DATA EVALUATION RECORD

(1) CHEMICAL: Trichlorfon.


(3) REVIEWED BY:

I. Cecil Felkner, Ph.D.
Project Scientist
Dynamac Corporation
1140 Rockville Pike
Rockville, MD 20852
301-468-2500

John R. Strange, Ph.D.
Department Director
Dynamac Corporation
1140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: ____________________________
Date: ____________________________

(4) APPROVED BY:

Irving Mauer, Ph.D.
EPA Scientist

Signature: ____________________________
Date: ____________________________

(5) STUDY TYPE: Acute/Chronic Toxicity.

(6) ACCESSION NO: Not available.

(7) MRID NO: 00075634.
DATA EVALUATION RECORD

(1) CHEMICAL: Trichlorfon.


(3) REVIEWED BY:

William L. McLellan, Ph.D.
Senior Scientist
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

John R. Strange, Ph.D.
Department Director
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: ____________________
Date: ____________________

Signature: ____________________
Date: ____________________

(4) APPROVED BY:

Irving Mauer, Ph.D.
EPA Scientist

Signature: ____________________
Date: ____________________

(5) STUDY TYPE: Carcinogenicity. (Rat?) (Species?)

(6) ACCESSION NO: Not available.

(7) MRID NO: Not available.
THE HEPATOTOXIC AND CARCINOGENIC EFFECT OF TRICHLORPHON

[Über die hepatotoxischen und carcinogenen Wirkungen des Trichlorphon]

K. Lehn and G. Gibel

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Translated for EPA by
SCHRAM (SCIENTIFIC TRANSLATION SERVICE)
Santa Barbara, California
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 trichlorophene, which supported the experiments described below in greater detail regarding the biological consequences of the alkylating effect of trichlorophen /1/. Meanwhile the question of a possible cancerogenic effect of trichlorophen has also been studied by R. Freussman /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 CNS as well as the formation of N-7-methyl-quinolin, and to draw from it conclusions on the 'long-term effects' of the DDVP poisoning /3/.

The trichlorophen which used /0,0-dimethyl-(1-hydroxy-2,2,2-trichloroethyl phosphonate) was approximately of 99% 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 trichlorophen 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 trichlorphene alone, or trichlorphene + croton oil. The trichlorphene 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 trichlorphen 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 degree 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 oesum of the rat we found both for oral and s.c. administration of trichlorphen, 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 oesum 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 larger 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 cancerogenic, 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 concept 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 fur Geschwulsforschung' (W. Gibel, Kh. Lohn, G. Wildner and D. Ziebarth).

BIBLIOGRAPHY

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