It has no flash point or fire point by ASTM procedures for Tag closed cup and Cleveland open cup tests. Limits of flammability of vapors of inhibited 1,1,1-trichloroethane have been found to be 10 to 15.5 percent in air with hot wire ignition. A considerable amount of energy is required for ignition. It will not sustain combustion (186).

2.18.3 Physiologic Response

Summary. The principal and first response from acute or chronic exposure to excessive amounts of methyl chloroform is depression of the central nervous system. It has little capacity to produce organ injury from either single or repeated exposures but at high levels can sensitize the heart to epinephrine.

The 1,1,1-trichloroethane isomer is considerably less toxic than the 1,1,2-trichloroethane isomer. Owing to an error in the literature, several authors have indicated the reverse. Torkelson et al. (187) have explained the circumstances and documented the literature.

Concentrations in excess of 14,000 to 15,000 ppm are fatal to animals. Human fatalities due to anesthesia (and/or cardiac arrhythmia) have occurred in confined spaces when exposures to high concentrations have not been promptly terminated. In cases where the victim has been alive when removed from the

high concentration, recovery has generally been rapid and complete. Abuse (sniffing) has also resulted in deaths. Several reviews have been published (188–190).

Single or Short-Term Exposure. ***Oral.*** Torkelson et al. (187) reported the oral LD_{50} for several species to be as follows: male rats, 12.3 g/kg; female rats, 10.3 g/kg; female mice, 11.24 g/kg; female rabbits, 5.66 g/kg; and male guinea pigs, 9.47 g/kg. Deaths were due primarily to anesthesia. Recovery was rapid and complete in surviving animals.

Eyes. The material caused only minor, transient irritation in the eyes of rabbits.

Skin. The skin shows only slight reddening and scaliness from contact. The reaction is somewhat increased on repeated exposures. Confinement of the liquid on the skin results in considerable pain and irritation (187).

Skin Absorption. Applied under a cuff for 24 hr, 3.9 g/kg was survived by all rabbits; 15.8 g/kg failed to kill all the rabbits treated with the undiluted liquid (187). Data on absorption of the liquid and vapor observations through human skin are presented in the section on observations in man.

Inhalation. Adams et al. (191) reported on the response of animals to acute exposure. Maximum time–concentrations in air survived by rats were as follows: 6 min at 30,000 ppm, 1½ hr at 15,000 ppm, and 7 hr at 8000 ppm. Maximum time–concentrations in air with no detectable injury in rats were as follows: 18 min at 18,000 ppm and 5 hr at 8000 ppm. It should be noted that the maximum level with no detectable injury is very close to the maximum level survived. This information has been confirmed by Torkelson et al. (187) using inhibited solvent. Others have reported similar low hepato- and renal toxicity in rats and other species (53, 192–194). Gehring (54) determined that at 13,500 ppm the LT_{50} was 595 min but that liver function as measured by SGOT was virtually unaffected unless exposures approached those causing anesthetic death.

Injection. Klaasen and Plaa reported an intraperitoneal LD_{50} of 3.9 g/kg in rats (194) and an LD_{50} of 120 m*M*/kg (16 g/kg) in mice (192).

Repeated or Prolonged Exposure. ***Inhalation.*** Adams et al. (191) exposed animals 7 hr/day, 5 days/week for 1 to 3 months. At 10,000 ppm rats showed staggering gait and weakness in 10 min. By 3 hr, they showed loss of color, irregular respiration, and semiconsciousness. Survivors had completely recovered by the following morning. For those that succumbed, death seemed to be due to either cardiac or respiratory failure. At 5000 ppm, there was definite

but mild narcotic effect within 1 hr. There was reduced activity. Rats survived for 31 exposures over 41 days without apparent injury. Rabbits showed slight retardation of growth at 5000 ppm. At 3000 ppm, rabbits and monkeys showed no response over a 2-month period. Guinea pigs showed a barely significant retardation of growth at 650 ppm.

Torkelson et al. (187) confirmed and extended these results, using inhibited material containing 2.4 to 3 percent dioxane, 0.12 to 0.3 percent butanol, and small amounts of ethylene dichloride, water, etc. Laboratory animals were exposed repeatedly to 500, 1000, 2000, or 10,000 ppm in order to establish conditions safe for repeated exposure. Rats, guinea pigs, rabbits, and monkeys were unaffected after 6 months of repeated 7-hr exposures 5 days/week to 500 ppm. Female guinea pigs, which were found to be the most sensitive in previous experiments, were able to tolerate 1000 ppm for 0.6 hr/day with no detectable adverse effects. Male rats tolerated exposure of 0.5 hr/day to 10,000 ppm with no organ injury.

The section on tetrachloroethylene describes the result of repeated exposure to a mixture of 1,1,1-trichloroethane and tetrachloroethylene (404).

Even continuous (24 hr/day) exposure for 14 weeks produced remarkably little injury to rats, mice, dogs, and monkeys at 1000 ppm and essentially no effect at 250 ppm except minor, apparently reversible cytoplasmic alterations in the livers of mice (124). After exposure to 1000 ppm dogs and monkeys were considered unaffected by the exposure but the rats and mice exhibited significant increases in liver weight and liver triglycerides and fatty and necrotic changes visible microscopically in the livers.

Quast et al. (195) repeatedly exposed groups of 96 rats of each sex to 875 or 1750 ppm 1,1,1-trichloroethane vapor 6 hr/day, 5 day/week for 1 year with no adverse effects (see section on carcinogenicity).

Teratogenesis Reproduction, Mutagenesis, and Carcinogenesis. ***Teratogenesis and Reproduction.*** Pregnant female rats and mice were exposed 7 hr/day on days 6 to 15 of gestation and the mothers and fetuses examined for teratological effects (63). The inhaled vapor concentration was 875 ppm of an inhibited formulation containing 5.5 percent inhibitors. No effects related to exposure were observed on either the mothers or fetuses. York et al. (473) repeatedly exposed female Long-Evans rats to 2100 ± 200 ppm of methyl chloroform vapors 2 weeks before breeding and until day 20 of gestation without effect on teratogenicity or subsequent neurobehavioral studies of the offspring allowed to deliver normally.

Riddle et al. (477) modified a multigeneration reproduction study to include screening for dominant lethal and teratogenic effects. Mice were fed water containing methyl chloroform so that daily dosage levels were 0, 99.4, 2640, or 8520 mg/kg. According to the authors, "There appeared to be no dose-dependent effects on fertility, gestation, viability, or lactation indices. Pup

survival and weight gain were not adversely affected. Gross necropsy of male and female F/O generation mice treated with 1,2-DCE or 1,1,1-TCE failed to reveal compound or dose-related effects."

Mutagenesis. Experimental results of mutagenic testing in vitro indicate negative results (11), or, at most, a very weak action. Similar to other chlorinated solvents small amounts of additional chemicals are frequently added to formulated products of methyl chloroform to stabilize against decomposition during use. Some of these stabilizers are electrophilic in nature and they may be responsible for the weakly positive findings in the Ames test reported sporadically (127). For example, in the case of trichloroethylene stabilized with epichlorohydrin, the stabilizer has been implicated as being responsible for the occasional positive results in in vitro and longer term animal carcinogenic studies. This is likely to remain a controversial issue but data available to date indicate that methyl chloroform per se is not likely to be positive in mutagenic tests. Methyl chloroform has been shown to be negative in a dominant lethal assay at daily doses as high as 8,500 mg/kg (477).

Carcinogenesis. Methyl chloroform has failed to demonstrate carcinogenic properties in two lifetime studies. When fed by gavage at daily doses of 1500 and 750 mg/kg/day for 2 years there was a significant increase in mortality in rats (197), possibly due to respiratory involvement related to the dosing technique. Mice were dosed in this NCI bioassay study with "time-weighted" average daily doses of 5615 and 2807 mg/kg. A moderate body weight depression occurred and survival was significantly decreased. No increase in tumors was observed but the massive doses fed caused so much mortality that the investigators were reluctant to assess the carcinogenicity from this study.

More reasonable yet high exposures were given by inhalation to male and female rats with no evidence of increased tumors (195). Male and female rats (96 of each sex) were exposed to either 1750 or 875 ppm of an inhibited 1,1,1-trichloroethane formulation 6 hr/day for 1 year and then kept for their lifetimes. No adverse effects on mortality, hematology, clinical chemistry, or gross and histopathology were observed, nor was there an increase in tumors of any type.

Extensive additional testing is currently underway on 1,1,1-trichloroethane. In our opinion the available data indicate it is very unlikely that carcinogenicity is of concern if exposure to 1,1,1-trichloroethane is kept below levels causing frank anesthesia.

Metabolism and Biologic Monitoring. The low systemic toxicity of methyl chloroform appears related to the small amount of metabolism which occurs in animals and man. Because of its low toxicity it has been used as a model compound in absorption–excretion studies (187, 198). In one of the first metabolic studies on this compound, Hake et al. (199) reported 97.6 percent of

radioactive methyl chloroform injected intraperitoneally was excreted unchanged by the lungs and only 0.85 percent of the radioactivity was found in the urine. This and subsequent studies on man and animals indicate that only small amounts of trichloroacetic acid and trichloroethanol may be found in the urine after injection or inhalation (200–203, 478), but that most of the dose is expired unchanged no matter what the route of administration. Enzymatic dechlorination by rat liver microsomes in vitro is very low and apparently not enhanced by enzyme inducers (204). The reaction is catalyzed by cytochrome P-450 in the presence of oxygen (205).

Stewart et al. (206), have produced a series of graphs making it possible to quantitate exposure based on expired air samples. Analysis of urine for metabolites probably has limited value. Monster (213) has also published extensive studies on biologic monitoring of 1,1,1-trichloroethane.

Observations in Man. Methyl chloroform has been evaluated as a surgical anesthetic but for several reasons, including lack of potency and effects on cardiac function, it was abandoned from serious consideration (207–209). It appears reasonable to assume that cardiac arrhythmias and fibrillations could be factors in some of the industrial deaths that have been reported from methyl chloroform. However, since industrial deaths have occurred in confined spaces as the result of exposures to obviously anesthetic levels, death could also have been due to anesthesia. If the subject has been alive when removed from exposure, recovery has generally been rapid and complete. In every fatality, misuse such as failure to prevent inhalation of high concentrations, failure to adequately ventilate confined spaces, or deliberate sniffing has apparently been involved.

Table 48.10 on the probable effects of exposure to humans to the vapor of methyl chloroform has been published for establishing emergency exposure limits (210).

Laboratory Studies. Numerous laboratory studies in man have permitted confirmation of much of the toxicologic data derived in animals. Stewart et al. in a series of papers have evaluated absorption and excretion following single and repeated inhalation exposures as well as dermal application. They have also evaluated the use of expired air for monitoring employee exposure and have produced a series of graphs based on expired air concentration following known exposures to various concentrations for different periods of time (206). These studies have also investigated metabolism and urinary excretion and evaluated clinical chemical parameters. Most important, however, are their studies to evaluate equilibrium, coordination, alertness, and other signs of anesthetic action. Based on these studies it has been concluded that, except for possible objections to odor, no untoward responses are observed even after repeated prolonged exposures of human subjects to 350 ppm. A few subjects

350,000 ppb billion

Table 48.10. Probable Result of Single Exposure to the Vapors of 1,1,1-Trichloroethane (210)

Exposure time (min)	Concentration in Air (ppm)	Expected Effect in Humans[a]
5	20,000	Complete incoordination and helplessness (R)
	10,000	Pronounced loss of coordination (R)
	5,000	Definite incoordination (R, M)
	2,000	Disturbance of equilibrium. Odor is unpleasant but tolerable (H)
15	10,000	Pronounced loss of coordination (R)
	2,000	Loss of equilibrium (H)
	1,000	Possible beginning loss of equilibrium (H)
30	10,000	Pronounced loss of coordination (R)
	5,000	Incoordination (R, M)
	2,000	Loss of equilibrium (H)
	1,000	Mild eye and nasal discomfort; possible slight loss of equilibrium (H)
60	20,000	Surgical anesthesia, possible death (R)
	10,000	Pronounced loss of coordination (R)
	5,000	Obvious loss of coordination (R, M)
	2,000	Loss of coordination (H)
	1,000	Very slight loss of equilibrium (H)
	500	No detectable effect, but odor is obvious (R, H)
	100	Apparent odor threshold (H)

[a] Expected effects are based on (H) human data, (M) monkey data, and (R) rat data.

may respond as concentrations approach 500 ppm, and if allowed to inhale 800 to 1000 ppm some subjects show minor CNS impairment. Other investigators (211) have found similar results but Gamberale and Hultengren (212) reported effects at lower vapor concentrations. Gamberale and Hultengren, however, used a mask to administer the vapors and this may have influenced their test results.

Monster (213) has published extensive studies on biologic monitoring of 1,1,1-trichloroethane, trichloroethylene, and perchloroethylene.

Liquid methyl chloroform has been shown by Stewart and Dodd (50) as well as Fukabori et al. (214) to be absorbed through the intact skin, but Riihimaki and Pfaffli (215) have shown that the vapors are not absorbed in toxicologically significant amounts.

Industrial Experience. Although chronic effects have been shown to be of little consequence in industrial exposure (216), failure to recognize the high vapor pressure of methyl chloroform and to prevent inhalation of high concentrations have resulted in reports of death. The number of deaths per year (two to three worldwide) appears to be decreasing relative to consumption, as proper precautions are being taken to avoid exposure. A few nonoccupational cases of deliberate sniffing have been reported, but generally a consistent pattern of use of the solvent in a confined space without regard for ventilation is the cause of industrial death. Stewart (188) discussed the consequences of overexposure and the treatment of overexposed subjects.

A rather extensive study of an industrial population exposed to methyl chloroform for up to 6 years confirms the data derived from animals (216). No effect of exposure was found in a matched-pair study of 151 subjects and 151 controls despite particular emphasis placed on hepato- and cardiotoxic effects.

2.18.4 Hygienic Standards of Permissible Exposure

The threshold limit value for methyl chloroform recommended by the ACGIH in 1980 was 350 ppm (1900 mg/m^3). This value provides a wide margin of safety from systemic injury. Peak concentrations should be limited to about 500 ppm to prevent beginning anesthesia in some subjects.

2.18.5 Odor and Warning Properties

Although methyl chloroform has a typical sweetish odor, it is not striking enough to be considered a good warning. The odor may be noticeable at concentrations near 100 ppm, well below those known to cause physiologic response. However, the odor at 500 ppm and even 1000 ppm is not so unpleasant as to discourage exposure. The odor has been described as strong and unpleasant at 1500 to 2000 ppm. Stewart et al. (206) reported female test

100,000 ppb.

subjects exposed to 350 ppm objected to the odor; however, this has not been an industrial problem.

2.19 1,1,2-Trichloroethane, Vinyl Trichloride, CAS 79-00-5

$$CHCl_2-CH_2Cl$$

2.19.1 Uses and Industrial Exposure

The use of 1,1,2-trichloroethane is quite restrictive. It is used to a slight extent as a speciality solvent and chemical intermediate, but the availability of other less toxic solvents discourages its use.

2.19.2 Physical and Chemical Properties

Physical state	Colorless liquid
Molecular weight	133.42
Specific gravity	1.443 (20/4°C)
Melting point	−36.7°C
Boiling point	113.5°C
Vapor pressure	25 torr (25°C)
Refractive index	1.4711 (20°C)
Percent in "saturated" air	3.3 (25°C)
Solubility	0.44 g/100 g water at 20°C; soluble in ethanol and ethyl ether
Flammability	Not flammable by standard tests in air

1 mg/liter ≏ 183 ppm and 1 ppm ≏ 5.46 mg/m^3 at 25°C, 760 torr

2.19.3 Physiologic Response

Summary. The principal physiologic responses to 1,1,2-trichloroethane are depression of the central nervous system and liver injury.

Similarity in chemical names has resulted in some confusion in older literature which misquoted work by Lazarew (217) and stated that the 1,1,2 compound was less toxic than 1,1,1-trichloroethane. Torkelson et al. (187) have explained the source of the error, which could be serious since 1,1,2-trichloroethane is much more hepatotoxic when given to animals by single or repeated doses. Consistent with the small quantity of the material used in industry and the care with which it is now generally handled, no published reports of human injury were found.

Single or Short-Term Exposure. ***Oral.*** Wright and Shaffer (218) reported that the oral lethal dose for dogs was 0.5 ml/kg. Irish (1) indicated an LD_{50} for rats of 0.1 to 0.2 g/kg. Liver and kidney pathology were seen at considerably lower doses. Gehring (54) included 1,1,2-trichloroethane in a series of chlorinated solvents evaluated for hepatotoxicity and considered it less hepatotoxic in the rat than carbon tetrachloride or chloroform, but markedly more toxic than 1,1,1-trichloroethane. Other investigators have confirmed this in mice as well as rats (194, 219). Kidney injury also occurs following oral and subcutaneous treatment of mice (196).

Skin and Eye. 1,1,2-trichloroethane is not highly irritating to the skin and eyes but, as with many other solvents, injures the skin by defatting.

Skin Absorption. Absorption of the liquid through the skin has been shown to occur in rabbits (11) and guinea pigs (220). In rabbits, three of four survived single 24-hr applications of 1 or 2 g/kg, but these dosages and 0.5 g/kg caused illness, delayed recovery, and liver and kidney injury. Jakobson and other coworkers also investigated the kinetics of absorption through the guinea pig skin as well as the nature of injury to the skin with prolonged contact (220, 221). Wahlberg (222) reported that repeated applications of 0.5 ml or more to the skin killed all the guinea pigs in 3 days, but 0.25 ml killed only 5 of 20 animals treated for a longer period of time. Although absorption does not appear to be a serious problem from acute exposure, prolonged or repeated exposure of the skin may result in manifestations of chronic toxicity.

Inhalation. Pozzani et al. (223) reported that a single 7-hr exposure to 500 ppm of the vapor was lethal to about half of the rats so exposed. Carpenter reported the acute lethal concentration for about half of the exposed rats to be 2000 ppm for a 4-hr exposure followed by a 14-day observation period.

Limited unpublished data (11) indicate a moderate to high toxicity in laboratory animals. Single 7-hr exposures to 500 and 250 ppm resulted in death of over half of groups of female rats. Autopsy of survivors showed marked injury to the liver and kidneys. Rats exposed to 250 ppm for 4 hr survived but also showed liver and kidney necrosis. Two- or 1-hr exposures apparently did not cause gross or microscopic injury. All rats survived a 7-hr exposure to 100 ppm but were not examined microscopically.

Repeated or Prolonged Exposure. Six months of repeated 7-hr exposures, 5 days/week to 15 ppm was tolerated by male and female rats, guinea pigs, and rabbits. No histopathological changes were observed on necropsy and the usual parameters of growth, mortality, organ weights, hemotology, and clinical chemistry were not affected (11).

However, 16 7-hr exposures to 30 ppm resulted in minor fatty changes and cloudy swelling in the livers of female rats. Male rats appeared unaffected, although pneumonitis was slightly higher in the 10 exposed rats than in the controls.

was not detectable at these levels. Thorough physiological examination of all who worked in these areas failed to show any indication of injury (organic injury or hematological effects) from the exposure (8).

Six months of industrial inhalation exposure of a young man to Orthosol, a product containing 95 percent of the ortho and 5 percent of the para isomer, resulted in severe pallor, exhaustion, and vomiting, with intense gastric pain and headache. Blood tests revealed a rapidly developing hemolytic anemia. Rapid and complete recovery followed cessation of exposure. Thirteen coworkers similarly exposed suffered no injury (38).

2.5.1 Skin

Eczematoid dermatitis of the hands, arms, and face of a 47-year-old glazier who worked with *o*-dichlorobenzene was described by Downing (39). Intense erythema and edema appeared promptly when the compound was applied locally to the skin of one arm. A large bullous lesion developed somewhat later.

2.6 Flammability

The explosive limits of *o*-dichlorobenzene are 2 to 9 percent by volume in air (8).

2.7 Odor and Warning Properties

The odor of *o*-dichlorobenzene is detectable by the average person at 50 ppm in air. Eye and nose irritation are not noted at this level. The odor becomes strong and the irritation noticeable at concentrations around 100 ppm. The compound has fair warning properties at this level, but the possibility of adaptation must be recognized (8). According to Varshavskaya (27) the threshold concentrations for odor and taste in water for *o*-dichlorobenzene are 0.002 and 0.0001 mg/liter, respectively.

2.8 Cancer

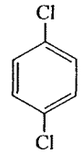
According to the June 1974 IARC report (31) on *o*- and *p*-dichlorobenzene, "No adequate studies on which to have an evaluation of carcinogenicity were available to the working group. . . . One report has suggested an association between leukemia and exposure to dichlorobenzenes, but this is insufficient evidence from which to assess the carcinogenic risk of this compound . . . ."

2.9 Hygienic Standards of Permissible Exposure

The threshold limit of *o*-dichlorobenzene adopted by the ACGIH in 1979 is 50 ppm (300 mg/liter). This concentration should not be exceeded, even instantaneously (25).

According to the 1980 *NIOSH–OSHA Pocket Guide to the Chemical Hazards* the permissible exposure limit is 50 ppm (300 mg/m^3); the immediately dangerous to life or health concentration (IDLH) is 1700 ppm (26).

3 *p*-DICHLOROBENZENE, $C_6H_4Cl_2$, 1,4-Dichlorobenzene



3.1 Uses and Industrial Exposures

p-Dichlorobenzene has been widely used as an insecticide, disinfectant, deodorant, and chemical intermediate. The potential for exposure exists for those involved in the manufacture, handling, and use of this compound.

3.2 Physical and Chemical Properties

Physical state	Colorless or white crystals
Molecular weight	147.01
Specific gravity	1.248 (55°C)
Melting point	53°C
Boiling point	174°C
Vapor density	5.07 (air = 1)
Solubility	Insoluble in water; soluble in benzene, alcohol, diethyl ether
Flash point	53.8°C (open cup)

1 mg liter = 166.3 ppm and 1 ppm = 6.01 mg/m^3 at 25°C, 760 mm Hg

3.3 Effect in Animals

3.3.1 Acute Toxicity

Oral administration of 1 g of *p*-dichlorobenzene/kg body weight to dogs for the treatment of intestinal worms produced no deleterious effect (40); however, Dikmans (41) reported that single doses of 0.5 or 1.0 g/kg produced severe signs of intoxication, and in one dog, death.

Hollingsworth et al. (1) fed *p*-dichlorobenzene to rats as a 20 percent solution in olive oil. The rats survived single doses of 1 g/kg of body weight, but all animals succumbed to a dose of 4 g/kg of body weight. Guinea pigs were fed a 50 percent solution and survived a single dose of 1.6 g/kg body weight, but succumbed to a dose of 2.8 g/kg of body weight (8).

The subcutaneous LD_{50} in 22- to 26-g dd-y mice was reported as 5145 mg/kg. The animals developed tremors within 2 to 3 hr, which continued for 3 or more days, and died of respiratory failure (42).

According to Varshavskaya (43) the oral LD_{50}s of *p*-dichlorobenzene and related compounds for mice, rats, rabbits, and guinea pigs are as shown in Table 49.4.

3.3.2 Subacute Toxicity

The intramuscular injection of 20 daily doses of 125 mg of *p*-dichlorobenzene in guinea pigs produced a state of coagulative deficiency as a result of reduced activity of the prothrombin complex and thrombokinase. The concurrent administration of lipotropic agents resulted in a protective action (44).

Totaro and Licari (45) also injected 125 mg daily doses for 20 days in guinea pigs and found this treatment to cause loss of body weight and an increase in blood serum transaminase activity. The concurrent administration of betaine, chlorine, or vitamin B_{12} (lipotropic agents) produced protective action.

According to the CMA report (7), Rimington and Ziegler (46) reported that feeding 1140 mg monochlorobenzene/kg, 455 mg *o*-dichlorobenzene/kg, or 770

Table 49.4. Oral LD_{50}s for Chlorobenzenes (43)

	LD_{50} (mg/kg Body Weight)		
Species	Monochlorobenzene	*o*-Chlorobenzene	*p*-Chlorobenzene
White mice	1445	2000	3220
White rats	2390	2138	2512
Rabbits	2250	1875	2812
Guinea pigs	5060	3375	7595

mg *p*-dichlorobenzene/kg to male white rats by gastric intubation for 5, 15, and 5 days, respectively, induced experimental hepatic porphyria. The treatment caused increased urinary coproporphyrin excretion, followed by increases in porphobilinogen and γ-aminolevulinic acid excretion. The mono and ortho compounds caused severe liver damage with intense necrosis and fatty changes. Rats with livers thus damaged displayed significantly decreased activities of liver catalase.

3.3.3 Chronic Toxicity

An extensive vapor study in animals was reported by Hollingswoth et al. (1) in 1956. They exposed the animals 5 days/week, 7 hr/day for extended periods of time. Rats, guinea pigs, and rabbits exposed to 798 ppm in air showed definite reactions of toxicity. Exposures ran from a few to as many as 69; an occasional animal died. Signs of intoxication included tremors, weakness, weight loss, eye irritation, and unkempt appearance; some became comatose. Histopathologically, the liver showed cloudy swelling and central necrosis. There was also a slight cloudy swelling of the tubular epithelium of the kidneys in some animals. Rabbits showed some lungs changes.

At a vapor concentration of 341 ppm, rats and guinea pigs survived for a period of 6 months. There was slight growth depression in male guinea pigs, a slight increase in average liver weight in male rats, and slight pathologic changes in the liver of male guinea pigs. At a concentration of 158 ppm, animals survived exposures lasting from 137 to 219 days. No adverse effects on growth or mortality were observed in rats, mice, rabbits, or monkeys. There was slight growth depression of the guinea pigs. Liver weights were slightly increased in male and female rats and in female guinea pigs; there was some questionable histophatologic changes in the liver. At a concentration of 96 ppm, rats, guinea pigs, rabbits, mice, and a monkey were exposed for periods up to 6 or 7 months. No adverse effects on many species of animal were observed (8).

Zupko and Edwards (47) exposed groups of rabbits, rats, and guinea pigs 20 to 30 min/day for up to 34 days to a *p*-dichlorobenzene vapor concentration of approximately 100 mg/liter of air. Each exposure induced intense irritation of eyes and nose, tremors and twitches of the extremities, loss of righting reflex, definite nystagmus, and rapid but labored respiration. The animals, as a rule, recovered from these signs of intoxication in 30 min to 2 hr; the use of the hind legs was always the last function to return to normal. Some animals died before the end of the exposure period. The compound was found to have a selective action on the granulocytes of the blood, producing a granulocytopenia in a majority of the animals. The total leukocytic (showing some increase in lymphocytes) and erythrocytic counts were not generally affected. The blood picture returned to normal within 30 days after the last exposure. Histological studies of 12 rabbits, 13 rats, and eight guinea pigs revealed lung damage and

a definite selective action on the kidneys. Every animal showed marked and extensive kidney damage. There was comparatively little liver damage or evidence of hepatitis.

Hollingsworth et al. (1) studied the effect of repeated oral administration of *p*-dichlorobenzene. Rats were fed 5 days/week, a total of 138 doses in 192 days. At a daily dose of 376 mg/kg, an increase in liver weight and a slight increase in kidney weight were observed. Microscopic examination of the liver revealed slight cirrhosis and focal necrosis. At 188 mg/kg, a slight increase in the average weight of the liver and kidneys occurred. No effects could be observed in rats at 18.8 mg/kg of body weight/dose. Similar liver and kidney changes were noted in rabbits following doses of 1000 mg/kg of body weight/dose; the effects were less intense, but there was definite injury at 500 mg/kg (8).

In 1958 Hollingsworth et al. (48) published their results on the effects of oral dosing (by stomach tube) of rats, five times a week for a total of 138 doses of 18.8, 188, and 376 mg of the para isomer per kilogram body weight. The lowest dose produced no deleterious effects. The 188 mg/kg dose caused a slight increase in liver and kidney weights. The repeated oral administration of the highest dose level resulted in a moderate increase in liver weight, together with slight cirrhosis and focal necrosis of the liver, a slight increase in kidney weight, and a slight decrease in the weight of the spleen.

Groups of rabbits were treated similarly with a dose of 500 mg/kg for as many as 263 doses over 367 days, and with 92 doses of 1000 mg/kg over a period of 219 days. Both dosage levels produced loss of body weight, tremors, weakness, cloudy swelling, and focal necrosis of the liver. The 1000 mg/kg dose caused some deaths (48).

3.4 Human Experience

3.4.1 Nonoccupational Exposure

The CMA report (7) summarized early *p*-dichlorobenzene intoxications, many of which were reported in the foreign literature.

A 62-year-old man, presumably because of home use of *p*-dichlorobenzene, began to suffer from dizziness, asthenia, anemia, and hypogranulocytosis. He recovered gradually after discontinuation of exposure (49).

A 19-year-old girl who worked for 18 months with an agent containing 90 percent of the para isomer and 10 percent of hexachloroethane suffered marked asthenia, dizziness, significant loss of body weight, a mild anemia, and hyperleukocytosis. She recovered rapidly after withdrawal from exposure. Two female workers who performed the same work suffered no abnormalities (50).

A 53-year-old woman who used *p*-dichlorobenzene crystals extensively in her home for 12 to 15 years suffered pulmonary granulomatosis. A lung biopsy revealed numerous small lesions which contained crystals physically similar to those of *p*-dichlorobenzene (51).

A number of similar intoxications were presented in some detail in the CMA report (7). Briefly, the signs and symptoms these individuals experienced included periorbital swelling, intense headache, and profuse rhinitis; or acute illness with nausea, headache, vomiting, weight loss, numbness, clumsiness, and a burning sensation in the legs. The latter subject lost 22.5 kg in 3 months, developed ascites, and died. One man, a 52-year-old trapper who used the compound on animal hides, suffered weakness, nausea, subacute yellow atrophy of the liver, jaundice with elevated serum bilirubin, and elevated alkaline phosphatase (52).

Campbell and Davidson (53) reported the unusual case history of a pregnant 21-year-old woman who developed a pica for the para isomer. She consumed, throughout pregnancy, one or two blocks of toilet air freshener per week, which were composed primarily of *p*-dichlorobenzene. She developed a severe hypochromic, microcytic anemia, with excessive polychromasia, and marginal nuclear hypersegmentation of the neutrophils. She recovered completely after withdrawal of the chemicals. Neonatal examination of the child revealed no abnormalities.

Statistics of poisonings in children disclosed *p*-dichlorobenzene to be the most frequent cause (4.9 percent) of all poisoning by household products in 1972 (54). For additional details of instances of intoxication refer to the CMA report (7).

According to Peterson and Liner (55) *p*-dichlorobenzene is the least toxic of the active ingredients in moth repellent products. Other ingredients are naphthalene and camphor; the latter was used particularly in the past. Naphthalene products look dry and are slowly soluble in cold ethanol whereas *p*-dichlorobenzene products appear wet and oily and are rapidly soluble in unheated ethanol. According to this report "ingestion of 20 g of *p*-dichlorobenzene has been well tolerated in man."

3.4.2 Occupational Exposure

The many incidents of intoxication that resulted from the household use of products containing *p*-dichlorobenzene contrast sharply with the scarcity of reports of industrial exposure to this compound.

According to the 1964 *Hygienic Guide Series* (56) on *p*-dichlorobenzene, voluntary industrial overexposure is unlikely. The most serious effects of overexposure are those of lung, liver, and kidney injury.

Hollingsworth et al. (1) reported on their extensive industrial experience in handling *p*-dichlorobenzene. They reported on 58 men who had worked continuously or intermittently on operations involving the handling of *p*-

dichlorobenzene for periods of 8 months to 25 years—an average of 4.75 years. Early investigations showed air concentrations ranging from 10 to 550 ppm, with an average of 85 ppm. A later study separated the job area into two ranges; one with concentrations from 100 to 725 ppm, with an average of 380 ppm; and another with concentrations from 5 to 275 ppm, with an average of 90 ppm.

A third survey was made after there had been some major changes in operations. The concentrations varied from 50 to 170 ppm, with an average of 105 ppm. Under these conditions, there were still some complaints of eye and nose irritation by the workmen. There were no complaints when air concentrations ranged from 15 to 85 ppm, with an average of 45 ppm. The men in these areas, throughout the different periods of study, were examined thoroughly. There was no evidence of organic injury, hematologic effects, or eye changes (8).

Von Oettingen in 1955 (4), and also Hollingsworth et al. in 1956 (1), reviewed the literature. According to Berliner (57) cataract formation followed exposure to a "mothproofing agent" containing *p*-dichlorobenzene. Considering also the publications of several other authors and the report by Pike (58) in particular, which stated that *p*-dichlorobenzene does not cause cataracts, and the report by Hollingsworth et al. (1) on industrial experience with this compound, it appears that Berliner's findings may have been due to chemicals other than *p*-dichlorobenzene, which were present in the "mothproofing agent" used (8).

Severe systemic effects were reported by Walgren (59) in eight workers employed in the production of moth deterrents with *p*-dichlorobenzene as the primary ingredient. The individuals developed irritation of the mucous membranes of eyes and throat, methemoglobinemia, and loss of appetite and body weight. Only one of the workers suffered an exposure that exceeded 1 year, and one worker only 1 month. Methemoglobin concentrations ranged between 0.12 and 0.29 g/100 ml blood. All cases showed increased muscle reflexes, ankle clonus, and fine finger tremors. Blood pressures were within the normal range. In the blood, slight diminution of erythrocytes and hemoglobin was observed, and relative lymphocytosis up to 63 percent. Four workers showed thrombocytopenia, and one workman had granulocytopenia. Sternal marrow was essentially normal. The interpretation of these data is difficult in the absence of the specific compounds involved other than *p*-dichlorobenzene in the working atmosphere.

3.5 Absorption, Metabolism, and Excretion

The compound is not absorbed through the intact skin in acutely hazardous amounts (4). Vapors of the compound are readily absorbed from the lungs. All indications are that absorption of the solid compound occurs readily from the gastroenteric tract. Fats and oils or organic solvents enhance absorption of the compound.

According to Azouz et al. (60), in the rabbit *p*-dichlorobenzene (0.5 g/kg) is oxidized mainly (approximately 30 percent) to 2,5-dichlorophenol, which is excreted conjugated. 2,5-Dichloroquinol is also formed (approximately 6 percent of the dose), but in contrast to the ortho derivative, no mercapturic acid or dichlorocatechol is formed. The excretion of the metabolites of *o*-dichlorobenzene is slow and appears to be complete in 5 to 6 days after feeding. With the para isomer the excretion of metabolites is incomplete, and is appreciable after 6 days.

Two metabolites appeared in the blood of male Wistar rats, fasted for more than 16 hr, then given orally 200 or 800 mg/kg of the para isomer (5.0 ml/kg dose, in a corn oil solution). The metabolites that remained in the blood for many hours after the para compound had practically disappeared were 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone. The authors (61) suggest that the storage and slow release of *p*-dichlorobenzene from the fatty body tissues is responsible for the prolonged presence of the metabolites in blood.

Carlson and Tardiff (62) studied the effect of chlorinated benzenes on the metabolism of foreign organic compounds. They found that 1,4-dichlorobenzene, 1,2,4-trichlorobenzene, 1-bromo-4-chlorobenzene, and hexachlorobenzene (but not chlorobenzene) decreased hexobarbital sleeping time immediately and/or to 14 days following treatment.

Cytochrome C reductase, cytochrome P-450, EPN detoxification, glucuronyl transferase, benzyopyrene hydroxylase, and azoreductase were increased to varying degrees by the administration for 14 days of these four chlorinated benzenes, at doses from 10 to 40 mg/kg per day. Administration of 1,4-dichlorobenzene or 1,2,4-trichlorobenzene for 90 days at these doses resulted in increases in EPN detoxification, benzopyrene hydroxylase, and azoreductase. The former two were still elevated 30 days after cessation of the administration of the compounds. 1,2,4-Trichlorobenzene was found to be a more potent inducer with cytochrome C reductase; cytochrome P-450 was also elevated and remained so through the 30-day recovery period. The authors concluded that even simple chlorinated benzenes can support the metabolism of foreign organic compounds (62).

Pagnotto and Walkley (63) investigated the value of measuring the urinary excretion of *p*-dichlorophenol as an index of industrial exposure to *p*-dichlorobenzene. Their study involved workers in a chemical manufacturing plant, in a household-products packaging factory, and in a plant where *p*-dichlorobenzene was employed in the manufacture of abrasive wheels. Exposure was almost exclusively due to vapor inhalation. The concentrations of *p*-dichlorobenzene in air ranged from 7.0 to 49.0 ppm (average 8 to 34 ppm). Spot air samples were collected during the work shift (usually 3 shifts/day).

Excretion of dichlorophenol in urine occurred as expected, starting very shortly after the exposure began and then rising to a maximum at the end of the exposure period. This was followed by an initial rapid decrease, then a more gradual reduction over a period of several days. In one instance, small but detectable amounts of dichlorophenol were found several weeks after cessation of exposure (63).

The presence of dichlorophenol in the urine is revealed also by its distinctive odor, which is noticeable at a level of 100 mg/liter and still detectable at about 20 mg/liter. The concentrations of dichlorophenol in the urine ranged from 10 to 233 mg/liter (average 14 to 103 mg/liter). No painful irritation of the eyes or nose was reported by the workers, except when there was direct contact with *p*-dichlorobenzene dust or crystals. These studies showed a fairly good correlation between the average air concentration of *p*-dichlorobenzene and the excretion of *p*-dichlorophenol at the end of an exposure period (63).

3.6 Eyes

Pike (58) exposed rabbits repeatedly for 8 hr to *p*-chlorobenzene vapor concentrations of 4.6 to 4.8 mg/liter (770 to 800 ppm). He also administered the compound orally to rabbits in repeated doses of 0.5 or 1.0 g/kg. His purpose for administering highly toxic doses was to observe possible harmful effects in the eyes of these animals. He noted "toxic eye-ground changes," but "no lens changes" in the rabbits. He concluded, based on the results in rabbits and his clinical experience, that these observations lead us to believe that cataracts are not produced by *p*-dichlorobenzene. He also administered naphthalene orally to rabbits and produced cataracts in these animals; hence it is very likely that earlier reports of cataract formation may have had their origin in other compounds used in the manufacture of "mothproofing agents."

Solid particles, vapors, or fumes of *p*-dichlorobenzene are very painful to the eyes and nose of man and animal. But in order for vapors to be painful, it is usually necessary for the material to be heated, or to be dispersed in such a way that there is a very large surface area for evaporation in a poorly ventilated area. *p*-Dichlorobenzene is painful to most people in concentrations between 50 and 80 ppm; the discomfort is quite severe at 160 ppm (8).

3.7 Skin

Solid *p*-dichlorobenzene causes very little irritation to the skin. It does produce a burning sensation when held in close contact with the skin for a prolonged period. Fumes from the surface of hot *p*-dichlorobenzene may irritate the skin slightly when the contact is repeated or prolonged. There is no evidence of significant absorption through the skin (8).

3.8 Odor, Taste, and Warning Properties

p-Dichlorobenzene has a very distinctive aromatic odor. The threshold of detection varies from 15 to 30 ppm in air. The odor becomes very strong at concentrations between 30 and 60 ppm. The vapors are painful to the eyes and nose at concentrations of 80 to 160 ppm. Above 160 ppm, they are intolerable to any person who has not been exposed to the compound long enough to have developed tolerance.

The odor and irritating effects are good warnings to prevent overexposure to *p*-dichlorobenzene. It should be recognized, however, that a person may become sufficiently accustomed to the odor to tolerate high concentrations (8).

Exposure of hens for 3 days to air containing 3.4 to 6.4 ppm of *p*-dichlorobenzene imparted an unpleasant, sweetish taste to the egg yolks. Ill effects in the hens were not noted and there was no reduction in egg production (64).

The threshold concentrations for odor and taste for *p*-dichlorobenzene in water were reported as 0.002 and 0.006 mg/liter, respectively (43).

3.9 Mutagenicity

Srivastava (65) studied the effect of *p*-dichlorobenzene on somatic chromasomes of *Vicia faba, V. narbonensis, V. hirsuta, Pisum arvense,* and *Lathyrus sativus.* Various mitotic anomalies were encountered. These included shortening and thickening of chromosomes, precocious separation of chromatids, tetraploid cells, binucleate cells, chromosome bridges, and chromosome breakage. Chromosome breaks generally took place at the heterochromatic regions.

3.10 Cancer

According to the International Agency for Research on Cancer (66), no adequate studies on which to base an evaluation of carcinogenicity were available to the "Working Group" at its meeting in Lyon, June 1974. ". . . One report has suggested an association between leukemia and exposure to dichlorobenzenes but this is insufficient evidence from which to assess the carcinogenic risk of this compound."

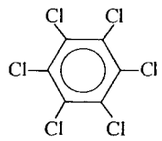
3.11 Hygienic Standards of Permissible Exposure

The threshold limits of *p*-dichlorobenzene adopted in 1979 by the ACGIH are TLV–TWA 75 ppm (450 mg/m^3) and TLV–STEL (tentative value) 110 ppm (675 mg/m^3). (25).

According to the 1978 *NIOSH–OSHA Pocket Guide to Chemical Hazards* the

permissible exposure limit is 75 ppm, and the immediately dangerous to life and health concentration is 1700 ppm (26).

4 HEXACHLOROBENZENE, C_6Cl_6, Perchlorobenzene



4.1 Uses and Industrial Exposure

Hexachlorobenzene is used as a fungicide to control wheat bunt and smut fungi of other grains. The technical grade used in agriculture contains 98 percent hexachlorobenzene, 1.8 percent pentachlorobenzene, and 0.2 percent 1,2,4,5-tetrachlorobenzene. Commercial formulations applied as dusts contain 10 to 40 percent hexachlorobenzene. Other applications include use as an additive for pyrotechnic compositions for the military, porosity controller in the manufacture of electrodes, intermediate in dye manufacture and organic synthesis, and wood preservative. Individuals engaged in the manufacture or handling of this compound are prone to industrial exposure. Aerial dispersion appears to be the major pathway for this compound entering the marine environment (67).

4.2 Physical and Chemical Properties

Physical state	White needles (monoclinic prisms)
Molecular weight	284.80
Specific gravity	1.5691 at 23.6°C
Melting point	230°C
Boiling point	322 (sublimes)
Vapor pressure	1 mm at 114.4°C
Vapor density	9.83
Solubility	Insoluble in water; slightly soluble in cold alcohol; soluble in benzene, chloroform, ether
Flash point	242°C
Fire hazard	Slight when exposed to heat or flame
Stability	Very stable, unreactive compound. There is no evidence that hexachlorobenzene is broken down by physical or chemical processes in the environment. It is "dangerous when heated to decomposition, it emits highly toxic fumes of chlorides" (EPA) (67)

1 mg/liter = 85.8 ppm and 1 ppm = 11.65 mg/m^3 at 25°C, 760 mm Hg

4.3 Effect in Animals, Absorption, Metabolism, and Excretion

4.3.1 Acute Toxicity

Hexachlorobenzene is of a low degree of toxicity. It is absorbed slowly from the gastroenteric tract, primarily via the lymphatic system. Oral LD_{50}s for laboratory animals are for cats, 1700 mg/kg; rabbits, 2600 mg/kg; rats, 3500 mg/kg; and mice, 4000 mg/kg. According to the EPA report, the average lethal oral dose for guinea pigs is 3000 mg/kg. For bluegill fish, rainbow trout, and channel catfish, the average lethal dose in water is given as more than 100 ppm (67).

4.3.2 Subacute Toxicity

Table 49.5 summarizes the subacute toxicity and signs of intoxication produced in rats, rabbits, mice, guinea pigs, chickens, and Japanese quail. This table was prepared by the EPA and is based on information from a 1975 report by the National Academy of Sciences (68).

4.3.3 Effect in Rats

Grant et al. (1974) (69) fed dietary concentrations of 10, 20, 40, 60, 80, and 160 ppm for 9 or 10 months to weanling male and female Sprague-Dawley rats; the 20 ppm dosage was about equal to 1 mg/kg body weight.

The response in the sexes differed to some extent, with the exception of hexachlorobenzene residues in the liver and the liver-to-body weight ratios in rats fed 80 and 160 ppm; these were dose-related but not sex-related. Also, the pharmacologic action of pentobarbital and zoxazolamine was shortened in both males and females fed 20 ppm and higher levels.

In males fed 40 ppm and higher concentrations, hepatic aniline hydroxylase and *N*-demethylase activities and cytochrome P-450 levels were increased; in females, these activities remained unaltered at all dietary levels.

In females fed 80 or 160 ppm, weight gains were reduced, and females but not males readily acquired chemical porphyria.

More recent reports include the investigation by Kuiper-Goodman et al. (70), who studied the subacute toxicity of hexachlorobenzene in Charles River strain rats fed a diet providing dosages of 0.5, 2, 8, and 32 mg of the compound in corn oil/kg body weight per day. Subgroups of rats were killed at 3, 6, 9, 12,