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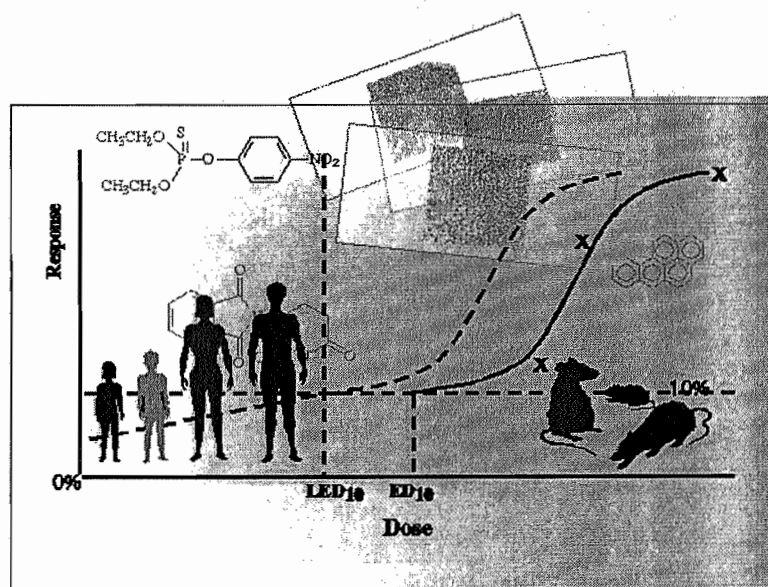
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HUMAN HEALTH RISK ASSESSMENT

ETHOPROP

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U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Kit Farwell, D.V.M., Risk Assessor
September 2, 1999

HUMAN HEALTH RISK ASSESSMENT

ETHOPROP

Phase 4

Risk Assessment Team:

Lead Risk Assessor: Kit Farwell, D.V.M., Toxicologist

Dietary Risk: Sheila Piper, Chemist
Christina Swartz, Chemist

Residue Chemistry: Sheila Piper, Chemist

Product Chemistry: Sheila Piper, Chemist

**Occupational and
Residential Exposure:** Catherine Joseph, MSPH, Industrial Hygienist

Toxicology: Kit Farwell, D.V.M., Toxicologist

Management:

Senior Scientist: Whang Phang, Ph.D.

Branch Chief: Michael Metzger

Division Director: Margaret J. Stasikowski, August 28, 1999

ETHOPROP REVISED RISK ASSESSMENT

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ETHOPROP

Executive Summary

Background

This document is the current update of Health Effects Division's (HED's) risk characterization for ethoprop. The attached disciplinary evaluations were written by Catherine Joseph (occupational and non-occupational exposure assessments), Sheila Piper (acute dietary exposure assessment), Christina Swartz (chronic dietary exposure assessment), and Kit Farwell (toxicology assessment).

A new dietary risk assessment was written because new anticipated residues were calculated. The occupational/non-occupational/residential exposure and risk assessment has been revised to incorporate a post-application assessment of golf course turf (including golfers) and cancer assessments for post-application golf course turf management professionals as well as golfers. Comments from USDA have been incorporated into these documents.

Two earlier versions of this document were written to incorporate public comments and to calculate the dietary risk assessment with and without the inclusion of several crops. As a result of public comments it was decided not to include the M1 metabolite of ethoprop in calculation of anticipated residues.

Uses

Ethoprop is an organophosphate insecticide and nematicide used on agricultural crops and golf course turf. With the exception of pineapples, it is applied pre-plant or pre-emergent. Ethoprop is formulated as a technical-grade manufacturing product (95.9% ai), as granular products (3%, 10% and 15% ai), emulsifiable concentrate (46% and 69.6% ai), two granular "Lock 'n Load" products (10% and 20% ai) and as a gel in water-soluble packaging (68.2% ai).

Residential exposure and chronic occupational exposure were not addressed in this risk assessment, because there are presently no registered residential uses or anticipated chronic occupational exposure scenarios for ethoprop. However, general public exposure from golfing following ethoprop treatment of a golf course may occur and an assessment was conducted. Cumulative risk assessment from other pesticides with a common mechanism of toxicity is not considered in this document.

Offspring Susceptibility

No increased susceptibility of offspring was noted in rat reproduction, rat developmental, or rabbit developmental studies and the HED FQPA Safety Factor Committee concluded that the 10x factor to account for enhanced sensitivity of infants and children should be reduced to 1x. A total uncertainty factor of 100x, based on uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability is adequate for acute and chronic dietary risk assessments.

Food Exposure

Acute dietary exposure resulting in less than 100% of the acute population adjusted dose (aPAD) is considered protective for ethoprop. **Acute dietary exposure** for ethoprop is **below the Agency's level of concern**. The population with the highest exposure was non-nursing infants < 1 year old with an estimated exposure of 80% of the aPAD.

Chronic dietary exposure resulting in less than 100% of the chronic PAD is considered protective for ethoprop. **Chronic dietary exposure** for ethoprop is significantly **below the Agency's level of concern**. The population subgroups with the highest exposure were non-nursing infants <1 year old and children 1-6 years old, with estimated exposures of 1% of the chronic PAD.

For dietary carcinogenic risk, the Agency's level of concern is one in a million excess cancers, or 1×10^{-6} . Estimated chronic **carcinogenic dietary risk** is **below the Agency's level of concern**, at 1.1×10^{-8} .

Water Exposure

Estimated drinking water concentrations for both surface and ground water **exceeded drinking water levels of comparison** for acute and chronic exposure. Drinking water levels of comparison ranged from 0.5 - 6 ppb for different population subgroups while estimated chronic surface water concentrations were ≥ 60 ppb and acute surface water concentrations were ≥ 135 ppb for different application scenarios.

Occupational and Non-Occupational Exposure

The occupational and non-occupational exposure assessment for this risk assessment used dermal and inhalation endpoints selected by the HED Hazard Identification Assessment Review Committee (Jess Rowland, 6/3/98 memo). The occupational exposure assessment also incorporates current HED policy of combining dermal and inhalation margins-of-exposure (MOEs) when the same endpoint is selected with different routes of exposure.

A MOE of 100 or greater is considered protective for ethoprop. None of the individual and professional short-term or intermediate-term handler exposure scenarios (even at the highest level of risk mitigation) had MOEs greater than 100. In fact, only three short-term and two intermediate-term handler exposure scenarios have combined MOEs greater than or equal to 10. The significant risk driver is the dermal exposure route. A cancer risk of less than 1×10^{-4} does not exceed the Agency's level of concern for occupational exposure; but at the highest level of mitigation available, one individual handler scenario and five professional handler scenarios had cancer risks greater than 1×10^{-4} . When feasible, the Agency seeks ways to reduce individual cancer risks to the greatest extent, preferably 10^{-6} or less.

Because ethoprop is used in pre-plant and pre-emergent applications and is normally soil incorporated or watered-in, there are generally no concerns for post-application exposure to agricultural workers. Two exceptions for this use pattern are sugarcane and pineapples. Sugarcane is mechanically transplanted and should have minimal post-application concerns. Ethoprop may be applied to pineapples at various points in the growing season. However, there is currently a 120 day pre-harvest interval for pineapples, so there should generally be minimal concern during harvesting.

Post-application exposure assessment was conducted for turf management professionals. When using both tractors and push-type mowers with application rates of 10 and 20 lb ai/A, it was determined that re-entry intervals (REIs) greater than 50 days were required before workers could re-enter for activities, such as mowing. At the highest level of mitigation available, the cancer risks associated with these activities were in the mid to high 10^{-5} range for re-entry on the day of treatment. Although these risks did not exceed the 10^{-4} level of concern, risks did not decline to the 10^{-6} range until more than 30 days following ethoprop treatment.

An assessment to quantify golfer risk following ethoprop treatment was also conducted. On the day of treatment for 20 and 10 lb ai/A, MOEs of 2 and 3 were calculated, respectively. More than 30 days needed to elapse before golfers could enter ethoprop treated areas to golf. In addition, the cancer risks associated with golfer exposures were in the low to mid 10^{-6} range for entry on the day of treatment.

Occupational and non-occupational risks **exceed** the Agency's level of concern for both cancer and non-cancer risks.

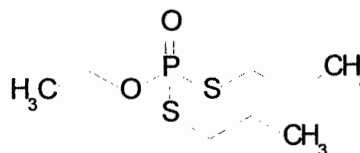
Aggregate Exposure

Aggregate risk calculations for acute and chronic exposure consisted of the drinking water levels of comparison mentioned above. Non-occupational or recreational (golfer) and dietary exposures to ethoprop were not combined for short-term and intermediate-term exposures because golfer risk alone exceeded a level of concern.

I. Physical/Chemical Properties

Ethoprop (O-ethyl S,S-dipropyl phosphorodithioate) is a colorless to yellow tinted liquid with a strong mercaptan odor and a boiling point of 86-91 C at 0.2 mm Hg. Ethoprop is only slightly soluble in water (843 ppm at 21 C), but is soluble in most organic solvents (hexane, xylene, acetone, and ethanol). (See Attachment 1, Product and Residue Chemistry Chapter.)

Empirical Formula: $C_8H_{19}O_2PS_2$
Molecular Weight: 242.3
CAS Registry No.: 13194-48-4
Shaughnessy No.: 041101



II. Hazard Characterization

A. Hazard Profile

Ethoprop is a potent cholinesterase inhibitor in acute toxicity category 1 by both oral and dermal routes (see Table 1). All test rabbits in the eye and dermal irritation studies died. The main toxic effects seen in the subchronic and chronic studies were decreased cholinesterase activity, cholinergic signs, anemia, and weight loss. Mild liver toxicity (see Table 2) also occurred in the chronic dog study. (Attachments 2 and 3, Toxicology Chapter and Addendum.)

The dose-response curve for ethoprop is steep. In the 1992 chronic toxicity/carcinogenicity study in rats, mortality occurred at doses only slightly higher than those causing clinical signs; the high dose of 600 ppm caused excess mortality in the first 2 weeks of the study, yet when the high dose was reduced to 400 ppm, this group of animals had increased survival compared to controls after two years of treatment. The NOAELs for plasma cholinesterase inhibition were the same as those for brain cholinesterase inhibition in the 21-day dermal rabbit study, the 1992 chronic toxicity/carcinogenicity study in rats, and the subchronic neurotoxicity study.

The dermal occupational endpoints are based on a 21-day dermal study in rabbits. This may provide a conservative estimate of risk as rabbits are approximately 50 times more sensitive than rats in terms of acute lethality from dermal exposure; the dermal LD50 for rats is 424 mg/kg compared to 8.5 mg/kg in rabbits. The relative sensitivity in humans is not known. No dermal absorption study is available for ethoprop. The possibility of calculating dermal absorption for cancer risk assessments by comparing oral and dermal endpoints was considered by the HED Hazard Identification Assessment Review Committee. Since ethoprop appears to be very well absorbed in rabbits, the 100% dermal absorption value was retained for use in occupational cancer risk assessments.

The HED Cancer Assessment Peer Review Committee (10/2/97 document) classified ethoprop as a "likely" human carcinogen due to the occurrence of malignant adrenal pheochromocytomas in male Sprague-Dawley rats. This classification was supported by the occurrence of thyroid C-cell adenomas and/or carcinomas in three different rat studies and evidence of clastogenicity by *in vitro* mutagenicity testing. The Q_1^* for ethoprop, in the absence of a complete tumor count in low- and mid-dose groups, is 2.81×10^{-2} mg/kg/day⁻¹ (Hugh M. Pettigrew memo, 1/15/98). Ethoprop was re-evaluated by the HED Cancer Assessment Review Committee because of new historical control data and arguments against ethoprop's cancer classification submitted by the registrant (Jess Rowland and Kit Farwell memo, 10/7/98). The committee retained the classification of ethoprop as a "likely" human carcinogen and recommended that adrenal slides in the low- and mid-dose groups be examined before the cancer classification would be reevaluated. These slides have not yet been examined by the registrant.

Previous toxicology reports for ethoprop used the terms NOEL and LOEL (no observed effect level and lowest observed effect level). NOAEL and LOAEL (no observed adverse effect level and lowest observed adverse effect level) are now used in order to be consistent with other Agency reports (Margaret Stasikowski, HED Director, 9/22/98).

B. Food Quality Protection Act (FQPA) Considerations

Ethoprop was evaluated by the HED Hazard Identification Assessment Review Committee and by the HED FQPA Safety Factor Committee as part of a comprehensive review of organophosphate pesticides.

In a rat developmental toxicity study, the maternal NOAEL was 2 mg/kg/day and the maternal LOAEL was 9 mg/kg/day based on decreased body weight gain and increased incidence of soft stools. No developmental toxicity occurred in this study and the developmental toxicity NOAEL was ≥ 18 mg/kg/day, the highest dose tested. There was no indication of increased sensitivity of offspring in this study.

In a rabbit developmental toxicity study, neither developmental nor maternal toxicity was observed and both maternal and developmental NOAELs were ≥ 2.5 mg/kg/day, the highest dose tested. Although no maternal or developmental toxicity was observed in this study, cholinesterase activity was not measured and likely would have been significantly inhibited based upon results from the 21-day dermal study in rabbits (LOAEL of 1.0 mg/kg/day based upon cholinesterase inhibition in plasma, red blood cells, and brain). There was no indication of increased sensitivity of offspring in this study.

In a 2-generation rat reproduction study, the parental NOAEL was 0.08 mg/kg/day and the parental LOAEL was 2.3 mg/kg/day based upon plasma cholinesterase inhibition. The offspring NOAEL was 2.3 mg/kg/day and the offspring LOAEL was 13 mg/kg/day based on body weight decrements. The NOAEL for offspring toxicity (2.3 mg/kg/day) was greater than the parental NOAEL (0.08 mg/kg/day) and there was no indication of a quantitative increase in susceptibility in this study. Pup mortality in the 24 mg/kg/day group was not considered indicative of qualitative susceptibility since this effect occurred only at the high dose in the presence of severe maternal toxicity (tremors and brain cholinesterase inhibition) and because pups were receiving a greater dosage of ethoprop than parents on post partum days 21-28 due to increased food consumption.

The neurotoxicity of ethoprop was also evaluated by the FQPA Committee. No changes in brain weight, brain dimensions, or nervous system histopathology were noted in acute and subchronic neurotoxicity studies, nor in chronic dog, rat, or mouse studies. No alterations in development of the central nervous system were observed in the rat and rabbit developmental studies. No observations indicative of neurotoxicity were reported in offspring in the 2-generation reproduction study in rats. Although the hen study was negative for delayed neurotoxicity, a neurotoxic esterase study was requested by the HED RfD Committee (5/8/96) because of structure-activity concerns. This study is confirmatory in nature and should not delay the reregistration process. The FQPA Committee did not recommend requiring a developmental neurotoxicity study for ethoprop.

As noted above, no increased susceptibility of offspring was shown in rat reproduction, rat developmental, or rabbit developmental studies. Although a confirmatory neurotoxic esterase study is required, there were no other toxicological datagaps, and the HED FQPA Safety Factor Committee concluded that the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be reduced to 1x. A total uncertainty factor of 100x, based on uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability is adequate for acute and chronic dietary risk assessments.

Table 1. Acute Toxicity: Technical Ethoprop

STUDY	MRID YEAR	RESULTS	TOXICITY CATEGORY
81-1 Acute Oral - Rat ^a	00078035 1965	M LD ₅₀ = 56.2 mg/kg F LD ₅₀ = 30.2 mg/kg	I
81-2 Acute Dermal - Rat	42979501 1987	M LD ₅₀ = 1280 mg/kg F LD ₅₀ = 424 mg/kg	II
81-2 Acute Dermal - Rabbit	42979502 1987	LD ₅₀ = 8.5 mg/kg	I
81-3 Acute Inhalation - Rat	070060 1980	LC ₅₀ = 0.123 mg/L	II
81-4 Eye Irritation - Rabbit	00078036 1965	0.1 mL killed all 3 rabbits	I
81-5 Skin Irritation - Rabbit	00048774 1977	0.5 mL killed all 6 rabbits.	I

M= male, F = Female

^aThese LD₅₀ values are from the review; slightly different values were reported in 1988 Reregistration Document.

Table 2. Toxicity Profile of Ethoprop

STUDY/MRID #	ENDPOINT	NOAEL	LOAEL
21-day Dermal Rabbit MRID 41304404	Systemic Plasma ChE RBC ChE Brain ChE	0.1 mg/kg/day 0.1 mg/kg/day 0.1 mg/kg/day 0.1 mg/kg/day	1.0 mg/kg/day (↓ body wt, ↓ kidney wt) 1.0 mg/kg/day 1.0 mg/kg/day 1.0 mg/kg/day
90-day Dog MRID 75240	Systemic Plasma ChE RBC ChE Brain ChE	0.025 mg/kg/day 0.025 mg/kg/day 1.0 mg/kg/day ---	0.075 mg/kg/day (emesis) 0.075 mg/kg/day 3.0 mg/kg/day ---
Combined 1-year/5 Month Dog MRID 263474, 41498601	Systemic Plasma ChE RBC ChE Brain ChE	0.025 mg/kg/day 0.01 mg/kg/day 0.025 mg/kg/day 1.0 mg/kg/day	1.0 mg/kg/day (anemia, liver toxicity) 0.025 mg/kg/day 1.0 mg/kg/day 10.0 mg/kg/day
Carcinogenicity - Mouse MRID 40356301, 43326001	Systemic Plasma ChE RBC ChE Brain ChE	0.254 mg/kg/day 0.026 mg/kg/day 0.026 mg/kg/day 0.254 mg/kg/day	3.96 mg/kg/day (↓ body weight) 0.254 mg/kg/day 0.254 mg/kg/day 3.96 mg/kg/day
Chronic Toxicity/ Carcinogenicity Rat MRID 42530201, 1992	Systemic Plasma ChE RBC ChE Brain ChE	2.44 mg/kg/day 0.04 mg/kg/day 0.04 mg/kg/day 0.04 mg/kg/day	18.38 mg/kg/day (↓ wt gain, anemia) 2.44 mg/kg/day 2.44 mg/kg/day 2.44 mg/kg/day
Chronic Toxicity/ Carcinogenicity Rat MRID 40291801, 1985 Supplementary, ungradable	Systemic Plasma ChE RBC ChE Brain ChE	≥ 4.19 mg/kg/day 0.041 mg/kg/day 0.041 mg/kg/day 0.40 mg/kg/day	> 4.19 mg/kg/day 0.40 mg/kg/day 0.40 mg/kg/day 4.19 mg/kg/day
Acute Neurotoxicity - Rat MRID 43197701	Systemic Plasma ChE RBC ChE Brain ChE	5 mg/kg < 5 mg/kg < 5 mg/kg ≥ 50 mg/kg	25 mg/kg (clinical signs, mortality) 5 mg/kg 5 mg/kg > 50 mg/kg
Rangefinding Acute Rat Neurotoxicity MRID 43197701	Systemic Plasma ChE RBC ChE Brain ChE	10 mg/kg < 2 mg/kg < 2 mg/kg 10 mg/kg	50 mg/kg (clinical signs, mortality) 2 mg/kg 2 mg/kg 50 mg/kg
Acute Neurotoxicity Rat Time-course Study MRID 43442402	Systemic Plasma ChE RBC ChE Brain ChE	15.7 mg/kg <15.7 mg/kg <15.7 mg/kg <15.7 mg/kg	33 mg/kg (clinical signs) 15.7 mg/kg 15.7 mg/kg 15.7 mg/kg
Subchronic Rat Neurotoxicity MRID 43424001	Systemic Plasma ChE RBC ChE Brain ChE	2.6 mg/kg/day 0.26 mg/kg/day 0.26 mg/kg/day 0.26 mg/kg/day	27 mg/kg/day (clinical signs) 2.6 mg/kg/day 2.6 mg/kg/day 2.6 mg/kg/day
2-generation Rat Reproduction MRID 41921200	Systemic Plasma ChE RBC ChE Brain ChE Offspring	2.3 mg/kg/day 0.08 mg/kg/day ≥ 13 mg/kg/day 0.08 mg/kg/day 2.3 mg/kg/day	13 mg/kg/day (↓ wt gain) 2.3 mg/kg/day > 13 mg/kg/day 2.3 mg/kg/day 13 mg/kg/day (↓ body wt)
Rat Developmental MRID 41304402	Systemic Offspring	2 mg/kg/day ≥ 18 mg/kg/day	9 mg/kg/day (↓ wt gain, soft stool) > 18 mg/kg/day
Rabbit Developmental MRID 41304403	Systemic Offspring	≥ 2.5 mg/kg/day ≥ 2.5 mg/kg/day	> 2.5 mg/kg/day > 2.5 mg/kg/day

Table 3. Mutagenicity and Metabolism Studies with Ethoprop

Mutagenicity studies Gene Mutation - <i>Salmonella</i> Gene Mutation - HGPRT Mouse Lymphoma Forward Gene Mutation <i>in vitro</i> CHO Cell Chromosomal Aberration <i>in vitro</i> CHO Cell Sister Chromatid Exchange <i>in vivo</i> Bone Marrow Cytogenetics Dominant Lethal Assay <i>in vitro</i> UDS (MRID 00160182) <i>in vitro</i> UDS (MRID 44038702)	Negative Negative Negative Positive with S9 activation. Positive with S9 activation. Negative. No interaction with target tissue due to severe toxicity. Negative. No interaction with target tissue due to severe toxicity. Negative Negative
METABOLISM - Rat MRID 41804301	Excretion by urinary ($\geq 50\%$), fecal (7-16%), and respiratory (11-19%) routes; essentially complete by 48 hours. Terminal elimination $t_{1/2}$ in blood was 92-135 hours. Metabolism was by hydrolysis of one or both S-propyl groups followed by conjugation with cell constituents.

C. Dose Response Assessment

The non-cancer endpoints for estimating risk from exposure to ethoprop are all based on cholinesterase inhibition. Toxicity endpoints and doses for risk assessment are shown in Table 4.

Previous risk assessments for ethoprop used the term RfD while the term PAD is used in this document. The chronic reference dose (RfD or cRfD) is an estimate of the level of daily dietary exposure to a pesticide residue which, over a 70-year human life span, is believed to have no significant deleterious effects. The acute reference dose (aRfD) is an estimate of the level of one-day dietary exposure to a pesticide residue which is believed to have no significant deleterious effects. Acute and chronic RfDs are determined by dividing the NOAEL from the selected study by uncertainty factors, which total 100 in the case of ethoprop.

The population adjusted dose (PAD) is new terminology and refers to an RfD which has been adjusted to take into account the FQPA safety factor. The PAD is determined by dividing the RfD by the FQPA safety factor. For ethoprop, the FQPA safety factor = 1, and the acute and chronic RfDs are equivalent to the acute and chronic PADs, respectively.

The acute population adjusted dose (aPAD) of 0.00025 mg/kg/day was selected from a subchronic dietary dog study. The NOAEL was 0.025 mg/kg/day and the LOAEL of 0.075 mg/kg/day was based upon plasma cholinesterase inhibition on the second day of the study.

The chronic PAD of 0.0001 mg/kg/day was obtained from the combined 5-month and 1-year dog gavage studies with a NOAEL of 0.01 mg/kg/day and LOAEL of 0.025 mg/kg/day based upon plasma cholinesterase inhibition. This endpoint is supported by the 1992 chronic toxicity/carcinogenicity study in rats with a NOAEL for plasma, red blood cell, and brain cholinesterase inhibition of 0.04 mg/kg/day and a LOAEL of 2.44 mg/kg/day. The rat 2-generation reproductive toxicity study had similar values with a NOAEL for plasma and brain cholinesterase inhibition of 0.08 mg/kg/day and a LOAEL of 2.3 mg/kg/day.

The occupational dermal exposure endpoints were selected from a 21-day dermal study in rabbits with a NOAEL of 0.1 mg/kg/day and a LOAEL of 1 mg/kg/day based upon plasma, red blood cell, and brain cholinesterase inhibition. This rabbit study may provide a conservative estimate of risk as rabbits were approximately 50x more sensitive than rats in acute dermal LD50 studies performed in rats and rabbits. The relative sensitivity in humans is not known.

The short-term inhalation endpoint was from a subchronic dietary dog study (the same study used for the acute PAD, above). The intermediate-term inhalation endpoint was from the combined 5-month and 1-year dog studies (the same study used for the chronic PAD, above).

Ethoprop was reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and an acceptable daily intake (ADI) of 0.0003 mg/kg/day was established in 1987.

Table 4. Toxicological Endpoints For Use in Human Risk Assessment

EXPOSURE	DOSE	ENDPOINT	STUDY
Acute PAD	NOAEL = 0.025 mg/kg/day	Plasma ChE Inhibition at 0.075 mg/kg/day on day 2.	90-day Dog Feeding Study
	UF =100	Acute PAD = 0.00025 mg/kg /day	
Chronic PAD	NOAEL = 0.01 mg/kg/day	Plasma ChE Inhibition at 0.025 mg/kg/day.	5-month and 1-Year Dog Gavage Studies
	UF =100	Chronic PAD = 0.0001 mg/kg/day	
Short-Term (Dermal)	Dermal NOAEL = 0.1 mg/kg/day	Plasma, RBC, Brain ChE Inhibition at 1.0 mg/kg/day.	21-day Dermal Rabbit
Short-Term (Inhalation)	Oral NOAEL = 0.025 mg/kg/day	Plasma ChE Inhibition at 0.075 mg/kg/day.	90-day Dog Feeding Study
Intermediate-Term (Dermal)	Dermal NOAEL = 0.1 mg/kg/day	Plasma, RBC, Brain ChE Inhibition at 1.0 mg/kg/day.	21-day Dermal Rabbit
Intermediate-Term (Inhalation)	Oral NOAEL = 0.01 mg/kg/day	Plasma ChE Inhibition at 0.025 mg/kg/day.	5-month and 1-Year Dog Gavage Studies
Long-Term (Dermal or Inhalation)	None	There are no long-term exposures; this risk assessment is not required for non-cancer risk assessments.	None

Dermal absorption is assumed equivalent to oral absorption for cancer risk assessment.
 MOE = 100 for dermal and inhalation risk assessments.

Cancer Classification: "likely" human carcinogen.
 Cancer Potency Factor (Q_1^*) = 2.81×10^{-2} mg/kg/day⁻¹.

III. Dietary Exposure Assessment

A. Summary of Registered Uses

Ethoprop is an organophosphate insecticide and nematicide. Pesticidal properties and toxicity are due to inhibition of acetylcholinesterase enzyme. Ethoprop is manufactured by Rhône-Poulenc Ag Company under the trade name Mocap® and is formulated as a technical-grade manufacturing product (95.9% ai), as granular products (3%, 10% and 15% ai), emulsifiable concentrates (46% and 69.6% ai), two granular "Lock 'n Load" products (10% and 20% ai) and as a gel in water-soluble packaging (68.2% ai). Ethoprop is applied pre-plant or pre-emergence and the insecticidal activity is highly dependent on incorporating the material into the soil (mechanically or with water) soon after application.

Ethoprop is registered for use on the following crops: bananas/plantains, beans (dry, snap and lima), cabbage, sweet and field corn, cucumber, peanuts, pineapples, citrus (non-bearing), sugarcane, sweet potato, white potato, and tobacco. It is also used on field-grown ornamentals (i.e., trees, shrubs, bulbs, lilies) and on golf course turf. There are no registered residential uses for ethoprop.

B. Food Exposure

The residues of toxicological concern in crops for non-cancer dietary risk assessments are ethoprop and two ethoprop metabolites, SME (O-ethyl-S-methyl-S-propylphosphorodithioate) and OME (O-ethyl-O-methyl-S-propylphosphorothioate). For cancer risk assessments, ethoprop, SME, OME, and M1 (O-ethyl-S-propylphosphorothioate) are of concern.

Residues in field trials were below the limit-of-detection (LOD) except for lima beans, snap beans and peanuts. Residue data were submitted only for parent and the M1 metabolite, however anticipated residues for risk assessment must reflect all the above-named residues of concern. The HED Chemistry Science Advisory Council (Chem SAC) met December 16, 1998 to determine how anticipated residues should be calculated when no residues were detected and only one metabolite was measured (Attachment 4, acute dietary exposure memo). The Chem SAC determined that in calculating anticipated residues for acute dietary risk assessments: (1) a ratio for similar crops of measured residues of parent only to the total residue of concern based on metabolism and/or confined rotational crops should be used; (2) for dissimilar crops apply an adjustment factor of 6.0x (highest adjustment factor for any crop) for single-serving non-blended commodities and the average 2.8x for blended commodities; and (3) where no detectable residues of any metabolites are observed, use half the LOQ/LOD and multiply by the appropriate adjustment

factor. Ratios of 2.8x for the chronic non-cancer risk assessment and 2.3x total residues of concern relative to parent and the M1 metabolite for the chronic cancer risk assessment were used.

Data from USDA's Pesticide Data Program could not be quantitatively used in the risk assessment. HED generally requires at least 100 samples to incorporate monitoring data into risk assessments, however, not enough samples were monitored in the crops for which there are tolerances. Furthermore, the LOD from the monitoring data (0.03) ppm gave a higher risk value than using field trial data which has an LOD of 0.003 ppm and therefore provides a less refined estimate of risk. FDA monitoring tested many samples with no detects. However, these data could not be quantitatively used in the risk assessment because the LOD from the FDA monitoring data (0.015 ppm) gave a higher risk value than using field trial data which has an LOD of 0.003 ppm and therefore also provides a less refined estimate of risk. Neither USDA nor FDA monitoring programs tested for ethoprop metabolites.

Data on % crop treated were provided by the Biological and Economic Assessment Division. The acute dietary analysis used the estimated maximum percent crop treated for relevant commodities and the chronic dietary assessments used the weighted average % crop treated.

Both the acute and chronic dietary risk assessments were conducted with the Dietary Exposure Evaluation Model (DEEM™) software and consumption data from USDA's 1989-1992 Continuing Survey of Food Intake by Individuals. A previous chronic dietary risk assessment calculated with the Dietary Risk Evaluation System (DRES) in the original risk characterization did not exceed the Agency's level of concern. However, DRES used outdated consumption data so a new dietary analysis with DEEM™ using more recent consumption data was conducted. The acute probabilistic (Monte Carlo) dietary exposure analysis used in this risk assessment was conducted by HED. A Monte Carlo assessment conducted by the registrant was not used because the registrant did not make changes in the assessment which were recommended by HED to increase the accuracy of the assessment. Rhone-Poulenc did not agree with HED policy for use of adjustment factors for metabolites when parent compound was not detected.

Although the Agency's analysis has been refined using percent crop treated information, the exposure estimates are largely based on residue values estimated from available field trial data and metabolism studies. The residue estimates are higher than tolerances, due to the inclusion of additional metabolites of concern. Further refinement of dietary risk is not possible unless the registrant submits additional residue data in which all residues of concern are quantified.

Acute dietary risk was calculated several ways (see Attachment 4). The results summarized in Table 5 assume that non-detectable residues are present at ½ the limit-of-detection, and include use of percent crop treated data, tolerance level residues for dry lima beans, and field trial data for all other registered commodities. **Acute dietary exposure** for ethoprop is **below the Agency's level of concern**. The population with the highest exposure was non-nursing infants < 1 year old with an estimated exposure of 80% of the aPAD. Since ethoprop residues are non-detectable for many commodities, and since conservative assumptions were used to account for metabolites not measured in field trials, these are conservative estimates of dietary risk.

The **chronic dietary analysis** indicates that dietary exposure and risk for ethoprop are **below the Agency's level of concern**. For chronic non-cancer effects, the Agency's level of concern is 100% of the population adjusted dose (PAD). The results of the chronic DEEM™ analysis indicate that the most highly exposed population subgroups are non-nursing infants <1 year old and children 1-6 years old, with exposures corresponding to approximately 1% of the chronic population adjusted dose (PAD) consumed. (See Attachment 5, chronic dietary exposure memo.)

For carcinogenic effects, the Agency's level of concern is one in a million excess cancers, or 1×10^{-6} . Estimated **carcinogenic dietary risk** for the general U.S. population is **below the Agency's one in a million level of concern**, at 1.1×10^{-8} . (See Attachment 5, chronic dietary exposure memo.)

Table 5. Dietary Exposure and Risk for Ethoprop¹

Population Subgroup	Acute Exposure		Chronic Exposure	
	Exposure (mg/kg/day)	Acute Risk % aPAD	Exposure (mg/kg/day)	Chronic Risk % PAD
U.S. Population-All Seasons	0.000096	38.51	0.000000	<1
All Infants (<1yr)	0.000188	75.37	0.000001	1.0
Nursing infants (<1 yr)	0.000058	23.27	0.000000	<1
Non-nursing infants (<1yr)	0.000200	80.10	0.000001	1.3
Children (1-6 yrs)	0.000168	67.17	0.000001	1.2
Children (7-12 yrs)	0.000088	35.34	0.000001	<1
Females (13+/preg/not nursing)	0.000036	14.24	0.000000	<1
Females (13+/ nursing)	0.000041	16.56	0.000000	<1
Females (13-19 yrs)	0.000054	21.66	0.000000	<1
Females (20+ yrs)	0.000050	20.03	0.000000	<1
Females (13-50 yrs)	0.000048	19.15	0.000000	<1
Males (13-19 yrs)	0.000057	22.63	0.000001	<1
Males (20+ yrs)	0.000046	18.58	0.000000	<1

¹Anticipated residues included tolerances for dry lima beans and field trial data for all other registered commodities and tolerances for dry lima beans.

Table 6. Cancer Dietary Risk Estimates for Ethoprop

Population Subgroup	Exposure (mg/kg/day)	Cancer Risk
General US Population	0.0000004	1.1×10^{-8}

C. Water Exposure

Ethoprop is mobile to very mobile in soil. The limited monitoring data for ethoprop in water were not linked to sites of ethoprop usage and therefore could not be used for risk assessments. Modeling on degradates was not conducted because of insufficient data on the environmental fate of the degradates; however, metabolites of concern were found at levels of less than 5% of parent in environmental fate studies (2/8/99 memo, Dana Spatz, Nick Federoff and 5/26/98 memo, Sid Abel).

Drinking water levels of comparison (DWLOCs) were calculated because suitable monitoring data were not available. The DWLOC_{acute} is the concentration in drinking water as a part of the aggregate acute exposure that

occupies no more than 100% of the acute PAD. The DWLOC_{chronic} is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic PAD. The DWLOC_{cancer} is the concentration in drinking water as a part of the aggregate chronic exposure that results in a negligible cancer risk. Default body weights and consumption values were used to calculate the DWLOCs: 2L/70 kg (adult male), 2L/60 kg (adult female), and 1L/10 kg (child/).

Drinking water estimated concentrations (DWECS) were modeled with SCI-GROW for ground water and PRZM-EXAMS for surface water. The DWLOCs were compared to DWECS calculated with a 20 lb a.i./acre application rate for golf course use and with a 6 lb a.i./acre application rate for sweet potato use, the 2 scenarios resulting in the highest DWECS (Tables 7, 8, and 9).

The DWECS (25 µg/L for ground water and 290 µg/L for surface water) exceed the DWLOCs for cancer risk (1 µg/L) and chronic risk (1 µg/L for non-nursing infants, 3 µg/L for females 13+/nursing, and 4 µg/L for the U.S. population. The DWECS (25 µg/L for ground water and 650 µg/L for surface water) exceed the DWLOCs for acute risk (0.5 µg/L for non-nursing infants, 5 µg/L for the U.S. population, and 6 µg/L for females 13-19). The DWECS are conservative, but suggest the Agency's level of concern for these risks could be exceeded when dietary food and water exposure are considered together.

Table 7. Summary of DWLOC Calculations for Acute Risk

Population Subgroup ¹	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Allowable Water Exposure (mg/kg/day)	SCI-GROW (µg/L) ²	PRZM-EXAMS (µg/L) ²	DWLOC (µg/L)
U.S. Population	0.00025	0.000096	0.000154	7.6/25	135/650	5
Females 13-19	0.00025	0.000054	0.000196	7.6/25	135/650	6
Non-nursing infants <1 yr	0.00025	0.000200	0.000050	7.6/25	135/650	0.5

Table 8. Summary of DWLOC Calculations for Chronic Risk

Population Subgroup ¹	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Allowable Water Exposure (mg/kg/day)	SCI-GROW (μg/l) ²	PRZM-EXAMS (μg/l) ²	DWLOC (μg/l)
U.S. Population	0.0001	0.000000	0.000100	7.6/25	60/290	4
Females 13+ nursing	0.0001	0.000000	0.000100	7.6/25	60/290	3
Non-nursing infants <1 yr	0.0001	0.000001	0.000099	7.6/25	60/290	1

Table 9. Summary of DWLOC Calculations for Cancer Risk

Population Subgroup	Q_1^* (mg/kg/day) ⁻¹	Food Exposure (mg/kg/day)	Allowable Water Exposure (mg/kg/day)	SCI-GROW (μg/L) ²	PRZM-EXAMS (μg/L) ¹	DWLOC (μg/L)
U.S. Population	2.81×10^{-2}	0.000004	0.000035	7.6/25	60/290	1

¹The infant/child subgroup and the female subgroup with the highest exposure were used. Assumed 70 kg body wt for U.S. population, 60 kg for females, and 10 kg for infants/children; water consumption of 2 L/day for adults and 1 L/day for infants/children.

²6# per acre rate application rate for sweet potatoes/20# per acre for golf course use.

Non-Cancer Calculations: allowable water exposure = PAD - chronic dietary exposure

$$\text{DWLOC} = \frac{\text{allowable water exposure} \times \text{body wt}}{\text{water consumption} \times 10^{-3} \text{ mg}/\mu\text{g}}$$

Cancer Calculations: allowable water exposure = $\frac{\text{Negligible Risk} - \text{dietary exposure}}{Q_1^*}$

$$\text{DWLOC} = \frac{\text{allowable water exposure} \times \text{body wt}}{\text{water consumption} \times 10^{-3} \text{ mg}/\mu\text{g}}$$

IV. Occupational and Non-Occupational Exposure

A. Occupational Exposure

Ethoprop is applied pre-plant or pre-emergence and the insecticidal activity is highly dependent on incorporating the material into the soil (mechanically or with water) soon after application. Applications can be made by aircraft (granular formulations – only to potatoes), chemigation, groundboom sprayers, hand-held sprayers (e.g., low-pressure handwand and backpack sprayers), push-type granular spreaders, tractor-drawn granular spreaders, and by slitting (i.e., subsurface insertion of granules into golf course turf). In addition, it can be applied as a dip for citrus seedlings, by hand (granular), and by hand-pouring of liquid concentrate from a measuring cup/vessel. The use of a belly grinder for application to turfgrass is prohibited.

Chemical-specific individual and professional pesticide applicator exposure data were not submitted in support of the reregistration of ethoprop. Therefore, analyses for both individual and professional short-term exposures, intermediate-term exposures and cancer risk (combined dermal and inhalation) were performed using the Pesticide Handlers Exposure Database (PHED), Version 1.1 (August, 1998). Chronic occupational exposures to ethoprop are not anticipated. Numerous mixer/loader, applicator, mixer/loader/applicator and flagger scenarios were evaluated. (See Attachment 6.)

The margin-of-exposure (MOE) is calculated by dividing the selected NOAEL by the estimated dose to which an individual is exposed. A MOE of 100 or greater is considered protective for ethoprop. **None of the individual and professional short-term and intermediate-term handler exposure scenarios (even at the highest level of appropriate risk mitigation) had MOEs greater than 100. All occupational risks exceed the Agency's level of concern.** Only three short-term and two intermediate-term exposure scenarios had combined MOEs which are greater than or equal to 10. Additionally, it should be noted that for each of the individual and professional short-term and intermediate-term handler exposure scenarios (with the one exception of flagging), the significant risk driver is the dermal exposure route.

A cancer risk of less than 1×10^{-4} does not exceed the Agency's level of concern for occupational exposure; but at the highest level of mitigation available, one individual handler scenario and five professional handler scenarios had cancer risks greater than 1×10^{-4} . When feasible, the Agency seeks ways to reduce individual cancer risks to 10^{-6} using mitigation (e.g. personal protective equipment or engineering controls). **Occupational cancer risk exceeds the Agency's level of concern.**

B. Post-Application Exposure

Because ethoprop is used in pre-plant and pre-emergent applications and is normally soil incorporated or watered-in, there are generally no concerns for post-application exposure to agricultural workers. Two exceptions for this use pattern are sugarcane and pineapples. Sugarcane is mechanically transplanted and should have minimal post-application concerns. Ethoprop may be applied to pineapples at various points in the growing season. However, there is currently a 120 day pre-harvest interval established for pineapples, so there should generally be minimal concern during harvesting.

Post-application exposure assessment was conducted for turf management professionals. When using both tractors and push-type mowers with application rates of 10 and 20 lb ai/A, it was determined that re-entry intervals (REIs) greater than 50 days were required before MOEs are > 100 and workers could re-enter for activities, such as mowing and maintenance. Specifically, REIs of 62 and 55 days, respectively, were calculated when mowing with a tractor following the application of 20 and 10 lb ai/A. REIs of 68 and 62 days were calculated when using a push-type mower following the application of 20 and 10 lb ai/A, respectively. In addition, post-application cancer risks were also calculated. At the highest level of mitigation available, the cancer risks associated with these activities were in the mid to high 10^{-5} range. Although these risks did not exceed the 10^{-4} level of concern, the risks did not lower to the 10^{-6} range until more than 32 and 44 days for tractors and push-type mowers, respectively.

C. Non-Occupational Exposure

An assessment to quantify golfer risk following ethoprop treatment was also conducted. On the day of ethoprop treatment for 20 and 10 lbs ai/A, MOEs of 2 and 3 were calculated, respectively. To exceed MOEs of 100, 40 and 33 days needed to elapse, respectively, before golfers could enter ethoprop treated areas to golf. In addition, the cancer risks associated with golfer exposures ranged from $1.8-3.5 \times 10^{-6}$ for use of 20 lbs ai and $1.2-5.1 \times 10^{-6}$ for use of 10 lbs ai. This variation is dependent upon the number of ethoprop treatments made to the golf course during the year.

Occupational and non-occupational risks **exceed** the Agency's level of concern for both cancer and non-cancer risks.

D. Incident Reports

The Review of Ethoprop Incident Reports had several occupational reports with 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.

V. Aggregate Exposure

Aggregate risk assessments include multiple routes of exposure, which for ethoprop are food, drinking water, and non-occupational/recreational (golfer) exposure. The **acute** aggregate assessment, by definition, includes only food and drinking water exposure. Since adequate monitoring data for water were not available, the acute aggregate assessment includes calculation of acute drinking water levels of comparison. As reported earlier in this document, the estimated drinking water concentrations exceeded drinking water levels of comparison and there may be a concern for drinking water exposure.

The **short-term** and **intermediate-term** aggregate assessments include food, drinking water, and non-occupational/recreational (golfer) routes of exposure. Since the MOEs for golfer exposure already exceeded the level of concern, food and non-occupational/recreational exposures were not combined.

Since chronic recreational exposure is not anticipated, a **chronic** aggregate assessment for ethoprop includes only food and drinking water routes of exposure. As reported earlier in this document, the estimated drinking water concentrations exceeded drinking water levels of comparison and there may be a concern for drinking water exposure.

The **carcinogenic** aggregate assessment includes food, drinking water and non-occupational/recreational (golfer) exposures. Because the Agency's level of concern was already exceeded for golfer risk, a carcinogenic aggregate assessment was not performed.

VI. Data Needs

The registrant is reportedly determining the cholinesterase activity of the M1 metabolite of ethoprop. A "confirmatory" neurotoxic esterase study is required. Neither of these two studies is expected to result in changes in calculated risk. The registrant is planning to conduct a 28-day dermal toxicity study in rabbits with a granular formulation of ethoprop. This study is not yet available, but the results may lead to refinement of occupational risks.

An exposure monitoring and biomonitoring study of workers is being conducted in the United Kingdom for granular application to potatoes. Additional information on slit placement techniques for turf and related exposure monitoring for workers and golfers is requested. Information on post-application techniques and appropriate exposure monitoring data for transplanting sugarcane and pineapple activities is requested.

VII. Attachments

ATTACHMENT 1. Ethoprop, Product and Residue Chemistry Chapters for the Reregistration Eligibility Decision (John Abbots, 3/27/98).

ATTACHMENT 2. Toxicology Chapter for the Reregistration Eligibility Document for Ethoprop (Kit Farwell, signed 4/17/98).

ATTACHMENT 3. Ethoprop. Addendum to toxicology chapter. Selection of Inhalation Endpoints. Assessment by the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee. (Kit Farwell, 8/31/98).

ATTACHMENT 4. Ethoprop (041101). Reregistration Case No 0106. Response to the USDA Comments to EPA's Monte Carlo Dietary Exposure Estimate for Ethoprop and Using Further Refinements. (Sheila Piper, 7/12/99).

ATTACHMENT 5. Ethoprop. List A Reregistration Case No. 0106/Chemical ID No. 041101. Revised Chronic Dietary Exposure Analyses for the HED Risk Assessment. DP Barcode No. D257828. (Christina Swartz, 7/21/99).

ATTACHMENT 6. Ethoprop: Revised Occupational/Non-occupational/Residential Exposure Assessment for the Reregistration Eligibility Decision (RED) Document [Case # 818841, PC Code 041101, DP Barcode D258251]

Attachment 1: Product and Residue Chemistry Chapters for the Reregistration Eligibility Decision

March 27, 1998

MEMORANDUM:

SUBJECT: Ethoprop (041101), Reregistration Case No. 0106.
Product and Residue Chemistry Chapters for the
Reregistration Eligibility Decision (RED).
DP Barcode No. D239294, No MRID.

FROM: John Abbotts, Chemist
Chemistry and Exposure Branch I
Health Effects Division [7509C]

THRU: Francis B. Suhre, Branch Senior Scientist
Chemistry and Exposure Branch I
Health Effects Division [7509C]

TO: Kit Farwell
Reregistration Branch I
Health Effects Division [7509C]

and

Judith Loranger
Reregistration Branch III
Special Review and Reregistration Division [7508W]

The Product and Residue Chemistry chapters for the Ethoprop RED are attached. The chapters were assembled by Dynamac Corporation under the supervision of CEBI, HED. The data assessment has undergone secondary review in the branch and has been revised to reflect Agency policies.

With regard to Product Chemistry, additional data are required for the 95.9% T to meet the new requirement concerning UV/visible absorption (OPPTS GLN 830.7050). Provided that the registrant submits the required data, and either certifies that the suppliers of beginning materials and the manufacturing processes have not changed since the last comprehensive product chemistry review, or submits completed updated product chemistry data packages, the Branch has no objections to the reregistration of Ethoprop with respect to product chemistry data requirements.

With regard to Residue Chemistry, requirements for plant and livestock metabolism have been satisfied. Requirements for field trials have been satisfied for a few crops. For other crops, submitted field trial data are not entirely consistent with maximum label use patterns; requirements may be satisfied by appropriate label amendments or additional residue data. Processing data are satisfied for most crops. Further details are provided in the endnotes to Table B in the Residue Chemistry chapter. Data also remain outstanding for field rotational crops; however, data requirements could be reduced by appropriate label restrictions on rotational crops. For several crops not being supported for reregistration, data requirements will be waived provided tolerances are revoked.

Tolerances are not established for 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.

With regard to dietary exposure assessment, the HED Metabolism Committee has determined that parent and three metabolites are residues of concern. Magnitude of the residue data have been submitted at most for parent and one metabolite. HED has previously made a commitment to conduct dietary exposure assessment using the best available data, making conservative assumptions from metabolism data to estimate all residues of concern. With the data available, it should be feasible to conduct a reasonably reliable dietary exposure assessment.

If additional information is required, please advise.

Attachment 1: Reregistration Eligibility Decision:
Product Chemistry Considerations

Attachment 2: Reregistration Eligibility Decision:
Residue Chemistry Considerations

cc(without Attachments):RF

cc(with Attachments): Abbotts, Ethoprop List A File

RDI:FBSuhre:3/23/98:ChemSAC:3/18/98

7509C:CEBI:JAbbotts:CM-2:Rm805B:305-6230: [3/25/98]

☐ethoprop.red

ETHOPROP
Shaughnessy No. 041101; Case 0106

Reregistration Eligibility Decision

January 16, 1998

Contract No. 68-D4-0010

Submitted to:
U.S. Environmental Protection Agency
Arlington, VA

Submitted by:
Dynamac Corporation
1910 Sedwick Road
Building 100, Suite B
Durham, NC 27713

ETHOPROP

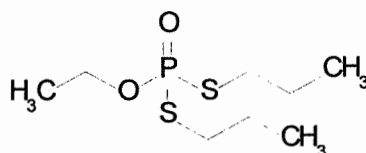
REREGISTRATION ELIGIBILITY DECISION:

PRODUCT CHEMISTRY CONSIDERATIONS

Shaughnessy No. 041101; Case No. 0106

DESCRIPTION OF CHEMICAL

Ethoprop (O-ethyl S,S-dipropyl phosphorodithioate) is a nematocide and insecticide registered for use on various fruit and vegetable crops.



Empirical Formula: $C_8H_{19}O_2PS_2$

Molecular Weight: 242.3

CAS Registry No.: 13194-48-4

Shaughnessy No.: 041101

IDENTIFICATION OF ACTIVE INGREDIENT

Ethoprop is a colorless to yellow tinted liquid with a strong mercaptan odor and a boiling point of 86-91 C at 0.2 mm Hg. Ethoprop is only slightly soluble in water (843 ppm at 21 C), but is soluble in most organic solvents (hexane, xylene, acetone, and ethanol).

MANUFACTURING-USE PRODUCTS

A search of the Reference Files System (REFS) conducted 11/10/97 identified a single ethoprop manufacturing-use product (MP) registered under Shaughnessy No. 041101: the Rhone-Poulenc Ag Company 95.9% technical product (T; EPA Reg. No. 264-456). Only the Rhone-Poulenc 95.9% T is subject to a reregistration eligibility decision.

REGULATORY BACKGROUND

Additional generic and product-specific product chemistry data for ethoprop were required in a registration standard issued 2/28/83 and a guidance document issued 6/83. The Ethoprop Final Registration Standard and Tolerance Reassessment (FRSTR) dated 10/20/87 and the subsequent Ethoprop Guidance Document dated 6/88 required that new or updated product chemistry data be submitted for the reregistration of ethoprop.

The current status of the product chemistry data requirements for the ethoprop 95.9% T is presented in the attached data summary table.

CONCLUSIONS

Pertinent data requirements have been satisfied for the Rhone-Poulenc 95.9% T (EPA Reg. No. 264-456), except that data are required concerning UV/visible absorption for the PAI (OPPTS 830.7050). Provided that the registrant submits the data required in the attached data summary table for the 95.9% T, and either certifies that the suppliers of beginning materials and the manufacturing process for the ethoprop MP have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, CBRS has no objections to the reregistration of ethoprop with respect to product chemistry data requirements.

AGENCY MEMORANDA CITED IN THIS DOCUMENT

CBRS No(s).: 5114
Subject: Rhone-Poulenc Ag Company - Response to Ethoprop Final
Registration Standard and Tolerance Reassessment Document -
Product Chemistry.
From: G. Makhijani
To: J. Ellenberger/B. Briscoe and W. Miller
Dated: 4/17/89
MRID(s): 41004401

CBRS No(s).: 5303
Subject: EPA Reg. No. 264-456: Ethoprop. Response to Final Registration
Standard and Tolerance Reassessment. Additional Product
Chemistry.
From: J. Garbus
To: B. Briscoe
Dated: 9/19/89
MRID(s): 41055301

CBRS No(s).: 8767
DP Barcode(s): D169998
Subject: Ethoprop. Rhone-Poulenc Response to the Guidance Document
Dated 6/88. Storage Stability.
From: L. Cheng
To: L. Rossi
Dated: 5/1/92
MRID(s): 42044801

CBRS No(s).: 12397
DP Barcode(s): D194353
Subject: Ethoprop. Data Waiver of Guideline 63-10.
From: F. Fort
To: S. Jennings/L. Schnaubelt
Dated: 9/29/93
MRID(s): 41055301

CBRS No(s).: 12705
DP Barcode(s): D195967
Subject: Ethoprop Reregistration: List A Chemical No. 041101; Case No.
0106. Rhone-Poulenc: Response to Data Requirements
Regarding Color (GLN No. 63-2) for Reregistration of Ethoprop
T/MP (EPA Reg. No. 264-456).
From: F. Toghrol
To: W. Waldrop
Dated: 11/19/93
MRID(s): 42953501

CBRS No(s).: 12396
DP Barcode(s): D194202
Subject: Response to the Ethoprop Reregistration Standard: Product
Chemistry.
From: R. Perfetti
To: E. Saito
Dated: 7/21/94
MRID(s): 41211203

CBRS No(s): 14437
DP Barcode(s): D207680
Subject: Ethoprop Reregistration. Rhone-Poulenc's Undated Response [62-2 data: CSF] to R. Perfetti 7/21/94 Review.
From: K. Dockter
To: L. Schnaubelt/S. Jennings
Dated: 5/8/95
MRID(s): Undated CSF

PRODUCT CHEMISTRY CITATIONS

Bibliographic citations include only MRIDs containing data which fulfill data requirements.

References (cited):

00142272 Orth, D. (1984) Product Chemistry Testing for Ethoprop Technical and Granular Formulation (MOCAP 10G): Final Report: Project Number 84-PL-34; 84-PL-28. Unpublished study prepared by Biospherics Inc. 12 p.

00152115 Beche, R. (1984) Ethoprop, Technical Grade Analysis and Certification of Product Ingredients. Unpublished study prepared by Rhone-Poulenc Agrochimie. 118 p.

41004401 Murayama, S. (1989) Ethoprop Technical: Product Identity and Composition: Proj. ID 783C10. Unpublished study prepared by Rhone-Poulenc Ag Co. 83 p.

41055301 Murayama, S. (1989) Ethoprop Technical: The Technical Grade of the Active Ingredient and the Manufacturing-Use Product: Physical and Chemical Properties: Project ID; 783C10; File No. 40485. Unpublished study prepared by Battelle, Columbus Div. 74 p.

42044801 Eubanks, M. (1991) Ethoprop Technical: Storage Stability Study: Lab Project Number: AC-90-016: 41033. Unpublished study prepared by Rhone-Poulenc Ag Co. 54 p.

42953501 Helfant, L. (1993) Ethoprop Technical: Product Chemistry Physical and Chemical Properties Series 63, Guideline 63-2 (Color): Lab Project Number: 44206: 93010LJH. Unpublished study prepared by Rhone-Poulenc Ag Co. 9 p.

41211203 Murayama, S. (1989) Ethoprop Technical: The Technical Grade of the Active Ingredient and the Manufacturing Use Product: Analysis and Certification of Product Ingredients: Laboratory Project ID 783C10. Unpublished study prepared by Rhone-Poulenc Ag Co. 103 p.

Case No. 0106
 Chemical No. 041101
 Case Name: Ethoprop
 Registrant: Rhone-Poulenc Ag Company
 Product(s): 95.9% T (EPA Reg. No. 264-456)

PRODUCT CHEMISTRY DATA SUMMARY

Guideline Number	Requirement	Are Data Requirements Fulfilled? ¹	MRID Number ²
830.1550	Product Identity and Disclosure of Ingredients	Y	00152115, 41004401
830.1600 830.1620 830.1650	Starting Materials and Manufacturing Process	Y	<u>41004401</u>
830.1670	Discussion of Formation of Impurities	Y	00152115, 41004401
830.1700	Preliminary Analysis	Y	00152115, 41211203 ³
830.1750	Certification of Ingredient Limits	Y	00152115, 41211203 ³ , Undated CSF ⁴ , CSF 8/21/96 ⁵
830.1800	Analytical Methods to Verify the Certified Limits	Y	00152115, 41211203 ³
830.6302	Color	Y	41055301 ⁶ , 42953501 ⁷
830.6303	Physical State	Y	41055301 ⁶
830.6304	Odor	Y	41055301 ⁶
830.6313	Stability	Y	41055301 ⁶
830.6314	Oxidation/Reduction	Y	00142272
830.6315	Flammability	Y	00142272
830.6316	Explosibility	Y	00142272, 00152115
830.6317	Storage Stability	Y	42044801 ⁸
830.6319	Miscibility	Y	00142272, 41055301 ⁶
830.6320	Corrosion Characteristics	Y	00142272
830.7000	pH	Y	00142272
830.7050	UV/Visible Absorption	N ⁹	
830.7100	Viscosity	Y	00142272
830.7200	Melting Point/Melting Range	N/A ¹⁰	
830.7220	Boiling Point/Boiling Range	Y	41055301 ⁶
830.7300	Density/Relative Density/Bulk Density	Y	00142272
830.7370	Dissociation Constant in Water	N/A ¹¹	
830.7550 830.7560 830.7570	Partition Coefficient (Octanol/Water)	Y	00142272
830.7840 830.7860	Solubility	Y	00142272
830.7950	Vapor Pressure	Y	00142272

¹ Y = Yes; N = No; N/A = Not Applicable.

² **Bolded** references were reviewed in the Ethoprop FRSTR dated 10/20/87; underlined references were reviewed under CBRS No. 5114, dated 4/17/89, by G. Makhijani; and all other references were reviewed as noted.

³ CBRS No. 12396, D194202, 7/21/94, R. Perfetti.

⁴ CBRS No. 14437, D207680, 5/8/95, K. Dockter.

⁵ CSF obtained from the product jacket.

⁶ CBRS No. 5303, 9/19/89, J. Garbus.

⁷ CBRS No. 12705, D195967, 11/19/93, F. Toghrol.

⁸ CBRS No. 8767, D169998, 5/1/92, L. Cheng.

⁹ The OPPTS Series 830, Product Properties Test Guidelines require data pertaining to UV/visible absorption for the PAI.

¹⁰ Data are not required because the TGAI/MP is a liquid at room temperature.

¹¹ Data requirements were waived (CBRS No. 12397, D194353, 9/29/93, F. Fort) because ethoprop does not contain any ionizable functional groups and does not dissociate in water.

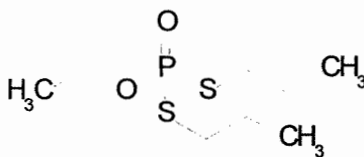
ETHOPROP

REREGISTRATION ELIGIBILITY DECISION

RESIDUE CHEMISTRY CONSIDERATIONS

Shaughnessy No. 041101; Case 0106

ETHOPROP



REREGISTRATION ELIGIBILITY DOCUMENT

RESIDUE CHEMISTRY CONSIDERATIONS

Shaughnessy No. 041101; Case 0106

INTRODUCTION

Ethoprop [S,S-dipropyl O-ethyl phosphorodithioate] is an insecticide/nematicide registered for use on bananas/plantains, beans (lima and snap), cabbage, citrus (non-bearing), corn, cucumbers, peanuts, pineapples, potatoes, sugarcane, sweet potatoes, and tobacco. Ethoprop is manufactured by Rhône-Poulenc Ag Company, the basic producer, under the trade name Mocap®. Ethoprop formulations registered for use on food/feed crops include emulsifiable concentrate (EC), soluble concentrate (SC/L), and granular (G) formulations. These products may be applied as broadcast or banded preplant to preemergence applications and as banded postemergence applications directed to the soil. Use directions specify the use of only ground equipment, except on potatoes where aerial applications are allowed.

REGULATORY BACKGROUND

Ethoprop is a List A reregistration chemical and was the subject of a Registration Standard dated 2/28/83, a Final Registration Standard and Tolerance Reassessment (FRSTR) dated 10/20/87, and their associated Guidance Documents (dated 6/83 and 6/88). These documents summarized regulatory conclusions on the available residue chemistry data and specified that additional data were required for reregistration purposes. Numerous submissions of data have been received since the FRSTR was issued. The information contained in this document outlines the current Residue Chemistry Science Assessments with respect to the reregistration of ethoprop.

Tolerances for ethoprop residues in/on food/feed commodities are currently expressed in terms of ethoprop, O-ethyl-S,S-dipropylphosphorodithioate, [40 CFR §185.262 (a) and (b)] and are 0.02 ppm (negligible residues) in/on all plant commodities. No tolerances have been established for residues in livestock commodities. Adequate methods are available for the enforcement of established tolerances, as currently defined.

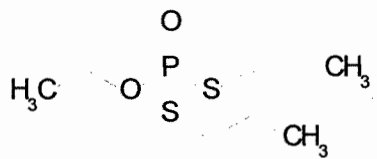
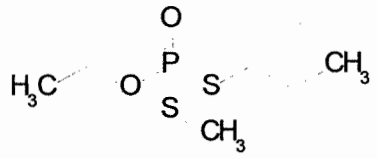
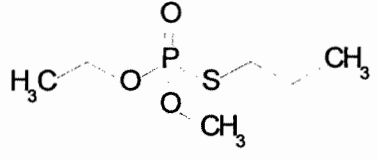
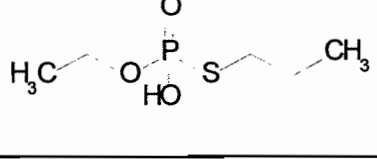
The HED Metabolism Committee (J. Abbotts, 10/17/96) concluded that the residues of toxicological concern for primary and rotational crops are ethoprop and Metabolites II, III and IV (see Figure A), and analytical methods capable of determining all residues of concern, as well as storage stability data, crop field trials, and processing studies reflecting determination of these residues, would be needed for reregistration. Following a meeting with the registrant regarding residue chemistry data requirements for reregistration, the Agency concluded that for the present, entirely new crop field trials and processing studies determining all residues of concern would not be required (Memos of 12/4/96 and 2/12/97, J. Abbotts). HED would conduct dietary exposure assessment using the available data on ethoprop and Metabolite IV, and making conservative assumptions regarding the levels of Metabolites II and III using data from the metabolism studies. However, for any field or processing studies initiated after 12/3/96, data would be required on all residues of concern along with methods for determining all residues of concern and supporting storage stability data.

The HED Metabolism Committee subsequently revised its conclusions (Memo, 2/6/98, K. Farwell). The Committee found that for acute and chronic non-cancer dietary risk, the residues of concern in crops were parent and metabolites II and III; for cancer dietary risk, residues of concern are parent and metabolites II through IV (see Figure A).

Regarding the regulation of ethoprop residues in livestock commodities, HED previously determined that a Category 3 situation [40 CFR 180.6(a)(3)] exists for livestock commodities based upon review of the livestock metabolism studies (R. Perfetti, 6/22/94). However, based on results from the confined rotational crop study, the Agency concluded that requirements for livestock feeding studies should be reevaluated once adequate field trial and processing data are received on all significant feed items.

The chemical names and structures of ethoprop and its metabolites of concern are depicted in Figure A.

Figure A. Chemical name and structure of ethoprop and its residues of concern in primary and rotational crops.

Common Name/Chemical Name	Chemical Structure
Ethoprop O-ethyl-S,S-dipropylphosphorodithioate	
Metabolite II O-ethyl-S-methyl-S-propylphosphorodithioate	
Metabolite III O-ethyl-O-methyl-S-propylphosphorothioate	
Metabolite IV; M1 O-ethyl-S-propylphosphorothioate	

SUMMARY OF SCIENCE FINDINGS

OPPTS GLN 860.1200: Directions for Use

A search of the Agency's Reference Files System (REFS) on 12/12/97 indicates that there are seven ethoprop end-use products (EPs) with uses on food/feed crops and two EPs with uses on tobacco registered to Rhône-Poulenc Ag Co. These EPs are presented below.

EPA Reg No.	Label Acceptance Date	Formulation Class	Product Name
264-457	6/93	15% G	MOCAP® 15% Granular Nematicide-Insecticide
264-458 ^a	8/95	6 lb/gal EC	MOCAP® EC Nematicide-Insecticide
264-459 ^b	6/93	10% G	MOCAP® Plus Nematicide-Insecticide
264-464 ^b	12/93	4 lb/gal EC	MOCAP® Plus 4-2 EC Nematicide-Insecticide
264-465 ^c	11/95	10% G	MOCAP® 10% Granular Nematicide-Insecticide
264-469	11/95	20 % G	MOCAP® 20% Granular Nematicide-Insecticide
264-475 ^d	12/93	3% G	MOCAP® PCNB 3-10 Granular Nematicide-Insecticide
264-521 ^e	4/93	10% G	HOLDEM® Brand Granular Nematicide-Insecticide
264-541	6/96	6 lb/gal SC/L	MOCAP® GEL Nematicide-Insecticide

^aIncludes the associated SLNs FL870001 and OR960018.

^bThese products are MAIs that also include disulfoton (5% G or 2 lb/gal EC) and are registered for use only on tobacco.

^cIncludes the associated SLNs FL850001, ME930003, OR840010, OR960017, PR920002, and WA 850008.

^dThis product is a MAI that also contains PCNB (10% G) and is registered for use only on peanuts.

^eThis product is a MAI that also contains Phorate (10% G) and is registered for use only on potatoes.

A review of the above labels and supporting residue data indicate that the following label amendments are required:

Use directions for potatoes and sweet potatoes on all labels should be amended to specify a maximum rate equivalent to 12 lb ai/treated acre for banded applications.

The label for the 15% G formulation (EPA Reg No. 264-457) must be amended to specify a REI.

Use directions for field and sweet corn should be amended to specify pre-plant or at planting application only. Additional residue data are required to support applications later in the season.

Use directions for peanuts on labels for the 3%, 10% and 15% G formulations (EPA Reg. Nos. 264-475, 264-465, and 264-457) should be amended to specify one pre-plant or at planting application.

Available data on sugarcane are adequate to support an application at planting at 15 lb ai/A. Labels should be limited to this effective rate per treated A at planting, or additional field trial data are required.

Data from the limited field rotational crop studies indicate that labels must be amended to include rotational crop restrictions, including a limit of 12 lb ai/A applied to primary crops.

A tabular summary of the residue chemistry science assessments for reregistration of ethoprop is presented in Table B. The conclusions listed in Table B regarding the reregistration eligibility of ethoprop food/feed uses are based on the use patterns registered by the basic producer, Rhône-Poulenc Ag Co., and apply to data on residues of parent and/or metabolite IV. When end-use product DCIs are developed (e.g., at issuance of the RED), RD should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the basic producer's labels.

OPPTS GLN 860.1300: Nature of the Residue in Plants

The qualitative nature of the residue in plants is adequately understood based on cabbage, corn, and potato metabolism studies. The HED Metabolism Committee (Memo, 2/6/98, K. Farwell) found that for acute and chronic non-cancer dietary risk, the residues of concern in crops were parent and metabolites II and III; for cancer dietary risk, residues of concern are parent and metabolites II through IV (see Figure A). The Metabolism Committee earlier concluded that the metabolite ethyl phosphate is not a residue of concern (Memo, 10/17/96, J. Abbotts).

OPPTS GLN 860.1300: Nature of the Residue in Livestock

The qualitative nature of the residue in livestock is adequately understood based upon acceptable ruminant and poultry metabolism studies. The Agency (R. Perfetti, 6/22/94) concluded that the data from the metabolism studies indicate that a Category 3 situation [40 CFR 180.6(a)(3)] exists for livestock commodities. Ethoprop was not detected in milk, eggs or tissues from goats and hens dosed orally for seven

consecutive days with [¹⁴C]ethoprop at levels equivalent to 32 ppm (865x) and 2.09 ppm (105x), respectively, in the diet. Maximum total radioactive residues were 9.26 ppm in goat liver and 1.22 ppm in chicken liver. Residues of potential concern detected were metabolites III and/or IV which together accounted for ≤2% of the total radioactive residues in liver of hens and goats.

OPPTS GLN 860.1340: Residue Analytical Methods

Adequate analytical methodology is available for data collection and enforcing tolerances of ethoprop as currently defined. Method I in the Pesticide Analytical Manual (PAM), Vol. II, is a GLC/ sulfur microcoulometric detection method that has undergone a successful EPA method validation. This method involves solvent extraction and clean-up by sweep co-distillation. Residues of ethoprop are determined by GLC using a sulfur microcoulometric detector. PAM, Vol. II also lists Method A, which uses the same principles as Method I, but employs different parameters for extraction and gas chromatography. The limit of quantitation for ethoprop in or on plant commodities is 0.01 ppm in each method.

A newer GC/FPD method has also been proposed as an enforcement method for determining residues of ethoprop and Metabolite IV in plant commodities. In this method, residues of ethoprop and Metabolite IV are extracted with methanol, filtered, and cleaned up using cation exchange resin and nuchar/attaclay. Residues are concentrated and redissolved in methanol. Diazomethane is added to methylate residues of Metabolite IV. Ethoprop and methylated Metabolite IV are partitioned into methylene chloride, concentrated, dissolved in methylene chloride, and further cleaned up using gel permeation and/or silica gel chromatography prior to analysis using GC/FPD in the phosphorus mode. This method was validated by an independent laboratory, with limits of quantitation at 0.01 ppm for each analyte in plant commodities. Review has noted that it could prove to the registrant's advantage to demonstrate that the methylation step does not alter metabolite III, since metabolite IV is converted to III by methylation (Figure A). Because of these uncertainties over the method's full capabilities, the method has not yet been submitted for Agency validation.

Data from analysis of ethoprop residues in plants have been collected using Method I and modifications of Method I, or more recently using variations of the GC/FPD method that has been proposed as an enforcement method.

Adequate methodology for determining Metabolites II and III in or on plant commodities is required in conjunction with any new residue studies.

OPPTS GLN 860.1360: Multiresidue Method Testing

The FDA PESTDATA database indicates that ethoprop is completely recovered using FDA Multiresidue Protocol D (PAM I Section 232.4) and partially recovered using FDA Multiresidue Protocol E for non-oily matrices (PAM I Section 211.1). Recovery of

ethoprop using Protocol E for oily matrices (PAM I Section 212.1) is small. The registrant has submitted data pertaining to the recovery of Metabolite IV through FDA Multiresidue Protocols, and these data have been forwarded to the FDA for review.

OPPTS GLN 860.1380: Storage Stability Data

For purposes of reregistration, the requirements for supporting storage stability data are satisfied for all acceptable residue studies. Generally, residues of ethoprop *per se* are more stable in frozen storage than are residues of Metabolite IV. Residues of ethoprop *per se* were stable in most matrices for at least 6 months of frozen storage; however, Metabolite IV was not stable in the majority of matrices following 3 months of storage at either -5 or -20 C. No storage stability data are presently available on the other two residues of concern, Metabolites II and III.

The available storage stability data indicate that ethoprop *per se* is stable in cabbage, potato, pineapple commodities, peanut commodities (except meal), and corn commodities for up to 6 to 12 months at -20 C, and in peanut meal for up to 3 months at -20 C. At storage temperatures of -5 C, ethoprop *per se* is stable for 6 to 12 months in the above commodities except for pineapple bran and pulp, peanut hulls, and corn grain dust, in which ethoprop is stable for <3 months.

Metabolite IV is stable for 6 to 12 months in the following matrices stored at -20 C: cabbage, potatoes, pineapple commodities (except bran), peanut oil and nutmeats, and corn forage, meal, oil, and grain dust. Metabolite IV is stable for ≤ 3 months at -20 C in pineapple bran, corn grain, corn fodder, corn starch, and in peanut meal, vine, hay, and hulls. At storage temperatures of -5 C, Metabolite IV is stable for up to 12 months in cabbage, pineapple juice, peanut nutmeat, peanut crude oil, and corn crude oil. Metabolite IV is stable at -5 C for ≤ 3 months in potatoes; pineapple fruit, bran, and pulp; peanut meal, vine, hay, hull, and refined oil; and corn grain, forage, fodder, starch, meal, grain dust, and refined oil.

Adequate storage stability data have also been submitted indicating that ethoprop and Metabolite IV are stable at -20 C in sugarcane and its processed commodities stored for up to 15 months.

The Agency has advised that concurrent storage stability studies should be conducted with any required field or processing studies; the demonstrated stability problems of Metabolite IV during frozen storage reinforce this requirement.

OPPTS GLN 860.1500: Magnitude of the Residue in Crop Plants

For purposes of reregistration, requirements for magnitude of the residue data in/on plants are fulfilled for the following crops, for residues of parent and/or metabolite IV: banana, beans (lima and snap), cabbage, cucumbers, and pineapples. Adequate field trial data depicting ethoprop residues in/on these crops following applications made

according to the maximum or proposed use patterns have been submitted. Geographical representation was adequate with sufficient numbers of trials reflecting representative formulation classes.

Available data on peanuts are adequate for residues of parent and/or metabolite IV, provided use directions for peanuts are amended to specify a single pre-plant or at-planting application. Residue data on field and sweet corn are adequate for residues of parent and metabolite IV, for applications at plant or earlier.

As noted above under Guideline 860.1200, residue data are adequate to support use on potatoes and sugarcane, at specified rates and conditions. Labels should be limited to these rates and conditions, or additional field trials will be required for all residues of concern.

OPPTS GLN 860.1500: Magnitude of the Residue in Crop Plants - Pending Petitions

PP#5E04491: The Interregional Research Project-4 submitted a petition for establishing tolerances for ethoprop in/on mint hay at 0.02 ppm. The proposed use pattern for mint specifies a single broadcast application of ethoprop (EC or G) at 6 lb ai/A to mint following the last harvest of the season. Following application, ethoprop would be incorporated into the soil using either irrigation or mechanical mixing. The proposed label would allow only one application per year and specify a 225 day PHI. This petition is currently in reject status (G. Otakie, 8/11/95 and 9/20/95) based upon the dietary exposure analysis. In addition, in response to a proposal that this use be considered at nonfood use, the Agency (W.J. Hazel, 9/16/97) has determined that the proposed use on mint is a food use.

OPPTS GLN 860.1520: Magnitude of the Residue in Processed Food/Feed

The reregistration requirements for processed food/feed commodities are fulfilled for residues of parent and metabolite IV for corn, peanut, pineapple, potato, and sugarcane. Adequate processing studies are available for corn, pineapple, potato, and sugarcane indicating that residues of ethoprop and Metabolite IV did not concentrate in processed commodities of these crops.

Two processing studies are also available for peanuts; however, neither study was deemed wholly acceptable (J. Abbotts, 9/4/97). In the first peanut processing study, peanut oil and meal were stored frozen prior to analysis for periods longer than ethoprop residues are stable in these commodities. In the second peanut processing study conducted at a 5x application rate, residues of ethoprop and metabolite IV were each <0.01 in peanut nutmeats and meal, and were respectively 0.018 ppm and <0.01 ppm in peanut oil. Frozen nutmeats were analyzed within 66 days of harvest and meal and oil samples were analyzed within 46 days of processing. Based upon these data, the Agency concluded that residues of ethoprop and metabolite IV do not concentrate in meal and that residues of ethoprop concentrate by $\geq 1.8x$ in oil; however,

concentration of metabolite IV in oil could not be determined due to questions about storage stability. The Agency concluded that the maximum theoretical concentration factor for peanut oil (2.8x) would be used for exposure assessment for peanut oil.

Based upon a 2.8x concentration factor for peanut oil, the 5x application rate used in the processing study, and the fact that residues of ethoprop and metabolite IV resulting from the **at-planting use** on peanuts are each nondetectable (<0.01 ppm), anticipated residues in peanut oil would be below the established tolerance for peanut nutmeats. Therefore a tolerance for residues in peanut oil is not required.

OPPTS GLN 860.1480: Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

No tolerances have been established for ethoprop residues in livestock commodities. The Agency (R. Perfetti, 6/22/94) concluded that the data from the metabolism studies indicates that a Category 3 situation [40 CFR 180.6(a)(3)] exists for livestock commodities. Ethoprop was not detected in milk, eggs or tissues from goats and hens dosed orally for seven consecutive days with [¹⁴C]ethoprop at levels equivalent to 32 ppm and 2.09 ppm, respectively, in the diet. Maximum total radioactive residues were 9.26 ppm in goat liver and 1.22 ppm in chicken liver. Residues of potential concern detected were metabolites III and/or IV which together accounted for ≤2% of the total radioactive residues in liver of hens and goats.

Based upon the currently registered uses and current or reassessed tolerances, the calculated maximum theoretical dietary burdens are 0.037 ppm for cattle and 0.02 ppm for poultry (see below). Therefore, feeding levels of ethoprop in the goat and poultry metabolism studies represent 865x and 105x the maximum theoretical dietary exposures, respectively.

Feed Commodity	% Dry Matter	% Diet ^a	Tolerance (ppm)	Dietary Contribution (ppm) ^c
Beef Cattle				
corn forage	40	40	0.02	0.02
corn grain	88	45	0.02	0.01
peanut meal	85	15	0.02	0.004
TOTAL BURDEN		100		0.034
Dairy Cattle				
corn forage	40	50	0.02	0.025
corn grain	88	35	0.02	0.008
peanut meal	85	15	0.02	0.004
TOTAL BURDEN		100		0.037
Poultry				
corn grain	N/A	80	0.02	0.016
peanut meal	N/A	20	0.02	0.004
TOTAL BURDEN		100		0.02
Swine				
corn grain	N/A	45	0.02	0.009
potato culls	N/A	40	0.02	0.008
peanut meal	N/A	15	0.02	0.003
TOTAL BURDEN		100		0.02

^aTable 1 (August 1996).

^bCurrent tolerance level from Table C.

^cContribution = [Reassessed tolerance / % DM (if cattle)] X % diet).

This information would support the conclusion that a Category 3 situation [40 CFR 180.6(a)(3)] exists for livestock commodities. However, data from the confined rotational crop study suggest that residues of concern may be present at higher levels in livestock feed items than indicated by current tolerances on primary crops. For the current time, tolerances for livestock commodities will not be required. However, the requirements for livestock feeding studies will be reevaluated once adequate field trial data and processing data are received on all significant feed items, including rotational feed crops.

OPPTS GLN 860.1400: Magnitude of the Residue in Water, Fish, and Irrigated Crops

Ethoprop is not registered for use on potable water or aquatic food and feed crops; therefore, no residue chemistry data are required under these guideline topics.

OPPTS GLN 860.1460: Magnitude of the Residue in Food-Handling Establishments

Ethoprop is not registered for use in food handling establishments; therefore, no residue chemistry data are required under these guideline topics.

OPPTS GLN 860.1850: Confined Accumulation in Rotational Crops

An adequate confined rotational crop study is available and indicates that residues of ethoprop in rotational crops are qualitatively similar to the residues resulting from the direct application of ethoprop to the primary crops. Ethoprop residues of concern were detected at >0.01 ppm in/on spinach from the 31-day plant-back interval (PBI), radish roots and wheat straw from 31- and 123-day PBIs, and wheat forage from 31-, 123, and 365-day PBIs. Based upon results of the confined rotational crop study, limited field accumulation studies in rotational crops were required.

OPPTS GLN 860.1900: Field Accumulation in Rotational Crops:

None of the registrant's labels currently specify any rotational crop restrictions pertaining to ethoprop. However, data from rotational crop limited field trials indicate that labels must be amended to include rotational crop restrictions. Depending on the restrictions placed on labels, extensive rotational crop field trials may be required.

TABLE A. FOOD/FEED USE PATTERNS SUBJECT TO REREGISTRATION FOR ETHOPROP (CASE)

Site	Application Type Application Timing Application Equipment ^a	Formulation [EPA Reg. No./ SLN No.]	Max. Single Application Rate ^b (ai)	Max. # Apps. ^c	Minimum Retreatment Interval (Days)	Use Limitations ^d
Food/Feed Crop Uses						
Bananas/Plantains						
	Basal application to soil within 30 inches of stem Ground equipment	10% G [264-465] 15% G [264-457] 6 lb/gal EC [264-458]	0.2 oz/plant	NS	6 months	
Beans (Lima and Snap)						
	Broadcast preplant or at planting application Ground equipment	10% G [264-465] 15% G [264-457] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	8 lb/A	1	NA	Labels for the 6 lb/gal EC and SC/L allow only one application per crop.
	Banded preplant or at planting application Ground equipment	10% G [264-465] 15% G [264-457] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	9 lb/treated acre (12" band) 8 lb/treated acre (12" band)			
Cabbage						
	Broadcast preplant or at planting application Ground equipment	10% G [264-465] 15% G [264-457] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	5 lb/A	1	NA	Labels for the 6 lb/gal EC and SC/L allow only one application per crop.
	Banded at planting application Ground equipment		5 lb/treated acre (12-15" band)			

Site	Application Type Application Timing Application Equipment ^a	Formulation [EPA Reg. No./ SLN No.]	Max. Single Application Rate ^b (ai)	Max. # Apps. ^c	Minimum Retreatment Interval (Days)	Use Limitations ^d
Corn (field and sweet)						
	Broadcast preplant or at-planting application Ground equipment	10% G [264-465] 15% G	6 lb/A	1	NA	No PHI is specified. Labels for the 20% G and 6 lb/gal EC and SC/L allow only one application per crop.
	Banded applications at planting through lay-by Ground Equipment	[264-457] 20% G [264-469]]	6.5 lb/treated acre (6" band)	NS	NS	
	Banded application at planting Ground Equipment	6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	6 lb/treated acre (6"-12" band)	1	NA	
Cucumbers						
	Banded preplant or at planting application Ground equipment	10% G [264-465] 15% G [264-457]	14 lb/treated acre (12" band)	1	NA	Labels for the 6 lb/gal EC and SC/L allow only one application per crop.
		6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	10.8 lb/treated acre (12" band)			
Peanuts						
	Broadcast preplant or at planting application Ground equipment	10% G [264-465] 15% G [264-457]	6 lb/A	1	NA	Label for the 6 lb/gal EC and SC/L specify one application per crop.
	Banded preplant or at planting application Ground equipment	6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	12 lb/treated acre (12" band)			
	Banded application at pegging Ground equipment	10% G [264-465] 15% G [264-457]	7.3 lb/treated acre (15" band)	1	NA	

Site	Application Type Application Timing Application Equipment ^a	Formulation [EPA Reg. No./ SLN No.]	Max. Single Application Rate ^b (ai)	Max. # Apps. ^c	Minimum Retreatment Interval (Days)	Use Limitations ^d
Pineapple	Postemergence broadcast or banded application at early pegging incorporated into the soil. Ground equipment	3% G [264-475]	3 lb/A 8.8 lb/treated acre (12" band)	1	NA	No PHI is specified.
	Chemigation through drip irrigation system beginning at planting.	6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	6 lb/A	8 - planting crop 5 - ratoon crop	2 months	For use only in Hawaii. A 120-day PHI is specified. A maximum of 8 applications or 48 lb ai/A can be applied to the planting crop and 5 applications or 30 lb ai/A can be applied to the ratoon crop.
	Banded preplant application over planting beds, with spot applications allowed 3- 6 months after planting Ground equipment	10% G [PR920002]	12 lb/A	NS	3 months	A 120-day PHI is specified. For use only in Puerto Rico.

Site	Application Type Application Timing Application Equipment ^a	Formulation [EPA Reg. No./ SLN No.]	Max. Single Application Rate ^b (ai)	Max. # Apps. ^c	Minimum Retreatment Interval (Days)	Use Limitations ^d
Potatoes						
	Broadcast preplant to preemergence application Ground or aerial equipment	10% G [264-465] [OR840010] [WA850008] 15% G [264-457] 20% G [264-469] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	12 lb/A	1	NA	Do not exceed 12 lb ai/A per season. Labels for the 6 lb/gal EC and SC/L specify one application per crop and prohibit aerial application. The label for the 15% G restricts the use to potatoes grown East of the Rocky Mountains. SLN ME930003 specifies one application per crop.
		10% G [264-465] 20% G [264-469] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	9 lb/treated acre (12" band)			
		15% G [264-457]	11 lb/treated acre (12" band)			
		10% G [ME930003]	22 lb/treated acre (5" band)			
	Banded application into open furrow at planting Ground equipment	10% G [264-521]	18.3 lb/treated acre (6" band)	1	NA	A 90-day PHI is specified. Do not apply more than once per year. Use a minimum row spacing of 32 inches

Site	Application Type Application Timing Application Equipment ^a	Formulation [EPA Reg. No./ SLN No.]	Max. Single Application Rate ^b (ai)	Max. # Apps. ^c	Minimum Retreatment Interval (Days)	Use Limitations ^d
Sugarcane						
	Broadcast application at planting Ground equipment	10% G [FL850001]	6 lb/A			
	Banded application at planting Ground equipment	10% G [264-465] [FL850001] 15% G [264-457] 20% G [264-469] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	24 lb/treated acre (12" band)	1	NA	Labels for the 6 lb/gal EC and SC/L allow only one application per crop.
Sweet Potatoes						
	Broadcast preplant application Ground equipment	10% G [264-465] 15% G [264-457] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	8 lb/A	1	NA	Labels for the 6 lb/gal EC and SC/L allow only one application per crop.
	Banded preplant application Ground equipment		14 lb/treated acre (12" band)			
Non food/feed Uses						
Citrus (seedlings or non-bearing trees)						
	30 minute bare root dip or soil drench of potted plants	6 lb/gal EC [264-458]	0.375 lb/50 gal	NS	NS	
	Banded application to soil between tree rows Ground equipment	6 lb/gal EC [FL870001]	5 lb/treated acre	2	NS	Apply only to non-bearing trees (trees that will not produce marketable fruit within 12 months). Do not apply more than twice per season.

Site	Application Type Application Timing Application Equipment ^a	Formulation [EPA Reg. No./ SLNI No.]	Max. Single Application Rate ^b (ai)	Max. # Apps. ^c	Minimum Retreatment Interval (Days)	Use Limitations ^d
Tobacco	Broadcast application preplant or at planting Ground equipment	10% G [264-459] 4 lb/gal EC [264-464]	8 lb/A	1	NA	Label for the 6 lb/gal EC and SC/L allow only one application per crop. The label for the 4 lb/gal EC prohibits applications through any type of irrigation system.
		10% G [264-465] 15% G [264-457] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	12 lb/A			
		10% G [264-459] 4 lb/gal EC [264-464]	14 lb/treated acre (18" band)			
	Banded application preplant or at planting Ground equipment	15% G [264-457] 10% G [264-465] 6 lb/gal EC [264-458] 6 lb/gal SC/L [264-541]	28 lb/treated acre (18" band)			

^aLabels for the 6 lb/gal EC (264-458) and the 6 lb/gal SC/L (264-541) allow applications through the following types of irrigation systems: center pivot, lateral move end tow, side (wheel) roll, traveler, big gun, solid set, or hand move sprinkler systems, or drip (trickle) irrigation systems.

^bFor banded applications, the maximum rate is expressed on a treated acre basis, and is calculated using the maximum rate per 1000 ft row and the minimum band width as follows: [(lb ai/1,000 ft row) ÷ (band width in feet)] * 43.56 = lb ai/treated acre.

^cMaximum number of applications at the maximum single application rate.

^dEthoprop must be incorporated into the soil with mechanical or irrigation equipment following application. Labels for EPA Reg. Nos. 264-459 and -521 specify a 24-hour restricted entry interval (REI). The labels for EPA Reg. Nos. 264-458, -464, -465, -469, -475, and -541 specify a 48-hour REI in areas receiving ≥25 inches of rain/year and 72-hour REI in areas receiving <25 inches of rain/year, except when material has been soil incorporated. The label for EPA Reg. No. 264-457 does not specify a REI. The following labels prohibit application in Long Island, NY: EPA Reg. Nos. 264-457, -458, -459, -464, -465, -469 and -541. None of the labels contain rotational crop restrictions pertaining to ethoprop.

Table B. Residue Chemistry Science Assessments for Reregistration of Ethoprop

OPPTS GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References ¹
860.1200: Directions for Use	N/A	Yes ²	See Table A.
860.1300: Nature of the Residue			
- Plants	N/A	No	00040380 00075252 00075253 00075254 00075255 00075256 00092103 40653205 41691001 ³ 41814001 ³ 41840801 ³ 41946001 ⁴ 43836401 ⁵ 43868701 ⁶
- Livestock	N/A	No	00092070 42923201 ⁷ 42962701 ⁷ 43209001 ⁸
860.1340: Residue Analytical Methods	N/A	Yes ⁹	00075245 00075246 00092079 00092080 00125395 00125397 00129928 00145970 00153065 00153326 00154203 00160441 42220601 ¹⁰ 43277502 ¹¹ 43373601 ¹¹ 44321501 ¹²
860.1360: Multiresidue Method	N/A	No	41270701 ¹³ 42242101 ¹⁴
860.1380: Storage Stability	N/A	No ¹⁵	00160441 43539401 ¹⁶ 43971501 ¹⁷
860.1500: Magnitude of the Residue in Crop Plants			
<u>Root and Tuber Vegetables Group</u>			
- Potatoes	0.02 (N) [§180.262(a)]	No	00153065 40028502
- Sweet potatoes	0.02 (N) [§180.262(a)]	No	00075252
<u>Brassica (Cole) Leafy Vegetables Group</u>			
- Cabbage	0.02 (N) [§180.262(a)]	No	00092068 00125397 43583201 ¹⁸
<u>Legume Vegetables (Succulent or Dried) Group</u>			
- Beans, lima	0.02 (N) [§180.262(a)]	No	40653204 43539601 ¹⁹
- Beans, snap	0.02 (N) [§180.262 (a)]	No	40653204 43538601 ¹⁹
- Soybeans	0.02 (N) [§180.262(a)]	Yes ²⁰	00076720 00092072 00092074
<u>Foliage of Legume Vegetables Group</u>			
- Beans, lima and snap, forage	0.02 (N) [§180.262(a)]	No ²¹	40653204

OPPTS GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References ¹
- Soybean, forage and hay	0.02 (N) [§180.262(a)]	Yes ²⁰	00076720 40653201
<u>Cucurbit Vegetables Group</u>			
- Cucumbers	0.02 (N) [§180.262(a)]	No	40653204 43484001 ²²
<u>Cereal Grains Group</u>			
- Corn, fresh (inc. sweet) (K+CWHR)	0.02 (N) [§180.262(a)]	Yes ²³	00075249 00075250 00092108 00092109 00092135 40653207 43491001 ²⁴ 43748203 ¹²
- Corn, grain (inc. pop)	0.02 (N) [§180.262(a)]	Yes ²³	00075249 00075250 00092108 00092109 00092135 40653207 43530901 ²⁵ 43748201 ¹²
<u>Forage, Fodder, and Straw of Cereal Grains Group</u>			
- Corn forage and fodder	0.02 (N) [§180.262(a)]	Yes ²³	00075249 00075250 00092108 00092109 00092135 40653207 43530901 ²⁵
<u>Miscellaneous Commodities</u>			
- Banana	0.02 (N) [§180.262(a)]	No	40653206
- Mushrooms	0.02 [§180.262(a)]	Yes ²⁶	00030481 ²⁷ 00030482 ²⁷
- Okra	0.02 [§180.262(b)]	Yes ²⁶	00125395
- Peanut	0.02 (N) [§180.262(a)]	Yes ²⁸	00092106 00092116 00129928 00141494 40653202 43539701 ²⁸ 44062401 ²⁸
- Peanut hay	0.02 (N) [§180.262(a)]	Yes ²⁸	00092106 00092116 00129928 00141494 40653202 43539701 ²⁸ 44062401 ²⁸
- Pineapple	0.02 (N) [§180.262(a)]	No	00092070 00154203 42901601 ²⁹
- Pineapple, fodder and forage	0.02 (N) [§180.262(a)]	No ³⁰	00092070 00154203
- Sugarcane	0.02 (N) [§180.262(a)]	Yes ³¹	40653203
- Sugarcane, fodder and forage	0.02 (N) [§180.262(a)]	No ³⁰	40653203

OPPTS GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References ¹
- Tobacco	NA	No	00145970 00153065 41809601 ³²
860.1520: Magnitude of the Residues in Processed Food/Feed			
- Corn	None	No	43748202 ¹²
- Peanut	None	No	43539801 ¹⁶ 44003301 ¹⁸
- Pineapple	None	No	42945501 ²⁹
- Potato	None	No	43373601 ¹¹
- Soybean	None	Yes ²⁰	
- Sugarcane	None	No	43277501 ³³ 43971501 ¹⁷
860.1480: Magnitude of the Residue in Meat, Milk, Poultry, and Eggs	None	Reserved ³⁴	00092101
860.1400: Magnitude of the Residue in water, fish, and irrigated crops	N/A	N/A	
860.1460: Magnitude of the Residue in Food Handling Establishments	N/A	N/A	
860.1850: Confined Accumulation in Rotational Crops	N/A	No	42197601 ⁷
860.1900: Field Accumulation in Rotational Crops	None	Yes ³⁵	44350201 ¹²

¹ **Bolded** references were cited in the Ethoprop Registration Standard dated 2/28/83 and *italicized* references were reviewed/cited in the Ethoprop FRSTR dated 10/20/87; Other references were reviewed as noted.

² Based upon the available residue data, the Agency is recommending specific changes to label directions for uses on peanuts. The peanut residue data are adequate to support application at plant. If any registrant desires to support application at-pegging, additional field trials are required. Labels for uses on field and sweet corn should be amended to limit application to at plant or earlier. Labels for use on potatoes, sweet potatoes, and sugarcane should be amended to limit application rates. Otherwise, additional field trial data are required. In addition, results from rotational crop limited field trials indicate that rotational crop restrictions are required. The recommended label amendments are listed in the SUMMARY OF SCIENCE FINDINGS, under OPPTS GLN 860.1200: Directions for Use.
Requirements for magnitude of the residue studies in this Table are pertinent to data on parent and/or metabolite IV (Figure A).

³ CBRS Nos. 7407, 7795, and 7933; DP Barcodes D149067, D163011, and D163888; 1/24/92; C. Olinger.

⁴ CBRS No. 8330, DP Barcode D167017, 4/22/92, J. Abbotts.

- 5 CBRS No. 16699, DP Barcode D221052, 7/11/96, J. Abbotts.
- 6 CBRS No. 16678, DP Barcode D221951, 7/11/96, J. Abbotts.
- 7 CBRS Nos. 11533, 12610, and 12797; DP Barcodes D188915, D195286, and D196126; 6/22/94; R. Perfetti.
- 8 CBRS No. 13604, DP Barcode D202608, 9/29/94, R. Perfetti.
- 9 A proposed GC/FPD enforcement method for determining residues of ethoprop and metabolite IV in plant commodities has been validated by an independent laboratory. Review has advised that it would be in the registrant's interests to determine if this method can also successfully determine residues of metabolite III. In addition, adequate methodology for determining metabolites II and III in or on plant commodities is required in conjunction with any new residue studies.
- 10 CBRS No. 9568, DP Barcode D175797, 7/16/92, B. Cropp-Kohlligian.
- 11 CBRS Nos. 14535 and 13949, DP Barcodes D207805 and D204975, 8/3/95, R. Perfetti.
- 12 MRID 44321501 on analytical method was reviewed in D237651, 11/26/97, J. Abbotts. MRIDs 43748201 on field corn, 43748203 on sweet corn, 43748202 on corn processing were reviewed in D218411, 235686, 1/8/98, J. Abbotts; data were adequate to support application at plant or earlier. MRID 44350201 on limited rotational crop field trials was reviewed in D238977, 1/23/98, J. Abbotts.
- 13 CB No. 6009, 1/19/90, M. Nelson.
- 14 CBRS No. 9812, DP Barcode D177243, 5/28/92, L. Cheng.
- 15 No additional storage stability data are required to support the existing field and processing studies; however, the Agency recommends conducting concurrent storage stability studies with any new residue studies.
- 16 CBRS No. 15114, DP Barcode D212132, 12/21/95, S. Knizner.
- 17 CBRS No. 17211, DP Barcode D225648, 11/14/97, J. Abbotts.
- 18 CBRS Nos. 15401 and 17234, DP Barcodes D213957 and D226333, 9/4/97, J. Abbotts.
- 19 CBRS No. 15264, DP Barcode D213113, 10/22/97, J. Abbotts.
- 20 Uses on soybeans have been deleted from the registrant's labels. Provided tolerances are revoked, no data will be required.
- 21 Forage of lima and snap beans is no longer considered a significant livestock feed item; therefore, residue data on these commodities are not required.
- 22 CBRS No. 14917, DP Barcode D210696, 3/13/97, C. Eiden.

- 23 Data on corn are adequate to support application at plant or earlier. Additional field trials and data on aspirated grain fractions are required to support applications later in the season.
- 24 CBRS No. 14917, DP Barcode D210696, 3/13/97, C. Eiden..
- 25 CBRS No. 15114, DP Barcode D212132, 12/21/95, S. Knizner.
- 26 The basic producer, Rhone Poulenc, has no registered uses on mushrooms or okra. Provided tolerances on these crops are revoked, residue data will not be required.
- 27 Reviews of these data could not be located.
- 28 DP Barcode D235830, 9/22/97, J. Abbotts. The data are adequate to support application at plant. If any registrant desires to support application at-pegging, additional field trials are required.
- 29 CBRS Nos. 12706 and 12578, DP Barcodes D195968 and D195127, 2/18/94, R. Perfetti.
- 30 Residue data on forage and fodder of pineapple and sugarcane are not required as these commodities are not considered to be significant livestock feed items (Table 1, OPPTS Guideline 860.1000).
- 31 In reviewing the registrant's response to the Ethoprop FRSTR, the Agency (R. Perfetti, 7/3/90) noted that residue data are available supporting application of ethoprop to sugarcane at rates up to 15 lb ai/A. However, current label directions for sugarcane allow for a banded application at a rate equivalent to 24 lb ai/treated acre. Residue data are required depicting all ethoprop residues of concern in/on sugarcane harvested at normal maturity following an at planting application of ethoprop at 1x the maximum label rate (24 lb ai/treated acre). Field trials should be conducted in accordance with current Agency guidelines (OPPTS Guideline 860.1500).
- 32 CBRS No. 7775, DP Barcode D162702, 1/24/92, C. Olinger; and CBRS No. 12816, DP Barcode D196279, , 7/19/95, C. Olinger.
- 33 CBRS Nos. 14535 and 13949, DP Barcodes D207805 and D204975, 8/3/95, R. Perfetti; and CBRS No. 17688, DP Barcode D231955, 2/19/97, J. Abbotts.
- 34 Data from the confined rotational crop study suggest that residues of concern may be present at higher levels in livestock feed items than indicated by current tolerances for primary plants (10/29/96, J. Abbotts). Tolerances for livestock commodities are not required at this time, but requirements for livestock feeding studies will be reevaluated once adequate field trial data and processing data are received on all significant feed items, including feed rotational crops.
- 35 Data are adequate for rotational crop limited field trials. Extensive field trials are required. Requirements can be reduced by label restrictions on crop rotation.

³⁵

Data are adequate for rotational crop limited field trials. Extensive field trials are required. Requirements can be reduced by label restrictions on crop rotation.

TOLERANCE REASSESSMENT SUMMARY

Tolerances for residues of ethoprop in/on plant RACs are currently expressed in terms of ethoprop *per se* [40 CFR §180.262 (a) and (b)]. No food/feed tolerances have been established for residues of ethoprop. The HED Metabolism Committee has concluded that the residues of toxicological concern for primary and rotational crops include ethoprop and Metabolites II through IV (Memo, 2/6/98, K. Farwell). However, submitted magnitude of the residue studies contained at best residue data on parent and Metabolite IV; and studies accepted by the FRSTR reported data on parent only. In addition, as noted under discussion on analytical method, it may be the case that methods which methylate Metabolite IV may also determine residues of metabolite III (Figure A).

It seems appropriate to change the current tolerance expression, so that Section 24(c) registrations and amended uses could not be approved on the basis of residue data for parent only. The current Division position is that studies initiated after 12/3/96 should report data on all residues of concern (CBRS 17755, 2/12/97, J. Abbotts). Such requirements should apply to both new and amended uses. In the interim, the tolerance expression for ethoprop should be amended as follows:

Tolerances are established for the combined residues of ethoprop (O-ethyl-S,S-dipropylphosphorodithioate) and its metabolite O-ethyl-S-propylphosphorothioate, each expressed as ethoprop.

As data are received on additional residues of concern, and/or as further information become available on the capability of methods to determine residues of metabolite II and III, tolerances can be revised for specific crops to include metabolites II and/or III. At the present, tolerances will be reassessed based on combined residues of parent and metabolite IV. For those crops where residue data on parent only were accepted by the FRSTR, the current tolerances at 0.02 ppm will be doubled to encompass residues of metabolite IV.

In addition, the "(N)" designation for negligible residues should be deleted from all 40 CFR §180.262 entries. A summary of the ethoprop tolerance reassessment and recommended modifications in commodity definitions are presented in Table C.

Tolerances Listed Under 40 CFR §180.262 (a):

Sufficient data are available to ascertain the adequacy of the established tolerances on bananas, beans (lima and snap), cabbage, cucumbers, and pineapples. The available residue data on bananas (parent only), lima beans, and pineapples adequately support the current 0.02 ppm tolerances on these commodities. Residue data on snap beans, cabbage, and cucumbers indicate that tolerances for ethoprop residues in/on these crops should be increased to 0.2, 0.05, and 0.1 ppm, respectively.

As noted above under Guideline 860.1200, label amendments and/or additional field trial data on all residues of concern are necessary before tolerances can be reassessed on corn grain, corn forage, corn fodder, peanuts, potatoes, sweet potatoes by translation from potatoes, and sugarcane.

As there are no registered uses on mushrooms or soybeans, tolerances for residues in/on mushrooms and soybean commodities should be revoked. In addition, tolerances for residues in/on lima and snap bean forage, pineapple fodder and forage, and sugarcane fodder and forage should be revoked as the Agency no longer considers these commodities to be significant livestock feed items (Table 1 in OPPTS Guideline 860.1000).

Tolerances Listed Under 40 CFR §180.262 (b):

A tolerance of 0.02 ppm parent is established with regional registration on okra. As there are currently no registered uses for ethoprop on okra, the tolerance for ethoprop residue in/on okra should be revoked.

Table C. Tolerance Reassessment Summary for Ethoprop

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/Correct Commodity Definition
Tolerances listed under 40 CFR §180.262 (a):			
Bananas	0.02 (N)	0.04	<i>Banana</i>
Beans, lima	0.02 (N)	0.02	<i>Bean, lima</i>
Beans, lima, forage	0.02 (N)	Revoke	No longer a regulated feed item.
Beans, snap	0.02 (N)	0.2	<i>Bean, snap</i>
Beans, snap, forage	0.02 (N)	Revoke	No longer a regulated feed item.
Cabbage	0.02 (N)	0.05	<i>Cabbage, fresh w/ wrapper leaves</i>
Corn, fodder	0.02 (N)	TBD ^a	<i>Corn, stover</i>
Corn, forage	0.02 (N)	TBD ^a	
Corn, fresh (inc. sweet) (K+CWHR)	0.02 (N)	TBD ^a	<i>Corn, sweet, K+CWHR</i>
Corn, grain	0.02 (N)	TBD ^a	
Cucumbers	0.02 (N)	0.1	<i>Cucumber</i>
Mushrooms	0.02	Revoke	No registered uses on mushrooms
Peanuts	0.02 (N)	TBD ^a	<i>Peanut, nutmeat</i>
Peanut, hay	0.02 (N)	TBD ^a	
Pineapples	0.02 (N)	0.02	<i>Pineapple</i>
Pineapples, fodder	0.02 (N)	Revoke	No longer regulated feed items.
Pineapples, forage	0.02 (N)		
Potatoes	0.02 (N)	TBD ^a	<i>Potato, tuber</i>
Soybeans	0.02 (N)	Revoke	Uses on soybeans have been deleted from all the registrant's labels.
Soybeans, forage	0.02 (N)		
Soybeans, hay	0.02 (N)		
Sugarcane	0.02 (N)	TBD ^a	<i>Sugarcane, cane</i>
Sugarcane, fodder	0.02 (N)	Revoke	No longer regulated feed items.
Sugarcane, forage	0.02 (N)		
Sweet potatoes	0.02 (N)	TBD ^a	Data can be translated from potatoes. <i>Sweet potato</i>
Tolerance with Regional Registration listed under 40 CFR §180.262 (b):			
Okra	0.02	Revoke	No registered uses on okra

^aTBD = To be determined. Tolerance cannot be determined at this time because label amendments or additional data on all residues of concern are required.

DIETARY EXPOSURE ASSESSMENT SUMMARY

For reregistration and risk assessment purposes, adequate plant and livestock metabolism data are available. Adequate magnitude of the residue data for ethoprop *per se* and/or for Metabolite IV are available for the registered commodities indicated in Table C. For other commodities, adequate residue data are available for label conditions less stringent than the maximum conditions. Adequate residue data are also available for all processed commodities currently registered in the U.S. As residue data on Metabolites II and III are not available, HED will conduct dietary exposure assessment using the available data on ethoprop and Metabolite IV, and making conservative assumptions regarding the levels of Metabolites II and III using data from the metabolism studies. A reasonably reliable risk assessment for the uses of ethoprop should be feasible at this time using available residue data.

CODEX HARMONIZATION

The Codex Alimentarius Commission has established maximum residue limits (MRLs) for ethoprophos (ethoprop) residues in/on various plant commodities (see *Guide to Codex Maximum Limits For Pesticide Residues, Part A.1, 1995*). Currently, the Codex MRL residue definition includes only parent ethoprophos. With the inclusion of Metabolites II through IV in the U.S. tolerance definition, Codex MRLs and U.S. tolerances will no longer be compatible.

A comparison of the Codex MRLs and the corresponding U.S. tolerances is presented in Table D.

Table D. Codex MRLs for ethoprophos and current U.S. tolerances

Codex			Current U.S. Tolerance (ppm)	Recommendation and Comments
Commodity (As Defined)	MRL (mg/kg)	Step		
Banana	0.02 (*) ^a	CXL	0.02	
Beetroot	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Cabbages, Head	0.02 (*)	CXL	0.02	
Cucumber	0.02 (*)	CXL	0.02	The tolerance for cucumber includes gherkins in the U.S.
Gherkin	0.02 (*)	CXL		
Grapes	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Lettuce, Head	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Maize	0.02 (*)	CXL	0.02	
Maize fodder	0.02 (*)	CXL		
Maize forage	0.02 (*)	CXL		
Melons, except watermelon	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Onion, Bulb	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Peanut	0.02 (*)	CXL	0.02	
Peanut fodder	0.02 (*)	CXL	0.02	
Peas	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Peppers	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Pineapple	0.02 (*)	CXL	0.02	
Pineapple fodder	0.02 (*)	CXL	None	No longer regulated as feed items in the U.S.
Pineapple forage	0.02 (*)	CXL	None	
Potato	0.02 (*)	CXL	0.02	
Soya bean fodder	0.02 (*)	CXL	None	Not registered for this use in the U.S.; tolerances should be revoked.
Soya bean (dry)	0.02 (*)	CXL	None	
Strawberry	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Sugar cane	0.02 (*)	CXL	0.02	
Sugar cane fodder	0.02 (*)	CXL	None	No longer regulated as feed items in the U.S.
Sugar cane forage	0.02 (*)	CXL	None	
Sweet potato	0.02 (*)	CXL	0.02	
Tomato	0.02 (*)	CXL	None	Not registered for this use in the U.S.
Turnip, Garden	0.02 (*)	CXL	None	Not registered for this use in the U.S.

^aAn asterisk (*) signifies that the MRL was established at or about the limit of detection.

AGENCY MEMORANDA CITED IN THIS DOCUMENT

CB No: 6009
DP Barcode: None
Subject: Multiresidue Protocol Data.
From: M. Nelson
To: J. Talarico
Dated: 1/19/90
MRID(s) 41270700 and 41270701

CB No: 6141
DP Barcode: None
Subject: Rhone-Poulenc, Inc. Response to the Ethoprop Reregistration Standard:
Residue Chemistry Requirements.
From: R. Perfetti
To: R. Engler/L. Rossi
Dated: 7/3/90
MRID(s) None

CBRS No: 7775
DP Barcode: D162702
Subject: Rhone-Poulenc Ag Company Response to the Reregistration Standard:
Residue Chemistry Data.
From: C. Olinger
To: L. Rossi
Dated: 1/24/92
MRID(s) 41809601

CBRS No: 7407, 7795, and 7933
DP Barcode: D14906, D163011, and D163888
Subject: Rhone-Poulenc Ag Company Response to the Reregistration Standard:
Plant Metabolism Data.
From: C. Olinger
To: L. Rossi
Dated: 1/24/92
MRID(s) 41691001, 41814001, and 41840801

CBRS No: 8330
DP Barcode: D167017
Subject: Rhone-Poulenc Ag company Response to the Reregistration Standard:
Plant Metabolism Data for Cabbage.
From: J. Abbotts
To: L. Rossi
Dated: 4/22/92
MRID(s) 41946001

CBRS No: 9812
DP Barcode: D177243
Subject: Multi-residue Methods Protocol.
From: L. Cheng
To: H. Hundley
Dated: 5/28/92
MRID(s) 42242101

CBRS No: 9568
DP Barcode: D175797
Subject: Reregistration of Ethoprop. Residue Analytical Method - Plants.
From: B. Cropp-Kohlligian
To: L. Rossi/L. Shnaubelt
Dated: 7/16/92
MRID(s) 42220601

CBRS No: 12706 and 12578
DP Barcode: D195968 and D195127
Subject: Response to the Ethoprop Reregistration Standard: Pineapple Residue and Processing Studies.
From: R. Perfetti
To: L. Rossi
Dated: 2/18/94
MRID(s) 42945501 and 42901601

CBRS No: 11533, 12610, and 12797
DP Barcode: D188915, D195286, and D196126
Subject: Response to the Ethoprop Reregistration Standard: Metabolism and rotational Crop Studies.
From: R. Perfetti
To: L. Rossi
Dated: 6/22/94
MRID(s) 42197601, 42923201, and 42962701

CBRS No: 13604
DP Barcode: D202608
Subject: Response to the Ethoprop Reregistration Standard: Metabolism Upgrade.
From: R. Perfetti
To: E. Saito
Dated: 9/29/94
MRID(s) 43209001

CBRS No: 12816
DP Barcode: 196279
Subject: Reregistration of Ethoprop: Response to CBRS Review of a Tobacco Pyrolysis Study.
From: C. Olinger
To: S. Jennings
Dated: 7/19/95
MRID(s) None

CBRS No: 14535 and 13949
DP Barcode: D207805 and D204975
Subject: Response to the Ethoprop Reregistration Standard: Methods and Processing Studies.
From: R. Perfetti
To: S. Jennings
Dated: 8/3/95
MRID(s) 43277501, 43277502, and 43373601

CBRS No: 15410
DP Barcode: D214091
Subject: PP#5E04491 - Ethoprop on Mint - Evaluation of Field Trial and Processing Residue Data.
From: G. Otakie
To: D. Edwards/C. Anderson/W. Hazel
Dated: 8/11/95
MRID(s) 43588801 and 43588802

CBRS No: 16089
DP Barcode: D218587
Subject: PP#5E04491 - Ethoprop on Mint. Evaluation of Revised Section F.
From: G. Otakie
To: H. Jamerson/W. Hazel
Dated: 9/20/95
MRID(s) None

CBRS No: 15114
DP Barcode: D212132
Subject: Magnitude of the Residue in Field Corn, Peanut Processing Study, and Storage Stability.
From: S. Knizner
To: S. Jennings
Dated: 12/21/95
MRID(s) 43539801, 43530901, and 43539401

CBRS No: 16678
DP Barcode: D221951
Subject: Ethoprop (041101). Metabolism in Corn, Supplemental.
From: J. Abbotts
To: P. Deschamp
Dated: 7/11/96
MRID(s) 43868701

CBRS No: 16699
DP Barcode: D221052
Subject: Ethoprop (041101). Metabolism in Potato, Supplemental.
From: J. Abbotts
To: P. Deschamp
Dated: 7/11/96
MRID(s) 43836401

CBRS No: None
DP Barcode: None
Subject: Issues to be presented at the 10/7/96 meeting of the HED Metabolism Committee.
From: J. Abbotts
To: HED Metabolism Committee
Dated: 10/1/96
MRID(s) None

CBRS No: None
DP Barcode: None
Subject: Results of the HED Metabolism Committee Meeting Held on 10/16/96: Ethoprop on Primary and Rotational Crops.
From: J. Abbotts
To: HED Metabolism Committee
Dated: 10/17/96
MRID(s) None

CBRS No: None
DP Barcode: None
Subject: Ethoprop. Decision on the HED Metabolism Committee, Residues to be Regulated in Primary and Rotational Crops.
From: J. Abbotts
To: P. Deschamp
Dated: 10/29/96
MRID(s) None

CBRS No: None
DP Barcode: None
Subject: Ethoprop. Meeting with Registrant Rhone-Poulenc, 12/3/96, on Residue Chemistry Requirements.
From: J. Abbotts
To: P. Deschamp
Dated: 12/4/96
MRID(s) None

CBRS No: 17755
DP Barcode: D232990
Subject: Ethoprop. Registrant Rhone-Poulenc, Letter on Residue Chemistry Requirements.
From: J. Abbotts
To: P. Deschamp
Dated: 2/12/97
MRID(s) None

CBRS No: 17688
DP Barcode: D231955
Subject: Registrant Rhone-Poulenc Ag Company. Sugarcane Processing.
From: J. Abbotts
To: T. Myers
Dated: 2/19/97
MRID(s) None

CBRS No: 14917
DP Barcode: D210696
Subject: Magnitude of the Residue in Sweet Corn and Cucumbers.
From: C. Eiden
To: P. Deschamp/S. Jennings/L. Schnaubelt
Dated: 3/13/97
MRID(s) 4349101 & 43484001

CBRS Nos: 15401 and 17234
DP Barcode: D213957 and D226333
Subject: Ethoprop. Cabbage Field Trials and Peanut Processing Data.
From: J. Abbotts
To: K. Farwell/J. Loranger
Dated: 9/4/97
MRID(s) 43583201 and 44003301

CBRS No: None
DP Barcode: D238745
Subject: Preplant application to mint: Is classification as a nonfood use appropriate?
From: J. Hazel
To: H. Jamerson/R. Forrest
Dated: 9/16/97
MRID(s) None

CBRS No: None
DP Barcode: D235830
Subject: Ethoprop. Peanut Field Trails.
From: J. Abbotts
To: K. Farwell/J. Loranger
Dated: 9/22/97
MRID(s) 43539701 and 44062401

CBRS No: 15264
DP Barcode: D213113
Subject: Ethoprop. Lima and Snap Bean Field Trails.
From: J. Abbotts
To: K. Farwell/J. Loranger
Dated: 9/22/97
MRID(s) 43538601 and 43539601

CBRS No: 17221
DP Barcode: D225648
Subject: Ethoprop. Storage Stability in Sugarcane, Sugarcane Processing.
From: J. Abbotts
To: K. Farwell/J. Loranger
Dated: 11/14/97
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Attachment 2: Toxicology Chapter for the Reregistration Eligibility Decision

MEMORANDUM

SUBJECT: Toxicology Chapter for the Reregistration Eligibility Document for ETHOPROP (Chemical 041101).

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

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

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

ACTION REQUESTED: Prepare Toxicology RED Chapter for Ethoprop.

SUMMARY: The toxicology chapter for the ethoprop RED is attached. Ethoprop (O-ethyl S,S-dipropyl phosphorodithioate) is a nematocide and insecticide for use on fruit and vegetable crops and golf course turfgrass.

The toxicology database for ethoprop is essentially complete, with two exceptions. Cholinesterase determinations for the M1 metabolite of ethoprop in an acute study are ongoing, however, the remainder of this study (MRID 44472501) has already been reviewed (see Acute Toxicity section of this chapter). A neurotoxic esterase study has been requested which is "confirmatory" in nature (see Neurotoxicity Studies section of this chapter). These results will not significantly change the understanding of the toxicity of ethoprop and should not delay the reregistration process.

The endpoints for acute and chronic dietary exposure as well as short-, intermediate-, and long-term dermal occupational or residential exposure are presented in this chapter. The HED Cancer Assessment Peer Review Committee (10/2/97 document) classified ethoprop as a "likely" human carcinogen with a Q₁* (see Carcinogenicity Classification section of this chapter). Recommendations for uncertainty factors as required under FQPA are included in the Dose Response Assessment section of this chapter.

CONTENTS OF ETHOPROP TOXICOLOGY CHAPTER

A. HAZARD ASSESSMENT

1. ACUTE TOXICITY STUDIES.

TABLE 2A. ACUTE TOXICITY: TECHNICAL ETHOPROP

TABLE 2B. COMPARATIVE ACUTE ORAL TOXICITY: ETHOPROP
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3. NEUROTOXICITY STUDIES: Acute Delayed Neurotoxicity Study in Hens (1986), Acute Neurotoxicity Study in Rats (1994), Special Acute Neurotoxicity Study in Rats (1994), Subchronic Neurotoxicity Study in Rats (1994).

4. CHRONIC TOXICITY STUDIES: Combined Chronic Feeding/Carcinogenicity Study in Rats (1992), Combined Chronic Feeding/Carcinogenicity Study in Rats (1985), Combined Chronic Feeding/Carcinogenicity Study in Rats by Feeding and Lactational Exposure (1983), Chronic Gavage Study in Dogs (1986 and 1990).

5. CARCINOGENICITY STUDIES: See Chronic Toxicity Studies for Rat Studies. Carcinogenicity Study in Mice (1984).

6. DEVELOPMENTAL TOXICITY STUDIES: Developmental Toxicity in Rats (1989), Developmental Toxicity in Rabbits (1989).

7. REPRODUCTIVE TOXICITY STUDIES: Reproductive Toxicity in Rats (1991).

8. MUTAGENICITY STUDIES.

TABLE 3. ACCEPTABLE MUTAGENICITY STUDIES

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10. METABOLISM: Metabolism Study in Rats (1990).

11. METABOLISM COMMITTEE CONCLUSIONS.

B. DOSE RESPONSE ASSESSMENT.

1. SENSITIVITY OF INFANTS AND CHILDREN.

a. 10X Factor for Protection of Infants and Children: Acute and Chronic Dietary Exposure.

b. Assessment of Need for a Developmental Neurotoxicity Study.

2. REFERENCE DOSE (RfD).

3. OTHER TOXICOLOGICAL ENDPOINTS

Table 4. Toxicological Endpoints

7. INHALATION EXPOSURE (any time period).

8. CARCINOGENIC CLASSIFICATION.

A. HAZARD ASSESSMENT.

1. ACUTE TOXICITY STUDIES. The acute toxicity of ethoprop is due to inhibition of acetylcholinesterase. Ethoprop is in Toxicity Class I based on an oral study in rats and a dermal study in rabbits. **Ethoprop is also in Toxicity Class I due to the eye and dermal irritation studies in which all rabbits died. The dose-response curve for ethoprop is steep, clinical signs appear at slightly lower doses than a lethal dose .** Rabbits were approximately 50x more susceptible than rats in dermal LD₅₀ studies, likely due to increased dermal absorption.

TABLE 2A. ACUTE TOXICITY: TECHNICAL ETHOPROP

GDLN	STUDY TYPE	MRID # YEAR	RESULTS	TOXICITY CATEGORY
81-1	Acute Oral - Rat ^a	00078035 1965	M LD ₅₀ = 56.2 mg/kg F LD ₅₀ = 30.2 mg/kg	I
81-2	Acute Dermal - Rabbit	42979502 1987	LD ₅₀ = 8.5 mg/kg	I
8-2	Acute Dermal - Rat	42979501 1987	LD ₅₀ = 1280 mg/kg M LD ₅₀ = 424 mg/kg F	II
81-3	Acute Inhalation - Rat	070060 1980	LC ₅₀ = 0.123 mg/L	II
81-4	Eye Irritation - Rabbit	00078036 1965	0.1 mL killed all 3 rabbits	I
81-5	Skin Irritation - Rabbit	00048774 1977	0.5 mL killed all 6 rabbits.	I
81-6	Dermal Sensitization ^b	N/A	N/A	N/A
81-7	Delayed Neuropathy - Hen	40609401 1986	Negative	N/A
81-8	Acute Neurotoxicity - Rat	43442402 43197701 1994	systemic NOEL/LOEL = 5/25 mg/kg (clinical signs), ChE NOEL <5 mg/kg	N/A

^aThese LD₅₀ values are from the review; slightly different values were reported in 1988 Reregistration Document. ^bRequirement for a Dermal Sensitization study waived due to high acute dermal toxicity of ethoprop in rabbits.

All acute studies are acceptable and the database is complete, with the exception of a portion of an ongoing acute toxicity study in rats with ethoprop metabolites. In the acute study with ethoprop metabolites, cholinesterase inhibition for the M1 metabolite of ethoprop (O-ethyl-S-propylphosphorothioate) has yet to be determined because of depletion of test material. The rest of the

study (MRID 44472501) has already been received by HED and reregistration should not be delayed.

The acute study with metabolites in rats (MRID 44472501) was conducted to determine if the M1 metabolite caused significant cholinergic toxicity. This study determined that the M1 metabolite was in Toxicity Category III and did not cause significant acute toxicity compared to parent ethoprop. M1 treatment required approximately 20x higher doses than ethoprop to cause similar mortality or clinical signs. Cholinesterase inhibition for M1 was not yet determined; test material was depleted due to the large quantities needed during LD₅₀ testing. SME treatment caused cholinesterase inhibition, clinical signs, and mortality at generally similar, but slightly lower doses than ethoprop. OME treatment caused clinical signs and mortality at approximately 1/3 to 1/2 the dose of ethoprop.

This study also showed the steep dose-response curve for ethoprop. Mortality at 50 mg/kg ethoprop was 3/10, at 60 mg/kg was 6/10, and at 75 mg/kg was 10/10. The number of animals with severe clinical signs (tremor or staggering gait) at 50 mg/kg ethoprop was 7/10 and at 60 mg/kg was 10/10. This study was successful in determining acute toxicity of the ethoprop metabolites and is classified **Acceptable/Guideline**.

TABLE 2B. COMPARATIVE ACUTE ORAL TOXICITY: ETHOPROP AND METABOLITES. (1998, MRID 44472501)

COMPOUND ¹	RESULTS	TOXICITY CATEGORY
ETHOPROP	LD ₅₀ = 55.8 mg/kg	II
SME	LD ₅₀ = 50.0 mg/kg	I
OME	LD ₅₀ = 22.4 mg/kg	I
M1	LD ₅₀ = 1608 mg/kg	III

¹SME = (O-ethyl-S-methyl-S-propylphosphorodithioate)

OME = (O-ethyl-O-methyl-S-propylphosphorothioate)

M1 = (O-ethyl-S-propylphosphorothioate)

2. SUBCHRONIC TOXICITY STUDIES. The database for subchronic toxicity is complete; no additional studies are required at this time. Principal toxicity in the subchronic dietary dog study and 21-day rabbit dermal study was inhibition of plasma, rbc, and brain cholinesterase (ChE) activity. Erythema also occurred in the 21-day rabbit dermal study. The ChE NOEL in the dietary dog study was 0.025 mg/kg/day. The ChE NOEL in the 21-day dermal rabbit study was 1 mg/kg/day. A subchronic neurotoxicity study is described in the Neurotoxicity Studies section of this document.

82-1(b) Subchronic Dietary Toxicity Study in Dogs (1967, MRID 00075240):

In a subchronic dietary study, technical ethoprop (% a.i. unknown) was administered to groups of 3 Beagle dogs/sex/dose group in the diet at dose levels of 0, 1.0, 3.0, or 100 ppm (0, 0.025, 0.075, or 2.5 mg/kg/day). No mortality was reported nor were changes noted in hematology, necropsy, histopathology, or organ weights. The only clinical sign which may have been related to treatment was emesis, seen once in two high-dose dogs. Plasma and rbc ChE activity was reported as % of pre-treatment value, statistical significance was not reported. Brain ChE activity was not determined. Plasma ChE inhibition occurred at 0.075 and 2.5 mg/kg/day on day 2, the earliest post-treatment determination. Mean plasma ChE activity for the 0.075 mg/kg/day male group was 75% of the pre-treatment value on day 2 and was 60% on day 4. Females in the 0.075 mg/kg/day group had 94% and 72% of pre-treatment activity on days 2 and 4. Males and females at 2.5 mg/kg/day had 32% and 35% of pre-treatment values for plasma cholinesterase on day 2. At termination, male and female values for plasma cholinesterase activity were 80% and 91% of pre-treatment values at 0.025 mg/kg/day, 60% and 63% at 0.075 mg/kg/day, and 40% and 35% at 2.5 mg/kg/day. At termination, male and female values for rbc cholinesterase activity were 106% and 112% of pre-treatment values at 0.025 mg/kg/day, 100% and 82% at 0.075 mg/kg/day, and 56% and 57% at 2.5 mg/kg/day. The **NOEL** is 1 ppm (0.025 mg/kg/day) and the **LOEL** is 3.0 ppm (0.075 mg/kg/day) based on decreases in plasma cholinesterase activity. This study is **Acceptable**.

82-2 21-day Dermal Toxicity Study in Rabbits (1989, MRID 41304404):

Ethoprop technical (95.6%) was applied to the shaved dorsal skin of groups of 10 Hra:(NZW)SPF rabbits of each sex at dose levels of 0, 0.03, 0.1, or 1 mg/kg/day, (5 days/week for 6 hr/day) for 3 weeks; controls received vehicle alone (4% carboxymethylcellulose in distilled water). The principal test compound-related effects were significant decreases, compared with controls, in the activities of plasma, erythrocyte, and brain cholinesterase in males and females dosed at 1 mg/kg/day. Cholinesterase activity for males and females in the 1 mg/kg/day group was 58% and 65% for plasma, 58% and 58% for erythrocyte, and 51% and 51% for brain when compared to respective controls. Compared with controls, other effects that may have been test compound-

related in rabbits dosed at 1 mg/kg/day were significantly lower mean body weights of females at weeks 2 and 4, and lower absolute weights of the kidneys of females (significant) and males (nonsignificant) at the end of the treatment period. Incidences of erythema at application sites were elevated, compared with controls, in high-dose animals of both sexes at day 9, and in mid- and high-dose animals of both sexes at later times of observation; the incidence of erythema was also marginally elevated in low-dose males at day 13. Mean scores for the severity of the erythema were elevated at all dose levels during the latter part of the treatment periods and, in general, were dose-related and increased with increasing time of animal exposure. There were no treatment-related effects upon mortality, clinical signs, body weight, food consumption, hematologic parameters, or gross or microscopic lesions in males or females, or body weights of males. The **NOEL** is 0.1 mg/kg/day and the **LOEL** is 1 mg/kg/day based on plasma, erythrocyte, and brain cholinesterase inhibition. On the basis of increased erythema at all doses, the 3-week repeated NOEL of dermal irritation was not established. Deficiencies included not reporting the stability, homogeneity, and concentrations of test material in dosing suspensions. Experimental animals were not healthy, 4 low-dose rabbits and 2 high-dose rabbits died or were sacrificed moribund due to illness with mucoid enteritis. The study is classified **Core Minimum**.

82-7 Subchronic Neurotoxicity Study in Rats (1994, MRID 43424001): This study is described in the Neurotoxicity Studies section of this chapter.

3. NEUROTOXICITY STUDIES. Acceptable acute and subchronic rat neurotoxicity studies and an acute delayed neurotoxicity study in hens were available. Although the hen study was negative for delayed neurotoxicity, a neurotoxic esterase study was requested by the HED RfD Committee (5/8/96) because of structure-activity concerns. This study is confirmatory in nature and should not delay the reregistration process.

Clinical signs indicative of ChE inhibition were seen as low as 25 mg/kg/day in the acute rat neurotoxicity study with a systemic NOEL of 5 mg/kg/day. The LOEL for ChE inhibition was 2.6 mg/kg/day with a NOEL of 0.26 mg/kg/day in the subchronic rat neurotoxicity study..

81-7 ACUTE DELAYED NEUROTOXICITY STUDY IN HENS (MRID 40609401): In an acute delayed neurotoxicity study, no clinical or histopathological signs of neurotoxicity were seen in hens given doses causing high mortality (6.5 mg/kg initially followed by a second oral dose of 5.3 mg/kg 21-days later).

81-8 ACUTE NEUROTOXICITY STUDY IN RATS (1994, MRID 43197701): In an acute neurotoxicity screening study, groups of 17 male and 17 female rats received a single gavage doses of Ethoprop in corn oil (males: 5, 50, or 75

mg/kg; females: 5, 25, or 50 mg/kg). Control rats received only vehicle. Twelve rats per group were subjected to functional observation battery (FOB) tests and motor activity tests at predose, 2 hours postdose (time-to-peak effect), and at 8 and 15 days postdose. Plasma cholinesterase (ChEP) and red blood cell cholinesterase (ChER) activities were determined at predose, and days 2, 8, and 15 for five rats/sex/group not used for FOB tests. Neuropathology examinations of all appropriate tissues were conducted on day 15 in 6 rats/sex/group not used for cholinesterase determinations. At 25 mg/kg, two females exhibited salivation, lip smacking, ataxia, negative pupillary response and/or tremors. At 50 mg/kg in females and 75 mg/kg in males, the incidence and frequency of these signs increased and in addition, negative corneal response, negative air drop reflex, negative startle response, increased latency until first step, paralytic gait abnormalities, reduced activity, prostration and labored or gasping respiration were observed in both sexes (incidence ranged from 4-9 animals affected). Motor activity was reduced in both sexes at 50 mg/kg (-50%, males and -79%, females). A total of 6 females died on day 1 or 2. At 75 mg/kg (males only), 2 males died on day 3. Two additional deaths (a mid-dose male, day 1 and a low-dose female, day 8) were not considered treatment-related. The **neurotoxicity LOEL** is 25 mg/kg, based on transient neurobehavioral signs in females related to cholinesterase inhibition. The **NOEL** is 5 mg/kg. In males at day 2, plasma ChE activity showed a dose-dependent inhibition at all doses (-45 to -94%; $p \leq 0.05$) and RBC activity was inhibited at 50 and 75 mg/kg. In females, plasma ChE decreased dose-dependently at day 2 (-49 to -94%; $p \leq 0.05$). At day 2, RBC ChE in females of all dose groups exhibited significant decreases (-32 to -49%; $p \leq 0.05$) although there was no dose relationship. Recovery was observed for plasma and RBC ChE although RBC values tended to be lower ($p < 0.05$, RBC ChE of high dose males at day 15). Brain ChE, measured only on day 15, was unaffected. Neuropathologic examinations revealed no remarkable findings in any of the treatment groups. The **cholinesterase LOEL** is 5 mg/kg, based on inhibition of plasma cholinesterase in both sexes and RBC cholinesterase in females. The **NOEL** is < 5 mg/kg. This study is classified **Acceptable/Guideline** for an acute neurotoxicity study in rats and satisfies guideline requirements for 81-8SS.

81-8 SPECIAL ACUTE NEUROTOXICITY STUDY IN RATS (time-course study, 1994, MRID 43442402): In an acute gavage study groups of 24 Sprague-Dawley rats/sex (approx. 6 weeks old) received a single doses of Ethoprop (95.7%) in corn oil (males: 0, 30 or 60 mg/kg target; 0, 24.2 or 52 mg/kg actual; females: 0, 20 or 40 mg/kg target; 0, 15.7 or 33 mg/kg actual). Animals were observed twice daily for mortality and clinical signs. Plasma, red blood cell and brain (caudate/putamen, hippocampus, frontal cortex and cerebellum) cholinesterase activities were determined on days 1, 3, 8 and 15 for 6 rats/sex/group. At 40 mg/kg, several females exhibited tremors, excessive salivation and low carriage (Day 1). One 20 mg/kg female was cold to the touch.

At 60 mg/kg, 1 male was sacrificed moribund on day 3. Some (1-4) males in the 60 mg/kg groups exhibited tremors of the head, limbs and body; hunched posture; yellow feces; labored and irregular breathing; rough and stained coat; red, clear, and cloudy ocular discharge; uncoordination; hypoactivity; excessive salivation; and were cold to the touch (Days 1-3). No treatment-related effects on body weight were observed. The **LOEL for clinical signs** in this study is 33 mg/kg (40 mg/kg/dose), based on cholinergic symptoms in females. The **NOEL** is 15.7 mg/kg (20 mg/kg dose). Statistically significant inhibition of plasma, RBC and brain ChE activity was observed in all treatment groups and was time-, tissue- and dose-dependent. In females at 20 mg/kg, inhibition of ChE relative to controls on day 1 (2-hr post-dosing) was 90% for plasma, 44% for RBC and from 50 - 72% for brain regions. In males at 30 mg/kg, inhibition of ChE relative to controls on day 1 was 83% for plasma, 43% for RBC and 45 - 48% for brain regions. At 40 mg/kg, females and 60 mg/kg, males, inhibition was slightly more pronounced for plasma and RBC and more sharply increased in brain (72 - 93% inhibition). Caudate/putamen ChE activity showed the greatest inhibition among the brain regions. Animals showed recovery from inhibition, but degree of recovery varied. By Day 15 plasma ChE levels were recovered but RBC levels remained marginally inhibited in males at 30 and 60 mg/kg (22 - 23%). In brain on Day 15, marginal but statistically significant inhibition was observed in the hippocampus in both sexes at high dose (17 - 18%) and frontal cortex ChE was marginally but significantly inhibited in males (19 - 27%). Caudate/putamen ChE activity remained slightly lower, but not significantly, in males at 60 mg/kg (32% inhibition) and females at 20 and 40 mg/kg (25% and 40%). The **cholinesterase LOEL** for this study is <15.7 mg/kg (20 mg/kg dose), based on inhibition of plasma, RBC and brain ChE in females. A **NOEL** was not determined. This acute oral cholinesterase study is classified **Acceptable/Non-guideline**. This study was not intended to fulfill a guideline requirement but was designed specifically to supplement the acute neurotoxicity screening study in rat (81-8ss) by investigating time-related effects of Ethoprop on ChE activities in plasma, red blood cells and four brain regions.

82-7 SUBCHRONIC NEUROTOXICITY STUDY IN RATS (1994, MRID

43442401): In a subchronic neurotoxicity study, 27 CD BR VAF/Plus rats/sex/dose were fed Ethoprop (tech., 95.7% a.i.) in the diet for 13 weeks at 0, 4, 40 or 400 ppm (0, 0.260, 2.648 or 27.113 mg/kg/day for males and 0, 0.306, 2.989 or 31.311 mg/kg/day for females, respectively). Twelve rats/sex/ dose were selected for functional observational battery (FOB) and motor activity (MA) testing, 15 animals/sex/dose for cholinesterase (ChE) analysis and 6/sex/dose were perfused for neuropathology. At 400 ppm, body weights were lowered by 13.1 to 16.2% for males and 5.7 to 8.3% for females; body weight gains were lowered by 64.2 to 24.7% for males and 44.4 to 10.2% for females. Food consumption was lowered at Week 1 by 21.6% for males and 7.9% for females. In males the following decreases were observed: hindlimb grip strength (28.4,

26.9 and 27.9% at Weeks 4, 8 and 13, respectively); analgesic reflex at Week 4 (6.8 sec less than controls) and MA (35.9, 30.0 and 26.0% at Weeks 4, 8 and 13, respectively; marginal decrease observed in females at Week 13). One male (week 4) and 1 female (week 8) showed an array of ChE-related symptoms, considered a possible marginal effect of treatment. No effects were observed at or below 40 ppm and no ethoprop-related neuropathological changes were observed. The **LOEL for systemic/neurobehavioral findings** is 400 ppm (27.113 mg/kg/day) based on decreased body weight gain/food consumption, decreased hindlimb grip strength, motor activity and analgesic response time in males, and possible cholinergic signs. The **NOEL** is 40 ppm (2.648 mg/kg/day). Plasma ChE activities were decreased by 53.8 to 90.0% for males at 40 and 400 ppm and 18.4 to 97.6% for females at 4, 40 and 400 ppm. Red blood cell ChE activities at 40 and 400 ppm were decreased by 23.4 to 40.3% in males and 19.2 to 39.9% (not significant) in females. Regional brain ChE activities were decreased by 22.6 to 82.3% at 40 and 400 ppm in males and 20.7 to 88.1% at 4, 40 and 400 ppm in females. The **LOEL for plasma and brain cholinesterase inhibition** is 4 ppm (0.306 mg/kg/day) based on decreases in females and the **LOEL for RBC ChE inhibition** is 40 ppm (2.648 mg/kg/day) based on decreases in both sexes. A **NOEL** for plasma and brain ChE was not determined and the **NOEL for RBC ChE inhibition** is 4 ppm. This subchronic neurotoxicity study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic oral study (82-7ss) in rats.

4. CHRONIC TOXICITY STUDIES. The database for chronic testing is complete; no additional studies are required at this time. Three chronic/carcinogenicity studies in rats were available. One study was acceptable while 2 studies were unacceptable, but upgradeable. In the rat studies, the **NOEL** for ChE inhibition was 0.04 mg/kg/day. Systemic effects included decreased weight gain, food consumption, and anemia with a systemic **NOEL** of 2.44 mg/kg/day.

Malignant adrenal pheochromocytomas were increased in the 1992 chronic rat study. Thyroid C-cell and/or parafollicular cell tumors were increased in all 3 rat studies. (See the Carcinogenic Classification section in the Dose Response Assessment section of this document.) Endometrial polyps were increased at the high dose in 2 studies.

The chronic dog study was followed up by a 5-month study to determine a **NOEL** for plasma ChE inhibition. Systemic effects at 1.0 mg/kg/day included anemia and evidence of liver injury with a systemic **NOEL** of 0.025 mg/kg/day. ChE inhibition occurred at 0.025 mg/kg/day and the ChE **NOEL** was 0.010 mg/kg/day.

83-1(a) Combined Chronic Feeding/Carcinogenicity Study in Rats (1992, MRID 42530201): In a combined chronic feeding/carcinogenicity study,

ethoprop (95.6%) was administered to Crl:CD rats, 80/sex/dose, at dose levels of 0, 1, 60, or 600 ppm for 105 weeks. Doses corresponded to 0, 0.04, 2.44, or 18.38 mg/kg/day in males and 0, 0.06, 3.56, or 23.98 mg/kg/day in females. Interim sacrifice was conducted at 52 weeks with 10 rats/sex/dose. An additional 10/sex in control and high-dose groups were treated for 52 weeks and sacrificed after a 4-week recovery period. The high-dose group had received 600 ppm for the first 2 weeks of the study. This dose was reduced to 400 ppm after 2 weeks due to toxicity in females (weight gain depression, tremors, ataxia, and 2 mortalities). The **systemic toxicity NOEL** for both males and females was 60 ppm (2.44 mg/kg/day in males and 3.56 mg/kg/day in females) and the **LOEL** for both males and females was 400 ppm (18.38 mg/kg/day in males and 23.98 mg/kg/day in females), based on reduced body weight gain, reduced food consumption, reduced erythrocyte count, reduced hemoglobin, and reduced hematocrit. The **NOEL for plasma, red blood cell and brain cholinesterase inhibition** in both males and females was 1 ppm (0.04 mg/kg/day in males and 0.06 mg/kg/day in females). The **LOEL** for plasma, red blood cell and brain cholinesterase inhibition in both males and females was 60 ppm (2.44 mg/kg/day in males and 3.56 mg/kg/day in females). **Adrenal gland malignant pheochromocytomas** were increased in males (0/41, 2/16, 2/18, 5/60 in their respective dose groups). **Thyroid C-cell carcinomas** were increased slightly in males (0/61, 0/63, 1/64, 3/66 in their respective dose groups). This chronic toxicity study in the rat is **acceptable**, and satisfies the guideline requirement for a chronic oral study (83-1(a)).

83-1(a) Combined Chronic Feeding/Carcinogenicity Study in Rats (1985, MRID 40291801): In a combined chronic feeding/carcinogenicity study (MRID 40291801) ethoprop (95%) was administered to F344 rats, 60/sex/dose, at dose levels of 0, 1, 10, or 100 ppm in the diet for 24 months. Doses corresponded to 0, 0.041, 0.40, or 4.19 mg/kg/day in males and 0, 0.052, 0.51, or 5.12 mg/kg/day in females. Interim sacrifices were conducted at 12 and 18 months with 10 rats/sex/dose in each interim sacrifice. The **systemic toxicity NOEL** for both males and females was ≥ 100 ppm (4.19 mg/kg/day in males and 5.12 mg/kg/day in females), the **highest dose level tested** in this study. The **NOEL for plasma and red blood cell cholinesterase inhibition** in both males and females was 1 ppm (0.041 mg/kg/day in males and 0.052 mg/kg/day in females). The **LOEL** for plasma and red blood cell cholinesterase inhibition in both males and females was 10 ppm (0.40 mg/kg/day in males and 0.51 mg/kg/day in females). The **NOEL** for brain cholinesterase inhibition in both males and females was 10 ppm (0.40 mg/kg/day in males and 0.51 mg/kg/day in females) with a **LOEL** of 100 ppm (4.19 mg/kg/day in males and 5.12 mg/kg/day in females). **Thyroid C-cell adenomas** were increased in high-dose males (8/49, 5/48, 5/50, 12/50 in the respective dose groups). **Thyroid C-cell carcinomas** were also increased slightly in high-dose males (0/49, 0/48, 1/50, 3/50 in the respective dose groups). Tumor incidence in females was comparable between controls and treated rats.

This study was classified **supplementary, upgradeable**.

83-1(a) Combined Chronic Feeding/Carcinogenicity Study in Rats by Feeding and Lactational Exposure (1983, MRID 00138636): Test animals (F1 generation) were exposed to ethoprop *in utero*, during lactation, and then by feeding. This was accomplished by administering technical ethoprop (95.3%) in the diet to parental F344 rats (F0 generation) at dietary concentrations of 0, 60.5, 131, or 262 ppm. After weaning, 60 F1 pups/sex/group were fed diets containing 0, 4.5, 9.0, or 18 ppm for 12 weeks and then placed on diets containing 0, 49, 98, or 196 ppm of ethoprop. Ten of the 60 F1 rats/group/sex were sacrificed at 52 weeks. Male rats had increasing trends for thyroid C-cell adenomas (2/46, 4/43, 1/41, 10/40; $p < 0.01$) as well for the pair wise comparison of the 196 ppm group with controls ($p < 0.01$). Female rats had increasing trends for uterine endometrial polyps (0/44, 4/45, 8/37, 13/42; $p < 0.01$) as well as for pair wise comparison of mid- and high-dose rats compared to controls ($p < 0.01$). Combined endometrial and stromal polyps showed increasing trends (8/44, 6/45, 10/37, 16/42; $p < 0.01$) as well as by pair-wise comparison of the high-dose group with controls ($p < 0.05$). This study was classified **Supplementary** because no NOEL was determined and the number of tissues examined microscopically was not evident to the reviewer. Other data requested included more data on analytical testing of diet, information on statistical methods used, and breeding and litter data. This study was **not evaluated by the RfD Committee** when it evaluated the ethoprop database on 5/9/96. The RfD Committee considered this study superseded by the 1992 toxicity study in rats (MRID 42530201). This study was evaluated by the Cancer Peer Review Committee on 6/25/97 and 8/20/97.

83-1(b) Chronic Gavage Study in Dogs (1986, MRID 00160179 and 1990, MRID 41498601):

In a 1-year capsule study in dogs (1986, MRID 00160179), groups of 4 female Beagle dogs per sex received capsules of ethoprop (96%) in peanut oil at doses of 0, 0.025, 1.0, or 10 mg/kg/day. Systemic effects at 1.0 mg/kg/day and above included decreases in red blood cell parameters in males and females and elevations in SGPT in males. At 10 mg/kg/day serum alkaline phosphatase was elevated in males, pathological changes occurred in the livers of males and females, and one treatment-related death occurred in one male. Plasma ChE was inhibited in all female treatment groups and in males at 1.0 and 10 mg/kg/day. Red blood cell ChE was inhibited in females at 1.0 and 10 mg/kg/day and in males at 10 mg/kg/day.

A 5-month study in dogs was later conducted to find a NOEL for plasma ChE inhibition. In the 5-month capsule study in dogs (1990, MRID 41498601), groups of 6 Beagle dogs per sex received capsules of ethoprop (95.6%) in corn oil at

doses of 0, 0.01, 0.025, or 1.0 mg/kg/day. In this study, there were no systemic effects attributed to treatment. Plasma, rbc, and brain ChE were inhibited at 0.025, 1.0, and 10.0 mg/kg/day, respectively, for both males and females.

The **NOEL for systemic toxicity** was 0.025 mg/kg/day and the **LOEL** for systemic toxicity was 1.0 mg/kg/day based on decreases in red blood cell parameters in males and females and elevations in SGPT in males. The **combined NOEL values for plasma, red blood cell and brain cholinesterase inhibition** were 0.010, 0.025 and 1.0 mg/kg/day, respectively, and **combined LOEL values** were 0.025, 1.0, and 10.0 mg/kg/day, respectively, for both males and females. Together these 2 studies are classified **Acceptable/Guideline** and satisfy the requirement for a chronic toxicity study in the dog.

5. CARCINOGENICITY STUDIES. The database for carcinogenicity testing is complete; no additional studies are required at this time. The chronic/carcinogenic studies are described in the Chronic Toxicity section of this document. Also, see the Carcinogenic Classification section in the Dose Response Assessment section of this document.

83-1(a) Carcinogenicity Studies in Rats (MRID 42530201, 40291801, 00138636): These studies are described in the Chronic Toxicity section above.

83-1(b) Carcinogenicity Study in Mice (1984, MRID 40356301 and 43326001): Ethoprop technical (>99% purity) was administered in the diet to 50 B6C3F1 mice per sex per group for 104 weeks at 0, 0.2, 2.0, or 30 ppm (Males: 0, 0.026, 0.254, or 3.96 mg/kg/day; Females: 0, 0.032, 0.318, or 4.9 mg/kg/day) in a carcinogenicity study (83-2b, MRID 43326001 & 40356301). Additional animals (30/sex/group) were added for 3 interim sacrifices (10 mice per sex) at weeks 26, 52, and 78. Survival was unaffected at any dose level. Body weight was reduced compared to controls in males (4-6%, $p \leq 0.05$) and females (6-8%, generally statistically significant to week 36) at the 30 ppm dose level during the first year of the study. Body weight gain was also statistically significantly decreased weeks 0 to 26 (males 13% below control and females 15% below control) but not week 26 to week 104 at the 30 ppm dose level. The slightly reduced body weight was accompanied by reduced efficiency of food utilization the first year of the study, but neither body weight nor food efficiency was reduced the second year of the study. Plasma and erythrocyte cholinesterase activities were inhibited in a dose-dependent fashion at 2 and 30 ppm for both males and females at weeks 26, 52, 78, and 104. Most of the decreases were statistically significant relative to controls. At 2 ppm, plasma cholinesterase inhibition ranged from 10% to 24% (males and females) and ranged from 64-77% (males and females) at 30 ppm. A similar pattern was seen at 2 and 30 ppm for erythrocyte cholinesterase inhibition. Brain cholinesterase was clearly inhibited and statistically significant at 30 ppm only in both sexes at week 26 and

104. Inhibition ranged from 17% to 36%. A dose related response and statistically significant increase was noted in kidney basophilic change (in older reports referred to as regenerating epithelium) in males (29% at 0.2 ppm and 57% at 30 ppm) at ≥ 0.2 ppm in males and calcium deposits in males (31%) and females (16%) at 30 ppm. However, both the kidney basophilia and the calcium deposits in males were close to the historical control mean of 26% and within historical control range (0% to 72%) for kidney calcification and 49% (0% to 87%) for basophilic changes and the apparent dose relationship may be due to the low control values (4% and 1%, respectively) or a real test material effect. In females, significant kidney calcium deposits were seen only at 30 ppm (16%) (historical control mean of 4.2% and range of 0% to 17%). Brain calcium deposits were statistically significantly increased in males at 30 ppm (62%) (historical control mean of 39% and range 0% to 78%). In females, hyaline bodies in the brain were statistically significantly increased at 30 ppm (53%) (historical control mean of 42% and range of 0% to 97%). **No statistically significant dose related incidence of tumors were seen in males or females.** All nominally elevated tumor incidence was within historical control range, except liver carcinoma that was nominally increased at 30 ppm in females 6/43 (14%) vs. controls at 2/38 (5.3%). Historical control data indicated a mean of 2.5% (range of 0% to 10% for females. For the tumor data in the historical control, the mean and range are based on 50 animals/experiment (page 325 and 348 of MRID 43326001). The **cholinesterase NOEL/LOEL in males** were 0.026/0.254 mg/kg/day and in females were 0.032/0.318 mg/kg/day based on decreased plasma and erythrocyte cholinesterase activity. The **systemic NOEL/LOEL in males** were 0.254/3.96 mg/kg/day and in females were 0.318/4.91 mg/kg/day based on body weight and body weight gain decreases. Brain cholinesterase activity was statistically significantly decreased in both sexes at the high dose. The doses were adequate to test for the carcinogenicity of ethoprop. The carcinogenicity study report (MRID 403356301 and 43326001) is **acceptable** for a Guideline 83-2b carcinogenicity study in mice.

7. DEVELOPMENTAL TOXICITY STUDIES. The database for developmental toxicity testing is complete; no additional studies are required at this time. No developmental toxicity occurred in either the rat or rabbit developmental studies.

83-3(a) Developmental Toxicity in Rats (1989, MRID 41304402): In a rat developmental toxicity study (1989, MRID 41304402), groups of 25 female SD rats received doses of 0, 2, 9, or 18 mg/kg/day ethoprop (95.6%) by gavage in corn oil on gestation days 6-15. The **maternal NOEL** was 2 mg/kg/day and the **maternal LOEL** was 9 mg/kg/day based on decreased body weight gain and increased incidence of soft stool. The **developmental toxicity NOEL** was ≥ 18 mg/kg/day, the **highest dose tested**. This study was **acceptable**.

83-3(b) Developmental Toxicity in Rabbits (1989, MRID 41304403): In a

rabbit developmental toxicity study (1989, MRID 41304403), groups of 20 NZW rabbits received doses of 0, 0.625, 1.25, or 2.5 mg/kg/day ethoprop (95.6%) in corn oil on gestation days 6-18. **Both the maternal and developmental NOELs were $\geq$ 2.5 mg/kg/day, the highest dose tested.** Although no maternal or developmental toxicity occurred in this study, dosing was considered adequate because the highest dose was close to a lethal dose. This study was classified **acceptable**.

8. REPRODUCTIVE TOXICITY STUDIES. The database for reproductive toxicity testing is complete; no additional studies are required at this time. No increased sensitivity of offspring compared to parents was noted in this study.

83-4 Reproductive Toxicity in Rats (1991, MRID 41921201): In a 2-generation reproduction study, groups of 28 male and 28 female Crl:CD BR rats received dietary doses of 0, 1, 30, or 300/150 ppm ethoprop (95.3%). Doses were equivalent to 0, 0.08, 2.3, and 24/13 mg/kg/day. The high dose of 300 ppm was reduced to 150 ppm due to excess mortality in the F1a litter. Systemic **parental toxicity** at 150 ppm was limited to body weight decrements; at 300 ppm there were also tremors and loose stools. The **parental NOEL for systemic toxicity** is 30 ppm (2.3 mg/kg/day) and the parental **LOEL** for systemic toxicity is 150 ppm (13 mg/kg/day). Cholinesterase activity was determined in adults at termination. The **NOEL values for parental plasma and brain cholinesterase inhibition** were 1 ppm (0.08 mg/kg/day); **LOEL** values for plasma and brain were 30 ppm (2.3 mg/kg/day). The **NOEL for red blood cell cholinesterase inhibition** was $\geq$ 13 mg/kg/day, the highest dose tested. **Offspring toxicity** in both generations included pup body weight decrements after gestation day 4 at 150 ppm (13 mg/kg/day) and 300 ppm (24 mg/kg/day). The high dose of 300 ppm was reduced to 150 ppm after 19 weeks due to increased pup mortality in the 300 ppm group between days 21 and 28 postpartum. Although increased pup mortality occurred at a dietary concentration which only caused clinical signs of toxicity in parents, this was not an indication of increased sensitivity because the pups were receiving a greater dosage of ethoprop than parents: during the period of mortality between days 21 and 28 post partum young rats consume approximately twice the diet per unit body weight as an adult rat consumes, and during that time period the pups were receiving lactational as well as dietary exposure (Hazard ID document dated 11/10/97.) No reproductive toxicity was noted. The **NOEL for offspring toxicity** was 30 ppm and the **LOEL** for offspring toxicity was 150 ppm (13 mg/kg/day). This study is **acceptable**.

9. MUTAGENICITY STUDIES. Both the pre-1991 and the current mutagenicity initial testing battery guidelines are satisfied. No additional studies are required at this time. Ethoprop is an *in vitro* clastogen with metabolic activation required for genotoxicity. Due to severe toxicity, it could not be determined whether ethoprop is an *in vivo* clastogen. Additional mutagenicity testing is not required

due to the limitations posed by toxicity. Results are in Table 3.

TABLE 3. ACCEPTABLE MUTAGENICITY STUDIES

MUTA STUDY	RESULTS
<u>Salmonella typhimurium</u> reverse gene mutation assay (MRID 00160180)	NEGATIVE
Chinese hamster ovary (CHO) cell HGPRT gene mutation assay (MRID 00160181)	NEGATIVE
Mouse lymphoma L5178Y forward gene mutation assay (MRID 44065001)	NEGATIVE
<u>In vitro</u> CHO cell chromosome aberration assay (MRID 00160183)	POSITIVE only with S9 activation.
<u>In vivo</u> bone marrow cytogenetic assay (MRID 41211202)	NEGATIVE in SD rats. No apparent interaction with target tissue; severe toxicity at highest dose.
Rat dominant lethal assay (MRID 40386901)	NEGATIVE in SD rats. No apparent interaction with target tissue; severe toxicity at highest dose.
<u>In vitro</u> unscheduled DNA synthesis in primary rat hepatocytes (MRID 00160182)	NEGATIVE
<u>In vitro</u> unscheduled DNA synthesis in primary rat hepatocytes (MRID 44038702)	NEGATIVE
<u>In vitro</u> CHO cell sister chromatid exchange assay (MRID 00160184)	POSITIVE only with S9 activation.

10. DERMAL ABSORPTION. No *in vivo* dermal absorption study with ethoprop is available. For purposes of risk assessment, 100% dermal absorption will be assumed.

11. METABOLISM. The database for metabolism testing is complete; no additional studies are required at this time. Conclusions of the Health Effects Division Metabolism Assessment Review Committee (1/27/98) are in the next section of this chapter.

85-1 METABOLISM STUDY IN RATS (1990, MRID 41804301): In a metabolism study, ethoprop was administered to CrI:CD(SD)BR rats as a single IV bolus (males and females); single oral bolus (females, metabolism and pharmacokinetic studies; males, metabolism only); or by multiple oral doses. Following oral administration, ethoprop was completely absorbed and completely metabolized. Excretion was by urinary ($\geq 50\%$ administered dose), fecal (7-16%), and respiratory (11-19%) routes and was essentially complete by 48 hours. Terminal elimination $t_{1/2}$ in blood was 92-135 hours. Metabolism was by dealkylation of one or both S-propyl groups, followed by hydroxylation and probably conjugation. Two urinary metabolites were identified by HPLC while 3

others were believed to be possible conjugates of those metabolites. The TLC profiles of fecal metabolites were similar to the profiles for urinary metabolites. This study is **acceptable**.

12. METABOLISM COMMITTEE CONCLUSIONS. The Health Effects Division Metabolism Assessment Review Committee met on January 27, 1998 to determine residues of concern for risk assessment purposes.

Interim results from an acute study (MRID 44472501, Covance 6224-246) with ethoprop and metabolites were reviewed by the HED Metabolism Committee. Although cholinesterase determinations for the M1 metabolite of ethoprop were not yet completed, the Metabolism Committee was able to determine residues of concern based upon interim toxicity testing results. (See Acute Toxicity section of this chapter.) Compounds evaluated by the Metabolism Committee were:

SME (O-ethyl-S-methyl-S-propylphosphorodithioate)
OME (O-ethyl-O-methyl-S-propylphosphorothioate)
M1 (O-ethyl-S-propylphosphorothioate)
S,S-dipropylphosphorodithioate

The Metabolism Committee's conclusions were:

For acute and chronic dietary non-cancer risk assessments, the residues of concern in crops are ethoprop, SME, and OME.

For water non-cancer risk assessments, the residues of concern are also ethoprop, SME, and OME.

For cancer risk assessments, the residues of concern in crops are ethoprop, SME, OME, and M1.

For cancer risk assessments, the residues of concern in water are ethoprop, SME, OME, M1, and S,S-dipropylphosphorodithioate.

B. DOSE RESPONSE ASSESSMENT. An RfD value for ethoprop was selected by the HED Reference Dose Peer Review Committee on 5/9/96. Endpoints for acute dietary exposure and occupational/residential exposure (short-, intermediate-, and long-term exposure by dermal or inhalation routes) were selected by the HED Toxicology Endpoint Selection Committee on 5/21/96. The HED Hazard Identification Assessment Review Committee evaluated the reproductive, developmental, and neurotoxicity data for ethoprop to address the sensitivity of infants and children on 11/4/97.

1. SENSITIVITY OF INFANTS AND CHILDREN. The Hazard Identification

Committee (11/4/97) evaluated the toxicology data base of Ethoprop with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Ethoprop as required by the Food Quality Protecting Act (FQPA) of 1996.

a. 10X Factor for Protection of Infants and Children. For acute and chronic dietary risk assessments, the HED Hazard ID Committee determined that the **10x factor** to account for enhanced sensitivity of infants and children **(as required by FQPA) should be removed because a Margin of Exposure of 100 is adequate** to ensure protection of this population from acute dietary exposure to Ethoprop.

The Committee based its decision upon the following reasons: (a) No increased sensitivity of fetuses as compared to maternal animals following *in utero* exposure in developmental toxicity studies. (b) No increased sensitivity of pups as compared to adults in a multigeneration reproduction study. © There are no data gaps. (See the Hazard Identification Assessment Review Committee Report, dated 11/10/97.)

b. Developmental Neurotoxicity. Based upon a weight-of-the-evidence consideration of the data base, the HED Hazard ID Committee determined that a **developmental neurotoxicity study** in rats is **not required**. There were sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Ethoprop including acceptable developmental toxicity studies in rats and rabbits as well as a 2-generation reproduction study in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hen or rats.

2. REFERENCE DOSE (RfD). Using a weight-of-the evidence approach, the HED RfD Committee (5/9/96) assigned an **RfD of 0.0001 mg/kg/day** from a **NOEL of 0.01 mg/kg/day** in the combined chronic and 5-month toxicity studies in dogs (MRID 00160179 and 41498601); the LOEL was 0.025 mg/kg/day based on plasma cholinesterase inhibition. An **uncertainty factor of 100** was applied to account for inter-species extrapolation and intra-species variability.

The HED Hazard ID Committee (11/4/97) determined that the **10x factor** to account for enhanced sensitivity of infants and children **(as required by FQPA) should be removed. An uncertainty factor of 100 is adequate** to ensure protection of this population from chronic exposure to Ethoprop (See section on 10X Factor for protection of infants and children, above).

The NOEL used for the RfD was also supported by a rat chronic toxicity study

(MRID 42530201) in which brain and red blood cell cholinesterase activities were inhibited at dose levels comparable to those causing plasma cholinesterase inhibition in dogs. In this rat study, the NOELs for plasma, red blood cell, and brain cholinesterase inhibition were 0.04 mg/kg/day with a LOEL of 2.44 and 3.56 mg/kg/day.

The FAO/WHO Joint Committee Meeting on Pesticide Residues assigned an acceptable daily intake of 0.0003 mg/kg/day for ethoprop in 1987.

3. OTHER TOXICOLOGICAL ENDPOINTS.

TABLE 4. TOXICOLOGICAL ENDPOINTS

EXPOSURE SCENARIO	NOEL (mg/kg/day)	ENDPOINT	STUDY MRID #	SAFETY FACTOR
ACUTE DIETARY	0.025	Plasma ChE Inhibition	Subchronic Dog . 00075240	100
SHORT-TERM DERMAL	0.1	Plasma, RBC, Brain ChE inhibition	21-day Rabbit 41304404	100
INTERMEDIATE-TERM DERMAL	0.1	Plasma, RBC, Brain ChE inhibition	21-day Rabbit 41304404	100
CHRONIC DERMAL	0.1	Plasma, RBC, Brain ChE inhibition	21-day Rabbit 41304404	100

7. INHALATION EXPOSURE (any time period). Except for an acute inhalation study ($LC_{50} = 0.123$ mg/L; Tox. Cat. II), no other inhalation studies with technical material are available. Therefore, for this risk assessment, the inhalation and dermal components should be added together in the calculation of the mixer/loader/applicator estimate of exposure. The per cent absorption should be 100% for inhalation (default value).

8. CARCINOGENIC CLASSIFICATION: The HED Cancer Assessment Peer Review Committee (10/2/97 document) classified ethoprop as a "**likely**" human carcinogen based on the following factors:

- (a) presence of a rare and life-threatening (malignant) tumor (pheochromocytoma of the adrenal glands) in male Sprague-Dawley rats at the low dose in the absence of cholinesterase inhibition;
- (b) occurrence of another type of tumor (C-cell carcinomas of the thyroid glands) in male rats in two strains (Sprague-Dawley and Fischer 344) in three different studies at doses that did cause cholinesterase inhibition;
- and

(c) evidence of clastogenicity *in vitro* mutagenicity testing.

The Committee recommended a linear low-dose approach for human risk characterization and extrapolation of risk should be based on the occurrence of malignant pheochromocytomas of the adrenal glands in male rats at all dose levels tested. This extrapolation is supported by: (i) lack of mode of action, (ii) evidence from the total data base [i.e., occurrence of other tumor types (C-cell carcinomas of the thyroid glands) at doses that caused cholinesterase inhibition], and (iii) confirmation of clastogenic activity in mutagenicity testing.

The Q_1^* for ethoprop, in the absence of a complete tumor count in low- and mid-dose groups, is calculated to be 2.81×10^{-2} mg/kg/day (Hugh M. Pettigrew memo, 1/15/98).

The HED Cancer Assessment Peer Review Committee reconvened on 4/1/98 to re-assess the carcinogenicity of ethoprop. The registrant submitted new historical control data on adrenal pheochromocytomas in rats and also argued against the carcinogenic classification of ethoprop, principally because of low survival in controls and a new statistical analysis of the critical study. The Committee concluded that the carcinogenic classification of ethoprop should not be changed because the carcinogenicity could not be fully evaluated until all adrenals in the 1992 rat study (MRID 42530201) had been examined. (The report for this meeting is still in progress at the time of writing the toxicological chapter.)

SignOff Date: 4/21/1998
DP Barcode: D239400
HED DOC Number: 012589
Toxicology Branch: RRB1

Attachment 3: Addendum to Toxicology Chapter

ADDENDUM MEMORANDUM

SUBJECT: ETHOPROP. ADDENDUM TO TOXICOLOGY CHAPTER. Selection of Inhalation Endpoints. Assessment by the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee.

DP Barcode: D248784 Submission: None.
PC Code: 041101 Tox Chem No: 434C

TO: Kathryn Boyle (7508W)
Special Review and Reregistration Division

FROM: Kit Farwell, D.V.M.
Reregistration Branch 1
Health Effects Division (7509C)

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

Ethoprop was evaluated by the Hazard Identification Assessment Review Committee (HIARC) and by the FQPA Safety Factor Committee as part of a comprehensive review of 40 organophosphates. This memo summarizes the committees' conclusions for ethoprop as reported in Hazard Assessment of the Organophosphates (Jess Rowland, 7/7/98) and FQPA Safety Factor Recommendations for the Organophosphates (Brenda Tarplee and Jess Rowland, 8/6/98).

The HIARC and the FQPA Safety Factor Committee recommended that: (1) The 10-fold safety factor mandated by the Food Quality Protection Act of 1996 for the protection of infants and children should be **removed** for ethoprop. (2) A developmental neurotoxicity study is **not** required for ethoprop. (3) A confirmatory neurotoxic esterase study is still required for ethoprop, but is not considered a major data gap. See the above mentioned memos for more details.

The HIARC also selected an endpoint for inhalation exposure as a selection had not previously been made by the Toxicity Endpoint Selection Committee (5/21/96). The oral equivalent for use in short term inhalation exposure is 0.025 mg/kg/day based on plasma cholinesterase inhibition on day 2 of the 90-day dog feeding study. The oral equivalent for use in intermediate and long term inhalation exposure is 0.01 mg/kg/day based on plasma cholinesterase inhibition from the combined 5 month and 1 year dog feeding studies. **The following 2 tables replace the corresponding Table 4 on page 19 of the Toxicology Chapter for Ethoprop (4/21/98, doc 012589):**

TABLE 4a. Toxicological Endpoints: Dietary Exposure

EXPOSURE SCENARIO	NOEL mg/kg/day	ENDPOINT	STUDY MRID #	SAFETY FACTOR
ACUTE RfD = 0.00025 mg/kg/day	0.025	Plasma ChE Inhibition	90-day Dog 00075240	100
CHRONIC RfD = 0.0001 mg/kg/day	0.01	Plasma ChE Inhibition	Combined 5-month/Chronic Dog 41498601, 00160179	100

TABLE 4b. Toxicological Endpoints: Residential or Occupational Exposure

EXPOSURE SCENARIO	NOEL mg/kg/day	ENDPOINT	STUDY MRID #	SAFETY FACTOR
SHORT-TERM DERMAL	0.1	Plasma, RBC, Brain ChE inhibition	21-day Dermal Rabbit 41304404	100
SHORT-TERM INHALATION	0.025	Plasma ChE Inhibition	90-day Dog 00075240	100
INTERMEDIATE-TERM DERMAL	0.1	Plasma, RBC, Brain ChE inhibition	21-day Dermal Rabbit 41304404	100
INTERMEDIATE-TERM INHALATION	0.01	Plasma ChE Inhibition	Combined 5-month/Chronic Dog 41498601, 00160179	100
CHRONIC DERMAL	0.1	Plasma, RBC, Brain ChE inhibition	21-day Dermal Rabbit 41304404	100
CHRONIC INHALATION	0.01	Plasma ChE Inhibition	Combined 5-month/Chronic Dog 41498601, 00160179	100

cc: Jeff Dawson, RRB1; Susan Hanley, RRB1; Kit Farwell RRB1; Caswell File KFarwell:RRB1:CM2:823H:7509C:305-6373; WPhang:Senior Scientist:RRB1

**Attachment 4: Response to the USDA
Comments to EPA's Monte Carlo Dietary
Exposure Estimate for Ethoprop and
Using Further Refinements**

MEMORANDUM

DATE: July 12, 1999

SUBJECT: Ethoprop (041101). Reregistration Case No 0106.
Response to the USDA Comments to EPA's Monte Carlo Acute
Dietary Exposure Estimate for Ethoprop and Using Further
Refinements.
MRID None. DP Barcode D257533.

FROM: Sheila Piper, Chemist
Chemistry & Exposure Branch 1
Health Effects Division (7509C)

THROUGH: Francis B. Suhre, Branch Senior Scientist
Chemistry & Exposure Branch 1
Health Effects Division (7509C)

TO: Kathryn Boyle, Chemical Review Manager
Reregistration Branch 3
Special Review and Registration Division (7508C)

and

Kit Farwell, Risk Assessor
Reregistration Branch 1
Health Effects Division (7509C)

In response to comments received by USDA, EPA revised the ethoprop acute dietary Monte Carlo assessment (S.Piper, D254325, 3/24/99). In this memorandum, HED provides a brief chronology of relevant data submissions and Agency decisions; results of DEEM analyses designed to determine which crop/residue combinations significantly affect exposure; and results of refined risk assessments which adjust non-detected residue values based on exaggerated application rates from field trials for potato, corn, pineapple and sugarcane, and the assumption that samples found that contain no measureable residue contain $\frac{1}{2}$ the LOD for that portion of the crop that is treated and zero for that portion of the crop that is not treated.

Background Information

Ethoprop (O-ethyl-S,S-dipropylphosphorodithioate)

Metabolite II: O-ethyl-S-methyl-S-propylphosphorodithioate (SME)

Metabolite III: O-ethyl-O-methyl-S-propylphosphorothioate (OME)

Metabolite IV: O-ethyl-S-propylphosphorothioate (M1)

- 6/83 Ethoprop is subject to a Registration Standard (Guidance Document).
- 10/20/87 Final Registration Standard and Tolerance Reassessment (FRSTR) based on studies for *parent only*. Also tolerances are established for *parent only* in the 40 CFR 180.262 (a) and (b) on plants. No tolerances are established for ethoprop residues in livestock commodities.
- 6/3/92 Reviews (C.Olinger; CBRS Nos. 7407, 7795, and 7933; 1/24/92) of plant metabolism studies submitted in response to the Guidance Document showed that the Metabolite M1 (O-ethyl-S-propylphosphorothioate) accounted for 2.5% for the total radioactive residues (TRR) in leafy cabbage, 1.5% of the TRR in potato vines, and 2.3% of the TRR in corn forage.
- 2/9/93 Rhone-Poulenc requested an extension of time to repeat crop field trials for ethoprop in 1993 due to the fact that the samples obtained in 1990 have been stored for two years and many of them were moldy. The registrant submitted a protocol for magnitude of the residue studies in plants which would analyzed parent and metabolite, M1 (R.Perfetti, D186110, 2/9/93).
- 10/1/96 Plant metabolism data on primary crops corn, potatoes, and cabbage, and on rotational crops radish, spinach, and wheat were evaluated (J.Abbotts, Issues to be Presented at the 10/7/96 meeting of the HED Metabolism Committee, 10/1/96) and are summarized below:

Ethoprop metabolites in CORN	Forage:		Fodder:		Grain:	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Ethoprop	7.8	0.17	0.5	0.01		
II. O-Ethyl-S-methyl-S-propylphosphorodithioate	0.3	0.01	1.1	0.02		
III. O-Ethyl-O-methyl-S-propylphosphorothioate	0.8	0.02	1.8	0.03		
IV. O-Ethyl-S-propylphosphorothioate	2.3	0.05	0.8	0.01		
Total, ppm		0.25		0.07		NC
Blank spaces indicate residues not detected. NC= ratio not calculated because residues of parent not detectable.						

Ethoprop metabolites in POTATO and CABBAGE	Potato tuber:		Cabbage leaves:		Cabbage heads:	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Ethoprop			4.0	0.62	0.8	0.02
II. O-Ethyl-S-methyl-S-propylphosphorodithioate			0.6	0.09	0.4	0.01
III. O-Ethyl-O-methyl-S-propylphosphorothioate			1.7	0.26	1.7	0.05
IV. O-Ethyl-S-propylphosphorothioate			2.5	0.39	0.3	0.01
Total, ppm	NC			1.36		0.09
Blank spaces indicate residues not detected. NC= ratio not calculated because residues of parent not detectable						

Metabolite: Residues of concern in RADISH ROOTS	31-DAT ^a		123-DAT		365-DAT	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
I. Ethoprop	7.6	0.33	5.1	0.07	--	--
II. O-Ethyl-S-methyl-S-propylphosphorodithioate	0.3	0.01	--	--	--	--
III. O-Ethyl-O-methyl-S-propylphosphorothioate	0.2	0.01	--	--	--	--
IV. O-Ethyl-S-propylphosphorothioate	21.0	0.91	--	--	--	--
Total, ppm		1.26		0.07		NC
^a Data are from a composite sample of radish tops and roots. Blank spaces indicate residues not detected. DAT= days after treatment for planting NC= ratio not calculated because residues of parent not detectable.						

Metabolite: Residues of concern in SPINACH	31-DAT		123-DAT		365-DAT	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
I. Ethoprop	0.4	0.08	--	--	--	--
II. O-Ethyl-S-methyl-S-propylphosphorodithioate	1.8	0.34	--	--	--	--
III. O-Ethyl-O-methyl-S-propylphosphorothioate	--	--	--	--	--	--
IV. O-Ethyl-S-propylphosphorothioate	--	--	--	--	--	--
Total, ppm		0.42		--		--
DAT=days after treatment for planting. NC= ratio not calculated because residues of parent not detectable.						

Metabolite: Residues of concern in WHEAT	31-DAT		123-DAT		365-DAT	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Wheat forage						
I. Ethoprop	6.5	1.82	4.9	0.25	--	--
II. O-Ethyl-S-methyl-S-propylphosphorodithioate	0.8	0.22	--	--	--	--
III. O-Ethyl-O-methyl-S-propylphosphorothioate	0.3	0.08	--	--	--	--
IV. O-Ethyl-S-propylphosphorothioate	--	--	10.5	0.53	5.4	0.03
Total, ppm		2.12		0.78		0.03
Wheat straw						
I. Ethoprop	1.3	0.62	0.3	0.13	--	--
II. O-Ethyl-S-methyl-S-propylphosphorodithioate	--	--	0.05	0.02	--	--
III. O-Ethyl-O-methyl-S-propylphosphorothioate	0.6	0.27	0.4	0.16	--	--
IV. O-Ethyl-S-propylphosphorothioate	--	--	0.2	0.09	--	--
Total, ppm		0.89		0.40		--
Wheat grain						
I. Ethoprop	--	--	--	--	--	--
II. O-Ethyl-S-methyl-S-propylphosphorodithioate	--	--	--	--	--	--
III. O-Ethyl-O-methyl-S-propylphosphorothioate	--	--	--	--	--	--
IV. O-Ethyl-S-propylphosphorothioate	--	--	0.7	0.04	--	--
Total, ppm		--		0.04		--
DAT=days after treatment for planting. NC= ratio not calculated because residues of parent not detectable						

- 10/29/96 HED Metabolism Committee concluded that residues of concern in primary and rotational crops are parent (ethoprop) and Metabolites, SME, OME and M1 (J.Abbotts, Decisions of the HED Metabolism Committee, Residues to be Regulated in Primary and Rotational Crops, 10/29/96).
- 12/4/96 Following a meeting with the registrant, Rhone-Poulenc, regarding residue chemistry data, the Agency concluded that new crop field trials and processing studies would not be required. However, for any field or processing studies initiated after 12/3/96, data would required all residues of concern to be analyzed.
- 6/25/97 Health Effects Division's Cancer Assessment Review Committee (CARC) evaluated 8/20/97 the carcinogenic potential of Ethoprop and in accordance with the *1996 Draft Guidelines for Carcinogen Risk Assessment* the Committee classified Ethoprop as a "likely" human carcinogen.
- 2/6/98 HED Metabolism Committee found that for acute and chronic non-cancer dietary risk, the residues of concern in crops are parent, SME and OME; for cancer dietary risk, the residue of concern are parent, SME, OME, and M1.
- 4/23/98 Anticipated residues for acute and chronic non-cancer dietary exposure assessment (S.Piper, D245022) were presented to ChemSac. Conclusion made by ChemSac: HED should conduct dietary exposure assessment using the available data on parent and M1; and estimate total exposure by making conservative assumptions regarding the levels of metabolites SME and OME using data from the metabolism studies.
- 6/19/98 Rhone-Poulenc submitted a probabilistic (Monte Carlo) dietary risk assessment for ethoprop and Metabolite, M1. To determine the total residue level in crops, from ethoprop metabolism studies, an average adjustment factor (2.8) was applied to the parent residue observed in field trials and no adjustment factor was used to adjust residues for those field trials for which the parent residue was reported as below the LOQ. Rhone-Poulenc cited the 99.9th percentile of the output distribution which showed acceptable MOE's (>100) for all subgroups. The registrant used reference dose of 0.025 mg/kg/day.
- 9/17/98 IR-4 request that HED reassess the acute dietary risk from existing uses of ethoprop and Metabolite, M1. In support of this request, Rhone-Poulenc submitted a probabilistic (Monte Carlo) dietary risk assessment for ethoprop. No adjustment factor was used to account for metabolites of concern for estimating an acute dietary risk. Rhone-Poulenc cited the 99th percentile of the output distribution which showed acceptable MOE's

(>100) for all subgroups. The reference dose used was 0.025 mg/kg/day. HED policy calls for using the 99.9th percentile exposure level which showed unacceptable MOEs (<100) for infants and children (1-6yrs).

- 10/25/98 Rhone-Poulenc sent in their rebuttal in response to deficiencies cited in S.Piper's memos, D245022 and D245574). HED agreed with Rhone-Poulenc in using *parent only* field trial data and Metabolite, M1 will not be used for calculating non-cancer acute dietary analyses.
- 12/1/98 Rhone-Poulenc met with HED to discussed ethoprop acute dietary risk assessment. They proposed: to used ratios calculated from metabolism studies where all metabolites are detected; to apply the adjustment factor to similar crops; not to apply an adjustment factor when no detectable residues of any metabolites are observed; and in absence of similar crop data, assume 3 times half LOQ/LOD value.
- 12/15/98 Following the 12/1/98 meeting with Rhone Poulenc, CEB1 asked ChemSac to consider the issue of which adjustment factors would be most appropriate. ChemSac concluded: use the metabolism study for the specific crop if available; for surrogate crops use the highest adjustment factor (6.0x) for non-blended corps and average (2.8x) for blended commodities. To account for all metabolites of concern for non-cancer risk identified by the HED Metabolism Committee (parent + Metabolites SME + OME), data from ethoprop metabolism and crop rotation studies were used to derive residue adjustment factors by dividing residues (parent + Metabolite SME + OME) by residues of (parent only). Adjustment factors ranged from 1.06x to 6.0x with the average being 2.8x (See data from tables on 10/29/96).
- Corn Forage= $0.20/0.17 = 1.18x$
 - Corn Fodder= $0.06/0.01 = 6.0x$
 - Cabbage Leaves= $0.97/0.62 = 1.56x$
 - Cabbage Heads= $0.08/0.02 = 4.0x$
 - Radish Roots= $0.35/0.33 = 1.06x$
 - Spinach= $0.42/0.08 = 5.25x$
 - Wheat forage= $2.12/1.82 = 1.16x$; $0.25/0.25 = 1.0x$; $\times = 1.08x$
 - Wheat straw= $0.89/0.62 = 1.44x$; $0.31/0.13 = 2.38x$; $\times = 1.91x$
- 2/10/99 At the request of SRRD, HED conducted an acute Monte Carlo analysis using 3/24/99 ChemSac's recommended modification to Rhone-Poulenc's protocol. The resulting ethoprop acute dietary risk exposure and risk estimates were above HED's level of concern for all subpopulations at the 99.9th percentile. The reference dose (RfD) of 0.00025 mg/kg/day, was derived from a NOAEL of 0.025 mg/kg bw/day. The uncertainty factors of 100 included a 10x for intra-species and 10 x for inter-species variation. The acute Population Adjusted Dose (aPAD) is 0.00025 mg/kg/day and is

equivalent to the acute RfD.

Presently HED has conducted numerous DEEM analyses for ethoprop to determine which assumptions and crop residues are driving the estimated risk. Refinements to the acute dietary risk were performed using multiple data sources and adjusting non-detected residue values based on exaggerated application rates from field trials for potato, corn, pineapple and sugarcane, and the assumption that samples found that contain no measureable residue contain $\frac{1}{2}$ the LOD for that portion of the crop that is treated and zero for that portion of the crop that is not treated.

Available Residue Data Sources

- I. PDP Monitoring Data (1994 only reflects commodities registered for ethoprop under 40 CFR 180.262).

Bananas= 71 samples all non-detects.

Sweet Corn= 34 samples all non-detects.

Green Beans= 57 samples all non-detects.

Potato= 36 samples all non-detects.

(HED's current policy requires at least 100 samples per commodity to use monitoring data)

Comments: *Parent only *Limited number of samples *No detects * $\frac{1}{2}$ LOD=0.015 ppm.

- II. FDA Monitoring Data (1992-98).

Bananas= 964 samples all non-detects.

Cabbage= 440 samples all non-detects.

Cucumber= 407 samples all non-detects.

Green Beans= 684 samples all non-detects; 1 sample trace residue (assigned LOQ=0.05 ppm)

Potato= 1301 samples all non-detects.

Field Corn= 140 samples all non-detects.

Sweet Potato= 279 samples all non-detects.

Comments: *Parent only *Many samples * No detects * $\frac{1}{2}$ LOD=0.0075 ppm.

- III. Field trials data.

Bananas= 1 sample in Costa Rica at LOQ=0.01 ppm

Cabbage= 27 samples at LOQ=0.01 ppm

Corn (field)= 96 samples at LOQ=0.01 ppm

Corn (sweet)= 60 samples at LOQ=0.01 ppm

Cucumber=42 samples at LOQ=0.01ppm

Green Beans= 30 samples at (<0.01-0.134 ppm)

Lima Beans= 30 samples at (<0.01-0.012 ppm)

Lima Beans (dry)= tolerance=0.02 ppm

Peanuts (nutmeat)= 20 samples at (<0.01-0.11 ppm)

Pineapples= 1 sample at LOD= 0.002 ppm

Potato= 1 sample at LOQ=0.01 ppm

Sweet Potato= data from potato

Sugar Cane= 1 sample at LOQ=0.01 ppm

Comments: *Parent and Metabolite IV (used parent only) *Limited data set with actual residue; on beans and peanuts only *1/2 LOQ=0.005 ppm.

Risk Estimates Using Various Residue Data Sources and Assumptions

Scenario I. Estimated dietary risk utilizing:

- * FDA monitoring data for bananas, cabbage, cucumber, green beans, potato, field corn, and sweet potato.
- * Field trial data for sweet corn, lima beans, peanuts, pineapples, and sugar cane.
- * Non-detected assumed $\frac{1}{2}$ LOD=0.0075 ppm for monitoring data and $\frac{1}{2}$ LOD=0.0015 ppm for field trial data.
- * Incorporated % crop treated.
- * Adjustment factors 6.0=surrogate crops; 2.8=blended crops; 4.0=cabbage (cabbage metabolism study); and 1.1= potato (radish metabolism study) were used to compensate for metabolites of concern.

ACUTE RESIDUE INFORMATION: U.S. Environmental Protection Agency Ver. 6.78
 DEEM Acute analysis for ETHOPROP 1989-92 data
 Residue file name: C:\deem\ethoppr.R96 Adjust. #2 NOT used
 Analysis Date 06-29-1999 Residue file dated: 06-29-1999/12:02:49/8
 Reference dose (aRfD) = 0.00025 mg/kg bw/day
 Comment: Using monitoring data

RDF indices and file names for Monte Carlo Analysis

1 C:\deem\ethoprop\BANANA.rdf
 2 C:\deem\ethoprop\CABBAGE.rdf
 3 C:\deem\ethoprop\CUCUMBER.rdf
 4 C:\deem\ethoprop\GREENBEAN.rdf
 5 C:\deem\ethoprop\LIMABEAN.rdf
 6 C:\deem\ethoprop\POTATO.rdf
 7 C:\deem\ethoprop\SCORN.rdf
 8 C:\deem\ethoprop\SPOTATO.rdf
 9 C:\deem\ethoprop\PINEAPPLE.rdf
 10 C:\deem\ethoprop\FCORN.rdf
 11 C:\deem\ethoprop\BANANA2.rdf

Food Crop	Grp	Food Name	RESIDUE (ppm)	RDF #	Adj. FactorsCode #1 #2
72	O	Bananas	0.045000	1	1.000 1.000
73	O	Bananas-dried	0.021000	11	3.900 1.000
89	O	Pineapples-peeled fruit	0.001200	9	1.000 1.000
90	O	Pineapples-dried	0.000030	0	5.000 1.000
91	O	Pineapples-juice	0.000030	0	1.700 1.000
94	O	Plantains-ripe	0.045000	1	1.000 1.000
148	9B	Cucumbers	0.045000	3	1.000 1.000
170	5A	Cabbage-green and red	0.030000	2	1.000 1.000
207	1C	Potatoes/white-whole	0.008000	6	1.000 1.000
208	1C	Potatoes/white-unspecified	0.008000	6	1.000 1.000
209	1C	Potatoes/white-peeled	0.008000	6	1.000 1.000
210	1C	Potatoes/white-dry	0.008000	6	6.500 1.000
211	1C	Potatoes/white-peel only	0.008000	6	1.000 1.000
218	1CD	Sweet potatoes (incl yams)	0.008000	8	1.000 1.000
229	6C	Beans-dry-lima	0.000560	0	1.000 1.000
233	6B	Beans-succulent-lima	0.072000	5	1.000 1.000
234	6A	Beans-succulent-green	0.300000	4	1.000 1.000
238	15	Corn/sweet	0.030000	7	1.000 1.000
266	15	Corn grain-endosperm	0.000030	10	1.000 1.000
267	15	Corn grain-bran	0.000030	10	1.000 1.000
268	15	Corn grain/sugar/hfcs	0.000030	10	1.500 1.000
283	O	Sugar-cane	0.000800	0	1.000 1.000
284	O	Sugar-cane/molasses	0.000800	0	1.000 1.000
289	15	Corn grain-oil	0.021000	10	1.000 1.000
293	O	Peanuts-oil	0.000960	0	2.800 1.000
378	O	Bananas-juice	0.021000	0	1.000 1.000
383	5B	Cabbage-savoy	0.030000	2	1.000 1.000
388	15	Corn grain/sugar-molasses	0.000030	10	1.500 1.000
403	O	Peanuts-butter	0.000960	0	1.890 1.000
406	O	Pineapples-juice-concentrate	0.000030	0	6.300 1.000
418	2	Sweet potatos-leaves	0.008000	8	1.000 1.000
480	O	Plantains-green	0.045000	1	1.000 1.000
481	O	Plantains-dried	0.045000	1	3.900 1.000
940	O	Peanuts-hulled	0.000960	0	1.000 1.000

U.S. Environmental Protection Agency
 DEEM ACUTE analysis for ETHOPROP
 Residue file: ethoppr.R96
 Analysis Date: 06-29-1999/15:56:44 Residue file dated: 06-29-1999/12:02:49/8
 Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: Using monitoring data

Ver. 6.78

(1989-92 data)

Adjustment factor #2 NOT used.

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:						
	0.000018	7.01	0.000092	36.82	0.000313	125.26
All infants (<1 year):						
	0.000046	18.33	0.000549	219.58	0.000843	337.14
Nursing infants (<1 year):						
	0.000002	0.79	0.000166	66.25	0.000241	96.46
Non-nursing infants (<1 yr):						
	0.000058	23.21	0.000640	255.94	0.000886	354.51
Children (1-6 years):						
	0.000043	17.15	0.000275	109.84	0.000540	215.92
Children (7-12 years):						
	0.000026	10.29	0.000138	55.25	0.000286	114.37
Females (13+/preg/not nsg):						
	0.000014	5.52	0.000094	37.79	0.000160	64.15
Females (13+/nursing):						
	0.000027	10.86	0.000100	39.87	0.000131	52.24
Females (13-19 yrs/np/nn):						
	0.000011	4.55	0.000079	31.64	0.000150	59.83
Females (20+ years/np/nn):						
	0.000015	6.01	0.000084	33.41	0.000165	66.02
Females (13-50 years):						
	0.000012	4.64	0.000079	31.75	0.000159	63.69
Males (13-19 years):						
	0.000017	6.65	0.000088	35.11	0.000215	86.04
Males (20+ years):						
	0.000014	5.78	0.000068	27.34	0.000156	62.51

Scenario II. Estimated dietary risk assessment utilizing **field trial data** included:

- * Field trial data for all registered commodities; Tolerance for dry lima beans.
- * Studies conducted at exaggerated rates resulted in non-detectable residues of ethoprop: corn grain/oil (5x); pineapples (5x); potato (2.6x); and sugar cane (2.5x).
- * Non-detected assumed $\frac{1}{2}$ LOQ=0.005 ppm.
- * Incorporated % crop treated.
- * Adjustment factors 6.0=surrogate crops; 2.8=blended crops; 4.0=cabbage (cabbage metabolism study); and 1.1= potato (radish metabolism study) were used to compensate for metabolites of concern.

ACUTE RESIDUE INFORMATION: U.S. Environmental Protection Agency Ver. 6.78
 DEEM Acute analysis for ETHOPROP 1989-92 data
 Residue file name: C:\deem\ethopro.R96 Adjust. #2 NOT used
 Analysis Date 06-29-1999 Residue file dated: 06-29-1999/11:07:09/8
 Reference dose (aRfD) = 0.00025 mg/kg bw/day
 Comment: Using field trials 1/2 LOQ

RDF indices and file names for Monte Carlo Analysis

1 C:\deem\041101\ban91.rdf
 2 C:\deem\041101\cabb91.rdf
 3 C:\deem\041101\cuk91.rdf
 4 C:\deem\041101\lima91.rdf
 5 C:\deem\041101\gbear91.rdf
 6 C:\deem\041101\pot91.rdf
 7 C:\deem\041101\scorn91.rdf
 8 C:\deem\041101\spot91.rdf
 9 C:\deem\041101\pine91.rdf

Food	Crop	Grp	Food Name	RESIDUE (ppm)	RDF #	Adj. FactorsCode	
						#1	#2
72	O		Bananas	0.030000	1	1.000	1.000
73	O		Bananas-dried	0.002000	0	3.900	1.000
89	O		Pineapples-peeled fruit	0.001200	9	1.000	1.000
90	O		Pineapples-dried	0.000030	0	5.000	1.000
91	O		Pineapples-juice	0.000030	0	1.700	1.000
94	O		Plantains-ripe	0.030000	1	1.000	1.000
148	9B		Cucumbers	0.030000	3	1.000	1.000
170	5A		Cabbage-green and red	0.020000	2	1.000	1.000
207	1C		Potatoes/white-whole	0.002000	6	1.000	1.000
208	1C		Potatoes/white-unspecified	0.002000	6	1.000	1.000
209	1C		Potatoes/white-peeled	0.002000	6	1.000	1.000
210	1C		Potatoes/white-dry	0.000100	0	6.500	1.000
211	1C		Potatoes/white-peel only	0.002000	6	1.000	1.000
218	1CD		Sweet potatoes (incl yams)	0.002000	8	1.000	1.000
229	6C		Beans-dry-lima	0.000560	0	1.000	1.000
233	6B		Beans-succulent-lima	0.030000	4	1.000	1.000
234	6A		Beans-succulent-green	0.030000	5	1.000	1.000
238	15		Corn/sweet	0.030000	7	1.000	1.000
266	15		Corn grain-endosperm	0.000030	0	1.000	1.000
267	15		Corn grain-bran	0.000030	0	1.000	1.000
268	15		Corn grain/sugar/hfcs	0.000030	0	1.500	1.000
283	O		Sugar-cane	0.000800	0	1.000	1.000
284	O		Sugar-cane/molasses	0.000800	0	1.000	1.000
289	15		Corn grain-oil	0.000030	0	1.000	1.000
293	O		Peanuts-oil	0.000960	0	2.800	1.000
378	O		Bananas-juice	0.002000	0	1.000	1.000
383	5B		Cabbage-savoy	0.020000	2	1.000	1.000
388	15		Corn grain/sugar-molasses	0.000030	0	1.500	1.000
403	O		Peanuts-butter	0.000960	0	1.890	1.000
406	O		Pineapples-juice-concentrate	0.000030	0	6.300	1.000
418	2		Sweet potatoes-leaves	0.002000	8	1.000	1.000
480	O		Plantains-green	0.030000	1	1.000	1.000
481	O		Plantains-dried	0.030000	1	3.900	1.000
940	O		Peanuts-hulled	0.000960	0	1.000	1.000

ACUTE DEEM ANALYSIS: U.S. Environmental Protection Agency Ver. 6.78
 DEEM ACUTE analysis for ETHOPROP (1989-92 data)
 Residue file: ethopro.R96 Adjustment factor #2 NOT used.
 Analysis Date: 06-29-1999/13:02:54 Residue file dated: 06-29-1999/11:07:09/8
 Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: Using field trials 1/2 LOQ

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:	0.000005	2.09	0.000066	26.36	0.000246	98.59
All infants (<1 year):	0.000014	5.65	0.000381	152.57	0.000611	244.38
Nursing infants (<1 year):	0.000017	6.79	0.000018	7.35	0.000190	76.14
Non-nursing infants (<1 yr):	0.000018	7.27	0.000418	167.27	0.000606	242.53
Children (1-6 years):	0.000015	5.97	0.000202	80.70	0.000417	166.63
Children (7-12 years):	0.000006	2.43	0.000102	40.83	0.000222	88.99
Females (13+/preg/not nsg):	0.000003	1.26	0.000067	26.92	0.000111	44.54
Females (13+/nursing):	0.000009	3.41	0.000067	26.76	0.000108	43.28
Females (13-19 yrs/np/nn):	0.000003	1.01	0.000055	21.88	0.000135	53.92
Females (20+ years/np/nn):	0.000004	1.77	0.000058	23.38	0.000139	55.78
Females (13-50 years):	0.000003	1.26	0.000056	22.33	0.000135	53.83
Males (13-19 years):	0.000004	1.60	0.000060	23.82	0.000175	69.85
Males (20+ years):	0.000004	1.56	0.000049	19.52	0.000127	50.80

Further Refinements

Scenario III. Estimated dietary risk utilizing:

- * FDA monitoring data for cabbage, cucumber, potato, field corn, and sweet potato; *excluding banana/plantain and green beans.*
- * Field trial data for sweet corn, lima beans, peanuts, pineapples, and sugar cane.
- * Non-detected assumed $\frac{1}{2}$ LOD=0.0075 ppm for monitoring data and $\frac{1}{2}$ LOD=0.0015 ppm for field trial data.
- * Incorporated % crop treated.
- * Adjustment factors 6.0=surrogate crops; 2.8=blended crops; 4.0=cabbage (cabbage metabolism study); and 1.1 = potato (radish metabolism study) were used to compensate for metabolites of concern.

ACUTE RESIDUE INFORMATION: U.S. Environmental Protection Agency Ver. 6.78
 DEEM Acute analysis for ETHOPROP 1989-92 data
 Residue file name: C:\deem\ethppr3.R96 Adjust. #2 NOT used
 Analysis Date 07-09-1999 Residue file dated: 07-09-1999/10:05:36/8
 Reference dose (aRfD) = 0.00025 mg/kg bw/day
 Comment: Using monitoring data; excluding banana/plantain and green beans

 RDF indices and file names for Monte Carlo Analysis

- 1 C:\deem\ethoprop\BANANA.rdf
- 2 C:\deem\ethoprop\CABBAGE.rdf
- 3 C:\deem\ethoprop\CUCUMBER.rdf
- 4 C:\deem\ethoprop\GREENBEAN.rdf
- 5 C:\deem\041101\lima92.rdf
- 6 C:\deem\ethoprop\POTATO.rdf
- 7 C:\deem\041101\scorn92.rdf
- 8 C:\deem\ethoprop\SPOTATO.rdf
- 9 C:\deem\041101\pine92.rdf
- 10 C:\deem\ethoprop\FCORN.rdf
- 11 C:\deem\ethoprop\BANANA2.rdf

Food Crop		RESIDUE	RDF	Adj.FactorsCode
Grp	Food Name	(ppm)	#	#1 #2
89 O	Pineapples-peeled fruit	0.001200	9	1.000 1.000
90 O	Pineapples-dried	0.000040	0	5.000 1.000
91 O	Pineapples-juice	0.000040	0	1.700 1.000
148 9B	Cucumbers	0.045000	3	1.000 1.000
170 5A	Cabbage-green and red	0.030000	2	1.000 1.000
207 1C	Potatoes/white-whole	0.008000	6	1.000 1.000
208 1C	Potatoes/white-unspecified	0.008000	6	1.000 1.000
209 1C	Potatoes/white-peeled	0.008000	6	1.000 1.000
210 1C	Potatoes/white-dry	0.008000	6	6.500 1.000
211 1C	Potatoes/white-peel only	0.008000	6	1.000 1.000
218 1CD	Sweet potatoes (incl yams)	0.008000	8	1.000 1.000
229 6C	Beans-dry-lima	0.000560	0	1.000 1.000
233 6B	Beans-succulent-lima	0.009000	5	1.000 1.000
238 15	Corn/sweet	0.009000	7	1.000 1.000
266 15	Corn grain-endosperm	0.000030	10	1.000 1.000
267 15	Corn grain-bran	0.000030	10	1.000 1.000
268 15	Corn grain/sugar/hfcs	0.000030	10	1.500 1.000
283 O	Sugar-cane	0.000600	0	1.000 1.000
284 O	Sugar-cane/molasses	0.000600	0	1.000 1.000
289 15	Corn grain-oil	0.021000	10	1.000 1.000
293 O	Peanuts-oil	0.000800	0	2.800 1.000
383 5B	Cabbage-savoy	0.030000	2	1.000 1.000
388 15	Corn grain/sugar-molasses	0.000030	10	1.500 1.000
403 O	Peanuts-butter	0.000800	0	1.890 1.000
406 O	Pineapples-juice-concentrate	0.000040	0	6.300 1.000
418 2	Sweet potatoes-leaves	0.008000	8	1.000 1.000
940 O	Peanuts-hulled	0.000800	0	1.000 1.000

ACUTE DEEM ANALYSIS: U.S. Environmental Protection Agency Ver. 6.78
 DEEM ACUTE analysis for ETHOPROP (1989-92 data)
 Residue file: ethppr3.R96 Adjustment factor #2 NOT used.
 Analysis Date: 07-09-1999/11:13:04 Residue file dated: 07-09-1999/10:05:36/8
 Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: Using monitoring data; excluding banana/plantain and green beans
 =====

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:	0.000005	2.08	0.000029	11.47	0.000088	35.11
All infants (<1 year):	0.000003	1.12	0.000057	22.85	0.000184	73.61
Nursing infants (<1 year):	0.000001	0.37	0.000008	3.09	0.000056	22.43
Non-nursing infants (<1 yr):	0.000003	1.27	0.000084	33.70	0.000205	81.90
Children (1-6 years):	0.000011	4.25	0.000059	23.54	0.000147	58.95
Children (7-12 years):	0.000010	3.98	0.000043	17.03	0.000108	43.03
Females (13+/preg/not nsg):	0.000003	1.33	0.000020	8.17	0.000047	18.80
Females (13+/nursing):	0.000005	2.19	0.000027	10.68	0.000091	36.56
Females (13-19 yrs/np/nn):	0.000005	1.92	0.000027	10.78	0.000069	27.51
Females (20+ years/np/nn):	0.000003	1.31	0.000021	8.58	0.000061	24.22
Females (13-50 years):	0.000004	1.41	0.000023	9.13	0.000062	24.68
Males (13-19 years):	0.000008	3.08	0.000033	13.01	0.000082	32.66
Males (20+ years):	0.000005	1.93	0.000023	9.06	0.000058	23.05

Scenario IV. Estimated dietary risk assessment utilizing:

- * *Field trial data excluding bananas/plantains and green beans.*
- * Field trials conducted at exaggerated rates resulted in non-detects and residues were adjusted using: corn grain/oil (5x); pineapples (5x); potato (2.6x); and sugar cane (2.5x).
- * Non-detected assumed $\frac{1}{2}$ LOQ=0.005 ppm.
- * Incorporated % crop treated.
- * Adjustment factors 6.0=surrogate crops; 2.8=blended crops; 4.0=cabbage (cabbage metabolism study); and 1.1= potato (radish metabolism study) were used to compensate for metabolites of concern.

ACUTE RESIDUE INFORMATION: U.S. Environmental Protection Agency Ver. 6.78
 DEEM Acute analysis for ETHOPROP 1989-92 data
 Residue file name: C:\deem\bethop2.R96 Adjust. #2 NOT used
 Analysis Date 07-06-1999 Residue file dated: 07-06-1999/10:58:01/8
 Reference dose (aRfD) = 0.00025 mg/kg bw/day
 Comment: Excluding banana/plantain and green beans

RDF indices and file names for Monte Carlo Analysis

1 C:\deem\041101\ban91.rdf
 2 C:\deem\041101\cabb91.rdf
 3 C:\deem\041101\cuk91.rdf
 4 C:\deem\041101\lima91.rdf
 5 C:\deem\041101\gbean91.rdf
 6 C:\deem\041101\pot91.rdf
 7 C:\deem\041101\scorn91.rdf
 8 C:\deem\041101\spot91.rdf
 9 C:\deem\041101\pine91.rdf

Food	Crop	Grp	Food Name	RESIDUE (ppm)	RDF #	Adj. Factors	Code #1 #2
89	O		Pineapples-peeled fruit	0.001200	9	1.000	1.000
90	O		Pineapples-dried	0.000030	0	5.000	1.000
91	O		Pineapples-juice	0.000030	0	1.700	1.000
148	9B		Cucumbers	0.030000	3	1.000	1.000
170	5A		Cabbage-green and red	0.020000	2	1.000	1.000
207	1C		Potatoes/white-whole	0.002000	6	1.000	1.000
208	1C		Potatoes/white-unspecified	0.002000	6	1.000	1.000
209	1C		Potatoes/white-peeled	0.002000	6	1.000	1.000
210	1C		Potatoes/white-dry	0.000100	0	6.500	1.000
211	1C		Potatoes/white-peel only	0.002000	6	1.000	1.000
218	1CD		Sweet potatoes (incl yams)	0.002000	8	1.000	1.000
229	6C		Beans-dry-lima	0.000560	0	1.000	1.000
233	6B		Beans-succulent-lima	0.030000	4	1.000	1.000
238	15		Corn/sweet	0.030000	7	1.000	1.000
266	15		Corn grain-endosperm	0.000030	0	1.000	1.000
267	15		Corn grain-bran	0.000030	0	1.000	1.000
268	15		Corn grain/sugar/hfcs	0.000030	0	1.500	1.000
283	O		Sugar-cane	0.000800	0	1.000	1.000
284	O		Sugar-cane/molasses	0.000800	0	1.000	1.000
289	15		Corn grain-oil	0.000030	0	1.000	1.000
293	O		Peanuts-oil	0.000960	0	2.800	1.000
383	5B		Cabbage-savoy	0.020000	2	1.000	1.000
388	15		Corn grain/sugar-molasses	0.000030	0	1.500	1.000
403	O		Peanuts-butter	0.000960	0	1.890	1.000
406	O		Pineapples-juice-concentrate	0.000030	0	6.300	1.000
418	2		Sweet potatos-leaves	0.002000	8	1.000	1.000
940	O		Peanuts-hulled	0.000960	0	1.000	1.000

ACUTE DEEM ANALYSIS: U.S. Environmental Protection Agency Ver. 6.78
 DEEM ACUTE analysis for ETHOPROP (1989-92 data)
 Residue file: bethop2.R96 Adjustment factor #2 NOT used.
 Analysis Date: 07-06-1999/12:04:55 Residue file dated: 07-06-1999/10:58:01/8
 Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: Excluding banana/plantain and green beans
 =====

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:						
	0.000002	0.98	0.000020	8.20	0.000122	48.99
All infants (<1 year):						
	0.000003	1.19	0.000006	2.39	0.000061	24.57
Nursing infants (<1 year):						
	0.000001	0.42	0.000002	0.92	0.000009	3.49
Non-nursing infants (<1 yr):						
	0.000003	1.21	0.000010	4.06	0.000130	51.92
Children (1-6 years):						
	0.000005	2.05	0.000061	24.25	0.000234	93.67
Children (7-12 years):						
	0.000003	1.28	0.000050	20.07	0.000147	58.82
Females (13+/preg/not nsg):						
	0.000002	0.65	0.000022	8.96	0.000077	30.67
Females (13+/nursing):						
	0.000002	0.97	0.000030	12.01	0.000092	36.78
Females (13-19 yrs/np/nn):						
	0.000001	0.60	0.000010	4.17	0.000121	48.42
Females (20+ years/np/nn):						
	0.000001	0.54	0.000016	6.53	0.000083	33.28
Females (13-50 years):						
	0.000001	0.57	0.000016	6.23	0.000093	37.04
Males (13-19 years):						
	0.000003	1.03	0.000030	11.96	0.000103	41.00
Males (20+ years):						
	0.000002	0.61	0.000016	6.59	0.000080	32.05

Scenario V. Estimated dietary risk assessment utilizing:

- * Field trial data for all registered commodities; Tolerance for dry lima beans.
- * *Non-detected assumed $\frac{1}{2}$ LOD=0.0015 ppm.*
- * Incorporated % crop treated.
- * Adjustment factors 6.0=surrogate crops; 2.8=blended crops; 4.0=cabbage (cabbage metabolism study); and 1.1 = potato (radish metabolism study) were used to compensate for metabolites of concern.

ACUTE RESIDUE INFORMATION: U.S. Environmental Protection Agency Ver. 6.78
 DEEM Acute analysis for ETHOPROP 1989-92 data
 Residue file name: C:\deem\etholod.R96 Adjust. #2 NOT used
 Analysis Date 06-30-1999 Residue file dated: 06-30-1999/14:31:45/8
 Reference dose (aRfD) = 0.00025 mg/kg bw/day
 Comment: Using field trials 1/2 LOD

 RDF indices and file names for Monte Carlo Analysis

1 C:\deem\041101\ban92.rdf
 2 C:\deem\041101\cabb92.rdf
 3 C:\deem\041101\cuk92.rdf
 4 C:\deem\041101\lima92.rdf
 5 C:\deem\041101\gbean92.rdf
 6 C:\deem\041101\pot92.rdf
 7 C:\deem\041101\scorn92.rdf
 8 C:\deem\041101\spot92.rdf
 9 C:\deem\041101\pine92.rdf

Food	Crop	Food Name	RESIDUE (ppm)	RDF #	Adj. Factors	Code
Grp					#1	#2
72	O	Bananas	0.009000	1	1.000	1.000
73	O	Bananas-dried	0.000700	0	3.900	1.000
89	O	Pineapples-peeled fruit	0.001800	9	1.000	1.000
90	O	Pineapples-dried	0.000040	0	5.000	1.000
91	O	Pineapples-juice	0.000040	0	1.700	1.000
94	O	Plantains-ripe	0.009000	1	1.000	1.000
148	9B	Cucumbers	0.009000	3	1.000	1.000
170	5A	Cabbage-green and red	0.006000	2	1.000	1.000
207	1C	Potatoes/white-whole	0.001700	6	1.000	1.000
208	1C	Potatoes/white-unspecified	0.001700	6	1.000	1.000
209	1C	Potatoes/white-peeled	0.001700	6	1.000	1.000
210	1C	Potatoes/white-dry	0.000080	0	6.500	1.000
211	1C	Potatoes/white-peel only	0.001700	6	1.000	1.000
218	1CD	Sweet potatoes (incl yams)	0.001700	8	1.000	1.000
229	6C	Beans-dry-lima	0.000560	0	1.000	1.000
233	6B	Beans-succulent-lima	0.009000	4	1.000	1.000
234	6A	Beans-succulent-green	0.030000	5	1.000	1.000
238	15	Corn/sweet	0.009000	7	1.000	1.000
266	15	Corn grain-endosperm	0.000040	0	1.000	1.000
267	15	Corn grain-bran	0.000040	0	1.000	1.000
268	15	Corn grain/sugar/hfcs	0.000040	0	1.500	1.000
283	O	Sugar-cane	0.000600	0	1.000	1.000
284	O	Sugar-cane/molasses	0.000600	0	1.000	1.000
289	15	Corn grain-oil	0.000040	0	1.000	1.000
293	O	Peanuts-oil	0.000800	0	2.800	1.000
378	O	Bananas-juice	0.000700	0	1.000	1.000
383	5B	Cabbage-savoy	0.006000	2	1.000	1.000
388	15	Corn grain/sugar-molasses	0.000040	0	1.500	1.000
403	O	Peanuts-butter	0.000800	0	1.890	1.000
406	O	Pineapples-juice-concentrate	0.000040	0	6.300	1.000
418	2	Sweet potatos-leaves	0.001700	8	1.000	1.000
480	O	Plantains-green	0.009000	1	1.000	1.000
481	O	Plantains-dried	0.009000	1	3.900	1.000
940	O	Peanuts-hulled	0.000800	0	1.000	1.000

ACUTE DEEM ANALYSIS: U.S. Environmental Protection Agency Ver. 6.78
 DEEM ACUTE analysis for ETHOPROP (1989-92 data)
 Residue file: etholod.R96 Adjustment factor #2 NOT used.
 Analysis Date: 06-30-1999/16:24:39 Residue file dated: 06-30-1999/14:31:45/8
 Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: Using field trials 1/2 LOD

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:						
	0.000004	1.45	0.000021	8.24	0.000096	38.51
All infants (<1 year):						
	0.000006	2.22	0.000118	47.37	0.000188	75.37
Nursing infants (<1 year):						
	0.000006	2.40	0.000008	3.05	0.000058	23.27
Non-nursing infants (<1 yr):						
	0.000008	3.06	0.000129	51.48	0.000200	80.10
Children (1-6 years):						
	0.000009	3.44	0.000061	24.59	0.000168	67.17
Children (7-12 years):						
	0.000004	1.68	0.000032	12.73	0.000088	35.34
Females (13+/preg/not nsg):						
	0.000002	0.92	0.000020	8.05	0.000036	14.24
Females (13+/nursing):						
	0.000005	2.00	0.000020	8.16	0.000041	16.56
Females (13-19 yrs/np/nn):						
	0.000002	0.73	0.000016	6.47	0.000054	21.66
Females (20+ years/np/nn):						
	0.000003	1.14	0.000018	7.16	0.000050	20.03
Females (13-50 years):						
	0.000002	0.86	0.000017	6.88	0.000048	19.15
Males (13-19 years):						
	0.000003	1.23	0.000018	7.32	0.000057	22.63
Males (20+ years):						
	0.000003	1.07	0.000015	6.04	0.000046	18.58

Scenario VI. Estimated dietary risk assessment utilizing:

- * Field trial data for lima beans, snap beans, and peanuts; Tolerance for dry lima beans.
- * *Non-detected assumed zeros.*
- * Incorporated % crop treated.
- * Adjustment factors 6.0=surrogate crops and 2.8=blended crops were used to compensate for metabolites of concern.

ACUTE RESIDUE INFORMATION: U.S. Environmental Protection Agency Ver. 6.78
 DEEM Acute analysis for ETHOPROP 1989-92 data
 Residue file name: C:\deem\ethozero.R96 Adjust. #2 NOT used
 Analysis Date 06-30-1999 Residue file dated: 06-30-1999/11:54:18/8
 Reference dose (aRfD) = 0.00025 mg/kg bw/day
 Comment: Adding zeros to non-detect commodities

 RDF indices and file names for Monte Carlo Analysis

1 C:\deem\041101\ban91.rdf
 2 C:\deem\041101\cabb91.rdf
 3 C:\deem\041101\cuk91.rdf
 4 C:\deem\041101\lima91.rdf
 5 C:\deem\041101\gbean91.rdf
 6 C:\deem\041101\pot91.rdf
 7 C:\deem\041101\scorn91.rdf
 8 C:\deem\041101\spot91.rdf
 9 C:\deem\041101\pine91.rdf

Food Crop	RESIDUE	RDF	Adj. Factors	Code
Grp Food Name	(ppm)	#	#1	#2
229 6C Beans-dry-lima	0.000560	0	1.000	1.000
233 6B Beans-succulent-lima	0.030000	4	1.000	1.000
234 6A Beans-succulent-green	0.030000	5	1.000	1.000
293 O Peanuts-oil	0.000960	0	2.800	1.000
403 O Peanuts-butter	0.000960	0	1.890	1.000
940 O Peanuts-hulled	0.000960	0	1.000	1.000

ACUTE DEEM ANALYSIS: U.S. Environmental Protection Agency Ver. 6.78
 DEEM ACUTE analysis for ETHOPROP (1989-92 data)
 Residue file: ethozero.R96 Adjustment factor #2 NOT used.
 Analysis Date: 06-30-1999/12:57:39 Residue file dated: 06-30-1999/11:54:18/8
 Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: Incorporating zeros for non-detects

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:						
	0.000001	0.37	0.000003	1.26	0.000088	35.04
All infants (<1 year):						
	0.000000	0.05	0.000000	0.17	0.000185	73.92
Nursing infants (<1 year):						
	0.000000	0.01	0.000000	0.03	0.000001	0.23
Non-nursing infants (<1 yr):						
	0.000000	0.07	0.000001	0.25	0.000249	99.49
Children (1-6 years):						
	0.000003	1.26	0.000007	2.89	0.000231	92.23
Children (7-12 years):						
	0.000002	0.69	0.000003	1.35	0.000112	44.66
Females (13+/preg/not nsg):						
	0.000001	0.29	0.000002	0.85	0.000063	25.16
Females (13+/nursing):						
	0.000001	0.40	0.000003	1.17	0.000077	30.90
Females (13-19 yrs/np/nn):						
	0.000001	0.30	0.000002	0.64	0.000077	30.84
Females (20+ years/np/nn):						
	0.000000	0.20	0.000002	0.72	0.000073	29.36
Females (13-50 years):						
	0.000001	0.22	0.000002	0.77	0.000065	26.20
Males (13-19 years):						
	0.000001	0.40	0.000002	0.96	0.000061	24.47
Males (20+ years):						
	0.000001	0.25	0.000002	0.67	0.000062	24.66

Summary

Dietary risk estimates summarized below show risks >100% of the aPAD for scenarios I and II and <100% of the aPAD for scenarios III through VI. It should be noted that these risk estimates are derived from data sets (FDA monitoring and field trials) which contain almost no detectable residues of ethoprop, per se. The primary factor affecting whether the estimate is above or below 100% of the aPAD is how one estimates the amount of pesticide residue in/on the food as consumed, e.g.

- * Ethoprop dietary risk estimate, based on FDA monitoring data which were not adjusted to reflect exaggerated rates of application and $\frac{1}{2}$ LOD (scenario I), resulted in estimated risks >100% of the aPAD.
- * Ethoprop dietary risk estimate, based on field trial data which were adjusted to reflect exaggerated rates of application and $\frac{1}{2}$ LOQ (scenario II), resulted in estimated risks >100% of the aPAD.
- * Ethoprop dietary risk estimate, based on the exclusion of specific raw agricultural commodities and $\frac{1}{2}$ LOQ (scenarios III and IV), resulted in estimated risks <100% of the aPAD.
- * Ethoprop dietary risk estimate, based on field trial residue data which were not adjusted to reflect exaggerated rates of application and $\frac{1}{2}$ LOD (scenario V), resulted in estimated risks <100% of the aPAD.
- * Ethoprop dietary risk estimate, based on assuming that non-detected samples contained no ethoprop residue of concern (scenario VI), resulted in estimated risks <100% of the aPAD.

Any meaningful refinements to these estimates requires residue data for all ethoprop residues of concern (ethoprop and Metabolites SME and OME) using very sensitive analytical measurement techniques, and post harvest studies on the affects of washing, peeling, and cooking raw agricultural commodities treated with ethoprop.

Scenarios	U.S. Population	All infants (<1yr)	Non-nursing infants (<1yr)	Children (1-6 yrs)	CEC*
% aPAD at the 99.9th percentile					
FDA Monitoring Data from Scenario I. (½ LOD)	123.63	341.81	355.38	218.49	Bananas and lima beans.
Field Trial Data from Scenario II. (½ LOQ)	98.59	244.38	242.53	166.63	Bananas and green beans.
FDA Monitoring Data from Scenario III. (Excluding bananas/plantains and green beans; ½ LOD)	35.11	73.61	81.90	58.95	Lima beans and corn (sweet/field).
Field Trial Data from Scenario IV. (Excluding bananas/plantains and green beans; ½ LOQ)	48.99	24.57	51.92	93.67	Lima beans and sweet corn.
Field Trial Data from Scenario V. (½ LOD)	38.51	75.37	80.10	67.17	Bananas, green beans, lima beans, and sweet corn.
Field Trial Data from Scenario VI. (Zeros for non-detects)	35.04	73.92	99.49	92.23	Lima and green beans.
aPAD=0.00025 mg/kg/day *CEC= Critical Exposure Contribution Analysis (These are the commodities listed in DEEM's CEC that are driving the risk assessment)					

cc: S.Piper, RF, SF, List A File

RDI: F.B.Suhre: 7/12/99

7509C: CEB1: CM-2:RM 810F: 308-2717: Ethoprop

Attachment 5: Revised Chronic Dietary Exposure Analyses for the HED Risk Assessment

July 21, 1999

MEMORANDUM

SUBJECT: Ethoprop. List A Reregistration Case No. 0106/Chemical ID No. 041101.
Revised Chronic Dietary Exposure Analyses for the HED Risk
Assessment. No MRID #. DP Barcode No. D257828.

FROM: Christina Swartz, Chemist
Reregistration Branch 1
Health Effects Division (7509C)

THRU: David Hrdy/Carol Christensen
Dietary Exposure Science Advisory Council

Whang Phang, Ph.D., Branch Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

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

and

Kathryn Boyle
Reregistration Branch 3
Special Review and Reregistration Division (7508W)

Executive Summary

Chronic (cancer and non-cancer) dietary exposure and risk for ethoprop are below HED's level of concern.

Background/Action Requested

In conjunction with the completion of the revised HED human health risk assessment for the ethoprop reregistration eligibility document (RED, K. Farwell memo dated 2/18/99, D252468), acute and chronic dietary exposure and risk analyses were conducted [acute: S. Piper, 3/26/99, D254325; chronic/cancer and non-cancer: C. Swartz, 2/9/99, D252421 and D252984 and C. Swartz, 4/16/99, D254774]. These analyses estimated potential exposure to ethoprop in the commodities supported through reregistration: banana, dry and succulent beans, snap beans, field and sweet corn, cabbage, cucumber, pineapple, potato, sugarcane; sweet potato and peanuts. Estimated chronic risk was below HED's level of concern.

To further characterize dietary exposure to ethoprop, and in response to comments submitted by USDA, additional chronic (cancer and non-cancer) anticipated residues (ARs) were generated (S. Piper, 7/12/99, D257533) using $\frac{1}{2}$ the extrapolated limit of detection (LOD) for non-detectable residues, rather than $\frac{1}{2}$ the limit of quantitation (LOQ). The new ARs should be used to generate revised cancer and non-cancer chronic dietary exposure and risk estimates using the Dietary Exposure Evaluation Model (DEEM™).

Although previous analyses incorporated the estimated maximum of percent crop treated (%CT) for relevant commodities, current HED policy supports use of the weighted average %CT in chronic dietary exposure analyses. Therefore, the revised analyses should incorporate weighted average %CT.

Conclusions (Current Assessment)

The revised chronic (cancer and non-cancer) analyses indicate that dietary exposure and risk for ethoprop are below the Agency's level of concern. For chronic non-cancer effects, the Agency's level of concern is 100% of the reference dose (RfD); for carcinogenic effects, the Agency's level of concern is one in a million excess cancers, or 1×10^{-6} . The results of the revised analysis, based on ARs calculated from the LOD, indicate the most highly exposed population subgroups are non-nursing infants <1 year old and children 1-6 years old, with exposures corresponding to approximately 1% of the chronic population adjusted dose (cPAD). Estimated chronic carcinogenic dietary risk is below the Agency's one in a million level of concern, at 1.1×10^{-8} .

DETAILED CONSIDERATIONS

Summary of Pertinent Toxicological Information

No changes have been made to the hazard inputs in the relevant dietary risk analyses; based on available toxicology data for ethoprop, the additional 10X safety factor required under FQPA has been removed. A reference dose (RfD) which includes the FQPA safety factor is now referred to as the acute or chronic population adjusted dose (aPAD or cPAD, respectively). The new terminology has been incorporated into the current assessment; since the FQPA factor was removed (reduced to 1X) for ethoprop, the cPAD is equivalent to the chronic RfD. Toxicological endpoints for dietary risk assessment are as follows:

TABLE 1. TOXICOLOGICAL ENDPOINTS

EXPOSURE SCENARIO	NOAEL (mg/kg/day)	ENDPOINT/STUDY	UF/Dose (mg/kg/day)
Acute Dietary	0.025	Plasma ChE (day 2)/ Subchronic, Dog	UF = 100 aRfD = 0.00025 aPAD = 0.00025
Chronic Dietary (Non-cancer)	0.01	Plasma ChE Inhibition/ Chronic, Dog	UF = 100 RfD = 0.0001 cPAD = 0.0001
Carcinogenic, Dietary	$Q_1^* = 0.0281 \text{ (mg/kg/day)}^{-1}$ [likely human carcinogen]		

ChE = cholinesterase

Residue Information

As stated in previous memoranda, the residues of concern for chronic non-cancer dietary risk assessments are parent and metabolites II and III: ethoprop, SME [O-ethyl-S-methyl-S-propylphosphorodithioate] and OME [O-ethyl-O-methyl-S-propylphosphorothioate].

For cancer risk assessment, the residues of concern in raw agricultural commodities are parent and metabolites II, III and IV: ethoprop, SME, OME and M1 [O-ethyl-S-propylphosphorothioate].

Tolerances for ethoprop residues in plant commodities are currently expressed in terms of ethoprop *per se* [40 CFR §180.262 (a) and (b)]. For all commodities supported through reregistration, tolerances are set at 0.02 ppm with a (N), or negligible residue notation. The current analysis includes only the tolerances/commodities supported through reregistration.

Residue data available for tolerance reassessment and dietary exposure analysis include either parent alone or parent and metabolite IV (M1). Therefore, HED concluded that tolerances will be reassessed based on combined residues of parent (chronic, non-cancer) or parent + metabolite IV (chronic, cancer), and making conservative assumptions with respect to levels of metabolites II and III based on metabolism data.

For chronic non-cancer dietary risk assessment, ARs are derived using the tolerance or available field trial residue values for the parent (ethoprop), multiplied by a ratio of 2.8; this ratio accounts for residues of parent + Metabolites II and III. In order to include residues of the M1 in the chronic cancer dietary exposure assessment, ARs are derived using the parent + M1 (where available) residue, which is multiplied by a ratio of 2.3.

In previous assessments, nondetectable ethoprop residues were assigned a residue value of ½ LOQ; the relevant ratios from metabolism studies were applied to obtain the

ARs. In order to further characterize dietary exposure/risk, revised ARs were generated using nondetectable ethoprop residues assigned a value of ½ the extrapolated LOD (i.e., LOQ/3/2) and the relevant ratios derived from metabolism studies, discussed above. The DEEM™ default processing factors (Adjustment Factor 1) were used in the analysis.

For banana, cabbage, corn (field and sweet), cucumber, potato, sugar cane, and sweet potato, the LOD was determined to be 1/3 the LOQ of 0.01, or 0.003. The residue value of ½ LOD (0.0015) was multiplied by the relevant ratio to determine the AR. For dry lima beans, the tolerance value of 0.02 ppm was used. For peanuts, snap beans and lima beans, the average of detected and nondetectable (0.0015 ppm) residue values from field trials was multiplied by the cancer and non-cancer ratios. For pineapple, the residue value of ½ the LOD of 0.002 ppm was multiplied by the ratios. The derivation of revised ARs and DEEM™ inputs for the current assessment are shown in Table 2:

Table 2. Ethoprop Anticipated Residues/Inputs to the DEEM™ Analysis

RAC	Average Residues (ppm)		Anticipated Residues: DEEM™ Residue Input ¹ (Average Residue x 2.3 or 2.8)		DEEM™ Adjustment Factor 2: Wtd. Ave. % Crop Treated ²
	Cancer (ppm)	Chronic (ppm)	Cancer AR (ppm)	Chronic AR (ppm)	
Banana	0.0015	0.0015	0.0035	0.0042	0.06
Beans, Lima, Dry	0.02	0.02	0.046	0.056	0.01
Beans, Lima, Succulent	0.002	0.002	0.005	0.006	0.01
Beans, Snap	0.011	0.011	0.025	0.031	0.01
Cabbage	0.0015	0.0015	0.0035	0.0042	0.01
Corn, Sweet	0.0015	0.0015	0.0035	0.0042	0.04
Corn, Grain	0.0015	0.0015	0.0035	0.0042	0.01
Cucumber	0.0015	0.0015	0.0035	0.0042	0.01
Peanuts	0.015	0.015	0.034	0.042	0.01
Pineapple	0.001	0.001	0.002	0.003	0.01
Potato	0.0015	0.0015	0.0035	0.0042	0.03
Sugarcane (molasses, sugar)	0.0015	0.0015	0.0035	0.0042	0.07
Sweet Potato	0.0015	0.0015	0.0035	0.0042	0.03

¹Chronic (non-cancer) residues calculated based on parent residues x 2.8; cancer

residues calculated based on (parent + M1 residues) x 2.3.

²Weighted average %CT, shown as a percentage, and entered into DEEM™ as Adjustment Factor 2, Comprehensive Quantitative Usage Analysis (QUA), J. Faulkner (BEAD/OPP), 2/2/99.

Results

Revised chronic (non-cancer) and chronic (cancer) exposure and risk analyses were performed using the anticipated residues and percent crop treated data shown in Table 2.

Dietary Risk for Carcinogenicity

The carcinogenic dietary risk for the general US population is calculated to be 1.1×10^{-8} (EPA does not consider cancer risk for specific population subgroups).

Dietary Risk for Chronic, Non-Cancer Effects

The results of the chronic (non-cancer) analysis are summarized in Table 3.

Table 3. Chronic (Non-Cancer) Dietary Risk Estimates for Ethoprop

Population Subgroup	Exposure (mg/kg/day)	Chronic Risk, %cPAD
General US Population	0.000000	<1
Infants (<1 Year)	0.000001	1.0
Nursing Infants	0.000000	<1
Non-Nursing Infants (<1 year old)	0.000001	1.3
Children (1-6 years)	0.000001	1.2
Children (7-12 years)	0.000001	<1
Females (13-19 years)	0.000000	<1
Females (20+ years)	0.000000	<1
Males (13-19 years)	0.000001	<1
Males (20+ years)	0.000000	<1

Discussion

Chronic dietary risk for ethoprop is below the Agency's level of concern. The results of the revised DEEM™ analysis indicate the most highly exposed population subgroups are non-nursing infants <1 year old and children 1-6 years old, with exposures corresponding to approximately 1% of the chronic Population Adjusted Dose (cPAD). Chronic carcinogenic dietary risk is below the Agency's one in a million level of concern, at 1.1×10^{-8} .

Attachments:

Attachment 1: Chronic Non-Cancer Dietary Exposure and Risk Analysis for Ethoprop.

Attachment 2: Carcinogenic Dietary Exposure and Risk Analysis for Ethoprop.

Secondary Review:

Dietary Exposure SAC Review:David Hrdy:07/19/99 Carol Christensen:07/20/99

cc: Reviewer, C. Swartz; LaShonia Richardson (HED/CEB1); List A Rereg. File
7509C:CSwartz:RRB1:CM2:Rm 722H:703 305 5877:07/16/99

U.S. Environmental Protection Agency
DEEM Chronic analysis for ETHOPROP
Residue file: C:\DRESSAC\041101rc.R96

Ver. 6.76
1989-92 data
Adjust. #2 used

Analysis Date 07-16-1999 Residue file dated: 07-16-1999/15:47:36/8
Reference dose (RfD) = 0.0001 mg/kg bw/day
Comment:UF includes 10X for intra- and 10X for inter-
Revised to include 1/2 LOD ARs and Wtd. %CT.

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj. Factors #1	Adj. Factors #2
72	O	Bananas	0.004200	1.000	0.060
73	O	Bananas-dried	0.004200	3.900	0.060
89	O	Pineapples-peeled fruit	0.003000	1.000	0.010
90	O	Pineapples-dried	0.003000	5.000	0.010
91	O	Pineapples-juice	0.003000	1.700	0.010
94	O	Plantains-ripe	0.004200	1.000	0.060
148	9B	Cucumbers	0.004200	1.000	0.010
170	5A	Cabbage-green and red	0.004200	1.000	0.010
207	1C	Potatoes/white-whole	0.004200	1.000	0.030
208	1C	Potatoes/white-unspecified	0.004200	1.000	0.030
209	1C	Potatoes/white-peeled	0.004200	1.000	0.030
210	1C	Potatoes/white-dry	0.004200	6.500	0.030
211	1C	Potatoes/white-peel only	0.004200	1.000	0.030
218	1CD	Sweet potatoes (incl yams)	0.004200	1.000	0.030
229	6C	Beans-dry-lima	0.056000	1.000	0.010
233	6B	Beans-succulent-lima	0.006000	1.000	0.010
234	6A	Beans-succulent-green	0.031000	1.000	0.010
238	15	Corn/sweet	0.004200	1.000	0.040
266	15	Corn grain-endosperm	0.004200	1.000	0.010
267	15	Corn grain-bran	0.004200	1.000	0.010
268	15	Corn grain/sugar/hfcs	0.004200	1.500	0.010
283	O	Sugar-cane	0.004200	1.000	0.070
284	O	Sugar-cane/molasses	0.004200	1.000	0.070
289	15	Corn grain-oil	0.004200	1.000	0.010
293	O	Peanuts-oil	0.042000	1.000	0.010
378	O	Bananas-juice	0.004200	1.000	0.060
383	5B	Cabbage-savoy	0.004200	1.000	0.010
388	15	Corn grain/sugar-molasses	0.004200	1.500	0.010
403	O	Peanuts-butter	0.042000	1.890	0.010
406	O	Pineapples-juice-concentrate	0.003000	6.300	0.010
452	5B	Bok choy	0.004200	1.000	0.010
480	O	Plantains-green	0.004200	1.000	0.060
481	O	Plantains-dried	0.004200	3.900	0.060
940	O	Peanuts-hulled	0.042000	1.000	0.010

U.S. Environmental Protection Agency Ver. 6.76
 DEEM Chronic analysis for ETHOPROP (1989-92 data)
 Residue file name: C:\DRESSAC\041101rc.R96 Adjustment factor #2 used.
 Analysis Date 07-16-1999/15:49:43 Residue file dated: 07-16-1999/15:47:36/8
 Reference dose (RfD, CHRONIC) = .0001 mg/kg bw/day
 COMMENT 1: UF includes 10X for intra- and 10X for inter-
 Revised to include 1/2 LOD ARs and Wtd. %CT.

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Total exposure by population subgroup

Population Subgroup	Total Exposure	
	mg/kg body wt/day	Percent of Rfd
U.S. Population (total)	0.000000	0.5%
U.S. Population (spring season)	0.000000	0.5%
U.S. Population (summer season)	0.000000	0.5%
U.S. Population (autumn season)	0.000000	0.5%
U.S. Population (winter season)	0.000001	0.5%
Northeast region	0.000000	0.5%
Midwest region	0.000001	0.5%
Southern region	0.000001	0.5%
Western region	0.000000	0.4%
Hispanics	0.000000	0.4%
Non-hispanic whites	0.000000	0.5%
Non-hispanic blacks	0.000001	0.5%
Non-hisp/non-white/non-black)	0.000000	0.5%
All infants (< 1 year)	0.000001	1.0%
Nursing infants	0.000000	0.3%
Non-nursing infants	0.000001	1.3%
Children 1-6 yrs	0.000001	1.2%
Children 7-12 yrs	0.000001	0.7%
Females 13-19(not preg or nursing)	0.000000	0.4%
Females 20+ (not preg or nursing)	0.000000	0.3%
Females 13-50 yrs	0.000000	0.3%
Females 13+ (preg/not nursing)	0.000000	0.3%
Females 13+ (nursing)	0.000000	0.5%
Males 13-19 yrs	0.000001	0.5%
Males 20+ yrs	0.000000	0.4%
Seniors 55+	0.000000	0.4%
Pacific Region	0.000000	0.4%

U.S. Environmental Protection Agency
 DEEM Chronic analysis for ETHOPROP
 Residue file: C:\DRESSAC\041101rq.R96
 Analysis Date 07-16-1999
 Q* = 0.0281

Ver. 6.76
 1989-92 data
 Adjust. #2 used
 Residue file dated: 07-16-1999/15:44:05/8

Comment:UF includes 10X for intra- and 10X for inter-
 Revised to reflect 1/2 LOD ARs, Wtd. Ave. %CT

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors	
				#1	#2
72	O	Bananas	0.003500	1.000	0.060
73	O	Bananas-dried	0.003500	3.900	0.060
89	O	Pineapples-peeled fruit	0.002000	1.000	0.010
90	O	Pineapples-dried	0.002000	5.000	0.010
91	O	Pineapples-juice	0.002000	1.700	0.010
94	O	Plantains-ripe	0.003500	1.000	0.060
148	9B	Cucumbers	0.003500	1.000	0.010
170	5A	Cabbage-green and red	0.003500	1.000	0.010
207	1C	Potatoes/white-whole	0.003500	1.000	0.030
208	1C	Potatoes/white-unspecified	0.003500	1.000	0.030
209	1C	Potatoes/white-peeled	0.003500	1.000	0.030
210	1C	Potatoes/white-dry	0.003500	6.500	0.030
211	1C	Potatoes/white-peel only	0.003500	1.000	0.030
218	1CD	Sweet potatoes (incl yams)	0.003500	1.000	0.030
229	6C	Beans-dry-lima	0.046000	1.000	0.010
233	6B	Beans-succulent-lima	0.005000	1.000	0.010
234	6A	Beans-succulent-green	0.025000	1.000	0.010
238	15	Corn/sweet	0.003500	1.000	0.040
266	15	Corn grain-endosperm	0.003500	1.000	0.010
267	15	Corn grain-bran	0.003500	1.000	0.010
268	15	Corn grain/sugar/hfcs	0.003500	1.500	0.010
283	O	Sugar-cane	0.003500	1.000	0.070
284	O	Sugar-cane/molasses	0.003500	1.000	0.070
289	15	Corn grain-oil	0.003500	1.000	0.010
293	O	Peanuts-oil	0.034000	1.000	0.010
378	O	Bananas-juice	0.003500	1.000	0.060
383	5B	Cabbage-savoy	0.003500	1.000	0.010
388	15	Corn grain/sugar-molasses	0.003500	1.500	0.010
403	O	Peanuts-butter	0.034000	1.890	0.010
406	O	Pineapples-juice-concentrate	0.002000	6.300	0.010
452	5B	Bok choy	0.003500	1.000	0.010
480	O	Plantains-green	0.003500	1.000	0.060
481	O	Plantains-dried	0.003500	3.900	0.060
940	O	Peanuts-hulled	0.034000	1.000	0.010

U.S. Environmental Protection Agency
 DEEM Chronic analysis for ETHOPROP
 Residue file name: C:\DRESSAC\041101rq.R96
 Analysis Date 07-16-1999/15:48:39
 Q* = 0.0281

Ver. 6.76
 (1989-92 data)
 Adjustment factor #2 used.
 Residue file dated: 07-16-1999/15:44:05/8

COMMENT 1: UF includes 10X for intra- and 10X for inter-
 Revised to reflect 1/2 LOD ARs, Wtd. Ave. %CT

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Total exposure by population subgroup

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Population Subgroup	Total Exposure	
	mg/kg body wt/day	Lifetime risk (Q* = .0281)
U.S. Population (total)	0.000000	1.12E-08

**Attachment 6: Revised
Occupational/Non-
Occupational/Residential Exposure
Assessment for the Reregistration
Eligibility Decision**

August 30, 1999

MEMORANDUM

SUBJECT: Ethoprop: Revised Occupational/Non-Occupational/Residential Exposure Assessment for the Reregistration Eligibility Decision (RED) Document
[Case # 818841, PC Code 041101, DP Barcode D258251]

FROM: Catherine Bodurow Joseph, MSPH, Industrial Hygienist
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Whang Phang, PhD, Branch Senior Scientist
Reregistration Branch I
Health Effects Division (7509C)

TO: Kit Farwell, DVM, Risk Assessor
Reregistration Branch I
Health Effects Division (7509C)

This document revises previous chapters submitted for ethoprop [(C. Joseph, dated 01/26/99, D252420) and (K. Boyle, dated 04/02/98, D239295)]. The document incorporates a post-application assessment of golf course turf, including golfers, and cancer assessments for post-application golf course turf management professionals as well as golfers. Comments from USDA have also been incorporated into this document. The document is intended to support the development of the Ethoprop Reregistration Eligibility Decision (RED) document and includes the results for HED's revised review of the potential human health effects associated with occupational/non-occupational/residential exposure to ethoprop. The document reflects current HED policy.cc: Whang Phang, Ph.D.; Kit Farwell, DVM; Kathryn Boyle

7509C: RRB1: CBJoseph: CBJ: CM#2: Room 722A: 308-1829: 08/26/99

RDI: Whang Phang, Ph.D. (08/26/99)

Reviewers: M. Collantes (08/30/99); S. Hanley (08/30/99); R. Sandvig (08/30/99).

1. Occupational/Non-Occupational/Residential Executive Summary for Ethoprop

Summary Description for Ethoprop:

Ethoprop, O-ethyl S,S-dipropylphosphorodithioate, is an organophosphate insecticide and nematicide used in agricultural settings and on golf course turf. Pesticidal properties and toxicity are due to inhibition of acetylcholinesterase enzyme. Ethoprop is manufactured by Rhône-Poulenc Ag Company under the trade name Mocap® and is formulated as a technical-grade manufacturing product (95.9% active ingredient [ai]), in a variety of granular products (3%, 10%, and 15% ai), as emulsifiable concentrates (46% and 69.6% ai), two granular Lock 'n Load™ products (10% and 20% ai) and as a gel in self-contained water-soluble packaging (68.2% ai). With the exception of pineapples, ethoprop is applied pre-plant or pre-emergence. The insecticidal activity is highly dependent on incorporating the material into the soil (mechanically or with water) soon after application.

Ethoprop is registered for use on the following crops: bananas, beans (dry, snap and lima), cabbage, citrus (non-bearing), sweet and field corn, cucumber, peanuts, pineapples, plantains, sugarcane, sweet potato, white potato, and tobacco. It is also used on field-grown ornamentals (i.e., trees, shrubs, bulbs, lilies) and on golf course turf. There are no registered residential uses for ethoprop. Therefore, no residential exposure assessment was conducted. However, general public exposure from golfing following ethoprop treatment of a golf course may occur and an assessment was conducted for golfers' exposure.

Based upon available pesticide survey usage information for the years 1987-1996, an annual estimate of ethoprop's total domestic usage averaged approximately 700,000 lb ai for a little over 200,000 acres treated. Most of the acreage is treated once per year with 6 lb ai/A or less. One exception is potatoes (regularly treated at 12 lb ai/A). Ethoprop's largest markets in terms of total lb ai are allocated to potatoes (35%; 3% total potato crop treated with ethoprop), sugarcane (28%; 7% total sugarcane crop treated with ethoprop) and tobacco (15%; 3% total tobacco crop treated with ethoprop). Most of the usage is in the Northwest and South, with some in the Midwest.

Applications can be made by aircraft (granular formulations – only to potatoes), chemigation, groundboom sprayers, hand-held sprayers (e.g., low-pressure handwand and backpack sprayers), push-type granular spreaders, tractor-drawn granular spreaders, and by slitting (i.e., subsurface insertion of granules into golf course turf). In addition, it can be applied as a dip for citrus seedlings, by hand (granular), and by hand-pouring of liquid concentrate from a measuring cup/vessel. The use of a belly grinder for application to turf grass is prohibited.

Toxicological NOAELs of Concern and Q_1^* for Assessments:

NOAEL_{ST,dermal} = 0.1 mg/kg/day
NOAEL_{ST,inhalation} = 0.025 mg/kg/day
NOAEL_{IT,dermal} = 0.1 mg/kg/day
NOAEL_{IT,inhalation} = 0.01 mg/kg/day
 Q_1^* is $2.81 \text{ E-02 (mg/kg/day)}^{-1}$

Individual and Professional Pesticide Applicator Risk Assessment:

Due to the frequency and duration of ethoprop uses, it was determined that uses of ethoprop by individual and professional pesticide applicators result in short-term and intermediate-term exposures of these applicators. However, the frequency and duration of these exposures do not exhibit a chronic exposure pattern (i.e., daily exposure which occurs for a minimum of several months). Therefore, exposure assessments were conducted for both short-term and intermediate-term exposures to individual and professional pesticide applicators while a long-term exposure assessment was not conducted.

Chemical-specific individual and professional pesticide applicator exposure data were not submitted in support of the reregistration of ethoprop. Therefore, analyses for both individual and professional short-term exposures, intermediate-term exposures and cancer risk (combined dermal and inhalation) were performed using the Pesticide Handlers Exposure Database (PHED), Version 1.1 (August 1998). Chronic occupational exposures to ethoprop are not anticipated. Numerous mixer/loader, applicator, mixer/loader/applicator and flagger scenarios were evaluated.

A Margin Of Exposure (MOE) of 100 or greater is considered protective for ethoprop. **None of the individual and professional short-term and intermediate-term handler exposure scenarios (even at the highest level of appropriate risk mitigation) had MOEs greater than 100. All occupational risks exceed HED's level of concern.** Only three short-term and two intermediate-term exposure scenarios have combined MOEs which are greater than or equal to 10. Additionally, it should be noted that for each of the individual and professional short-term and intermediate-term handler exposure scenarios (with the one exception of flagging), the significant risk driver is the dermal exposure route.

Short-Term Combined MOEs greater than or equal to 10 (this is one-tenth the acceptable MOE):

Baseline: **None**

PPE: **None**

Engineering Controls:

(1b) Mixer/Loader; Loading granulars for application with a tractor-drawn mechanical

- spreader; 2 lb ai/A; 80 A; **Combined MOE = 30**; using Lock 'n Load™ products; based upon high confidence in inhalation data, low confidence in dermal/hand data, and the use of protection factors for dermal and inhalation exposures.
- (3b) Applicator; Applying granulars with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 15**; based upon high confidence in hand and inhalation data and low confidence in dermal data.
- (10) Flagger; Flagging granular applications with fixed-wing aircraft; 6 lb ai/A; 350 A; **Combined MOE = 11**; using enclosed cab; medium confidence in dermal data and low confidence in hand and inhalation data.

Intermediate-Term Combined MOEs greater than or equal to 10 (this is one-tenth the acceptable MOE):

Baseline: None

PPE: None

Engineering Controls:

- (1b) Mixer/Loader; Loading granulars for application with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 18**; using Lock 'n Load™ products; based upon high confidence in inhalation data, low confidence in dermal/hand data, and the use of protection factors for dermal and inhalation exposures.
- (3b) Applicator; Applying granulars with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 10**; based upon high confidence in hand and inhalation data and low confidence in dermal data.

A cancer risk of less than 1×10^{-4} does not exceed HED's level of concern for occupational exposure; but at the highest level of mitigation available, one individual and five professional pesticide applicator scenarios had cancer risks greater than 1×10^{-4} . When feasible, the Agency seeks ways to reduce individual cancer risks to 10^{-6} or less using mitigation (e.g., personal protective equipment or engineering controls).

Occupational cancer risk exceeds HED's level of concern.

Post-Application Worker Risk Assessment:

Because ethoprop is used in pre-plant or pre-emergent applications and is normally soil incorporated or watered-in, there are generally no concerns for post-application exposure to agricultural workers. Two exceptions for this use pattern are sugarcane and pineapples. Sugarcane is mechanically transplanted and should have minimal post-application concerns. In order to refine the potential post-application exposure assessment for sugarcane, appropriate exposure monitoring data are requested to determine workers' exposure. Ethoprop may be applied to pineapples at various points in the growing season. However, there is currently a 120 day pre-harvest interval established for pineapples, so there should generally be minimal concern during harvesting.

Post-application exposure assessment was conducted for turf management professionals. When using both tractors and push-type mowers, following applications made at the rates of 10 lb ai/A and 20 lb ai/A, it was determined that re-entry intervals (REIs) greater than 50 days were required before MOEs exceed 100 and workers could re-enter treated areas for mowing and maintenance. Specifically, REIs of 62 and 55 days, respectively, were calculated when mowing with a tractor following the application of 20 lb ai/A and 10 lb ai/A. Respectively, REIs of 68 and 62 days were calculated when using a push-type mower following the application of 20 lb ai/A and 10 lb ai/A. In addition, post-application cancer risks were also calculated. At the highest level of mitigation available, the cancer risks associated with these activities were in the mid to high 10^{-5} range. Although these risks did not exceed the 10^{-4} level of concern, the risks did not lower to the 10^{-6} range until more than 32 and 44 days for tractors and push-type mowers, respectively.

Non-Occupational/Recreational Risk Assessment:

An assessment to quantify golfer risk following ethoprop treatment was also conducted. On the day of ethoprop treatment for 20 lb ai/A and 10 lb ai/A, MOEs of 2 and 3 were calculated, respectively. To exceed MOEs of 100, 40 and 33 days needed to elapse, respectively, before golfers could enter ethoprop treated areas to golf. In addition, the cancer risks associated with golfer exposures ranged from $1.8-3.5 \times 10^{-6}$ for use of 20 lb ai/A and $1.2-5.1 \times 10^{-6}$ for use of 10 lb ai/A. This variation is dependent upon the number of ethoprop treatments made to the golf course turf during the year.

Occupational and non-occupational risks exceed HED's level of concern for both cancer and non-cancer risks.

Incident Reports:

The Review of Ethoprop Incident Reports had several occupational reports with symptoms of cholinesterase inhibition. According to Poison Control Centers data (1985-1996), ethoprop had an above average level of risk (e.g., hospitalization) when compared with other organophosphate and carbamate compounds. 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.

Data Needs:

The registrant is planning to conduct a 28-day dermal toxicity study in rabbits with a granular formulation of ethoprop. This study is not yet available, but may result in refinement of occupational risks. An exposure monitoring and biomonitoring study of workers is being conducted in the United Kingdom for granular application to potatoes.

Additional information on slit placement techniques for turf and related exposure monitoring for workers and golfers is requested. Information on post-application techniques and appropriate exposure monitoring data for transplanting sugarcane and pineapple activities is requested.

2. Background Information

This revised document is based upon the following referenced documents.

Referenced Documents:

Ethoprop. Addendum to Toxicology Chapter. Selection of Inhalation Endpoints. Assessment by the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee; Author: Kit Farwell, DVM, Toxicologist and Risk Assessor RRBI/HED/OPP; Chapter directed to Kathryn Boyle of SRRD/OPP (08/31/98) [HED DOC # 012836, PC Code 041101, DP Barcode D248784].

Ethoprop: Revised Occupational and Residential Exposure (ORE) Assessment for the Reregistration Eligibility Decision (RED) document; Author: Catherine Joseph, MSPH, Industrial Hygienist RRBI/HED/OPP; Chapter directed to Kit Farwell, DVM, Toxicologist and Risk Assessor RRBI/HED/OPP (01/26/99) [PC Code 041101, DP Barcode D252420].

Letter entitled *Ethoprop/PHED Information/Occupational Exposure Risk Assessments*, Letter sent from Lizbeth R. Simila, Registration Manager of Rhone-Poulenc to Kathryn Boyle, SRRD/OPP (dated 12/03/98).

Letter entitled *Ethoprop/Bananas*, Letter sent from Lizbeth R. Simila, Registration Manager of Rhone-Poulenc to Kathryn Boyle, SRRD/OPP (dated 12/14/98).

Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Ethoprop; Author: Kathryn Boyle, Chemist RRBI/HED/OPP; Chapter directed to Kit Farwell, DVM, Toxicologist and Risk Assessor RRBI/HED/OPP (04/02/98) [PC Code 041101, DP Barcode D239295].

Review of Ethoprop Incident Reports; Authors: Jerome Blondell, PhD and Monica Spann, MPH (Signed 03/09/98); Chapter directed to Kathryn Boyle of RRBI/HED/OPP (03/09/98) [PC Code 041101, Case #0106, DP Barcode D243371].

EPA Registration Numbers:

Currently "active" as reported by registrant:

264-456, 264-457, 264-458, 264-465, 264-469, 264-546, and 34704-710

Currently "inactive" as reported by registrant (as labels do exist, these formulations are included in the ORE assessment):

264-459, 264-464, 264-475, 264-521, 264-541, and 51036-80

PHED: Yes, Version 1.1 (August 1998)

3. Occupational/Non-Occupational/Residential Exposure and Risk Characterization

An occupational and/or residential exposure assessment is required for an active ingredient if: (1) certain toxicological criteria are triggered **and** (2) there is potential exposure to handlers (i.e., mixers, loaders, applicators, etc.) during use or to persons entering treated areas after application is completed. Ethoprop meets both criteria. Ethoprop is a potent cholinesterase inhibitor in acute toxicity category I by both oral and dermal routes, and there is potential exposure from agricultural uses. There are no registered residential uses for ethoprop; however, the general public may be exposed to ethoprop from golfing following ethoprop treatment of a golf course. The 10 percent (%) granular golf course turf product 264-546 contains the statement "not for use on domestic turf grass."

3.a. Summary of Use Patterns and Formulations

Ethoprop, O-ethyl S,S-dipropylphosphorodithioate, is an organophosphate insecticide and nematicide used in agricultural settings and on golf course turf. Ethoprop is formulated as a technical-grade manufacturing product (95.9% active ingredient [ai]), in a variety of granular products (3%, 10%, and 15% ai), as emulsifiable concentrates (46% and 69.6% ai), two granular Lock 'n Load™ products (10% and 20% ai) and as a gel in water-soluble packaging (68.2% ai). The following formulations are labeled for "Restricted Use": 264-457, 264-458, 264-459, 264-464, 264-469, 264-521, 264-541, and 34704-710.

Ethoprop is registered for use on the following crops: bananas, beans (dry, snap and lima), cabbage, citrus (non-bearing), sweet and field corn, cucumber, peanuts, pineapple, plantains, sugarcane, sweet potato, tobacco, and white potato. It is also used on field-grown ornamentals (i.e., trees, shrubs, bulbs) and on golf course turf. The table in Appendix A summarizes ethoprop labels. Both the products which the registrant has indicated as "in active use" and those "not in active use" are listed in the table. Note that the registrant has indicated in letters dated December 16, 1997, and February 6, 1998, that the use on citrus seedlings will be deleted, that the "Special Local Need" (SLN) registrations on lilies will be canceled, that peanut pegging will be deleted, and that the SLN registration for citrus in Florida will be canceled.

Based upon available pesticide survey usage information for the years 1987-1996, an annual estimate of ethoprop's total domestic usage averaged approximately

700,000 lb ai for a little over 200,000 acres treated. Most of the acreage is treated once per year with 6 lb ai/A or less. One exception is potatoes (regularly treated at 12 lb ai/A). Ethoprop's largest markets in terms of total lb ai are allocated to potatoes (35%; 3% total potato crop treated with ethoprop), sugarcane (28%; 7% total sugarcane crop treated with ethoprop) and tobacco (15%; 3% total tobacco crop treated with ethoprop). Most of the usage is in the Northwest and South, with some in the Midwest.

Ethoprop is applied pre-plant or pre-emergence and the insecticidal activity is highly dependent on incorporating the material into the soil (mechanically or with water) soon after application. Ethoprop can be applied by aircraft (granular formulations – only to potatoes), chemigation, groundboom sprayers, hand-held sprayers (e.g., low-pressure handwand and backpack sprayers), push-type granular spreaders, tractor-drawn granular spreaders, and by slitting (i.e., subsurface insertion of granules into golf course turf). In addition, it can be applied as a dip for citrus seedlings, by hand (granular), and by hand-pouring of liquid concentrate from a measuring cup/vessel. The use of a belly grinder for application to turf grass is prohibited.

Aerial application of the granular formulation to potatoes is specified on three labels (i.e., EPA Registration Numbers 264-457, 264-465, and 264-469). Hence, aerial application exposures and risks are addressed in this document only with regard to the use of the granular product on potatoes. The emulsifiable concentrate ethoprop label states that aerial application on potatoes is specifically prohibited.

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.”

The following paragraphs describe two different formulation types of ethoprop (granular and emulsifiable concentrate), the crops on which they are used, their application rates, and the corresponding number of treatments per season. The reported application rates are the maximum amount of product active ingredient (ai) applied in a single treatment and not seasonal rates.

Granular Products

There are two Lock 'n Load™ granular formulations (10% and 20% ai) with the latter labeled for restricted use only. There are also one 15% granular product, two 10% granular products and one 3% granular product available in open packaging. One of the latter is labeled for use on field or sweet corn only while the other is only labeled for golf course turf. Of seven SLN registrations, six (sweet corn, white potato, sugarcane and pineapple) are for the 10% granular formulations available in open packaging, and one (field-grown lily bulbs) is for a different 10% granular formulation in open packaging.

The lowest recommended label application rate is one pound active ingredient per acre (lb ai/A) on corn, and the highest recommended label application rate is 12 lb ai/A on white/Irish potatoes and tobacco. Maximum application rates range from 2 to 12 lb ai/A depending upon the crop. Rhone-Poulenc has provided HED information which states the maximum application rate for hand application of granules around banana/plantain is 5.5 lb ai/A. The range of recommended label application rates on golf course turf is 10 to 20 lb ai/A. [Note: granular products are not labeled for use on nursery ornamentals, with the single exception of a SLN on field-grown lily bulbs.]

Maximum Granular Application Rates:

- Banana & plantain (5.5 lb ai/A; repeat application in 6 months); **Rhone-Poulenc has provided HED a letter which states the application rate is 5.5 lb ai/A and a maximum of 2 applications per year (Rhone-Poulenc letter dated 12/14/98); this information must be included on all future label modifications;**
- Beans (snap and lima) (8 lb ai/A; from 3 days before planting to at-planting);
- Cabbage (5 lb ai/A; from one week before planting to at planting);
- Corn (6 lb ai/A; at cultivation after plant emergence until layby or 3 days before planting to at planting);
- Cucumber (2 lb ai/A; at or just before planting);
- SLN Field-grown lilies (4 lb ai/A; at planting);
- Peanut (6 lb ai/A; one week before or at planting; at pegging);
- SLN Pineapple (1.2 lb ai/A; pre-plant, spot applications as necessary 3 to 6 months after planting, but not within 120 days to harvest);
- Potato (12 lb ai/A; from 2 weeks before to at planting; before potato emergence);
- SLN Sugarcane (6 lb ai/A; at planting);
- Sugarcane (4 lb ai/A; at planting);
- Sweet potato (8 lb ai/A; 2-3 weeks before planting);
- Tobacco (12 lb ai/A; 1 week before to at planting); and
- Golf course turf (20 lb ai/A; with repeat applications "as needed" up to 40 lb ai/A/yr).

Emulsifiable Concentrates

There are two emulsifiable concentrate (EC) formulations 69.6% (restricted use) and a 46% ethoprop product labeled for use on tobacco. There is also a 68.2% Gel-Tec Water Soluble Pak. There are two SLN registrations: one for sweet corn and one for non-bearing citrus seedlings.

The lowest recommended label application rate is 1 lb ai/A on corn, and the highest recommended label application rate is 12 lb ai/A on white/Irish potatoes and tobacco. Maximum application rates range from 2 to 12 lb ai/A depending upon the crop. Rhone-Poulenc has provided HED information which states the maximum application rate for hand application of undiluted EC around banana/plantain is 5.5 lb

ai/A. EC ethoprop products are also used on field-grown ornamentals (from 3 to 6 lb ai/A). A SLN for use on non-bearing citrus by dipping, by pot drench, and by spraying soil surfaces and citrus tree trunks results in an application rate of 4.957 lb ai/A according to the Agency's Label Use Information System (LUIS) report. EC products are not labeled for use on golf course turf.

Maximum EC Spray Application Rates:

- Banana & Plantain (5.5 lb ai/A; repeat application in 6 months); **Rhone-Poulenc has provided HED a letter which states the application rate is 5.5 lb ai/A and a maximum of 2 applications per year (Rhone-Poulenc letter dated 12/14/98); this information must be included on all future label modifications;**
- Beans - Snap & Lima (8 lb ai/A; up to 3 days before or at planting; one application per crop);
- Cabbage (5 lb ai/A; up to 1 week before or at planting; one application per crop);
- Non-bearing Citrus (5 lb ai/A; bare root or tuber dip pre-plant or pot-drench);
- SLN Non-bearing Citrus (5 lb ai/A; at least 12 months before fruiting, by band, broadcast spray or irrigation, no more than two applications per season);
- Corn - Field and Sweet (4 lb ai/A; at planting, one application per crop);
- SLN Corn- Sweet (6 lb ai/A; at 1 week pre-plant or at planting, one appl per crop);
- Cucumber (2 lb ai/A; at or just before planting, one application per crop);
- Field nursery stock ornamentals (6 lb ai/A; soil broadcast treatment 72 hours prior to planting);
- Peanut (6 lb ai/A; up to 1 week before or at planting, one application per crop);
- Pineapple (6 lb ai/A; at or within 2 months of planting via drip irrigation, reapply every two months, with limit of 8 applications (8 gallons EC/A) per plant crop and 5 applications (5 gallons EC/A) per ratoon crop);
- Potato (12 lb ai/A; within 2 weeks prior to or at planting or until prior to crop emergence, one application per crop);
- Sugarcane (8 lb ai/A; at planting, one application per crop);
- Sweet Potato (8 lb ai/A; 2-3 weeks before planting, one application per crop); and
- Tobacco (12 lb ai/A; from 1 to 2 weeks prior to transplanting time to transplanting time, one application per crop).

Note: The Agency recently received hypothetical future use information from the Pineapple Growers Association of Hawaii for the post-plant application of ethoprop EC to pineapples in Hawaii. Although the Agency has not yet carefully evaluated this information, it is not anticipated that an exposure assessment using this information will alter the current RED document recommendations.

3.a.i. Modifications Based upon Agency's Revisions, USDA Comments, and/or Rhone-Poulenc's Comments

Minor HED-based modifications (regarding application rates) are included in this section of the assessment. HED has also included information provided by Rhone-Poulenc regarding banana acres treated (letter dated 12/14/98). Even though the backpack application of granulars is an exposure scenario, HED has no data to evaluate this scenario. The information submitted by Rhone-Poulenc will be incorporated into any future risk assessment completed by HED, should appropriate data become available. **Please note that acceptance of Rhone-Poulenc's information for this risk assessment requires the modification of all labels which currently reflect application rates greater than 5.5 lb ai/A for bananas and plantains.**

3.b. Occupational and Non-Occupational/Recreational Exposure and Risk Assessment

HED has determined that there is a potential for exposure in occupational settings from handling ethoprop products during the application process (i.e., mixer/loader, applicator and mixer/loader/applicator) and from entering previously treated areas. As a result, risk assessments have been completed for individual and professional pesticide applicator scenarios. In addition, HED has determined that there is potential for exposure to golfers who enter golf courses following ethoprop treatment.

3.b.i. Calculations/Endpoints Used in the Exposure and Risk Assessments

A series of toxicological endpoints and calculations were used to complete the individual and professional pesticide applicator risk assessments, post-application assessments and non-occupational assessments. The endpoints and equations which have been used are presented in this section. All endpoints were selected by the Hazard Identification Assessment Review Committee (HIARC). HIARC determined that the uncertainty factor (UF) for all scenarios was 100 (10x for intra-species variability and 10x for inter-species variability).

Acute Toxicology Categories

Guideline studies for acute toxicity indicate that the technical grade of ethoprop is classified as category I for acute oral and acute dermal toxicity, category II for acute inhalation toxicity, and category I for primary eye irritation and primary skin irritation. There are no data on dermal sensitization; the 1988 Reregistration Standard waived this data requirement due to mortality during primary skin irritation tests.

Toxicological Endpoints of Concern

During the exposure assessment process, it was determined that uses of ethoprop by individual and professional pesticide applicators result in short-term and intermediate-term exposures of these applicators. However, the frequency and

duration of these exposures do not exhibit a chronic exposure pattern (i.e., daily exposure which occurs for a minimum of several months). Therefore, performing a chronic occupational assessment is not appropriate and toxicological endpoints of a chronic nature will not be discussed in this section.

Dermal Exposure: For the short-term and intermediate-term dermal occupational exposure scenarios, a No Observed Adverse Effect Level (NOAEL) of 0.1 milligrams/kilograms/day (mg/kg/day) will be used for calculating the Margin Of Exposure (MOE). These exposure scenarios are based upon plasma, red blood cell, and brain cholinesterase inhibition endpoints. Since the short-term and intermediate-term NOAELs were selected based upon a 21-day dermal rabbit study, no dermal absorption adjustment is required for these assessments.

Inhalation Exposure: For the short-term and intermediate-term inhalation occupational exposure scenarios, a NOAEL of 0.025 and 0.01 mg/kg/day, respectively, will be used for calculating the MOE. These exposure scenarios are also based upon plasma cholinesterase endpoints from dog feeding studies (90-day and combined 5-month/chronic, respectively). It was assumed that the inhalation toxicity was equivalent to the oral toxicity.

Carcinogenic Potential: Ethoprop is classified as a "likely" human carcinogen. The cancer potency value or Q_1^* (also known as the cancer slope factor) is $2.81 \text{ E-}02 \text{ (mg/kg/day)}^{-1}$ for ethoprop. A 100% absorption factor is assumed for both the dermal and inhalation exposure routes in this risk assessment. A cancer risk which incorporates both dermal and inhalation exposures is considered acceptable if less than 1×10^{-4} for occupationally exposed populations and less than 1×10^{-6} for the general population.

Toxicological NOAELs of Concern and Q_1^* for Assessments

NOAEL_{ST,dermal} = 0.1 mg/kg/day
NOAEL_{ST,inhalation} = 0.025 mg/kg/day
NOAEL_{IT,dermal} = 0.1 mg/kg/day
NOAEL_{IT,inhalation} = 0.01 mg/kg/day
 Q_1^* is $2.81 \text{ E-}02 \text{ (mg/kg/day)}^{-1}$

Individual and Professional Pesticide Applicator Exposure and Risk Equations

Daily dermal and inhalation exposures, potential daily doses, and risks are calculated as described below. The first step is to calculate daily dermal and inhalation exposures.

Daily dermal exposure is calculated:

Daily dermal exposure (mg ai/day) =

Unit exposure (mg ai/lb ai) x Application rate (lb ai/A) x Daily treatment (A/day)

Where:

Daily dermal exposure = amount deposited on the surface of the skin that is available for dermal absorption, also referred to as potential dose (mg ai/day);

Unit exposure = normalized exposure value derived from February, 1998 PHED Surrogate Exposure Table, no chemical-specific data were available for this assessment (mg ai/lb ai applied);

Application rate = normalized application rate based on a logical unit treatment such as acres, a maximum value is generally used (lb ai/A); and

Daily treatment = normalized application area based on a logical unit treatment such as acres (A/day).

[Note: (lb ai/acre) and (A/day) are replaced, respectively, with (lb ai/gal) and (gal/day) when appropriate.]

Daily inhalation exposure is calculated:

Daily inhalation exposure (mg ai/day) =

[Unit exposure (μ g/lb ai) x Application rate (lb ai/A) x Daily treatment (A/day)] / (1000 μ g/mg)

Where:

Daily inhalation exposure = amount available for absorption, also referred to as potential dose (mg ai/day);

Unit exposure = normalized exposure value derived from February, 1998 PHED Surrogate Exposure Table, no chemical-specific handler data were available for this assessment (μ g ai/lb ai applied);

Application rate = normalized rate based on a logical unit treatment such as acres, a maximum value is generally used (lb ai/A); and

Daily treatment = normalized area based on a logical unit treatment such as acres (A/day).

Potential daily dermal and inhalation doses are then calculated by normalizing the daily dermal and inhalation exposures by body weight. For individual and professional pesticide applicators using ethoprop, a body weight of 70 kg (default adult body weight) was used for all exposure scenarios because the effects observed in the

toxicological studies were not sex-specific.

Since the toxicity endpoint is based upon a 21-day dermal study, use of a dermal absorption factor is not needed. It was assumed that the inhalation toxicity was equivalent to the oral toxicity from the 90-day and 5-month feeding studies. Daily inhalation exposure levels were calculated for inclusion into the PHED surrogate exposure tables and presented as ($\mu\text{g}/\text{lb ai}$) based on a human inhalation rate of 29 L/minute and an 8-hour working day. The absorbed dermal and inhalation doses for short- and intermediate-term scenarios were calculated using the following equation.

Potential Daily Dose is calculated:

$$\text{Potential daily dermal or inhalation dose (mg ai/kg/day)} = \frac{\text{Daily dermal or inhalation exposure (mg ai/day)}}{\text{body weight}}$$

[Note: 70 kg human assumed for both short-term and intermediate-term exposures; calculates a potential biologically-available dose resulting from dermal or inhalation exposure.]

Once the route-specific potential daily doses are calculated, the dermal and inhalation Margins of Exposure (MOEs) are calculated as follows.

Margin of Exposure is calculated:

$$\text{MOE (unitless)} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Potential Daily Dose (mg/kg/day)}}$$

[Note: NOAEL and potential daily dose are for the same route of exposure and exposure duration (e.g., both dermal or both inhalation and both short-term or both intermediate-term).]

Because exposures from both the dermal and inhalation routes have the same toxicological effect (i.e., plasma cholinesterase inhibition), the route-specific MOEs can be combined to express a total risk from ethoprop exposure. That is, once $\text{MOE}_{\text{ST,dermal}}$, $\text{MOE}_{\text{ST,inhalation}}$, $\text{MOE}_{\text{IT,dermal}}$ and $\text{MOE}_{\text{IT,inhalation}}$ have been calculated for each exposure scenario, the short-term MOEs and intermediate-term MOEs can be combined using the following equations.

Combined Dermal and Inhalation Margin of Exposures are calculated:

$$\begin{aligned} \text{MOE}_{\text{ST,Combined}} &= \frac{1}{\left(\frac{1}{\text{MOE}_{\text{ST,dermal}}} + \frac{1}{\text{MOE}_{\text{ST,inhalation}}} \right)} \\ \text{MOE}_{\text{IT,Combined}} &= \frac{1}{\left(\frac{1}{\text{MOE}_{\text{IT,dermal}}} + \frac{1}{\text{MOE}_{\text{IT,inhalation}}} \right)} \end{aligned}$$

The HED Cancer Peer Review Committee determined ethoprop to be a “likely” human carcinogen and calculated a potency value or Q_1^* of $2.81 \text{ E-02 (mg/kg/day)}^{-1}$. A 100 percent absorption factor is assumed for both the dermal and inhalation exposure routes in this risk assessment. A cancer risk which incorporates both dermal and inhalation exposures is considered acceptable, if in the range of 10^{-4} or lower for occupationally-exposed populations and 1×10^{-6} (one in a million) for the general population. The Agency closely examines occupational cancer risks in the 1×10^{-4} to 1×10^{-6} range and seeks ways to reduce individual cancer risks to the greatest extent feasible, preferably 10^{-6} or less.

When cancer risk is quantified using a Q_1^* , risk is expressed as a probability. For example, the probability frequently considered to represent an acceptable risk level is 1×10^{-6} (one in a million) for the general population. When this approach is used, the implicit assumptions are that any exposure will lead to some level of risk and that risk is directly and linearly proportional to exposure, regardless of the dosing schedule.

Average daily doses are calculated by summing the potential daily doses from dermal and inhalation routes. Once the Average daily dose is calculated, a Lifetime Average Daily Dose (LADD) can be calculated. To obtain the cancer risk associated with a specific exposure scenario, the LADD is multiplied by Q_1^* .

Average Daily Dose is calculated:

$$\text{Average Daily Dose (mg/kg/day)} = \text{Potential daily dose}_{\text{Dermal}} \text{ (mg/kg/day)} + \text{Potential daily dose}_{\text{Inhalation}} \text{ (mg/kg/day)}$$

Lifetime Average Daily Dose is calculated:

$$\text{Lifetime Average Daily Dose (mg/kg/day)} = \text{Average Daily Dose (mg/kg/day)} \times (\# \text{ days worked}/365 \text{ days per year}) \times (35 \text{ years worked}/70 \text{ year lifetime})$$

[Note: the # days worked by professional pesticide applicators generally averages 10 times that of individual pesticide applicator.]

Cancer Risk is calculated:

$$\text{Cancer Risk} = \text{LADD (mg/kg/day)} \times Q_1^* \text{ (mg/kg/day)}^{-1}$$

Post-Application Worker Exposure and Risk Calculations

Because ethoprop is used in pre-plant and pre-emergent applications and is normally soil incorporated or watered-in, there are generally no concerns for post-application exposure to agricultural workers. Two exceptions are sugarcane and pineapples. Sugarcane is mechanically transplanted and should have minimal post-application concerns. In order to refine the potential post-application exposure assessment for sugarcane, appropriate exposure monitoring data are requested to determine workers' exposure. Ethoprop may be applied to pineapples at various points in the growing season. However, there is currently a 120 day pre-harvest interval established for pineapples, so there should generally be minimal concern during harvesting.

HED is concerned about potential occupational post-application exposure to ethoprop for activities on golf courses, such as mowing and maintenance. As a result, a post-application risk assessment was conducted for turf management professionals.

The calculations used to estimate daily dermal dose, MOE and cancer risk for the dermal post-application scenarios are similar to those described previously for the applicator scenarios. The only significant differences are: (1) the manner in which daily dermal dose is calculated using transfer coefficient, transferable residue levels, and accounting for the dissipation of ethoprop over time and (2) inhalation exposures were not calculated for the post-application scenarios (i.e. potential daily dose and MOE calculations only represent dose levels from dermal exposures, because inhalation exposures have been shown to account for a negligible percentage of the overall body burden).

Chemical-specific turf transferable residue data were not available when this document was completed. Therefore, a range finder assessment is presented in this document to illustrate HED's concern for post-application activities on golf courses, such as mowing and maintenance. The use of both tractors and push-type mowers are presented in this document. The equations for calculating turf transferable residue and dermal dose follow.

Turf transferable residue is calculated:

Turf transferable residue ($\mu\text{g}/\text{cm}^2$) =

Application rate (lb ai/A) x 11.209 $\mu\text{g}/\text{cm}^2$ per lb ai/A conversion x Residue % available

Where:

Turf transferable residue (TTR) = transferable residue that represents the amount of residue on turf that is available for dermal exposure at time (t) [$\mu\text{g}/\text{cm}^2$];

Application rate = normalized application rate based on a logical unit treatment such as acres, a maximum value is generally used (lb ai/A); and

Residue % available = percentage of residue present on turf at time (t).

[Note: two application rates (10 lb ai/A and 20 lb ai/A) were used in this assessment; residue of 5% assumed after treatment; residue dissipation of 10% assumed per day.]

Dermal dose is calculated:

Dermal dose (mg ai/kg/day) =

$$(\text{TTR}(t) [\mu\text{g}/\text{cm}^2] \times \text{Tc} (\text{cm}^2/\text{hr}) \times \text{DA} \times 0.001 \text{ mg}/\mu\text{g} \text{ conversion} \times \# \text{ hours worked/day}) / \text{body weight (kg)}$$

Where:

Dermal dose (t) = dermal dose attributable to exposure at time (t) when engaged in a specific mechanical activity or job function (mg ai/kg/day);

Turf transferable residue (TTR) = transferable residue that represents the amount of residue on turf that is available for dermal exposure at time (t) [$\mu\text{g}/\text{cm}^2$]; as defined above;

Tc = transfer coefficient or measure of the relationship of exposure to transferable residue concentrations while engaged in a specific mechanical activity or job function;

DA = dermal absorption (%);

Hours worked/day = exposure duration or hours engaged in specific mechanical activity (hrs/day); and

Body weight = body weight (kg).

[Note: transfer coefficients of 1000 and 500 were assumed for push-type mowers and tractors, respectively; 100% dermal absorption was assumed (as previously described in this document); 70 kg human assumed.]

Non-Occupational/Recreational Exposure and Risk Calculations

HED is concerned about potential non-occupational/recreational exposure to golfers following ethoprop treatment of golf courses. As a result, a risk assessment was conducted for golfers. Although chemical-specific data were not available to complete this assessment, a range finder assessment is presented in this document for non-occupational/recreational exposure.

The calculations used to estimate daily dermal dose and MOEs for the dermal non-occupational/recreational scenarios are similar to those described previously for the post-application worker scenarios. The only differences in calculating the dermal dose of golfers were: (1) the duration of golfing 18 holes was estimated at 4 hours and (2) the use of 100 as a transfer coefficient. Golfers' dermal exposure is anticipated to be significantly lower than post-application workers, and golfers' exposures are anticipated to occur through minimal hand contact with the golf ball and dermal exposure to the lower legs. As a result, a transfer coefficient of 100 is consistent with low potential for dermal transfer. As is the case for post-application workers, a body weight of a 70 kg was used in the calculations and inhalation exposures were not calculated. In addition, no potential hand-to-mouth exposures were estimated for non-occupational/recreational exposures.

The method to calculate golfers' cancer risk varied slightly from the previous described methods. It was assumed that individuals golf 26 times per year. However, golfers are not anticipated to have potential ethoprop exposure every time they golf due to the following: (1) ethoprop may be applied at a maximum of 40 lb ai/A/year (e.g., 4 applications of 10 lb ai/A or 2 applications of 20 lb ai/A) and (2) the dissipation of ethoprop over time will reduce golfers' exposures and risk. It was assumed that ethoprop would dissipate to levels which would cause negligible exposure to golfers after 60 days (e.g., estimated TTR levels approximate $0.01 \mu\text{g}/\text{cm}^2$ at 60 days for both application rates). As a result, the calculated TTR over a 60-day period were averaged. Then it was assumed that no overlapping treatments (within the 60-day period) would be made. For the 10 lb ai/A application, it was assumed that 1, 2, 3 or 4 applications would be made per year. On the remainder of the days in the year, it was assumed that, due to dissipation, there was no potential ethoprop exposure. An average dose was then calculated. Similar calculations were made for the 20 lb ai/A application which can be applied twice per year. Again, it was assumed that no overlapping treatments (within the 60-day period) would be made and on the remainder of the days in the year, due to dissipation, there was no potential ethoprop exposure. These average daily dermal doses were used to calculate golfers' cancer risk. This method was used to account for typical dermal exposures rather than high- or low- level exposures.

3.b.ii. Modifications Based upon Agency's Revisions, USDA Comments, and/or Rhone-Poulenc's Comments

HIARC reviewed the toxicological endpoints for ethoprop and decided to retain the same endpoints for the dermal exposure route (i.e., cholinesterase inhibition in a 21-day rabbit dermal study for both the short-term and intermediate term endpoints: 0.1 mg/kg/day). However, HIARC selected new endpoints for the inhalation exposure route (i.e., cholinesterase inhibition in a 90-day dog feeding study for the short-term endpoint: 0.025 mg/kg/day; and cholinesterase inhibition in a combined 5-month/chronic dog feeding study for intermediate-term endpoint: 0.01 mg/kg/day). The toxicological effect in each of these scenarios is the same for each route and the uncertainty factors applied to each scenario (short-term and intermediate-term) are the same (i.e., 100).

The HIARC also retained the dermal absorption factor of 100.

The calculations for individual and professional pesticide applicator exposures have been modified from the original risk assessment, as a result of the modifications in the hazard aspects of the ethoprop risk assessment. Instead of calculating risks from the dermal and inhalation routes by summing the potential daily doses attributed to dermal and inhalation exposures, the current HED methodology (presented in the previous section) is used.

A golfer exposure and risk assessment has been incorporated into this document.

No changes were included in this section as a result of HED accepting Rhone-Poulenc's comments to the initial RED document of May 1998.

3.b.iii. Risk Assessment Assumptions and Factors

The following assumptions and factors were used to complete the occupational, post-application and non-occupational/recreational (e.g., golfer) assessments:

- Average body weight of an adult handler is 70 kg. This body weight is used in all assessments within this document, since the endpoint of concern is not sex-specific (i.e., cholinesterase inhibition can be assumed to occur in both males and females).
- Average work day interval for occupational and post-application scenarios represents an 8-hour workday (e.g., the acres treated, volume of spray solution prepared in a day or number of hours involved in post-application activity [such as mowing and maintenance]).
- Daily acreage and volumes (as appropriate) to be treated in each scenario include:
 - Granules by fixed-wing aircraft: -potatoes - 350 acres
 - Granules by tractor-drawn spreader: -agricultural - 80 acres
 - golf course turf - 40 acres
 - Granules by hand (banana/plantain): -agricultural - 1 acre
 - Granules by push-type spreader to turf: -golf course turf - 5 acres
 - Liquids by chemigation: -agricultural - 350 or
 - agricultural - 80 acres
 - Liquids by groundboom spray: -agricultural - 80 acres
 - Liquids by low-pressure handwand: -agricultural - 5 acres
 - Liquids by backpack sprayer: -agricultural - 5 acres
 - Liquids with sprinkler can: -agricultural - 1 acre
- To evaluate risk levels associated with the various use patterns, calculations are

completed for a range of maximum application rates to various agricultural crops (i.e., low-range, mid-range and high range are maximum rates for specific crop types; and the maximum application rate for golf course turf) as listed on current, available ethoprop labels. *Save bananas, no use data were provided by the registrant concerning the actual or typical application rates that may be commonly used for ethoprop on various crops.*

- Due to a lack of scenario-specific data, HED often calculates unit exposure values using generic protection factors (PF) that are applied to represent various risk mitigation options (i.e., the use of personal protective equipment [PPE] and engineering controls). PPE protection factors include those representing a double layer of clothing (50% PF), chemically-resistant gloves (90% PF), and appropriate respiratory protection (80 to 90% PF, depending upon the type of respirator used). Engineering controls are generally assigned a protection factor of 90 to 98 percent, depending upon the type of engineering controls selected. Engineering controls may include: closed mixing/loading systems, closed cabs/cockpits, and Lock 'n Load™ type systems for granulars. When protection factors are used in estimating exposure, it is noted in the footnotes.
- For the occupational, post-application and non-occupational exposure assessments, a Margin of Exposure (MOE) of 100 was assigned by HIARC (10X for intra-species variability and 10X for inter-species variability).
- Several assumptions were made for the post-application and non-occupational exposure assessments: two application rates were used (10 lb ai/A and 20 lb ai/A), an initial residue of 5% was assumed after treatment, residue dissipation of 10% was assumed per day, a transfer coefficient of 100 was assumed for the non-occupational/recreational assessment, and transfer coefficients of 1000 and 500 were assumed for push-type mowers and tractors for the post-application assessment, respectively.
- For the non-occupational/recreational assessment numerous assumptions were made: it was assumed that individuals golf 26 times per year; the duration of golfing 18 holes was estimated at 4 hours; 100 was used as a transfer coefficient; ethoprop may be applied at a maximum of 40 lb ai/A/year (e.g., 4 applications of 10 lb ai/A or 2 applications of 20 lb ai/A); it was assumed that ethoprop would dissipate to levels which would cause negligible exposure to golfers after 60 days; it was assumed that no overlapping treatments (within the 60-day period) would be made; for the 10 lb ai/A formulation, it was assumed that 1, 2, 3 and 4 applications were made per year and for the 20 lb ai/A that 1 and 2 applications were made per year; and on the remainder days in the year, it was assumed that there was no potential exposure to ethoprop.
- For the occupational cancer assessment, the scenarios represent: 1) typical exposures experienced by individual pesticide applicators who apply ethoprop to

their own fields and 2) ten times the number of applications per season which represents typical exposures experienced by professional pesticide applicators. Most individual pesticide applicators make 1-2 applications per year. Most professional pesticide applicators make 10-20 applications per year. For the post-application cancer risk assessment, it was assumed that mowing and maintenance activities would occur following 4 applications of 10 lb ai/A or 2 applications of 20 lb ai/A (40 lb ai/A/year maximum on golf course turf).

- For the occupational and post-application cancer assessment, it was also assumed that workers are exposed for 35 years over a 70 year lifetime. For the non-occupational/recreational assessment, it was assumed that golfers are exposed for 50 years over a 70 year lifetime.

3.b.iv. Modifications Based upon Agency's Revisions, USDA Comments, and/or Rhone-Poulenc's Comments

Current HED policy estimates the application of granules by push-type spreader to golf course turf as 5 acres. This is modified from 8 acres and has been incorporated into the revised assessment. Rhone-Poulenc provided HED several PHED analyses (letter dated 12/03/98) which have been incorporated into the revised ethoprop ORE assessment. The Rhone-Poulenc PHED data output is included in Appendix C. HED agrees with Rhone-Poulenc's unit exposure values for Mixer/Loaders in Groundboom Applications. However, HED does not agree with Rhone-Poulenc's approach in the determination of their unit exposure values for Applicators in Groundboom Applications. Therefore, Rhone-Poulenc's values have been included in this assessment for illustrative purposes only. It should also be noted that risk values are similar to those calculated by HED and that these revised unit exposures should not influence the results of the risk assessment. No additional changes were included in this section of the assessment, as a result of HED accepting Rhone-Poulenc's comments to the initial RED document of May 1998.

3.b.v. Handler Exposure Data Sources

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted to the Agency in support of the reregistration of ethoprop. When chemical-specific exposure data are unavailable, it is HED's policy to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions.

PHED was designed by a task force of representatives from the US EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts – a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database

contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based upon the central assumption that the magnitude of handler exposures to pesticides are primarily a function of task (e.g., mixing/loading/applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and levels of personal protective clothing worn by the individual and professional pesticide applicator (e.g., gloves, double layer of clothing).

Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (e.g., chest, upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based upon the number of observations and the available quality control data. These evaluation criteria and the caveats specific to each exposure scenario are summarized in Table 5. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposures for many occupational scenarios that can be used to ensure consistency in exposure assessments.

3.b.vi. Personal Protective Equipment Summary

Two common risk mitigation approaches HED considers for reducing occupational exposures are the use of personal protective equipment [PPE] (i.e., chemically-resistant gloves, double layer of clothing) and the use of engineering controls (i.e., closed tractor cabs, closed mixing/loading/transfer systems, and water-soluble packets). Occupational exposure assessments are completed by HED through a tiered approach using a baseline exposure scenario and, if required, increasing the levels of risk mitigation (use of PPE and engineering controls) to achieve an acceptable

margin of exposure or cancer risk. [Note: administrative controls are generally not considered in exposure assessments, because exposure assessments are conducted with respect to the current registered labels.]

The baseline clothing/PPE outfit for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemically-resistant gloves and no respiratory protection (exceptions are otherwise noted). The first level of mitigation generally considered in the exposure assessment is the use of PPE. As is used in this exposure assessment, PPE involves the use of an additional layer of clothing, chemically-resistant gloves and appropriate respiratory protection beyond the baseline outfit (i.e., long pants and long-sleeved shirt). The next level of mitigation considered in the assessment is the use of engineering controls (when feasible for the application method). The currently accepted ethoprop labels require the use of the following PPE.

For liquid formulations:

- coveralls over long-sleeved shirt and long pants
- chemically-resistant gloves
- chemically-resistant footwear and socks
- protective eyewear
- chemically-resistant headwear for overhead exposure
- chemically-resistant apron when cleaning equipment, mixing or loading
- respiratory protection (organic vapor with pesticide pre-filter or pesticide canister)

For granular formulations in agricultural settings:

- coveralls over long- or short-sleeved shirts and long or short pants
- waterproof gloves
- chemically-resistant footwear and socks
- protective eyewear
- chemically-resistant headgear for overhead exposure
- chemically-resistant apron when cleaning equipment, mixing or loading
- respiratory protection (dust/mist respirator)

For granular formulations on golf courses:

- mixers/loaders use coveralls over short-sleeved shirt and short pants, waterproof gloves, shoes and socks, and dust/mist respirator
- applicators use long-sleeved shirt, long pants, shoes and socks

For granular formulations in Lock 'n Load™

(qualify as closed loading system under the Worker Protection Standard):

- long-sleeved shirt and long pants
- shoes and socks
- chemically-resistant apron
- waterproof gloves

3.b.vii. Occupational Handler Risk Assessment

HED has determined that individual and professional pesticide applicators (i.e. mixers, loaders, applicators, flaggers) are likely to be exposed during ethoprop use. Due to the frequency and duration of ethoprop uses, it was determined that uses of ethoprop by individual and professional pesticide applicators result in short-term and intermediate-term exposures to these applicators. However, the frequency and duration of these exposures do not exhibit a chronic exposure pattern (i.e., daily exposure which occurs for a minimum of several months). The anticipated use patterns and current labeling indicate numerous exposure scenarios based upon the types of equipment that potentially can be used to make ethoprop applications. These scenarios serve as the basis for the quantitative exposure and risk assessments. These scenarios include:

- 1a loading granulars for aerial application;
- 1b loading granulars for tractor-drawn spreader application;
- 2a mixing/loading liquids for chemigation application;
- 2b mixing/loading liquids for groundboom application;
- 2* Rhone-Poulenc PHED analysis of mixing/loading liquids for groundboom application;
- 3a applying granulars with fixed-wing aircraft;
- 3b applying granulars with a tractor-drawn spreader;
- 4 applying sprays with a groundboom sprayer;
- 4* Rhone-Poulenc PHED analysis for applying sprays with a groundboom sprayer;
- 5a loading/applying granules with a push-type granular spreader;
- 5b loading/applying granules by hand (includes information provided by Rhone-Poulenc for banana acres treated);
- 6a mixing/loading/applying sprays with a low pressure handwand;
- 6b mixing/loading/applying sprays with a backpack sprayer;
- 7 mixing/loading/applying liquids with a sprinkler can;
- 8 mixing/loading/applying liquid concentrate by handheld measuring container;
- 9 dipping seedlings in liquid formulations; and
- 10 flagging for granular application with fixed-wing aircraft.

[Note: Exposure data from the Pesticide Handler Exposure Database (PHED) Version 1.1 garden hose-end sprayer scenario are used as surrogate data for the sprinkler can scenario (#7). There are neither exposure data nor pesticide application information available for scenarios 8 and 9. These scenarios are referenced in the tables found in Appendix A as *No Data*.]

The risk assessment has been completed based upon the exposure data available to HED. The handler exposure and risk calculations are presented in the tables contained in Appendix B entitled *Ethoprop Handler Exposure and Risk Assessment Tables*. These results are for both individual and professional pesticide applicators. The exposure factors (i.e., scenario descriptors, application rates, and

daily treatment), unit exposure values at varying levels of mitigation, and toxicological parameters used in the assessment are presented in Table 1 of Appendix B. The calculation of daily exposure in milligrams/day (mg/day) at the baseline risk mitigation level, potential daily dose (mg/kg/day) and combined dermal and inhalation MOEs using ST and IT NOAELs are presented in Table 2. Tables 3 and 4 contain similar calculations for increased levels of risk mitigation -- use of additional mitigation in the form of personal protective equipment (PPE) are presented in Table 3 and use of engineering controls are presented in Table 4. The format of these tables is similar to Table 2. The only differences are the unit exposure values taken from Table 1 which represent different levels of risk mitigation.

Table 5 summarizes the parameters and caveats specific to the PHED exposure data used for each exposure scenario and corresponding exposure/risk assessment. These caveats include the descriptions of the source of the data and an assessment of the overall quality of the data. Generally, the assessment of the data is based upon the number of observations and the available quality control data. Quality control data are assessed based upon a grading criteria established by the PHED Task Force. Additionally, it should be noted that all calculations were completed based on current HED policies pertaining to the completion of occupational and residential exposure/risk assessments (e.g., rounding, exposure factors and acceptable data sources).

The Average Daily Doses (ADD) of baseline, PPE and engineering controls are presented for each exposure scenario in Table 6 of Appendix B. The Potential Daily Doses (PDDs) found in Tables 2, 3 and 4 were used to calculate these ADDs. The lifetime average daily dose and cancer risk values are presented in Table 7 at baseline, PPE and engineering controls mitigation levels for each exposure scenario. As noted in Table 7, the number of treatments per crop per season are included for both individual and professional pesticide applicators.

3.b.viii. Post-Application Occupational Risk Assessment

There is low potential for occupational post-application exposure when pre-plant and pre-emergence insecticides are used. Ethoprop is applied to the soil directly and is soil incorporated or watered-in at the time of application. The timing of the application of ethoprop can greatly reduce the potential for post-application exposure. Also, most agricultural operations mechanically plant early in the season, which minimizes the potential for dermal contact. Minimal exposure during harvesting or any other late season activities is anticipated since ethoprop is applied pre-plant or pre-emergence. Therefore, HED does not require a post-application occupational exposure assessment for ethoprop on agricultural crops (HED Exposure Science Advisory Council Policy No. 008).

Although there are generally no concerns for post-application exposure to agricultural workers, two exceptions for this use pattern are sugarcane and pineapples. Sugarcane is mechanically transplanted and should have minimal post-application

concerns. However, in order to refine the potential post-application exposure assessment for sugarcane, appropriate exposure monitoring data are requested to determine workers' exposures. Ethoprop may also be applied to pineapples at various points in the growing season. There is, however, a 120 day pre-harvest interval on current labels for pineapples, so there should generally be minimal concern during harvesting.

HED is concerned about potential occupational post-application exposure to ethoprop for activities on golf courses, such as mowing and maintenance. As a result, a post-application risk assessment was conducted for turf management professionals.

A re-entry interval (REI) is defined as the time it takes for residues to decline to a level that entry into a previously treated area and engaging in a task or activity would not result in exposures that exceed the Agency's level of concern. When chemical-specific data are available, REIs are established on a chemical-, crop-, and activity-specific basis. No chemical-specific data were available for this assessment. As a result, REIs and cancer risks for post-application activities were calculated using default values and equations previously described in section 3.b.i. REIs and cancer risks for the mowing and maintenance of golf course turf using both tractors and push-type mowers were calculated. The results are presented in the tables contained in Appendix D entitled *Ethoprop Post-Application Worker Exposure and Risk Assessment Tables*. Table 1 contains REIs and cancer risks following the application of 10 lb ai/A on golf course turf, and Table 2 contains REIs and cancer risks following the application of 20 lb ai/A on golf course turf.

3.b.ix. Modifications Based upon Agency's Revisions, USDA Comments, and/or Rhone-Poulenc's Comments

The Agency did not conduct post-application exposure and risk assessments in previous versions of the occupational document.

3.b.x. Non-Occupational/Recreational Risk Assessment

HED is concerned about potential non-occupational/recreational exposure to golfers following ethoprop treatment of golf courses. As a result, a risk assessment was conducted for golfers. Although chemical-specific data were not available to complete this assessment, a range finder assessment is presented in this document for non-occupational/recreational exposure.

As no chemical-specific data were available for this assessment, MOEs and cancer risks for golfers were calculated using default values and equations previously described in section 3.b.i. The results are presented in the tables contained in Appendix E entitled *Ethoprop Non-Occupational/Recreational Exposure and Risk Assessment Tables*. Table 1 contains MOEs and cancer risks following the application

of 10 lb ai/A on golf course turf, and Table 2 contains MOEs and cancer risks following the application of 20 lb ai/A on golf course turf.

3.b.xi. Modifications Based upon Agency's Revisions, USDA Comments, and/or Rhone-Poulenc's Comments

The Agency did not conduct non-occupational/recreational exposure and risk assessments in previous versions of the occupational document.

3.c. Occupational and Non-Occupational Risk Assessment/Characterization

The occupational and non-occupational risk assessments are summarized herein. Please refer to the appropriate tables as stated in the text. These tables are the basis for the risk assessments.

3.c.i. General Risk Characterization Considerations

Several issues must be considered when interpreting the results of the occupational and non-occupational assessments. These include:

- ☐ No chemical-specific handler exposure data were submitted. As a result, all analyses were completed using exposure data from PHED Version 1.1 and default data. Several handler assessments were completed using "low quality" PHED data due to the lack of a more acceptable data set. The PHED unit exposures range between the geometric mean and the median of the available exposure data.
- ☐ No chemical-specific post-application and non-occupational exposure data were submitted. As a result, default values were used to estimate potential exposures and doses for workers entering treated golf courses and individuals golfing following ethoprop treatment. Default transfer coefficient values are based upon published empirical data and are generally considered by HED to represent reasonable estimates of potential dermal exposure.
- ☐ Several generic protection factors were used to calculate handler exposures. The protection factors used for clothing layers and gloves have not been completed evaluated by HED. The key element being evaluated by HED is the protection factor for clothing. The protection factors used for respiratory protection are based upon NIOSH's *Respirator Decision Logic* and the protection factor for gloves is in the range which OSHA and NIOSH often use.
- ☐ In some cases, exposure factors used to calculate daily occupational exposures to handlers are based upon the best professional judgment (due to lack of pertinent data). In other cases, exposure factors have been referenced from the

3.c.ii. Handler Risk Characterization Results

Combined Short-term Dermal and Inhalation Non-Cancer Risks

The calculations of combined short-term dermal and inhalation risks indicate that MOEs do not exceed 100 for any exposure scenarios (*even at the highest level of risk mitigation available*). The following ranges of combined short-term dermal and inhalation MOEs were calculated for baseline, PPE and engineering controls scenarios. **All of the Combined MOEs were below 100. None of the HED-calculated Combined MOEs exceeded 30, and none of the MOEs calculated using Rhone-Poulenc's PHED analyses exceeded 11.**

Short-Term Scenario	Lowest Combined MOE	Highest Combined MOE
Baseline	0.00059	3.0
PPE	0.033	9.0
Engineering Controls	0.17	30
R-P PHED analysis for Groundboom Applications	1.7	11

Legend:

M/L = Mixer/Loader; A = Applicator; M/L/A = Mixer/Loader/Applicator; and F = Flagger

Note:

The **MOE uncertainty factor = 100** but for illustrative purposes, the following scenarios are presented which have MOEs greater than or equal to **10**.

Baseline & PPE

None

Engineering Controls

- (1b) M/L; Loading granulars for application with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 30**; using Lock 'n Load™ products; based upon high confidence in inhalation data, low confidence in dermal/hand data, and the use of protection factors for dermal and inhalation exposures.
- (3b) A; Applying granulars with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 15**; based upon high confidence in hand and inhalation data and low confidence in dermal data.
- (10) F; Flagging granular applications with fixed-wing aircraft; 6 lb ai/A; 350 A; **Combined MOE = 11**; using enclosed cab; medium confidence in dermal data and low confidence in hand and inhalation data.

Combined Intermediate-term Dermal and Inhalation Non-Cancer Risks

The calculations of combined intermediate-term dermal and inhalation risks indicate that MOEs do not exceed 100 for any exposure scenarios (*even at the highest level of risk mitigation available*). The following ranges of combined intermediate-term dermal and inhalation MOEs were calculated for baseline, PPE and engineering controls scenarios. **All of the Combined MOEs were below 100. None of the HED-calculated Combined MOEs exceeded 18, and none of the MOEs calculated using Rhone-Poulenc's PHED analyses exceeded 10.**

Intermediate-Term Scenario	Lowest Combined MOE	Highest Combined MOE
Baseline	0.00059	2.0
PPE	0.033	7.9
Engineering Controls	0.11	18
R-P PHED analysis for Groundboom Applications	1.5	10

Legend:

M/L = Mixer/Loader; A = Applicator; M/L/A = Mixer/Loader/Applicator; and F = Flagger

Note:

The **MOE uncertainty factor = 100** but for illustrative purposes, the following scenarios are presented which have MOEs greater than or equal to **10**.

Baseline & PPE

None

Engineering Controls

- (1b) M/L; Loading granulars for application with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 18**; using Lock 'n Load™ products; based upon high confidence in inhalation data, low confidence in dermal/hand data, and the use of protection factors for dermal and inhalation exposures.
- (3b) A; Applying granulars with a tractor-drawn mechanical spreader; 2 lb ai/A; 80 A; **Combined MOE = 10**; based upon high confidence in hand and inhalation data and low confidence in dermal data.

It should be noted that in each of the short-term and intermediate-term exposure scenarios (with the one exception of flagging) the significant risk driver is the dermal exposure route.

Combined Dermal and Inhalation Cancer Risks

The following two tables and descriptions summarize individual and professional pesticide applicator cancer risks for all ethoprop handler exposure scenarios in this assessment. Exposure scenarios for which combined dermal and inhalation cancer risks exceed 1×10^{-4} are presented.

At the highest level of mitigation available, one individual pesticide applicator exposure scenario and five professional pesticide applicator exposure scenarios yielded cancer risks greater than 1×10^{-4} .

Individual Pesticide Applicators' Table

Individual Scenario	Lowest Cancer Risk	Highest Cancer Risk
Baseline	8.1E-7	2.7E-2
PPE	3.6E-7	7.9E-4
Engineering Controls	8.1E-8	8.4E-5
R-P PHED analysis for Groundboom Applications	3.4E-7	2.0E-6

Legend:

M/L = Mixer/Loader; A = Applicator; M/L/A = Mixer/Loader/Applicator; and F = Flagger

Note:

The following scenarios have cancer risks greater than 1×10^{-4} .

Baseline

- (2a) M/L; Mixing/Loading Liquids for Chemigation; 2, 6 & 12 lb ai/A; 1, 2 & 8 treatments per crop per season; 350 & 80 A; based upon high confidence in inhalation, dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (2b) M/L; Mixing/Loading Liquids for Groundboom Applications; 2, 6 & 12 lb ai/A; 1 treatment per crop per season; 80 A; based upon high confidence in inhalation, dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (5a) M/L/A; Loading/Applying Granulars with a Push-type Granular Spreader; 20 lb ai/A; 2 treatments per crop per season; 5 A; based upon high confidence in inhalation, low to medium confidence in dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (5b) M/L/A; Loading/Applying Granulars by Hand; 5.5 lb ai/A; 1 & 2 treatments per crop per season; 1 A; based upon medium confidence in inhalation and dermal data; baseline data includes chemically-resistant gloves; hand data without gloves are calculated by using a 90% protection factor.

- (6a) M/L/A; Mixing/Loading/Applying Liquids with a Low-pressure Handwand Sprayer; 5 lb ai/A; 2 treatments per crop per season; 5 A; based upon low confidence in inhalation, dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (7) M/L/A; Mixing/Loading/Applying Liquids with a Sprinkler Can; 6 lb ai/A; 1 treatment per crop per season; 1 A; based upon low confidence in inhalation, dermal and hand data, and 50% protection factor was required to define the unit exposure which represents the use of a single layer of clothing.

PPE

- (2a) M/L; Mixing/Loading Liquids for Chemigation; 6 lb ai/A; 8 treatments per crop per season; 350 A; based upon high confidence in hand data, and the use of protection factors of 50% for dermal and of 90% for inhalation exposures from baseline data.
- (5b) M/L/A; Loading/Applying Granulars by Hand; 5.5 lb ai/A; 1 & 2 treatments per crop per season; 1 A; based upon medium confidence in hand data; use of protection factors of 50% for dermal and of 90% for inhalation exposures from baseline data.

Engineering Controls

None

Professional Pesticide Applicators' Table

Professional Scenario	Lowest Cancer Risk	Highest Cancer Risk
Baseline	9.8E-6	2.7E-1
PPE	3.9E-6	2.3E-3
Engineering Controls	8.1E-7	8.4E-4
R-P PHED analysis for Groundboom Applications	3.4E-6	2.0E-5

Legend:

M/L = Mixer/Loader; A = Applicator; M/L/A = Mixer/Loader/Applicator; and F = Flagger

Note:

The following scenarios have cancer risks greater than 1×10^{-4} .

Baseline

- (1a) M/L; Loading Granulars for Application by Fixed-Wing Aircraft; 6 & 12 lb ai/A; 10 treatments per crop per season; 350 A; based upon high confidence in inhalation, low confidence in dermal and hand data, and no use of protection factors for dermal and inhalation exposures.

- (2a) M/L; Mixing/Loading Liquids for Chemigation; 2, 6 & 12 lb ai/A; 10, 20 & 80 treatments per crop per season; 350 & 80 A; based upon high confidence in inhalation, dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (2b) M/L; Mixing/Loading Liquids for Groundboom Applications; 2, 6 & 12 lb ai/A; 10 treatments per crop per season; 80 A; based upon high confidence in inhalation, dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (5a) M/L/A; Loading/Applying Granulars with a Push-type Granular Spreader; 20 lb ai/A; 20 treatments per crop per season; 5 A; based upon high confidence in inhalation, low to medium confidence in dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (5b) M/L/A; Loading/Applying Granulars by Hand; 5.5 lb ai/A; 10 & 20 treatments per crop per season; 1 A; based upon medium confidence in inhalation and dermal data; baseline data includes chemically-resistant gloves; hand data without gloves are calculated by using a 90% protection factor.
- (6a) M/L/A; Mixing/Loading/Applying Liquids with a Low-pressure Handwand Sprayer; 5 lb ai/A; 20 treatments per crop per season; 5 A; based upon low confidence in inhalation, dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (6b) M/L/A; Mixing/Loading/Applying Liquids with a Backpack Sprayer; 5 lb ai/A; 20 treatments per crop per season; 5 A; based upon low confidence in inhalation, dermal and hand data; baseline data includes chemically-resistant gloves; no use of protection factors for dermal and inhalation exposures.
- (7) M/L/A; Mixing/Loading/Applying Liquids with a Sprinkler Can; 3 & 6 lb ai/A; 10 treatments per crop per season; 1 A; based upon low confidence in inhalation, dermal and hand data, and 50% protection factor was required to define the unit exposure which represents the use of a single layer of clothing.

PPE

- (1a) M/L; Loading Granulars for Application by Fixed-Wing Aircraft; 12 lb ai/A; 10 treatments per crop per season; 350 A; based upon high confidence in inhalation, low confidence in dermal and hand data, and no use of protection factors for dermal and inhalation exposures.
- (2a) M/L; Mixing/Loading Liquids for Chemigation; 6 & 12 lb ai/A; 10, 20 & 80 treatments per crop per season; 350 & 80 A; based upon high confidence in hand data, and the use of protection factors of 50% for dermal and of 90% for inhalation exposures from baseline data.
- (5a) M/L/A; Loading/Applying Granulars with a Push-type Granular Spreader; 20 lb ai/A; 20 treatments per crop per season; 5 A; based upon high confidence in inhalation data, low to medium confidence in dermal and hand data; and no use of protection factors for dermal and inhalation exposures.
- (5b) M/L/A; Loading/Applying Granulars by Hand; 5.5 lb ai/A; 10 & 20 treatments per crop per season; 1 A; based upon medium confidence in hand data; use of protection factors of 50% for dermal and of 90% for inhalation exposures from

- baseline data.
- (6a) M/L/A; Mixing/Loading/Applying Liquids with a Low-pressure Handwand Sprayer; 5 lb ai/A; 20 treatments per crop per season; 5 A; based upon baseline data; and use of protection factors of 50% for dermal and of 90% for inhalation exposures from baseline data.
 - (6b) M/L/A; Mixing/Loading/Applying Liquids with a Backpack Sprayer; 5 lb ai/A; 20 treatments per crop per season; 5 A; based upon baseline data; and use of protection factors of 50% for dermal and of 90% for inhalation exposures from baseline data.
 - (7) M/L/A; Mixing/Loading/Applying Liquids with a Sprinkler Can; 6 lb ai/A; 10 treatments per crop per season; 1 A; based upon baseline data; and use of protection factors of 50% for non-hand dermal data, 90% for hand data to account for use of chemically-resistant gloves, and of 90% for inhalation exposures from baseline data.

Engineering Controls

- (2a) M/L; Mixing/Loading Liquids for Chemigation; 6 & 12 lb ai/A; 10, 20 & 80 treatments per crop per season; 350 & 80 A; Mechanical transfer or Gel-Tec self-contained water-soluble packaging; high confidence in inhalation, dermal and hand data; gloves were worn during the use of engineering controls.

3.c.iii. Post-Application Risk Characterization Results

Because ethoprop is used in pre-plant or pre-emergent applications and is normally soil incorporated or watered-in, there are generally no concerns for post-application exposure to agricultural workers. Two exceptions for this use pattern are sugarcane and pineapples. Sugarcane is mechanically transplanted and should have minimal post-application concerns. In order to refine the potential post-application exposure assessment for sugarcane, appropriate exposure monitoring data are requested to determine workers' exposure. Ethoprop may be applied to pineapples at various points in the growing season. However, there is currently a 120 day pre-harvest interval established for pineapples, so there should generally be minimal concern during harvesting.

Post-application exposure assessment was conducted for turf management professionals. When using both tractors and push-type mowers, following applications made at the rates of 10 lb ai/A and 20 lb ai/A, it was determined that re-entry intervals (REIs) greater than 50 days were required before MOEs exceed 100 and workers could re-enter treated areas for mowing and maintenance. Specifically, REIs of 62 and 55 days, respectively, were calculated when mowing with a tractor following the application of 20 lb ai/A and 10 lb ai/A. Respectively, REIs of 68 and 62 days were calculated when using a push-type mower following the application of 20 lb ai/A and 10 lb ai/A. In addition, post-application cancer risks were also calculated. At the highest level of mitigation available, the cancer risks associated with these activities were in the mid to high 10^{-5} range. Although these risks did not exceed the 10^{-4} level of concern, the risks

did not lower to the 10^{-6} range until more than 32 and 44 days for tractors and push-type mowers, respectively.

The following table summarizes the post-application risks for turf management professionals.

Task	Days After Treatment	MOE	Cancer Risk
Tractor			4.9×10^{-5}
Mowing after 20 lb ai/A	62	107	
Mowing after 10 lb ai/A	55	103	
Push-type mower			9.9×10^{-5}
Mowing after 20 lb ai/A	68	101	
Mowing after 10 lb ai/A	62	107	

3.c.iv. Non-Occupational/Recreational Risk Characterization Results

An assessment to quantify golfer risk following ethoprop treatment was also conducted. On the day of ethoprop treatment for 20 lb ai/A and 10 lb ai/A, MOEs of 2 and 3 were calculated, respectively. To exceed MOEs of 100, 40 and 33 days needed to elapse, respectively, before golfers could enter ethoprop treated areas to golf. In addition, the cancer risks associated with golfer exposures ranged from $1.8\text{-}3.5 \times 10^{-6}$ for use of 20 lb ai/A and $1.2\text{-}5.1 \times 10^{-6}$ for use of 10 lb ai/A. This variation is dependent upon the number of ethoprop treatments made to the golf course turf during the year. The following table summarizes golfer non-cancer and cancer risks.

Application Rate	Days After Treatment	MOE	Cancer Risk
20 lb ai/A			$1.8\text{-}3.5 \times 10^{-6}$
	0	2	
	40	106	
10 lb ai/A			$1.2\text{-}5.1 \times 10^{-6}$
	0	3	
	33	101	

3.c.v. Modifications Based upon Agency's Revisions, USDA Comments, and/or Rhone-Poulenc's Comments

As previously stated, the calculations of handler exposures and risks have been modified from the original risk assessment, as a result of the modifications in the hazard aspects of the ethoprop risk assessment. Instead of calculating risks from the dermal and inhalation routes by summing the potential daily doses attributed to dermal and inhalation exposures, the current HED methodology was used. As a result, combined dermal and inhalation MOEs have been reduced relative to the original risk assessment. *No additional changes were included in this section of the assessment, as a result of HED accepting Rhone-Poulenc's comments to the initial RED document of May 1998.*

Again, Rhone-Poulenc provided HED several PHED analyses which have been incorporated into this risk assessment (Rhone-Poulenc letter dated 12/03/98). These are included in Appendix C. The resulting risks did not vary significantly from the risks calculated by HED. Indeed, the analyses using Rhone-Poulenc's values do not alter HED's assessment.

3.d. Incident Reports

3.d.i. General Summary

EPA has obtained incident information concerning ethoprop from four sources: 1) the Office of Pesticide Programs (OPP) Incident Data System (IDS), 2) Poison Control Centers (PCC), 3) the California Department of Food and Agriculture (CDFA); replaced by the Department of Pesticide Regulation in 1991), and 4) the National Pesticide Telecommunications Network (NPTN; a toll-free information service supported by OPP). The IDS contains reports of incidents submitted to OPP since 1992 from various sources, including registrants, other federal and state health and environmental agencies, and individual consumers. PCC provides OPP data as a result of Data-Call-Ins issued in 1993. This data covers the years 1985 through 1996 for 28 organophosphates and carbamate chemicals. The CDFA data consists of uniform reports, required by statute since 1982, from physicians on suspected pesticide poisonings and all illnesses suspected of being related to exposure to pesticides. The NPTN data consists of a tabulation of the top 200 categories of human incidents, animal incidents, calls for information, and others.

A memorandum entitled *Review of Ethoprop Incident Reports* is included in Appendix F.

3.d.ii. IDS Data

Six incidents were reported to IDS. Exposures ranged from ingestion by an adult

and child to pesticide handler exposures. Two of the pesticide handler incidents did not report specific symptoms. The other two incidents reported dizziness, nausea, headaches, vomiting and pinpoint/constricted pupils. No further information on the disposition of these cases was reported.

3.d.iii. PCC Data

An analysis of the PCC data was performed by Dr. Jerome Blondell (see Appendix F). The following is a summary of his findings. "Compared to other organophosphate and carbamate insecticides, ethoprop had above average evidence of effects, though for some measures (percent with symptoms or life-threatening symptoms) the number of cases was too few to provide reliable percentages (Table 1). **For both the occupational and non-occupational categories, ethoprop cases were nearly twice as likely to require hospitalization as did cases due to other cholinesterase inhibitors.**"

3.d.iv. CDFA Data

During the period 1982-1995, 11 cases involving the sole use of ethoprop were reported. All of these cases were reported in 1989. A total of 8 persons had systemic illnesses from ethoprop exposure and only 1 person was disabled and hospitalized. Of these 8 persons, one was exposed when performing ground application and the remaining 7 were exposed by drift. Drift was associated with the majority of the illnesses which included symptoms of shortness of breath, asthma, headaches, nausea, diarrhea, and burning eyes. Ethoprop was ranked 76th as a cause of systemic poisoning in California.

A detailed investigation of the drift incident was performed by the California Department of Health Services and published in the Archives of Environmental Health (Volume 46, pages 213-217) by Richard Ames, PhD, MPH and James Stratton, MD, MPH and entitled *Acute Health Effects from Community Exposure to n-Propyl Mercaptan from an Ethoprop-Treated Potato Field in Siskiyou County, California*. Ethoprop was applied at 12 lb ai/A by air blasting onto the soil, tilling it in and then irrigating the field. The study concluded that the effects reported by households (400 returned questionnaires) were due to the strong odor of n-propyl mercaptan which is a contaminant and degradation product of ethoprop. The authors recommended that human exposures be minimized to the extent practical "through pesticide use restrictions or modifications of agricultural practices."

3.d.v. NPTN Data

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, ethoprop was ranked 182nd with 13 incidents in humans reported and 3 incidents in animals (mostly pets).

3.d.vi. Incident Data Conclusions

Relatively few incidents of illnesses have been reported due to ethoprop. The investigation of a drift incident revealed that most effects were due to the strong odor of n-propyl mercaptan (ethoprop contaminant and degradation product). PCC data suggest that exposures to ethoprop are more likely to require hospitalization than other cholinesterase inhibitors.

3.d.vii. Incident Data Recommendations

Ethoprop demonstrates a profile suggesting greater than average toxicity for a cholinesterase inhibitor. Application methods which prevent drift into 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.

3.e. Data Needs

Several areas of the risk assessment and characterization would improve with more data. Areas of data needs include:

- ☐ Chemical-specific exposure studies for occupational and non-occupational exposures. Rhone-Poulenc is conducting an exposure monitoring and biomonitoring study of workers in the United Kingdom for granular application to potatoes. Other such studies are encouraged.
- ☐ Specific data on typical use, types of mixing and loading completed for application equipment, types of packaging available to individual and professional pesticide applicators, types of potential engineering controls, additional information on slit-placement techniques for turf applications, and information on post-application techniques for transplanting sugarcane and pineapple activities.
- ☐ Rhone-Poulenc is a member of the Agriculture Re-entry Task Force (ARTF). This task force united in response to a data-call-in made by EPA. Studies have been conducted on post-application pesticide residues and transfer coefficients associated with agricultural field activities. Submission and review of the ARTF study data could change the occupational risk assessment results for ethoprop.
- ☐ The registrant is planning to conduct a 28-day dermal toxicity study in rabbits with a granular formulation of ethoprop. This study is not yet available, but may result in refinement of occupational risks.
- ☐ The registrant is planning to gather additional information with regard to ethoprop carcinogenicity. This information may result in refinement of cancer risks.