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THE HALOGENATED HYDROCARBONS OF INDUSTRIAL AND TOXICOLOGICAL IMPORTANCE

by

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HOFMANN, A. H., *Münch. med. Wschr.*, 69 (1922) 159.
HOTON, *J. Méd. Paris*, 19 (1907) 7.
KOCHMANN, M. and W. STRECKER, *Biochem. Z.*, 43 (1912) 412.
KÖNIG, R., *Arch. klin. Chir.*, 99 (1913) 147.
LARGE, S. A. and E. D. BROWN, *Laryngoscope*, 15 (1905) 883.
LAZAREW, N. W., *Arch. exp. Path. Pharmakol.*, 141 (1929) 19.
LEHMANN, K. B. and L. SCHMIDT-KEHL, *Arch. Hyg.*, 116 (1936) 157.
LOTHEISSEN, G., *Münch. med. Wschr.*, 47 (1900) 601.
MAASS, TH. A., *Ther. Monatsh.*, 21 (1907) 303.
MANUFACTURING CHEMISTS ASSOCIATION, *Safety Data Sheet*, SD–50, 1953.
MÉRAT and DE LENS (quoted from TH. A. MAASS, 1907).
MÜLLER, B., *Arch. klin. Chir.*, 75 (1905) 896.
NUCKOLLS, A. H., *Underwriters' Lab. Rep.*, No. 2375, Nov. 1933.
OETTINGEN, W. F. VON, C. C. POWELL, N. E. SHARPLESS, W. C. ALFORD and L. J. PECORA, *Nat. Inst. Hlth. Bull.*, No. 191 (1949); *Arch. int. Pharmacodyn.*, 81 (1950) 17.
RENNER, *Dtsch. med. Wschr.*, 44 (1918) 578.
SAYERS, R. R., W. P. YANT, C. P. WAITE and F. A. PATTY, *Publ. Hlth. Rep. (Wash.)*, 45 (1930) 225.
SCHOTT, E., *Arch. exp. Path. Pharmakol.*, 87 (1920) 309.
SCOTTI-FOGLIENI, L., *C. R. Soc. Biol.*, 105 (1930) 959, 961; 106 (1931) 222.
SEIFFERT, E., *Dtsch. med. Wschr.*, 49 (1923) 55.
SEITZ, J., *Correspondenzbl. Schweiz. Ärzte*, 31 (1901) 97, 411.
WEBSTER, W., *Amer. J. Physiol.*, 27 (1910) 328.
ZOEPFFEL, R., *Arch. exp. Path. Pharmakol.*, 49 (1903) 89.

10. ETHYLENE DICHLORIDE

Chemistry

Ethylene dichloride, *sym.*-dichloroethane, 1,2-dichloroethane, ethylene chloride, Dutch liquid, Brocide, ClH_2CCH_2Cl, has the molecular weight 98.97. It is a colorless liquid of pleasant odor and sweetish taste of the specific gravity 1.253 20°/4°, solidifies at —35.3° C and boils at 83.5° C. It is soluble in 100 parts of water to the extent of 0.9 parts at 0° and is freely miscible with alcohol, ether and most organic solvents.

When heated with alcoholic solution of potassium hydroxide, chloroethylene (vinyl chloride) is formed. In contrast to its isomer, ethylidene chloride, it is indifferent to cold and concentrated sulfuric acid, it does not react with Fehling solution, and does not give the isonitrile reaction of chloroform.

Ethylene dichloride is flammable and is classified as such (inflammable) by the Interstate Commerce Commission. Its flashpoint is 13.33° C (56° F) by the closed cup method and 18.33° C (65° F) by the open cup method. In contact with open flames it is decomposed with the formation of hydrochloric acid and other irritant vapors (Manufacturing Chemists Association, 1947). Its explosive limits in air are between 6.2 and 15.9% in air.

Manufacture

Ethylene dichloride is made commercially by treating ethylene with chlorine. In order to restrict the reaction to the formation of ethylene dichloride the temperature and/or the pressure are reduced and to increase the yield catalysts such as ferric chloride, bromine or lead are used.

Uses

Ethylene dichloride is used as a solvent for oils, fats, paraffin, casein, resins and gums, for the extraction of fats and oils, degreasing of machinery, and as a cleaning agent in soaps and scouring compounds. It is used as a coupling agent in ethyl antiknock fluids and in fumigant mixtures for insect control.

Determination in air

According to Bogatkow (1942) ethylene dichloride may be determined in air by passing the vapor–air mixture through manganese dioxide and determining the chlorine formed nephelometrically as silver chloride. Malnikow and Ssenilow (1940)

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heated the air sample for 2 h with sodium alcoholate and determined the chloride formed by Volhard's method.

Absorption, fate and excretion

Ethylene dichloride is absorbed through the lungs, from the gastro-intestinal tract, and, as shown by Schwander (1936) in mice, to a moderate extent also through the intact skin. It is not known whether it is decomposed in the organism, and whether it is excreted by other routes than through the lungs. As to its distribution in the organism Ollivier *et al.* (1954) found in a case of poisoning on a per kg organ weight basis, 140 mg in the brain, 110 mg in the kidneys, 85 mg in the liver, the same amount in the lungs, only traces in the blood, and none in spleen, stomach, and intestine.

Determination in biological materials

Ethylene dichloride may be determined in biological specimens by the method of Gettler and Siegel (1935) who described a special distillation apparatus and micro-rectification flask which can be used satisfactorily for this purpose.

Effect on laboratory animals

The effect of ethylene dichloride on laboratory animals is characterized by a depression of the central nervous system and according to Müller (1925) it ranks in this respect between chloroform and carbon tetrachloride which was confirmed by Lazarew (1929) who determined the narcotic concentration for mice as 0.00021 moles/l, that for chloroform as 0.00017 and that for carbon tetrachloride as 0.00032 moles/l. Similar results were reported by Lehmann and Schmidt-Kehl (1936) who noted that concentrations causing light and deep narcosis are very close together. Kistler and Luckhardt (1929) reported that in dogs narcosis is preceded by a period of marked excitement and copious salivation, that it takes 30 min for regaining consciousness from full narcosis, and that with narcosis for 15 min toxic

effects become apparent. According to these authors the intravenous injection of 0.5 ml/kg causes in dogs deep narcosis, slowing of the respiration, slow and weak heart beat and loss of reflexes in 8 min, the animals dying after 6 h without regaining consciousness. With one half this dose the narcosis lasted only 4 min, the animal regained consciousness in 20 min, but nevertheless died within 24 h. Doses of 0.125 ml/kg caused no narcosis, but only excitement and incoordination from which the animals recovered. The oral administration of 0.3 ml/kg caused temporary respiratory arrest and Cheyne-Stokes respiration.

As to the effect of ethylene dichloride on the circulation Führer (1921) showed that concentrations of 0.031 moles/l of saline caused arrest of the isolated frog heart, ethylene dichloride being in this respect inferior to chloroform and superior to ethyl chloride for which the corresponding concentrations were 0.007 and 0.046 moles/l respectively. Similar findings were reported by Kiessling (1921). Kistler and Luckhardt (1929) noted after oral administration to dogs a fall of the blood pressure proportionate to the dose, which, when not marked, returned to normal within a few minutes.

Regarding the toxicity of ethylene dichloride for laboratory animals Müller (1925) believed it to be less toxic than chloroform and carbon tetrachloride and more toxic than methylene chloride, Heppel *et al.* (1946) considered it as one of the more toxic chlorinated hydrocarbons, and Sayers *et al.* (1930) thought that it is of the same order of toxicity as chloroform and carbon tetrachloride with exposure for 1 hour, but less toxic than these with shorter exposures. Lazarew (1929) determined the minimal fatal concentration with 2 h exposure for mice as 35 mg/l. Sayers *et al.* studied its toxicity as illustrated in Table XXVII. Heppel *et al.* (1945b) found that single exposure for 7 h to 3,000 ppm (0.3% or 12.4 mg/l) was fatal to mice, rats, guinea pigs, and rabbits, the animals showing varying degrees of narcosis during the exposure, increasing weakness, and dyspnea before death, racoons and cats being somewhat more resistant.

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TABLE XXVII

THE TOXICITY OF ETHYLENE DICHLORIDE FOR GUINEA PIGS
(Sayers *et al.*, 1930)

Concentration (vol.%)	*Symptoms*
10–20	fatal within a few min
6	after 10 min irritation of eyes and nose, vertigo, static and motor ataxia, retching movements, semi-consciousness progressing to unconsciousness, and death after 30 min
1	the same symptoms delayed for 15–20 min
0.4– 0.6	dangerous to life in 30–60 min
0.35	highest concentration which could be tolerated for 60 min
0.12	no symptoms during 8 h exposure, no death

Spencer *et al.* (1951) determined the toxicity for rats with single exposures as follows:

LD_{50}: 12,000 ppm for 31.8 min; 3,000 ppm for 165 min; 1,000 ppm for 432 min

$LD_{0.01}$: 12,000 ppm for 13.8 min; 3,000 ppm for 61.2 min; 1,000 ppm for 222 min

No adverse effects: 12,000 ppm for 6 min; 3,000 ppm for 18 min; 1,000 ppm for 90 min.

Animals exposed to these concentrations showed depression of the central nervous system, pulmonary irritation and injury of liver, kidneys, and adrenal glands.

As to the effects of repeated exposure Heppel *et al.* (1946) found that 1,000 ppm were fatal to rats, guinea pigs and rabbits after a few 7 hours' exposures, dogs being somewhat more resistant. Daily exposure for 7 h to 400 ppm was tolerated by dogs for a period of 8 months without apparent symptoms but at

autopsy they showed slight fatty degeneration of the liver. With this type of exposure there were some fatalities among rats, guinea pigs, and rabbits. All animals studied tolerated repeated exposures to 100 ppm. According to Spencer *et al.* (1951) the maximum concentration of ethylene dichloride in air with 7 h exposure on 5 days per week for 6 months causing no adverse effects is for rabbits 400 ppm; for rats 200 ppm; and for monkeys and guinea pigs 100 ppm.

Data on the toxicity of ethylene dichloride by other routes of administration are scanty. According to Highman *et al.* (1951), the subcutaneous injection of 1 ml/kg in young white rats is fatal to 35% of the animals within 24 h. Wright and Schaffer (1932) found that in dogs oral doses of 3.7 ml/kg cause retching, vomiting, salivation, and marked incoordination followed by rapid recovery. McCollister *et al.* (1956) gave the oral LD_{50} as 680 mg/kg. Barsoum and Saad (1934) gave the minimal lethal dose for dogs with oral administration as 2.5 g (3.13 ml)/kg, and with intravenous injection as 0.175 g (0.22 ml)/kg killing the animals within 30 min. They gave the minimal lethal dose for rabbits with subcutaneous injection as 1.6 g (2.98 ml)/kg, the animals dying in 24 h.

One peculiar phenomenon of exposure to ethylene dichloride is cloudiness of the cornea observed in dogs and foxes as reported by Dubois and Roux (1887), Dubois (1888), Panas (1888), and Steindorff (1922). In the opinion of Heppel *et al.* (1944) the basic lesion is an injury of the posterior or endothelial surface of the cornea without evidence of histological lesions, interfering with the deturgescent state of the cornea.

Following exposure to ethylene dichloride animals may show the following histo-pathological changes which vary with the intensity of the exposure. As shown by Maloff (1928), Wright and Schaffer (1932), Heppel *et al.* (1946), and Spencer *et al.* (1951) the liver may show fatty degeneration, or slight congestion with slight parenchymatous degeneration. With moderate exposure the kidney may show signs of moderate irritation and

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in more severe poisoning varying degrees of tubular damage ranging from slight parenchymatous degeneration to complete necrosis with interstitial edema, congestion and hemorrhages as reported by the same investigators. Heppel *et al.* (1946) saw occasionally necroses and hemorrhages in the adrenal cortex, and Wright and Schaffer (1932) and Kistler and Luckhardt (1929) noted after oral doses and after inhalation irritation of the gastro-intestinal tract and hemorrhages in the mesentery and in the mucosa of the intestine. The lungs may be congested and slightly edematous as reported by these investigators and according to Heppel *et al.* (1946) after continuous exposure the heart may show degenerative changes in the myocardium.

Heppel *et al.* (1945a) studied the effect of various diets on the toxic action of ethylene dichloride. They found that diets low in choline and protein (casein) increased the susceptibility, which could be corrected by addition of choline, methionine, and increase of the casein content in the diet. Animals kept on a low protein–high fat diet showed the highest incidence of hemorrhagic necroses in the adrenal cortex, premedication with *p*-amino-benzoic acid, methionine, aniline, and sulfonamide giving some protection. Heppel *et al.* (1947) found that addition of *l*-cysteine and *dl*-methionine to a low-casein–high-fat diet offered some protection which was not produced by addition of choline hydrochloride. Of other substances studied, addition of sodium sulfate, sodium thiosulfate, cysteic acid, and aurine, and S-benzyl-*l*-cysteine had no protective effect in contrast to that of thiourea, thiouracil, 2-thiobarbituric acid, β, β′-dithiodipropionic acid and *l*-cysteine hydrochloride. It appears, therefore, that the protective action is bound to the ability of such compounds to furnish sulfhydrylic groups. As shown by Highman *et al.* (1951) the mortality and the incidence of fatty degeneration of heart, liver and kidneys was reduced in rats by the oral administration of methionine, BAL (2,3-dimercapto-l-propanol) and cysteine if given immediately after the subcutaneous injection of ethylene dichloride. The incidence of renal

necrosis was increased by addition of methionine and administration of thiourea increased the mortality rate when given immediately after the injection of ethylene dichloride. It appears, therefore, that the protective action of certain chemicals does not extend to the same degree to liver and kidneys.

Toxicity for humans

Intimate contact of ethylene dichloride with the skin may give rise to dermatitis as reported by Wirtschafter and Schwartz (1939).

Most cases of ethylene dichloride poisoning in humans have resulted from its accidental ingestion as reported by Hueper (1935), Hueper and Smith (1935), Ienistea and Mezinesco (1943), Van Meurs (1944), Keyser (1944), Noetzel (1944), Hulst *et al.* (1946), Roubal (1947), Stuhlert (1949), Lochhead and Close (1951), Hubbs and Prusmack (1955), Weiss (1957), and Morozow (1958). In most instances the amount ingested was not known but the ingestion of 20 and 60 ml have resulted in death.

Depending upon the amount of food in the stomach, several hours may elapse before signs and symptoms of poisoning become manifest. Sooner or later the patient becomes nauseated and vomits, this may be very persistent, the vomitus containing blood. Not infrequently this is followed by diarrhea, associated with epigastric pain and cramps. Sooner or later the patient feels dizzy, sometimes inebriated, he suffers from headache, his gait becomes staggering, and he becomes somnolent, unconscious, and later stuporous. As his condition becomes worse, the respiration becomes stridulous, râles appear over the lungs and signs of pulmonary edema may develop. If the patient is in stupor the body temperature may be lowered and the pupils are dilated and nonreactive. In delayed poisoning signs of liver injury such as jaundice and of kidney injury such as albuminuria with casts may develop. Death is due to respiratory and/or circulatory failure and if delayed for several days to hepatic coma, and may ensue after hours, mostly after one

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day and occasionally after several days.

The pathological changes seen in oral poisonings consist in irritation of the gastro-intestinal tract characterized by hemorrhagic gastritis, inflammation of esophagus and duodenum and the latter may exhibit hemorrhages and contain blood exudation. The liver is hyperemic and may show fatty degeneration and diffuse necrosis and offer the picture of toxic hepatitis. The kidneys are hyperemic and may show the picture of toxic nephrosis with degeneration of the epithelium of the contorted tubules. The spleen may be hyperemic. The lungs are usually congested with small hemorrhages and may show emphysematous, edematous, pneumonic, and atelectatic changes. The heart may be dilated to the right, show infarcts, pericardial hemorrhages, and fatty degenerative changes of the myocardium. The brain is frequently hyperemic and edematous, it may exhibit perivascular hemorrhages and may offer the picture of meningitis.

Poisonings from inhalation of ethylene chloride, mostly of occupational character, were reported by Korelova (1937), Wirtschafter and Schwartz (1939), McNally and Fostvedt (1941), Holtzmann (1943), Baader (1950), Ollivier *et al.* (1954), and Menschick (1957). With the exception of the cases of Holtzmann and Menschick these were of comparatively light nature; the former's patient died after one day and the two of the latter developed liver injury of several months' duration. Victims of ethylene dichloride poisoning from inhalation experience fatigue, become drowsy, suffer from headache, nervousness, sometimes from sleeplessness and not infrequently from tremors. They may be nauseated, suffer from anorexia and vomiting, and may lose weight. With more severe exposure the liver may be enlarged and tender and this may be associated with epigastric pain. There may be a moderate leukocytosis, the heart beat may be slowed, and the blood pressure low. Some patients may exhibit nystagmus and in severe poisoning clonic-tonic convulsions have been reported. In the opinion of McCollister *et al.*

(1956) concentrations of 200 ppm can be tolerated for 7 h, 1,000 ppm for 1 h and 3,000 ppm for 6 min without untoward effects.

Treatment

In case of ingestion of ethylene dichloride and if seen early the stomach should be washed and saline cathartics should be given if the condition of the patient permits. In poisoning from inhalation the victim should be transferred to fresh air, kept comfortably warm and at rest. If the respiration is impaired oxygen should be given, if necessary with artificial respiration. If the blood pressure is low, no attempts should be made to improve it by vasopressor agents such as epinephrine. In case liver injury should develop a high-protein–high-carbohydrate diet should be given. Otherwise the treatment is symptomatic and supportive.

Prevention of poisoning

Operations in which ethylene dichloride is handled should be supplied with adequate exhaust ventilation to keep its concentration below the threshold limit value of 50 ppm (200 mg/m^3) as proposed by the American Conference of Governmental Industrial Hygienists (1962). As pointed out in the Safety Data Sheet SD–18 published by the Manufacturing Chemists Association (1947), processes in which it is handled should not be located near open flames. If it is necessary to enter small enclosures such as tanks, these should be washed and ventilated first and such premises should only be entered with protection by an open air or self-contained oxygen mask, together with rescue harness and lifeline and under supervision of a person familiar with first aid work. It should also be remembered that ethylene dichloride is a flammable material and may form explosive mixtures with air so that open flames or electric tools which may spark should not be used under these conditions.

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