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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ETHOPROP HED RED Chapter.

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TO: Judy Loranger
Reregistration Branch 3
Special Review and Reregistration Division (7508W)

FROM: Kit Farwell
Reregistration Branch 1
Health Effects Division (7509C)

Kit Farwell 5-21-98

THRU: Whang Phang, Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

Whang Phang 5/21/98

BACKGROUND: This memo comprises the Health Effects Division (HED) risk characterization for ethoprop. Attached are Toxicology, Chemistry, and Occupational Exposure Chapters, a Dietary Risk Evaluation System (DRES) analysis, and a Review of Ethoprop Incident Reports. Residential exposure was not assessed because there are presently no residential uses for ethoprop. Drinking water assessment has **not** been incorporated into this risk characterization. Aggregate exposure, including drinking water will be calculated at a later date.

Ethoprop is an organophosphate insecticide, nematocide, and fungicide used on agricultural crops and golf-course turf. Cumulative risk assessment from other pesticides with a common mechanism of toxicity is not considered in this memo.

SUMMARY OF RISK (Non-cancer): Ethoprop is a potent cholinesterase inhibitor with acute toxicity category 1 by both oral and dermal routes; all test rabbits in the eye and dermal irritation studies died. Due to the acute toxicity of ethoprop, with few apparent clinical signs before death, most studies used low doses. The main toxic effect seen at lower doses was decreased cholinesterase activity and related clinical signs. Mild liver toxicity also occurred in dogs. The non-cancer endpoints for estimating risk from exposure to ethoprop were all based on

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cholinesterase inhibition. (See Toxicology Chapter.)

TABLE 1. ACUTE TOXICITY: TECHNICAL ETHOPROP

STUDY	RESULTS	TOXICITY CATEGORY
81-1 Acute Oral - Rat	M LD ₅₀ = 56.2 mg/kg F LD ₅₀ = 30.2 mg/kg	I
81-2 Acute Dermal - Rabbit	LD ₅₀ = 8.5 mg/kg	I
81-2 Acute Dermal - Rat	M LD ₅₀ = 1280 mg/kg F LD ₅₀ = 424 mg/kg	II
81-3 Acute Inhalation - Rat	LC ₅₀ = 0.123 mg/L	II
81-4 Eye Irritation - Rabbit	0.1 mL killed all 3 rabbits	I
81-5 Skin Irritation - Rabbit	0.5 mL killed all 6 rabbits.	I

M= male, F = Female

TABLE 2. TOXICOLOGICAL ENDPOINTS

EXPOSURE SCENARIO	NOEL (mg/kg/day)	ENDPOINT	STUDY
ACUTE DIETARY	0.025	Plasma ChE (day 2)	Subchronic Dog
CHRONIC DIETARY RfD = 0.0001 mg/kg/day	0.01	Plasma ChE Inhibition	Chronic Dog
SHORT and INTERMEDIATE TERM DERMAL	0.1	Plasma, RBC, Brain ChE	21-day Dermal Rabbit
SHORT and INTERMEDIATE TERM INHALATION	0.025	Plasma ChE	Subchronic Dog
CHRONIC DERMAL/INHALATION	Risk assessment not performed, no chronic uses.		

ChE = cholinesterase

The **acute dietary exposure endpoint** was selected from a subchronic dietary dog study with doses of 0, 0.025, 0.075, or 2.5 mg/kg/day. The NOEL was 0.025 mg/kg/day. The LOEL was 0.075 mg/kg/day and was based upon plasma cholinesterase inhibition on the second day of the study. This study provided the most sensitive indicator for acute cholinesterase inhibition.

The **reference dose (RfD)** used in the chronic dietary risk assessment was obtained from combined 5-month and 1-year dog studies with a NOEL of 0.01 mg/kg/day. The LOEL of 0.025 mg/kg/day was based upon plasma cholinesterase inhibition. At 1.0 mg/kg/day and above, red blood cell cholinesterase was inhibited, anemia occurred, and liver enzymes were elevated. At 10 mg/kg/day and above, brain cholinesterase was inhibited, gross and microscopic liver pathology occurred, and one male died.

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The **occupational dermal exposure endpoints** were selected from a 21-day dermal study in rabbits with doses of 0, 0.03, 0.1, or 1 mg/kg/day. The no observed effect level (NOEL) was 0.1 mg/kg/day. The lowest observed effect level (LOEL) was 1 mg/kg/day and was based upon plasma, red blood cell, and brain cholinesterase inhibition. Erythema occurred at the application site in all treatment groups. The **occupational inhalation exposure endpoints** used the acute dietary endpoint above.

SUMMARY OF RISK (Cancer): The Cancer Assessment Peer Review Committee determined that ethoprop was a "likely" human carcinogen to be regulated by linear low dose extrapolation. The Q_1^* (in the absence of a complete tumor count in low- and mid-dose groups) was calculated to be $2.81 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ and was based upon malignant adrenal gland pheochromocytomas in male rats (See Toxicology Chapter.)

SENSITIVITY OF INFANTS AND CHILDREN: No increased sensitivity of fetuses or pups compared to adults was shown in rat or rabbit developmental studies or the 2-generation reproduction study. Since there was no indication of an increased sensitivity of infants and children, the Hazard Identification Committee recommended that for dietary risk assessments, the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA) be removed. A margin of exposure of 100 is adequate for acute and chronic dietary risk assessments. (See Hazard ID Report, 11/10/97.)

OCCUPATIONAL AND RESIDENTIAL RISK (non-cancer): At this time, ethoprop is intended for occupational uses only, and a risk assessment for home use was not conducted. A chronic occupational exposure assessment was not performed since no chronic exposure scenarios exist. Calculation of post-application risks will be postponed until risks for pesticide handlers are determined not to be of concern.

No chemical-specific handler exposure data were submitted in support of the reregistration of ethoprop. Therefore, the exposure assessment was developed with surrogate values of varying reliability using the Pesticide Handlers Exposure Database. Refinement of the occupational exposure assessment may be possible with ethoprop-specific handler studies.

There are concerns for short-term and intermediate term occupational exposures. A margin of exposure (MOE) of 100 or greater is considered adequately protective for occupational exposure. Most of the combined dermal/inhalation MOEs were less than 1 whether personal protective equipment or engineering controls were assumed. (See pages 17-24 and 39 of the Occupational Exposure Chapter.)

OCCUPATIONAL CARCINOGENIC RISK: The Agency's level of concern for occupational carcinogenicity risk is in the range of 10^{-4} to 10^{-6} . Four exposure scenarios had a carcinogenic risk of 10^{-3} or greater and exceeded the Agency's level of concern. These scenarios were with personal protective equipment and combined dermal and inhalation exposure. The four scenarios which exceeded the Agency's level of concern were for mixing/loading liquid

formulations for chemigation (2.3×10^{-3}), loading/applying granular with a push-type granular spreader (1.3×10^{-3}), loading/applying granular by hand (1.1×10^{-2} and 1.1×10^{-1}), and mixing/loading/applying liquid formulation with low-pressure handwand sprayer (1.4×10^{-3}). (See pages 25-34 and 39 of the Occupational Exposure Chapter.)

ACUTE DIETARY RISK: Acute dietary risk was assessed by HED using the Dietary Risk Evaluation System (DRES). Anticipated residues were calculated from plant metabolism studies because residue data and monitoring data were not available for all residues of concern.

Using DRES, acute dietary risk for ethoprop exceeds the Agency's level of concern for the general U.S. population and all subgroups. With the RfD approach, the % acute RfD occupied by acute dietary exposure should be less than 100%. However, the % acute RfD values for ethoprop were all at least 1,200%. (See pages 4 and 5 of the Acute and Chronic Dietary Risk Analysis.)

The registrant has performed a Monte Carlo acute dietary analysis which is presently under review. Preliminary review indicates that the registrant used several different assumptions than did HED's DRES analysis. The registrant used different values for anticipated residues and % crop treated than did HED. Bananas, potatoes, sugar cane, and sweet potatoes were apparently not included in the registrant's analysis (no values for anticipated residues). This study is currently under review and cannot be considered in the risk assessment for ethoprop.

CHRONIC DIETARY RISK: Chronic dietary risk was assessed using DRES, anticipated residues, and % crop treated data provided by BEAD. Chronic dietary risk is below the Agency's level of concern for the general U.S. population and for all subgroups. The most highly exposed population subgroup, based on the results of the DRES analysis, is non-nursing infants (<1 year old), for which 97.6% of the RfD is occupied. Approximately 95% of the RfD for non-nursing infants (<1 year) is occupied by bananas/plantains. It was assumed that % crop treated was 100% for bananas/plantains. Drinking water was not included in the assessment, and it is possible that with aggregate human risk analysis, the exposure could be greater than 100% of the RfD. (See pages 4 and 5 of the Acute and Chronic Dietary Risk Analysis.)

DIETARY CARCINOGENICITY RISK: Dietary risk analysis with DRES found chronic carcinogenicity dietary risk to be below the Agency's one in a million level of concern for dietary risk, at 0.7×10^{-6} . Much of this risk is due to bananas/plantains for which the carcinogenicity risk is approximately 0.66×10^{-6} . However, drinking water was not included in the assessment and it is possible that aggregate carcinogenic risk could be greater than 10^{-6} . (See page 5 of the Acute and Chronic Dietary Risk Analysis.)

ETHOPROP INCIDENT REPORTS: The Review of Ethoprop Incident Reports had several occupational reports with possible symptoms of cholinesterase inhibition. In addition, the Report included a drift incident investigated by the California Department of Environmental Health. In this drift incident, reports of headache, diarrhea, runny nose, sore throat, burning/itching eyes,

fever, and hay fever or asthma attacks were attributed to n-propyl mercaptan, an ethoprop contaminate/degradate with a strong, offensive odor.

The Review of Ethoprop Incident Reports recommended that application methods to prevent the odor of n-propyl mercaptan drifting to residential areas should be considered. Alternatively, reducing the content of the contaminant n-propyl mercaptan, if practical, would be expected to reduce the complaints related to the strong odor. (See pages 7-9 of the Review of Ethoprop Incident Reports.)

DATA REQUIREMENTS: Following are comments on data requirements from the various disciplinary chapters.

Product and Residue Chemistry Chapter (John Abbotts memo, 3/27/98):

For Residue Chemistry, submitted field trial data for some crops are not entirely consistent with maximum label use patterns; requirements may be satisfied by appropriate label amendments or additional residue data. Data also remain outstanding for field rotational crops; however, data requirements could be reduced by appropriate label restrictions on rotational crops.

Tolerances are not established for residues in livestock commodities, and will not be required at present. However, once adequate residue data are available on all livestock feed items, the requirement for livestock feeding studies will be reevaluated to determine if additional data are needed.

Since residue data have not been submitted for all metabolites of concern, anticipated residues were calculated, using conservative assumptions from metabolism studies, for use in the dietary exposure assessments.

Regarding Product Chemistry, there will be no objection to reregistration of ethoprop once the registrant has submitted required data for the 95.9% T to meet new requirements for UV/visible absorption.

Toxicology Chapter (Kit Farwell memo, signed 4/17/98, page 1):

The toxicology database for ethoprop is essentially complete, with the exception of cholinesterase determinations for the M1 metabolite of ethoprop in an acute study and a "confirmatory" neurotoxic esterase study. These results will not significantly change the understanding of the toxicity of ethoprop and should not interfere with the reregistration process.

Occupational Exposure Assessment (Kathryn Boyle memo, signed 4/2/98, page 2)
recommended that aerial use, greenhouse use, and sod farm scenarios should be addressed during

label development to ensure that these use scenarios are not permitted without a further assessment:

Aerial application seems unlikely for most of the registered crops, since the product must be immediately incorporated following application and is often applied as a band treatment. The emulsifiable concentrate ethoprop label, specifically prohibits aerial application on potatoes, however, aerial application of the granular formulation to potatoes is specified on three labels. Exposure and risks were calculated for use of the granular product on potatoes.

According to the registrant, greenhouse use is "negligible or nonexistent" even though labeling does not preclude this use pattern.

Sod farm uses are also not referenced on any label except the technical product, which is labeled for "commercial turf."

ATTACHMENTS

Toxicology Chapter for the Reregistration Eligibility Document for Ethoprop (Kit Farwell, signed 4/17/98).

Ethoprop - FQPA Requirement - Report of the Hazard Identification Committee (Jess Rowland, 11/10/97).

Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Ethoprop (Kathryn Boyle, 4/2/98).

Ethoprop. Acute and Chronic Dietary Risk Analyses for the HED RED Chapter (Christina Swartz, 5/5/98).

Review of Ethoprop Incident Reports (Jerome Blondell, 3/9/98).

Ethoprop, Product and Residue Chemistry Chapters for the Reregistration Eligibility Decision (John Abbots, 3/27/98).

Ethoprop. Anticipated Residues for Acute and Chronic Non-Cancer Dietary Exposure (Sheila Piper, 4/23/98).

Ethoprop. Anticipated Residues for Chronic (Cancer) Dietary Exposure (Sheila Piper, 4/29/98).

Secondary Review: Whang Phang, Sr. Scientist:5/13/98, 5/20/98;
Kathryn Boyle, Exposure:5/12/98; Christina Swartz, Dietary:5/11/98

7509C:KFarwell:RRB1:CM2:Rm 823H:703-305-6373:5/21/98