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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Fortress (Chlorethoxyfos). Review of Protocols for Inhalation Range-finding Study, Repeated-Dose Inhalation Toxicity Study, and Repeated-Dose Dermal Toxicity Study.

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Kit Farwell 9-27-96

THRU: Karl Baetke
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9/27/96

ACTION REQUESTED: Toxicology Branch I received 3 study protocols from DuPont Agricultural Products for review. A range-finding inhalation study and a 7-day repeated-dose inhalation toxicity study will use technical Fortress. A 21-day repeated-dose dermal toxicity study will use Fortress 5G formulation. These studies were required in the HED Risk Assessment for Chlorethoxyfos (8/21/95). Important endpoints to be determined are NOEL and LOEL values for plasma, rbc, and brain cholinesterase inhibition.

CONCLUSIONS: The studies will be suitable for risk assessment purposes as required in the HED Risk Assessment for Chlorethoxyfos (Fortress), dated 8/21/96, if performed as planned in the draft protocols and if NOEL and LOEL values for cholinesterase inhibition are determined. The methodology for determination of cholinesterase activity should be consistent with the "round robin" on cholinesterase methodology. Comments on the studies follow.

Range-finding Inhalation Study: The range-finding inhalation study will determine plasma cholinesterase activity after exposure to technical Fortress. The purpose of the study is to determine exposure concentrations for the repeated-dose

inhalation study. This range-finding study will use several single-exposure groups and one multiple-exposure group.

The protocol says that gas chromatography will be used to measure the test atmosphere concentration and that the analytical method will be described in the study report. It is important that the ability to measure the test atmosphere concentration be determined in this range-finding study before beginning the repeated-dose study.

Particle sizes need to be determined in the range-finding study to ensure that particle sizes are small enough during the repeated-dose study.

Methodology for determination of cholinesterase activity should be described in the study report and should be consistent with the "round robin" on cholinesterase methodology.

Repeated-Dose Inhalation Toxicity Study: This study will use technical Fortress. The main purpose of the study is to determine NOEL and LOEL values for plasma, rbc, and brain cholinesterase inhibition. Also noted will be changes in body weights, clinical signs, and gross and microscopic changes in the respiratory tract.

The concentration of test atmosphere was not accurately determined in previously conducted acute inhalation studies with Fortress. Although the acute inhalation studies were able to determine the toxicity category, the purpose of the repeated-dose inhalation study is to determine NOEL and LOEL values. It is therefore very important to accurately determine exposure concentrations in this study.

The gas chromatographic method used should measure concentration of test material in the breathing zone of the animals. Toxicology Branch I should be consulted before performing the repeated-dose inhalation study if the range-finding study encountered problems in accurately determining concentration of test atmosphere in the breathing zone.

Particle size analysis should be conducted with mass median aerodynamic particle size (MMAD) and distribution reported. MMADs should ideally be 1-3 microns.

The protocol says that brains will be frozen for later analysis of cholinesterase activity. Activity should be determined as soon as possible after dissection to avoid re-activation of enzyme, which has happened in blood.

The protocol says that the final report will include items cited in CFR 40, Part 792. Part 792 describes reporting requirements for compounds regulated under the Toxic Substances Control Act.

2

The reporting requirements for this study are listed in Subdivision F, Pesticide Assessment Guidelines.

Methodology for determination of cholinesterase activity should be described in the study report and should be consistent with the "round robin" on cholinesterase methodology.

Since this is a 7-day study, rather than a 21-day study, this study may not be acceptable under OPP Guideline requirements. However, the study will be suitable for risk assessment purposes if NOEL and LOEL values for cholinesterase inhibition are determined.

Repeated-dose Dermal Toxicity Study: This study will use Fortress 5G formulation. The study will follow general 82-2 Guideline requirements and will determine NOEL and LOEL values for plasma, rbc, and brain cholinesterase inhibition. A range-finding study will precede the main study.

Plasma and rbc cholinesterase activity should be determined at 7 days, as well as 21 days, in the main study. This will provide more confidence in interpretation of results and this time point will be useful for risk assessment purposes.

The protocol says that brains will be frozen for later analysis of cholinesterase activity. Activity should be determined as soon as possible after dissection to avoid re-activation of enzyme, which has happened in blood.

Clinical chemistries, hematology, urinalysis, and microscopic examination of skin, liver, and kidneys are not planned for this study because changes in clinical pathology or histopathology were not noted in previous oral studies. These omissions may mean that the study does not meet OPP Guideline requirements for an acceptable study. However, the study will be suitable for risk assessment purposes if NOEL and LOEL values for cholinesterase inhibition are determined.

Methodology for determination of cholinesterase activity should be described in the study report and should be consistent with the "round robin" on cholinesterase methodology.

cc: Beth Edward, RD