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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: **CHLORETHOXYFOS - *RE-EVALUATION OF Toxicology Endpoint Selection -***

FROM: Jess Rowland
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Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Steve Knizner
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PC Code: 129006

SUMMARY: In the preliminary risk assessment done in August 1997, an oral NOEL was used for dermal occupational dermal exposure risk assessments. Since then the Agency has received, reviewed and accepted a 21-day dermal toxicity study in rats. The NOEL of 25 mg/kg/day in this study is based on inhibition of erythrocyte cholinesterase activity. This NOEL was selected for short and intermediate-term dermal occupational exposure risk assessments because: 1) the study tested the formulation product (granular) of concern for exposure; 2) the study was conducted in the sex (females) that was shown to be more sensitive to the effects of chlroethoxyfos; 3) the most sensitive endpoint (cholinesterase inhibition) was demonstrated via the route of exposure of concern (dermal); 4) the endpoint (cholinesterase inhibition) was observed 7 and 21 days post-treatment which is appropriate for the exposure periods of concern (1-21 days); and 5) the study design (dermal exposure) simulates real-life exposure scenario.

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I. BACKGROUND

On November 16, 1994, the Health Effects Division's Toxicology Endpoint Selection Committee (TESC) met and selected the doses and endpoints for dietary and non dietary exposure risk assessments. At that meeting, the TESC selected an oral NOEL 0.06 mg/kg/day based on plasma cholinesterase inhibition observed in both sexes of dogs in a 6-month ocular toxicity study. The Agency used this oral NOEL and a 50% dermal absorption rate (for route-to-route extrapolation) to conduct its preliminary risk assessments for occupational dermal exposure HED Risk Assessment for Chlorethoxyfos (Fortress®, From: S.Robbins, HED to D. Edwards,RD dated August 21, 1995).

II. REVIEW OF A 21-DAY DERMAL TOXICITY STUDY

The Registrant, recently, submitted a 21-day dermal toxicity study in which adult female Crl:CD rats received 15 repeated dermal administration of Fortress 5G (approximately 5% chlorethoyxfos) at doses of 0 (vehicle control, deionized water), 0 (granular control, Fortress granules that did not contain chlorethoyxfos) at 25, 75 or 300 mg/kg, 6 hours/day for 21 consecutive days. This study was conducted with female rats only because previous studies have shown females to be more sensitive to the effects of chlorethoxyfos than males. The test substance, small water insoluble granules, was spread as thinly as possible onto a gauze dressing that was pre-moistened with 1 mL of deionized water. Cholinesterase measurements were done pre exposure and on study days 7 and 21. At the high dose (300 mg/kg/day) there were statistically significantly decreases in plasm and red blood cell (RB) cholinesterase activity on days 7 and 21 and in brain cholinesterase activity on day 7. At the mid dose (75 mg/kg/day), plasma and RBC cholinesterase activity was inhibited, however, only the depression in RBC reached statistical significance on day 21. The NOEL was 25 mg/kg/day and the LOEL was 75 mg/kg/day based on erythrocyte cholinesterase inhibition.

III. SELECTION OF DOSE FOR OCCUPATIONAL DERMAL RISK ASSESSMENTS

The NOEL of 25 mg/kg/day in this study is based on inhibition of erythrocyte cholinesterase activity. This NOEL was selected for short and intermediate-term dermal occupational exposure risk assessments because: 1) the study tested the formulation product (granular) of concern for exposure; 2) the study was conducted in the sex (females) that was shown to be more sensitive to the effects of chlroethoxyfos; 3) the most sensitive endpoint (cholinesterase inhibition) was demonstrated via the route of exposure of concern (dermal); 4) the endpoint (cholinesterase inhibition) was observed 7 and 21 days post- treatment which is appropriate for the exposure periods of concern (1-21 days); and 5) the study design (dermal exposure) simulates real-life exposure scenario.

NOTE: THE DOSES AND ENDPOINTS SELECTED FOR ACUTE AND CHRONIC DIETARY AS WELL AS INHALATION EXPOSURE RISK ASSESSMENTS BY THE TOXICOLOGY ENDPOINT SELECTION COMMITTEE (TES Document 11/16/94) REMAINS UNCHANGED.

IV. TOXICOLOGY ENDPOINT SELECTION

The toxicology endpoints selected for dietary and non-dietary risk assessments are presented below.

Exposure Duration	Exposure Route	Dose	Endpoint	Comments
Acute	Dietary	Acute RfD= 0.0006 mg/kg	Plasma cholinesterase	NOEL=0.06 mg/kg/day of and an Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Chronic	Dietary	Chronic RfD= 0.0006 mg/kg/day	Overall Cholinesterase inhibition (ChEI)	NOEL=0.061 mg/kg/day based on ChEI in the 90-day, 6-month and 1-year studies in dogs. An Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Short-Term (1-7 Days)	Dermal	NOEL = 25	Erythrocyte ChEI	A MOE of 100 is adequate for occupational exposure risk assessments. **There are no residential uses.**
Intermediate-Term (7-90 days)	Dermal	NOEL = 25	Erythrocyte ChEI	A MOE of 100 is adequate for occupational exposure risk assessments. **There are no residential uses.**
Long-Term (several months to life-time)	Dermal	None	None	Based on the use pattern (1 application/year), there is no potential long-term dermal exposure. Therefore, this risk assessment is not required.
Short,-Intermediate	Inhalation	NOEL= 0.06 mg/kg/day	Plasma cholinesterase inhibition	Oral NOEL selected due to lack of an appropriate inhalation study and the oral LD_{50} and inhalation LC_{50} for the technical and the formulation product (Fortress 5G) are both in Toxicity Category I. On this basis, the Agency has no reason to believe that chlorethoxyfos is less potent in term of toxicity by the inhalation route. Since an oral NOEL was selected, the use of 100% (default) inhalation absorption rate is required for risk assessment. A MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.
Long-Term (several months to life-time)	Inhalation	None	None	Based on the use pattern (1 application/year), there is no potential long-term dermal exposure. Therefore, this risk assessment is not required.

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