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TOXICITY OF CHLORINATED DIPHENYL

PRELIMINARY REPORT[1]

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The chlorinated hydrocarbons of the aliphatic series have been extensively studied and their toxic action (narcosis, hepatic and renal damage) has been firmly established. The chlorinated aryl compounds, however, have received relatively little attention. Industrial processes involving the use of chlorinated naphthalene have been recognized for some time as the cause of a characteristic acne-like dermatitis involving principally the sebaceous glands of the exposed parts of the body (1, 4, 7, 8). Recently, chlorinated diphenyl compounds used in commercial processes have been reported to be the cause of similar skin changes (5, 6).

Only two references to animal experiments with chlorinated conjugated aromatic compounds have been found. K. B. Lehmann (4) noted that animals dying as a result of inhalation or feeding of chlorinated naphthalene showed liver changes similar to those due to tetrachlorethane. He was unable to produce in animals skin lesions similar to those found in humans. Flinn and Jarvik (2) reported that certain commercial chlorinated naphthalenes when injected subcutaneously produced yellow atrophy of the liver in rabbits. The starting point of their investiga-

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tion was the observation that three cases of yellow atrophy of the liver had occurred in three widely separated plants, in all of which however the men were exposed to a chlorinated naphthalene heated above its melting point and giving off fumes. No animal experiments appear to have been reported on chlorinated diphenyl compounds.

The experiments described below were planned to test the effect on animals of a commercial chlorinated diphenyl compound when applied to the skin or inhaled as vapor from the atmosphere. This compound is a viscous, almost water-clear oil at room temperatures, approximating the formula $C_{12}H_7Cl_3$. It is a mixture of isomers of diphenyls chlorinated to different extents and in different positions, with an approximate chlorine content of 42 percent. It is insoluble in water, soluble in mineral and vegetable oils, benzene, other chlorinated hydrocarbons, and fat solvents. Because of its low inflammability (flash point 176° to 180° C.), its high dielectric capacity, and a combination of other physical properties, this substance has found wide industrial use in the manufacture of plastics and in the electrical industry.

SKIN TESTS

An area between the shoulders of guinea pigs was clipped and approximately 1/40 cc (two drops delivered from a syringe fitted with a No. 24 needle) of commercial chlorinated diphenyl undiluted or dissolved

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in mineral oil, was allowed to fall on the clipped area, where it spread immediately without rubbing. This treatment was repeated daily for 11 days. At the same time and under the same conditions, 20 control animals were treated daily with mineral oil alone. There were no signs of local irritation of any sort on the control animals, and of the 6 animals in the control group that died during the duration of the experiment, all appeared, upon autopsy, to have died from pneumonia.

A slight erythema appeared an hour or two after the application of a solution containing 10 percent or more of chlorinated diphenyl. The erythema ~~persisted~~ lasted as long as treatment continued and usually disappeared within a day or two after discontinuing treatment. Small scales, resembling dandruff, appeared on the clipped area after the first five or six applications, and persisted until the death of the animal.

Application of solutions containing more than 10 percent of chlorinated diphenyl was followed by a gradual loss of vigor which began to be apparent after 4 to 7 days, the time being dependent upon the concentration. Treated animals ate less than usual, generally

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FIGURE I. - Survival time of guinea pigs treated with various concentrations of chlorinated diphenyl.

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TABLE 1. - Number of deaths and number of survivors in groups of 20 guinea pigs, treated with various concentrations of chlorinated diphenyl.

Days	Concentration of chlorinated diphenyl, percent								Controls	
	100		50		10		1			
	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors
Number at start	-	20	-	20	-	20	-	20	-	20
8	-	20	-	20	1	19	-	20	1	19
9	1	19	1	19	-	19	-	20	1	18
10	1	18	-	19	-	19	-	20		18
11	2	16	2	17	-	19	-	20		18
12	3	13	2	15	-	19	-	20		18
13	5	8	2	13	1	18	-	20		18
14	4	4	1	12	-	18	-	20		18
15	-	4	6	6	1	17	-	20	1	17
16	1	3	1	5	-	17	-	20		17
17	-	3	2	3	-	17	-	20		17
18	1	2	1	2	1	16	-	20		17
19	1	1	1	1	2	14	-	20		17
20	-	1	-	1	2	12	-	20		17
21-22	1	0	1	0	1	11	1	19		17
23-24					1	10	-	19		17
25-26					2	8	-	19	1	16
27-28					2	6	-	19		16
29-30					2	4	2	17	1	15
31-32					1	3	1	16		15
33-34					1	2		16	1	14
35-36						2		16		14
37-38						2		16		14
39-40						2		16		14
41-42						2		16		14
43-44						2	1	15		14

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losing weight, and huddled together closely in a corner of their cage.

(Insert table 1 and figure 1)

All guinea pigs treated with 100 percent or 50 percent chlorinated diphenyl died, the average survival times being 13.6 $\pm$ .27 and 14.6 $\pm$ .27 days, respectively. Reduction of the concentration to 10 percent increased the survival time of the test animals (table 1 and figure 1), and two of the twenty guinea pigs survived until the end of the 60-day observation period when they were killed for study. Reducing the concentration to 1 percent resulted in survival times that did not differ greatly from those of the controls. Of the five animals which died subsequent to the application of a 1 percent solution all showed symptoms of a type of respiratory congestion that caused the death of guinea pigs in neighboring cages, including some of the controls. Two of the five guinea pigs showed autopsy findings similar to those found in animals exposed to high concentrations.

Autopsy of the guinea pigs that died following treatment with chlorinated diphenyl either by skin application, inhalation, or injection, revealed retrograde changes in the liver on gross examination.

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The liver was pale yellowish-brown in color.with scattered, irregular yellowish-gray areas of varying sizes over its surface. Minute, dark-red areas were closely and uniformly distributed throughout the liver substance and were most prominent over the capsule. The gall bladder was often distended with bloody bile. No gross changes in the other visceral organs were observed. No cases of lung congestion of the type referred to in an earlier section of this paper were found among animals killed by exposure to high concentrations of chlorinated diphenyl. Usually the animals were emaciated, with but little subcutaneous fat and only a small amount of peritoneal fat.

These tests clearly demonstrate that death may follow application of chlorinated diphenyl to the skin. They provide, however, no means for deciding whether this compound entered the body through the skin or through the lungs. To provide information on these two possibilities, two series of experiments were carried out. In one, chlorinated diphenyl was supplied as a vapor, and in the other it was injected into the body in various ways and in various amounts.

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INHALATION TESTS

In order to test the toxicity of the vapors of chlorinated diphenyl, eight guinea pigs were confined in bell jars[1/] containing gauze pads saturated with this substance. These pads were mounted on the inside upper surface of the jars, protected by coarse metal screens, so that the animals could not come into direct contact with chlorinated diphenyl in any way. The bell jars were supported on two wooden strips, 1/4 by 1 inch, which in turn rested on a layer of shavings, and this opening at the bottom provided ventilation. No measurements of the concentration of chlorinated diphenyl were made. Two control animals were confined for 29 days in bell jars arranged in this way (but without exposure to chlorinated diphenyl) without showing ill effects of any sort. All of the eight animals exposed to the vapors of chlorinated diphenyl died, the time of survival ranging from 6 to 23 days, averaging 15.5 ± .6 days.

1/ The bell jars were ~~6 inches~~ 15 cm tall, inside measure, and had a volume of approximately 4 liters.

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Autopsy of guinea pigs which died as a result of inhalation of chlorinated diphenyl revealed the same type of liver pathology that followed application to the skin. No other visceral organs appeared to be affected.

Since quantitative measurements of vapor concentration were not made, these experiments give no clue as to the amount of chlorinated diphenyl to which man or other mammals may be safely exposed. The experiments indicate, however, that death can result from inhalation of the vapors of chlorinated diphenyl.

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TABLE 2. - Survival times of guinea pigs receiving subcutaneous injections of undiluted chlorinated diphenyl.

Dosage cc	Number of animals tested	Average survival time days
1.0	3	3
0.5	11	8.4
0.2	6	18.5
0.1	11	21.3

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INJECTION TESTS

Subcutaneous injection of undiluted chlorinated diphenyl resulted in the death of all animals tested. The survival time varied inversely with the dosage.

(Take in Table 2)

When this substance was injected subcutaneously a nodule was formed whose diameter varied from 0.5 to 2 cm., depending upon the dosage. The nodule was firm, not easily movable, and on section was found to consist of an encapsulated mass of thick, yellowish-white, necrotic material with which was mixed a small quantity of the injected substance.

When injected intradermally, a superficial nodule resulted which usually broke down, allowing the contents to escape, leaving a punched-out ulcer. Crust formation and rapid healing of these lesions generally followed.

Intraperitoneal injection of this material induced death somewhat sooner than other types of treatment, and produced numerous visceral and omental adhesions, indicating peritoneal irritation.

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Further work is in progress to test the toxicity of various commercial chlorinated diphenyl compounds and of pure chemical compounds known to be constituents of the commercial materials. Experiments are also in progress to determine quantitatively the range of concentrations of chlorinated diphenyl vapor which produce toxic symptoms. A more complete pathological report is also in process of preparation.

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SUMMARY

Toxicity tests of commercial chlorinated diphenyl containing approximately 42 percent of chlorine are reported. These tests included application to the unbroken skin, inhalation of the vapors arising from this material at room temperature, and subcutaneous injection.

All guinea pigs treated with this commercial chlorinated diphenyl

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in undiluted form and in any of these three ways died. Retrograde changes of the liver constituted the characteristic type of pathology observed on gross examination.

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