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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 28, 2000

SUBJECT: Dichlorvos: Review of Protocol for a 7-Day Oral Toxicity Study in the Rat

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TASK ID: DP Code: D268079 Submission: S583642 P.C. Code: 084001
Case: 819293

REGISTRANT: AMVAC

Action Requested: Review of protocol for a 7-day oral toxicity study in the rat

Agency's Response: The registrant for Dichlorvos, AMVAC, has submitted a protocol for a short-term toxicity study to investigate the toxicity of the test compound to male and female rats over a 7-day dosing period.

The Agency has reviewed the details of the submitted protocol in view of the mechanism of pesticidal action of dichlorvos as an inhibitor of cholinesterase, the results of the acute oral neurotoxicity study in rats (MRID # 42655301) and/or other relevant data.

Based on the submitted information it is concluded that the protocol is unacceptable because it lacks sufficient details. The recommended changes to the protocol should not be misconstrued as a commitment on the part of the Agency to accept the outcome of the proposed study. The revised protocol may be submitted to the Agency for review prior to study initiation. The final

decision regarding the acceptability of the study will depend upon the submission of the full study and its review by the Agency. The results of the proposed study will be reviewed and evaluated by the HIARC in order to make any changes in the endpoints selected for risk assessment.

Detailed Considerations: Dichlorvos is an organophosphate. The mechanism of its neurotoxicity occurs via inhibition of cholinesterase. The available toxicity studies suggests that dichlorvos inhibits cholinesterase at low levels in various species and the nervous system is the target for dichlorvos toxicity. Although the protocol stated that the dose levels have been selected from an acute oral toxicity study and other relevant data, the dose levels were not provided.

The selection of strain, test species, number animals/dose group, the route of administration as well as parameters such as observations for clinical signs, measurements of body weight gains, food consumption and changes in organ weights and gross and histopathology are appropriately included. The changes in weight and histopathology would be indicative of toxicity. However, the protocol provides only the outline for the conduct of the study but lacks the specific details such as specific purpose of the study, source of the test material, purity, storage conditions and the doses selected. Given the fact that dichlorvos is an organophosphate, an assessment of cholinesterase activity in the various compartments is required.

The selection of both male and female rats in the proposed study seems appropriate since it would be helpful to assess the sex-related differences in response. Animals should be specifically observed for cholinergic signs. Among clinical chemistry parameters to be measured, the Registrant should conduct measurements of plasma and RBC cholinesterase levels on the same animals at various interim sampling intervals including pre test (to determine the baseline levels), and for example, at 1, 3 and 7 days. Measurements during post exposure should be performed to determine the reversibility of the cholinesterase inhibition. Brain cholinesterase measurements should be conducted also. The acceptable analytical method should be used and described in details. These measurements for an assessement of dose response, time to onset, and steady state for both plasma and RBC cholinesterase levels are required. It would also determine whether the cholinesterase inhibition increases or changes with time. At necropsy, brain weights and gross and histopathological changes in the brain and neural tissues should be examined. Registrant may wish to consider using tissues from animals prepared by *in situ* perfusion.

Although the cover letter stated that the purpose of the study is to refine the no observed adverse effect level in the rat, it is unclear whether the registrant intends to use the refined NOAEL for use in risk assessment for acute dietary or short-term non-dietary exposure scenarios. Also the basis for the NOAEL was not specified. If the study is intended to refine the NOAEL for cholinesterase inhibition for short-term duration risk assessment, then in view of the intended changes in the definition of short-term duration (which will be 1-30 days rather than 1-7 days) by the HIARC, may wish to consider extending the study period up to 30 days. In that case the

cholinesterase measurements should be conducted at various sampling intervals including pretest, 1, 7, 14, 21, 30 days and during post exposure period.

cc: Ray Kent, Branch Chief, RRB4/HED