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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: *DICHLORVOS (DDVP)- RE-EVALUATION - Report of the Hazard Identification Assessment Review Committee.*

FROM: Jess Rowland *Jess Rowland 6/3/98*  
Executive Secretary,  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, *K. Clark Swentzel 6/3/98*  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

TO: Christina Scheltema, Risk Assessor  
Risk Characterization and Analysis Branch  
Health Effects Division (7509C)

PC Code: 084001

On May 7, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to review the findings of the Pathology Work Group that evaluated the results of the acute and subchronic studies in hens as requested by this Committee at the November 18, 1997 meeting. The HIARC also reviewed a developmental toxicity study in guinea pigs from the open literature. The Committee's conclusions are presented in this report.



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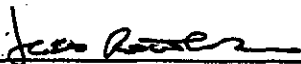
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Committee Members in Attendance

Members in attendance were: Karl Baetcke, William Burnam, Robert Fricke, Nancy McCarroll, Mike Metzger, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Member in absentia: Karen Hamernik, Susan Makris and Melba Morrow.

Other HED members also present were: Ghazi Dannan of Toxicology Branch 2, Jocelyn Stewart of Registration Action Branch 2, Christina Scheltema of Risk Characterization and Analysis Branch, and William Sette of Science Analysis Branch.

Report preparation:

  
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Jess Rowland  
Executive Secretary

## I. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met on November 13 and 18, 1997, evaluated the toxicology data base of Dichlorvos and selected the doses and toxicological endpoints for dietary and non-dietary exposure risk assessments. In addition, the HIARC also assesses the potential enhanced susceptibility to infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions of the meeting were presented in the HIARC Report (*Memorandum: G. Ghali, HED to S. Lewis, RD, dated December 19, 1997; HED Document No. 012448*). A summary of the toxicological endpoints and doses selected are tabulated in this report.

On May 7, 1998, the HIARC met to review the findings of the Pathology Work Group that evaluated the results of a 28-day neurotoxicity study in hens as requested by this Committee at the November 18, 1997 meeting. The HIARC also reviewed a developmental toxicity study in guinea pigs from the open literature. The Committee's conclusions from this meeting are presented in this report.

## II. RESULTS OF THE PATHOLOGY WORKING GROUP.

An acute delayed neurotoxicity study in hens (MRID 41004702) exhibited lesions of the sciatic nerve similar to that observed in positive control (TOCP) treated birds, in one of ten hens given an acute dose of 16.5 mg/kg of Dichlorvos. Because of this finding, the Agency required that a 28 day hen study be conducted according to its guidelines and data requirements. This study (28-day study in hens) was conducted and submitted to the Agency (MRID 43433501).

In the 28-day study, the study pathologist reported spinal cord lesions in a number of hens given 1 or 3 mg/kg of Dichlorvos at a grade level she defined as biologically significant. However, no NTE inhibition was seen at any dose, suggesting that any effects were not related to OPIDN. Last, the only clinical motor signs seen in the Dichlorvos treated hens seemed more related to acute effects of exposure and did not persist beyond the exposure period, as would be expected with OPIDN or with results of lesions. However, no clinical signs were seen in the positive control hens, either, which might call their observational sensitivity into question.

A second pathology report was subsequently submitted that consists of a re-read of the spinal cord slides from positive control and Dichlorvos exposed hens in the 28 day study by a noted expert neuropathologist with specific expertise in OPIDN (Jortner 1994). In brief, he found no evidence either of OPIDN or treatment related spinal cord lesions from Dichlorvos exposure.

These conflicting reviews of the histopathology data were considered to pose a number of problems for the HIARC in determining the appropriate scientific conclusions to be made for this study. The Committee therefore recommended that the registrant be asked to follow a procedure OPP has established for obtaining consensus in pathology re-reads submitted to the Agency, (PR Notice 94-5), for this study. In this case, target tissues included all neural tissues collected (peripheral nerves, spinal cord, and brain).

The Pathology working group consisted of the reviewing pathologist (Dr. Jortner), and 5 other pathologists, several with widely known expertise in neuropathology and OPIDN. The original study pathologist was said to be unavailable. They examined all sections of cerebellum and spinal cord examined in the first 2 readings of the slides. All members of the PWG examined slides coded so that the exposure group was not known at the time of grading.

Emphasis was limited to axonal degeneration. Each lesion was discussed and a consensus diagnosis recorded based on a majority view. The consensus findings were that for hens exposed to Dichlorvos a few scattered degenerating fibers were seen in both controls and treated hens (without any increase in incidence in any treated group). Further, these were not seen to involve a specific level of cord or to have a consistent pattern of distribution. They were mostly noted in the myelinated fibers of the white matter in longitudinal sections and occasionally in cross sections. This pattern was contrasted with that seen in the positive control hens, where more marked degeneration was seen in a pattern typically noted with OPIDN ( e.g., upper cervical nucleus gracilis; lumbo-sacral spinocerebellar tract).

The PWG, based on the consensus evaluation of several pathologists who have examined the slides from this study, concluded that no treatment related increase in neuropathological lesions in spinal cord or cerebellum were seen in this study.

Accepting the negative conclusion of this report, in turn leads to the more general conclusion that the weight of all of the available evidence on Dichlorvos do not support concern for OPIDN or other spinal cord or peripheral nerve pathology resulting from exposures to Dichlorvos (excepting supra-lethal doses described in the literature and noted below).

The HIARC believes that the PWG's review is basically sound and their conclusions acceptable. However, it is unfortunate that their re-examination did not focus as recommended more broadly on other possible effects, or on all of the nervous tissues available. It is also regrettable that the study pathologist was not part of this review group, though her results were presented in the report.

A number of literature citations have previously noted some neuropathology from DDVP exposures. The first found alterations under electron microscopy in spinal cord and cerebellum of rats given 10 daily injections of 3 mg/kg (Hasan, M, Maitra SC, Ali SF; 1979). In contrast, no neuropathological changes in rat nervous system were seen at the light microscope level in the recent 90 day rat neurotoxicity study, where rats received up to 15 mg/kg/day orally (MRID 429581-01).

Two studies in hens reported that OPIDN was seen following massive acute doses (100 mg/kg, s.c.; or 2 doses of 10 times the LD50) in hens ( Caroldi & Lotti, 1981; Johnson, 1981). But together with the present studies in hens which failed to show evidence of OPIDN in clinical signs or NTE inhibition, or neuropathology related or unrelated to OPIDN (rat and hen studies), the weight of the evidence available to EPA does not support the potential for such hazards at less than lethal doses.

### III. REVIEW OF THE PRENATAL DEVELOPMENTAL TOXICITY STUDY IN GUINEA PIGS.

The HIARC evaluated a prenatal developmental toxicity study in guinea pigs published in the open literature by Mehl et al., 1994.

Trichlorfon (125 mg/kg), DDVP (15 mg/kg, once or twice/day) and several other organophosphates (dimethoate, TOCP, Soman, and ethyl trichlorfon) were administered (route unspecified) to pregnant outbred albino guinea pigs (Ssc: AL, MOI:DHF) between day 42 and 46 of gestation. Offspring were born between day 69 and 72 of gestation. Brain weights were determined of pups within 24 hours of birth. Brain regions dissected and weighed were: medulla oblongata; cerebellum; superior and inferior colliculi; hippocampus; and thalamus and hypothalamus. The brain regions were homogenized in 0.32 M sucrose and analyzed for choline acetyltransferase, acetyl cholinesterase (Ellman method), and glutamate decarboxylase.

A dose of 15 mg/kg DDVP was considered the largest dose that could be given without causing cholinergic symptoms in the pregnant dams, but it was noted that the mother of the litter that received 15 mg/kg once in 24 hours had slight symptoms.

Dosing of the dams resulted in the exposure of 19 pups receiving saline on days 42-45; 10 pups receiving trichlorfon on days 42-44 (125 mg/kg), and 4 pups each receiving DDVP at either 15 mg/kg/day on days 42-44 (3 pups), 15 mg/kg/12 hours on days 42-44, or 15 mg/kg/12 hours on days 44-46. No effects on body weight were found. Trichlorfon caused significant decreases in total brain weight (29%), and significant decreases in cerebellum, medulla, thalamus/hypothalamus, the colliculi, and the cerebral cortex.

DDVP, in both groups dosed twice/day produced significant decreases in total brain weight (12-14%) and significant decreases in cerebellum, medulla, thalamus/hypothalamus, and the colliculi. In the DDVP given 15 mg/kg once daily, total brain weight decreases (6%) were not statistically significantly decreased, and only the thalamus/hypothalamus (19%) was significantly decreased. For dams given Trichlorfon, RBC cholinesterase inhibition (ChEI) was 64% at 1 hour, with recovery at 24 hours. There were no significant decreases in brain levels of AChEI, glutamate decarboxylase, or choline acetyltransferase.

Neither soman, a much more potent ChE inhibitor, nor TOCP, a potent NTE inhibitor, caused any effect. Ethyl trichlorfon, a more potent ChE inhibitor and analogue of trichlorfon, did not cause decreases in brain weight, and atropine given with trichlorfon did not prevent the decrease in brain weights (data not shown). The article mentions seven articles by a variety of labs in several countries in which decreases in brain weights of pups from trichlorfon have been noted in guinea pigs and pigs, but not rats. It has been shown that 1-10% of trichlorfon is metabolized to DDVP, which is generally regarded as the active moiety in its antihelmintic and ChEI activities.

Based on these findings, the HIARC concluded that a developmental toxicity study in guinea pigs should be conducted with certain protocol modifications (including examination of brain weight) to replicate/confirm the findings of Mehl, et al., 1994

#### IV. DETERMINATION OF THE UNCERTAINTY FACTOR FOR RISK ASSESSMENTS

At the November 18, 1998 meeting HIARC concluded that "a three-fold uncertainty factor should be used for the protection of infants and children" because the acute and subchronic neurotoxicity studies in hens showed "inconclusive" evidence of neuropathology. The Committee, however, determined that these results require further interpretation, e.g., review by a Pathology Working Group (PWG). Based on this recommendation, the PWG review was conducted and the PWG concluded that there were no treatment-related increases in neuropathological lesions in spinal cord or cerebellum in hens following repeated oral dosing of Dichlorvos.

Based on these findings, the HIARC is recommending the removal of the additional 3 x factor applied at the earlier meeting due to the "inconclusive" evidence of neuropathology in the subchronic hen study. The need for the additional 10 x factor for the enhanced susceptibility of infants and children (as required by FQPA) will be determined by the FQPA Safety Factor Committee.

#### V. TOXICOLOGICAL ENDPOINTS SELECTED FOR RISK ASSESSMENTS.

Provided below are the doses and toxicological endpoints selected for various exposure risk assessments at the November 18, 1997 HIARC meeting. For Executive Summaries and rationale for the endpoints selected, the reader is referred to the HIARC Report HED Doc. No. 012248.

EXPOSURE SCENARIO	DOSE (mg/kg/day) and UF	ENDPOINT	STUDY
Acute Dietary	NOEL = 0.5	Red blood cell cholinesterase inhibition	Acute- Human
	UF=10	Acute RfD = 0.05 mg/kg	
Chronic Dietary	NOEL = 0.05	Plasma and RBC cholinesterase inhibition in both sexes and brain cholinesterase inhibition in males	1-Year Dog
	UF = 100	Chronic RfD = 0.0005 mg/kg/day	
Short-Term (Dermal) (a)	Oral NOEL= 0.5	Red blood cell cholinesterase inhibition	Acute -Human
	UF = 10		
Intermediate-Term (Dermal) (a)	Oral LOEL= 0.1	Red blood cell cholinesterase inhibition	Repeated Dose Human
	UF=30		
Long-Term (Dermal)	None	The use pattern does not indicate a potential Long-Term dermal exposure; this risk assessment is not required	None
Inhalation (Any Time Period)	0.00005 mg/L	Plasma, RBC and Brain cholinesterase inhibition.	2-Year Rat
	UF=100		

- (a) Since an oral NOEL was selected for these exposure periods, a dermal absorption factor of 11% (determined from a dermal absorption study, MRID No. 41435201) should be used for these exposure risk assessments.

References

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Johnson MK 1981. Delayed neurotoxicity-do trichlorophon and/or dichlorvos cause delayed neuropathy in man or in test animals? *Acta Pharmacol Toxicol (Copenh)* 49 Suppl 5: 87-98.

Mehl A, Schanke TM, Johnsen BA, and Fonnum F. 1994. The Effects of Trichlorfon and Other Organophosphates on Prenatal Brain Development in the Guinea Pig. *Neurochemical Research* 19:5, pp.569-74.