UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

7 JUL 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Dichlorvos (DDVP): Reconsideration of quantification of human risk

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The Health Effects Division (HED) Reference Dose Committee (RfDC) met on April 8, 1993 at the request of Toxicology Branch I to consider recommendations made by the CRAVE Work Group with respect to quantification of human risk resulting from dermal exposure to dichlorvos. Specifically, the RfD Committee was requested to address the question of whether it is appropriate to extrapolate carcinogenicity data generated by oral administration for the purpose of quantifying the potential carcinogenicity risk of the dermal exposure. Particularly, since the oral data was considered inappropriate to quantify the risk resulting from the inhalation exposure to dichlorvos.

A. Background

On July 19, 1989 the HED Carcinogenicity Peer Review Committee (CPRC) classified Dichlorvos as a "Group C", possible human carcinogen with a recommendation for quantification of human risk for all routes of exposure other than inhalation (i.e. using the dietary and dermal routes only). The classification was based on increased incidences of mononuclear cell leukemia in male Fisher 344 rats and of forestomach squamous cell tumors in high dose female B6C3F1 mice in NTP gavage studies. The potency estimate Q^*_1 was calculated based on the geometric mean of these tumor types. In that meeting, the Committee also considered an inhalation carcinogenicity study performed on CFE rats. In this study, the treatment did not result in increased incidence of tumors. The exclusions of the inhalation route in the quantification of the carcinogenic risk was based mainly on the fact that carcinogenicity

(1)

testing conducted by this route did not alter the spontaneous tumor profile in this strain of rats, i. e. did not induce carcinogenic response.

It should be noted that the FIFRA Scientific Advisory Panel (SAP) has also classified Dichlorvos as a "Group C" carcinogen on two occasions. Later, the Office of Policy, Planing and Evaluation (OPPE) raised the issue of the acceptability of a negative rat inhalation carcinogenicity study.

In October 1991, the issue of DDVP's carcinogenic potential, including the inhalation carcinogenicity study, was discussed by the CRAVE Workgroup. The Workgroup concurred with the HED's classification of Dichlorvos as a "Group C" carcinogen, but requested information and discussion from HED and Human Health Assessment Group (HHAG) with respect to deriving an inhalation risk from the oral data. This discussion took place on March 31, 1992. At that time, based on the information presented with respect to the uncertainties regarding (1) the quality of the oral carcinogenicity data (2) the route specificity of the target organs and (3) the reliability and accuracy in estimating the target organ dose, the CRAVE Workgroup accepted HED's quantification by the oral route only and considered the inhalation route to be inappropriate under these circumstances. The CRAVE document was revised to reflect the March 31 discussion, and was submitted to the CRAVE Workgroup Chair on October 30, 1992.

The CRAVE decision and the issue of the appropriateness of the extrapolation of the carcinogenicity data generated by oral gavage administration for the purpose of quantifying human risk resulting from dermal exposure was then presented to the RfD Committee for consideration.

B. Conclusion

The RfD Committee concluded that it was inappropriate, at least in this particular case, to extrapolate carcinogenicity data generated by oral gavage administration for the purpose of quantifying human risk resulting from dermal exposure. This decision was based on the following considerations: 1) there was no dose response in the leukemia observed in male Fisher 344 rats, a tumor with a high and variable background in this strain of rats, 2) the tumors observed in female B6C3F1 mice were contact site tumors, the relevance of which to humans is unknown and in which the tumor incidence at all dose levels, including the concurrent controls, were outside the NTP's historical control range, 3) the dynamics of absorption, distribution, metabolism and excretion does not favor retention of the chemical in animal tissues and makes it difficult to determine accurately the concentration at the target site, and finally 4) it is not expected that topically applied doses would reach the target organ(s) in sufficient quantity to produce a carcinogenic response or would be sufficient to alkylate macromolecules in the target tissues to produce contact site tumors.

B. Individuals in Attendance

1. Peer Review Committee Members and Associates (signature indicates concurrence with the peer review unless otherwise stated).

William L. Burnam

Reto Engler

Karl Baetcke

Henry Spencer

Stephen Dapson

John Tice

Whang Phang

George Ghali

Rick Whiting

2. Peer Review Members and Associates in Absentia (committee members and associates who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee).

Marcia Van Gemert

3. Scientific Reviewer (committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Joycelyn Stewart

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Esther Saito
Karl Baetcke
Joycelyn Stewart
Mike Beringer
Karen Whitby

C. Weight of the Evidence

The Health Effects Division RfD/Peer Review Committee in their meeting of April 8, 1993 concluded that it was inappropriate in this particular case to extrapolate carcinogenicity data generated by oral gavage administration for the purpose of quantifying human risk resulting from dermal exposure. The Committee considered the following to be of significance in the weight of the evidence determination and in arriving at this conclusion:

1. The questionable nature of some of the carcinogenic responses observed in the oral gavage studies:

a) The forestomach tumors observed in the mouse study might have been the result of direct contact of the chemical and/or breakdown products with the target site. Pancreatic tumors observed in the rat study and was later dismissed as not treatment-related, are known to have some casual association with the vehicle solvent (corn oil) used in this study. Such circumstances may not exist in the case of other routes of exposure, i. e. inhalation exposure or dermal application of dichlorvos. This was evident in the inhalation carcinogenicity study where no carcinogenic response was observed.

b) There was a lack of a dose-response relationship for the mononuclear cell leukemia (observed in male rats), a tumor known to have a high and variable incidence in control male Fisher 344 rats. The mononuclear cell leukemia is the only end-point for the quantification of human risk, resulting from the exposure to dichlorvos, by any route.

2. Bio-availability and the concentration of dichlorvos and/or its breakdown products at the target site as a function of biodynamic factors (including absorption, distribution, biotransformation and elimination):

a) Absorption and distribution:

Daily administration of dichlorvos in a gavage oral bolus dose most likely deposits a large initial concentration of the chemical to the blood and possibly to the target tissue(s) and is expected to result in large fluctuations in blood levels. Thus, it would be difficult to establish exactly how much of the chemical is likely to reach the target site(s). On the other hand, dermal administration, like inhalation exposure can be expected to result in steady state and lower blood concentrations.

Approximately 84 to 93 percent of the administered dose was absorbed from the gastrointestinal tract after administration of a single low or high oral dose, or repeated low oral doses of the test material to rats. Only 10% of the topically applied C^{14} labelled dichlorvos was absorbed after 120 hours. The maximum blood level did not exceed 0.20 percent of the dose at different

intervals (10 to 120 hours) regardless of the amount applied. Thus, after 120 hours, very little or no dichlorvos penetrated the skin and entered the blood circulation.

Gavage administration is expected to deposit a large initial dose in blood circulation while dermal administration normally results in a lower steady-state concentration.

Thus, if it is assumed that the target sites are similar for both oral and dermal administration of dichlorvos, then it is possible that the gavage administration and the dermal application would vary significantly in the concentration of dichlorvos reaching the target site(s). In the gavage administration the chemical is expected to reach the target site in sufficient concentration. On the other hand, in the case of dermal exposure it is very unlikely that the chemical would reach an effective level at the target site(s) to produce tumors.

b) Biotransformation and DNA Alkylation:

Metabolism data demonstrate that orally administered dichlorvos is readily absorbed, and rapidly metabolized. There are two metabolic pathways involved in the biotransformation of dichlorvos:

A predominate pathway via the hydrolytic cleavage of the ester link to a short-lived reactive intermediate, dichloroacetaldehyde, which is subsequently reduced to dichloroethanol and excreted as a glucuronide conjugate or taken up into the two carbon pool through dechlorination. These reactions are catalyzed by large amounts of esterases present in the cytosol of mammalian cells and in the blood. Dichlorvos has been shown to be metabolized in the blood, adrenal gland, kidney, lung and spleen.

A second minor pathway exists via the oxidative demethylation which leads to the alkylation of DNA. However, this alkylation most likely exists when the hydrolytic enzyme systems are saturated, i. e. when dichlorvos is available in a high concentration. Data exist to demonstrate that the ratio between this minor pathway and the major metabolic pathway is $1:3 \times 10^7$ in favor of the esterase catalyzed hydrolysis.

Dichlorvos is metabolized much more rapidly when administered by inhalation. A half life of 13.5 minutes in the kidney was observed when dichlorvos was administered to rats by inhalation for 4 hours. At the same time only 57% of an oral dose was eliminated (in the urine, feces and expired air) within 24 hours.

Given the very slow rate of absorption of the topically applied dose coupled with the rapid rate of degradation of dichlorvos, it is not expected that a dose of dichlorvos administered by dermal application (or by inhalation) would be biologically equivalent to a similar oral gavage dose and it is

very unlikely under these circumstances that the second metabolic pathway, the activation process, would come into play. Therefore, it is not expected that the topically applied doses would reach the target organ(s) in sufficient quantity to produce a carcinogenic response at the target site.