THE HALOGENATED ALIPHATIC, OLEFINIC, CYCLIC, AROMATIC, AND ALIPHATIC-AROMATIC HYDROCARBONS INCLUDING THE HALOGENATED INSECTICIDES, THEIR TOXICITY AND POTENTIAL DANGERS

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PREFACE

Since the short review, "The halogenated hydrocarbons: their toxicity and potential dangers," was published in 1937 (J. Ind. Hyg. Tox., *19*, 340, 1937), much investigative work on the mechanism of their action and numerous reports on their toxicity have been published.

Since that time not only new halogenated aliphatic hydrocarbons have found new fields of use in industry and our daily life but also cyclic and aromatic hydrocarbons have gained in importance from both the practical and the toxicological point of view. It appears, therefore, timely that these are included in the present review, especially since there exists no synopsis of their toxicology.

In the following pages the chemistry, analytical procedures, potential uses, investigative toxicology, clinical toxicology, and the prophylaxis and treatment of such poisonings will be discussed. It is hoped that this review will help to reduce the incidences of such poisonings, facilitate their diagnosis and treatment, and stimulate research on the many problems which still remain unanswered.

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BENZOCHLORODIFLUORIDE

Benzochlorodifluoride, α-chlorodifluorotoluene,

has, according to Swarts (1898), the molecular weight 162.99 and is a colorless liquid of irritant odor and a density of 1.25445 13° which boils at 142.6° C. (770 mm.) and which is somewhat hygroscopic.

According to Lehmann (1928) doses of 0.7 to 1.0 mM (114 to 163 mg.) per 100 gm. body weight are fatal to frogs, causing paralysis without increased motor activity, increased reflex excitability, and convulsions.

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4. HALOGENATED XYLENE DERIVATIVES

Of the halogenated xylene derivatives only *bromoxylene* has been investigated toxicologically. Whereas the pure product has not been studied, Flury and Zernik (1931) stated that a mixture of $C_6H_4CH_3Br$-CH_2Br and $C_6H_4CH_2CHBr_2$ has been used as lacrimator in chemical warfare under the name of T-stoff or lilac gas, which has a boiling range of 216° to 220° C. and, according to Uttermark (1937), a specific gravity 1.31.

The vapors of bromoxylene produce in animals severe irritation of the eyes and a less severe irritation of the lungs. High concentrations will produce edema of the mucous membranes, pulmonary edema, and, after several days, somnolence, loss of appetite, and death.

Man can tolerate concentrations of 40 mm.³ per m.³ (0.56 mg./liter) for only one minute and, according to Vedder (1925), concentrations of 0.00378 mg. per liter render a man unable to fight. As stated by Uttermark (1937) concentrations of 0.015 mg. per liter are intolerable and such of 0.0018 mg. per liter are the lower limit causing irritation.

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Uttermark, W., Die chemischen Kampf stoffe u. Industriegifte, O. Meissner, Hamburg, 1937.
Vedder, E. B., The medical aspects of chemical warfare, Williams and Wilkins, Baltimore, 1925.

5. HALOGENATED DIPHENYL DERIVATIVES

A. Monohalogenated Diphenyl Derivatives

MONOCHLORODIPHENYL

Monochlorodiphenyl exists in 3 isomeric forms, depending upon the position of the chlorine atom in 1 of the 6-carbon rings.

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o-Chlorodiphenyl,

has the molecular weight 188.65 and forms crystals which melt at 34° and boil at 267° to 268° C. and which are insoluble in water but very soluble in ligroine.

m-Chlorodiphenyl,

has the molecular weight 188.65 and forms crystals which melt at 89° and boil at 284° to 285° C.

p-Chlorodiphenyl,

has the molecular weight 188.65 and forms leaflets which melt at 77.5° C. and boil at 282° C., and which are insoluble in water but soluble in ligroine.

Smyth (1931) studied the toxicity of the ortho- and para-compounds in rabbits and guinea pigs and found that the former killed animals within 20 to 40 hours with doses of 2.5 gm. per kg., causing mild convulsions, whereas the latter was fatal in 40 hours in doses of 3.5 gm. per kg. without causing convulsions.

REFERENCE

Smyth, H. F., J. Ind. Hyg., *13*, 87, 1931.

B. Dihalogenated Diphenyl Derivatives

Of the dihalogenated diphenyl derivatives only difluorodiphenyl has been studied to some extent. It exists in two isomeric forms, of which only the p,p′ derivative has been studied toxicologically.

p,p′-Difluorodiphenyl,

has the molecular weight 190.18. It forms monoclinic columns of the specific gravity 1.236 25°/4° which melt at 90° to 95° C., and boil at 254 to 255° C., and which are insoluble in water and soluble in alcohol, ether, and chloroform.

Kempf, Greenwood, and Nelson (1937) reported that rats kept on a diet containing 0.05 percent of this material (calculated as fluorine) developed neither mottled enamel of the teeth nor changes of the red blood cell count or of the hemoglobin.

REFERENCE

Kempf, G. A., D. A. Greenwood, and V. H. Nelson, J. Lab. Clin. Med., *22*, 1133, 1937.

C. Polychlorinated Diphenyl Derivatives

Polychlorinated diphenyl derivatives are of considerable toxicological interest because they are constituents, together with chloronaphthalenes, of certain synthetic waxes used extensively in industry as for the insulation of electrical equipment.

Penning (1939) described the process by which these products are prepared. In the course of this procedure first a mixture of 2- and 4-chlorodiphenyl is formed, and as the chlorination proceeds the mixture becomes more and more viscous and finally solid. These products are marketed under the name of "Aroclor" and represent mixtures of different isomers. "Aroclor" is insoluble in water and glycerol, not very soluble in lower alcohols, but very soluble in oils and other organic solvents. The "Aroclors" are solvents for sulfur, rubber, asphalt, paraffin, and natural waxes, and are used for protective coating, waterproofing of wood, and for electric insulation.

The toxicological evaluation of these products is difficult because of their variable composition. Drinker, Warren, and Bennett (1937) used a preparation which contained 65 percent of chlorine and Miller (1944) used a viscous, almost white material of the empirical formula $C_{12}H_4Cl_6$ of a specific gravity 1.374 to 1.383.

The toxicity of chlorodiphenyl for experimental animals was first studied by Smyth and Smyth (1931) who found that their product proved nontoxic by oral administration to guinea pigs and rabbits in doses of 4 gm. per kg. given as a paste. Drinker, Warren, and Bennett (1937) and Bennett, Drinker, and Warren (1938) found that feeding rats about 0.3 gm. daily was highly toxic when given over a period of 6 days, and that even 0.05 gm. per rat was definitely toxic, causing injury to the liver, although no yellow atrophy of the liver was observed. Miller (1944) found that feeding guinea pigs 9 doses of 69 mg. 1 week apart was fatal in 11 to 29 days after the first dose, and that the animals showed marked liver changes.

Miller (1944) reported that the *subcutaneous injection* of a single dose of 0.5 cc. (69 mg.) caused in guinea pigs local necroses at the site of injection, followed by encapsulation, and after 8 days fatty infiltration of the liver, moderate central atrophy and, rarely, focal necroses and some congestion of the kidneys. These injuries were more severe after doses of 0.1 to 0.5 cc. (138 to 690 mg.) and, when given as a 50 percent solution in oil, 345 mg. killed all animals within 18 days. The subcutaneous injection of 63 mg. into rabbits produces fatty infiltration of the liver earlier than observed in guinea pigs but with less marked central atrophy. On the other hand, congestion of the spleen was seen more frequently and often there was a myelosis of the pulp. Doses of 690 mg. produced marked fatty changes in the liver and considerable hypertrophy of the spleen. With *repeated administration* 10 doses of 69 mg. gave definite pathologic changes in the liver, and 10 doses of 690 mg. and of 1380 mg. given on consecutive days caused delayed death and marked fatty infiltration and sometimes focal necroses of the liver.

With *cutaneous application* Miller (1944) found that in guinea pigs daily doses of 34.5 mg. for 11 days were fatal after various intervals

up to 21 days, the animals showing essentially the same pathologic changes in liver and other organs as observed with subcutaneous injection. The skin at the site of the application showed occasionally congestion of the capillaries, thickening of the epidermis, edema of the dermis surrounding the blood vessels, and with prolonged administration destruction of the epidermis.

The *topical application to the cornea* of rats on 25 consecutive days caused no local changes but slight central atrophy of the liver and slight cavernous venous congestion of the spleen.

The *toxicity of chlorodiphenyl by inhalation* was studied by Drinker, Warren, and Bennett (1937) and Bennett, Drinker, and Warren (1938) in rats. They found that exposure of rats for 10 hours daily to an average concentration of 0.57 mg. per m.^{3} or for 8 hours daily to 0.93 mg. per m.^{3} for a prolonged period of time caused no apparent ill effects during life, but when the animals were killed after various periods of exposure they showed pale, slightly yellow, somewhat mottled livers, hyaline degeneration of the liver cells, increased prominence of cytoplasmic granules, and increased vacuolization. The same authors thought that chlorodiphenyl is more toxic than chlorinated naphthalenes and believed that the hepatotoxic action of chlorodiphenyl increased with the percentage of chlorine in the molecule.

There are no reports on human poisoning from exposure to chlorodiphenyl alone, although numerous poisonings have resulted from its mixture with chlorinated naphthalenes. The American Conference of Government Industrial Hygienists (1953) accepted a concentration of 1 mg. per m.^{3} as threshold limit for continued exposure.

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Smyth, H. F. and H. F. Smyth, Jr., J. Ind. Hyg., *13*, 87, 1931.

6. HALOGENATED NAPHTHALENE DERIVATIVES

A. Monohalogenated Naphthalene Derivatives

MONOCHLORONAPHTHALENE

Monochloronaphthalene exists in 2 isomeric forms, alpha- and beta-chloronaphthalene, depending on the position of the chlorine atom in the double ring.

Alphachloronaphthalene, α-naphthyl chloride,

has the molecular weight 162.61. It is a colorless liquid of the specific gravity 1.194 20°/4° which solidifies at −20° C. and boils at 259.3° C. and which is insoluble in water, soluble in alcohol, and miscible with benzene, carbon disulfide, and ether.

Beta-chloronaphthalene, β-naphthyl chloride,

has the molecular weight 162.61 and forms leaflets of specific gravity 1.266 16° which melt at 56° to 57° C. and boil at 264° to 266° C. (751 mm.) and which are insoluble in water and very soluble in alcohol and ether.

None of these compounds has been studied toxicologically, but Gavandan, Gavandan, and Durand (1939) found that the vapors of alpha-chloronaphthalene affect the roots of *Triticum vulgare* with exposures of 1 to 2 hours, causing karyokinesis.

REFERENCE

Gavandan, P., N. Gavandan, and J. F. Durand. Compt. rend. soc. biol., *130*, 1443, 1939.

Fluoronaphthalene

Alpha-fluoronaphthalene, naphthyl fluoride,

has the molecular weight 146.16 and is a liquid of the specific gravity 1.133 19.5°/4° which solidifies at −8° C. and boils at 212° to 216° C. and is soluble in benzene, alcohol, acetone, and chloroform.

Kempf, Greenwood, and Nelson (1937) fed rats levels of 0.1 and 0.05 percent (as fluorine) in the diet. Animals kept on the higher concentration died within 90 days without developing abnormalities of the teeth, but those kept for a longer period of time on a diet containing 0.05 percent of fluoronaphthalene developed mottled enamel. They did not reproduce, but showed no changes in the red blood cell count or in the hemoglobin.

REFERENCE

Kempf, C. A., D. A. Greenwood, and V. H. Nelson, J. Lab. Clin. Med., *22*, 1123, 1937.

B. Polyhalogenated Naphthalene Derivatives

Trichloronaphthalene

Trichloronaphthalene exists in the form of two isomers differing in the distribution of the 3 chlorine atoms in the 6 ring.

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