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(5) STUDY TYPE: Acute/Chronic Toxicity. — Species ? Route ??

(6) ACCESSION NO: Not available.

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6 pages

In this study a complete [illegible] was not recorded [illegible] you may place the classification [illegible] and reason (although the study reflects these findings) the study is invalid because

DATA EVALUATION RECORD
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(1) CHEMICAL: Trichlorfon.

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(5) STUDY TYPE: Carcinogenicity.

(6) ACCESSION NO: Not available.

(7) MRID NO: Not available.

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# THE HEPATOTOXIC AND CANCEROGENIC EFFECT OF TRICHLORPHON

[Ueber die hepatoxische und cancerogene Wirkung des Trichlorphon]

Duplicate data

Kh. Lohs and W. Gibel

GS0104154

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pp. 515-517

Translated for EPA by
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For years, the phosphorylation processes related to the enzymatic inhibition and the conclusions to be derived for the development of antidote preparations was the center of interest to toxicologists and pharmacologists, as well as to clinical medicine. The partially strong alkylating properties, especially of methyl esters of phosphoric, thiophosphoric, and phosphonic acid derivatives was indicated by chemists or experimental proofs were put forward, but only very recently was attention given to explaining psychopathological and neurological delayed damages, as well as to the clarification of possible relations between the alkylation effect and the pathogenesis of certain organic cancers through the reaction behavior of such compounds.

In the working group of one of us (K. L), recently various investigations were carried out on trichlorphone, which suggested the experiments described below in greater detail regarding the biological consequences of the alkylating effect of trichlorphon /1/. Meanwhile the question of a possible cancerogenic effect of trichlorphon has also been studied by R. Preussman /2/.

Our in vivo findings are being given particular importance because of the studies carried out in Stockholm with DDVP by G. Lofroth. Lofroth was able to prove the alkylation of the DNS as well as the formation of N-7-methyl-guanine, and to draw from it conclusions on the 'long-term effects' of the DDVP poisoning. /3/.

The trichlorphon wh used /0,0-dimethyl-(1-hydroxy-2,2,2-trichlorethyl phosphonate) was approximately of 98% purity.

For the experiment we used Wistar rats and mice, each time of both sexes. (The animals were taken for the experiment at two months, weighed weekly, and the trichlorphon was administered three times a week in a dose of 30 mg/kg up to the end of the mouse's life or applied s.c.. In mice the cutaneous application was undertaken both as an administration of trichlorphon alone, or trichlorphon + croton oil. The trichlorphon was given 3 times a week altogether for 5 months, croton oil in drops once a week

for 6 months). The number of animals for probe and s.c application tests was 80 for each, cutaneous application was made on 20 mice each. In evaluating the findings, only those animals were considered, who were tested for more than 6 months.

The application of trichlorphon was fairly well tolerated during the first months (no acute toxic reactions were observed). All test animals which were included in the experiment for more than 6 months showed--independently of the type of application--pathological alterations of the liver clearly depending on the dose administered. These liver conditions extended from steatosis of the most different degrees of gravity, through enlarged yellow hard liver with clear emphasis on the lobular structure as a result of central necrosis combined with hyperemia and hemorrhages up to the typical postnecrotic cirrhosis of the liver. A liver cell carcinoma was observed after 17 months of cutaneous application, another after 14 months of cutaneous application + croton oil. The cutaneous application with simultaneous administration of croton oil also led to a 2cm x 2cm sarcoma of the abdomen. The s.c. application did not give any local tumors.

In the omasum of the rat we found both for oral and s.c. administration of trichlorphon, partly single, partly multiple exophytically growing papilloma. In all 3 forms of application, histologically different degrees of liver cell damage were produced.

It is with in the range of possibilities, that the number of liver tumors would be greater if the massive destruction of the liver through the partly simultaneous necrosis had not led to the animal's death before the manifestation of the tumor. It is also worth mentioning the papilloma developing especially on the omasum of the rat, the more so that each papilloma may be considered as a potential preliminary stage of a carcinoma. Naturally we cannot transfer these results obtained in the screening animal test schematically to the conditions in the human organism, without completing these investigations with a longer number of animals and other species of animals. But at present it appears to us already necessary to indicate the dangers related to the use

of trichlorphon, above all in order that the corresponding measures of protection in the work for production and application of trichlorphon may be improved. On the basis of the investigation results obtained up to now, we consider it hardly likely, that the users will be in any danger if they ingest foodstuff that has come into contact with trichlorphon.

On the whole therefore it appeared to us urgently necessary to call for more attention to be paid than heretofore to the possible consequences of using phosphoro-organic esters with alkylating effect and also to consider the application specific formulations of such esters from the point of view of the danger of cancerogonic, cocancerogenic, as well as mutagenic manifestations.

The basic statements made by Kagan at this Symposium on the problem of delayed damages are fully consistent with our concepts and stress the need for considering the metabolism of phosphoro-organic compounds which change the toxicity, as an area of research to be given priority, both for chemical toxicology and preventive medicine.

A detailed description of our findings is soon to appear in the 'Archiv fuer Geschwulstforschung' (W. Gibel, Kh. Lohs, G. Wildner and D. Ziebarth).

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[2] Preussmann, R., Food Cosmet. Toxicol. 6, 576 (1968).
Preussmann, R., H. Schneider u. F. Epple, Arzneimittelforsch. 19, 1059 (1969).

[3] Lofroth, G., Naturwissenschaften 57, 393 (1970).