OCCUPATIONAL CHLORACNE CAUSED BY AROMATIC CYCLIC ETHERS

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Thirty-one cases of chloracne were found among workers engaged in the production of 2,4,5-trichlorophenol and in the conversion of the latter into 2,4,5-trichlorophenoxyacetic acid and its esters. Animal experiments, carried out by painting rabbits' ears, have shown the cause of chloracne to be not trichlorophenol itself, but toxic by-products formed in the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene into 2,4,5-trichlorophenol. Compounds that may arise in this process were synthesized, and tri- and tetrachlorodibenzofuran and tetrachlorodibenzodioxin were found to be highly active. Furthermore, 2,3,6,7-tetrachlorodibenzodioxin was isolated as a by-product formed in the manufacture of trichlorophenol, and the possibility of its formation from sodium trichlorophenoxide was established.

Chlorinated compounds, used as industrial materials or formed as by-products, occupy an important position among the chemical and physical intoxicants capable of producing acne and folliculitis.

The first cases caused by these compounds were observed at the beginning of the century with the introduction of the electrolytic chlorine process. The view put forward, and later corrected, by Herxheimer, according to which the disease is caused by free chlorine, has led to the confusing but common designation "chloracne".

Since the introduction of chlorinated naphthalenes, used in various branches of industry on account of their useful properties (resistance to acids, non-inflammability, waterproofness, good insulation), contact with these compounds has often resulted in chloracne[2,3,8]. Both Wauer[9] and Teleky[8] have suggested the term "Pernakrankheit" ("perchloronaphthalene disease"), which again is unsatisfactory in many respects.

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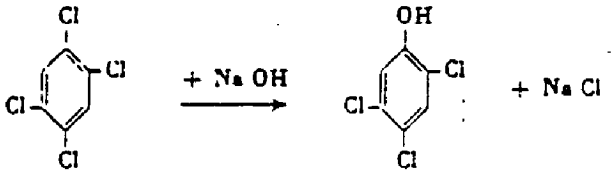
aving been used with more than 100 substances in the past two years, the rabbit-ear test enables the chloracne-inducing activity of a substance to be ascertained with high probability.

The first results were reported by one of us[7] at the 23rd Congress of German Dermatologists in Vienna. It was first shown that, contrary to previous assumptions, 2,4,5-trichlorophenol was not to be considered as the chloracne-inducing factor. This emerged from the observation that the expected symptoms were not produced on the rabbits' ears with a 5% solution of pure 2,4,5-trichlorophenol in polyglycol, but they were produced by the technical product. Since the starting material, 1,2,4,5-tetrachlorobenzene, was inactive on the rabbits' ears, it was to be assumed that the intoxicant was among the by-products formed in the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene into 2,4,5-trichlorophenol.



1,2,4,5-tetrachlorobenzene — 2,4,5-trichlorophenol

Since the distillation residue could not at first be separated, a number of such synthetic compounds were selected for testing, which were likely to be formed in the hydrolysis of tetrachlorobenzene at 180°C, these compounds being the chlorine derivatives of diphenyl ether and of dibenzofuran (diphenylene oxide).

Whilst the chlorine derivatives of diphenyl ether and unsubstituted and monochlorinated dibenzofuran were inactive in the animal experiments, trichloro- and tetrachlorodibenzofuran resulted in the expected symptoms, even when they were applied in 0.05% solutions.

In addition to the above symptoms, both compounds exhibited strong hepatotoxic properties. The oral administration of a single dose of 0.5 to 1 mg/kg led to severe hepatic conditions in rabbits. However, chlorinated dibenzofurans could not be detected as a by-product in the production.

The clinical examination of a laboratory assistant who developed a severe case of chloracne after contact with tetrachlorodibenzodioxin indicated the possible causative function of chlorinated dibenzodioxins (diphenylene dioxides). Further experiments with rabbits' ears showed tetrachlorodibenzodioxins, especially 2,3,6,7-tetrachlorodibenzodioxin, to be very highly active. Three or four painting with 0.01 - 0.005% solutions, applied at intervals of 3 to 4 days, were found to be sufficient to produce severe inflammation and follicular hyperkeratosis. A single dose of 0.05 - 0.1 mg/kg (per os) resulted in severe hepatic conditions, and, in most cases, in death within 8 to 20 days. Autopsy revealed distended necrotic tissues and engorgement of the liver.