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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: October 19, 2005

MEMORANDUM

SUBJECT: **Fenpropimorph** HED Human Health Risk Assessment to Support Tolerance on Imported Bananas (Petition No. 7E4874).

PC Code:	121402
DP Barcode:	D309498
Regulatory Action:	Tolerance without Registration
Risk Assessment Type:	Single Chemical No Aggregate
Trade Names:	Volley™ 880L
Chemical Class:	Systemic Morpholine Fungicide

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OCT 21 2005

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1.0 Executive Summary

BASF Corporation's Agricultural Products Division has submitted a petition (PP#7E4874) for the establishment of a permanent tolerance for residues of the fungicide fenpropimorph in imported bananas. Fenpropimorph, an inhibitor of ergosterol biosynthesis, is a systemic morpholine fungicide with protectant and eradicant activity. The petitioner proposes the use of VOLLEY™ 88OL Fungicide, an oil-miscible liquid (OL) formulation of fenpropimorph with 880 grams per liter (g/L) active ingredient (ai), for the control of Sigatoka diseases (*Mycosphaerella spp.*) in bananas and plantains imported into the US. Registration is proposed for Mexico, Guatemala, Belize, El Salvador, Honduras, Columbia, Nicaragua, Costa Rica, and Panama. There are currently no U.S. tolerances established for residues of fenpropimorph in plant or animal commodities and BASF is not proposing any uses for fenpropimorph on bananas grown in the US.

Toxicology

The toxicology data base for fenpropimorph is adequate to support the proposed tolerance on imported bananas, and there are no data gaps at this time. The scientific quality of the database for fenpropimorph is high, and the toxicity profile can be characterized for all effects, including potential developmental, reproductive and neurotoxic effects.

A complete battery of acute studies for both the active ingredient (91%) and end-use product (5.4% WOLSIN LP 13762, 5.85% of technical containing 93% active) was submitted to the EPA. Fenpropimorph has low acute toxicity via the oral and dermal routes of exposure (Toxicity Category III). Fenpropimorph also has low acute toxicity via the inhalation route of exposure (Toxicity Category III), and the end use product acute inhalation toxicity was lower (Category IV). Acute eye irritation with the active ingredient was classified as Toxicity Category II; however, the end-use product was classified as Toxicity Category I (severely irritating). The acute dermal irritation studies in rabbits with both the active ingredient and end-use product, showed severe irritation after one hour exposure (Toxicity Category I). Dermal sensitization studies (guinea pig) were not provided. There is no evidence of delayed neurotoxicity following exposure to fenpropimorph.

The liver was affected by the administration of fenpropimorph in the 90-day (increase in absolute and relative liver weights) and chronic/carcinogenicity rat (alternations in hepatocytes) studies. No liver effects were noted in the 90-day dog study; however, in the 12-month dog study, there was ≥ 200% increase in the liver enzyme alanine aminotransferase (ALT). No liver changes were reported for any of the other studies.

The chronic dog and chronic rat studies were considered co-critical for endpoint selection for chronic dietary risk assessment. The chronic reference dose (cRfD) is derived from the NOAEL of 3.2 mg/kg/day based on liver effects (histopathology, relative liver weight changes) at LOAELs of 9-11 mg/kg/day in the 2-year rat study.

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), fenpropimorph was classified as, "not likely to be carcinogenic to humans." There were no

increased incidences of benign or malignant tumors in either a rat chronic/carcinogenicity or a mouse carcinogenicity study.

Two rat developmental toxicity studies were submitted in support of this action. The maternal effects consisted of vaginal bleeding and decreased body weight as well as body weight gain. The developmental effects resulted in decreased number of live fetuses/dam, increased resorptions, increased % postimplantation loss as well as decreased mean litter size, number of live pups and survival indices and increased incidence of cleft palate. The maternal and developmental effects were observed at the same doses (LOAELs) of 40 mg/kg/day, and the NOAELs were the same (10 mg/kg/day).

There were also two developmental rabbit studies submitted. The maternal effects in the more recent study consisted of swelling of the anus during gestation days 15-29, mortality, abortions and clinical signs of toxicity at the LOAEL of 30 mg/kg/day. The developmental effects consisted of an increased incidence of cleft palate, increased incidences of resorptions, and external anomalies and skeletal variations/retardations, also at the LOAEL of 30 mg/kg/day. The maternal and developmental NOAELs were the same, 15 mg/kg/day.

An appropriate endpoint attributable to a single exposure was identified from the oral toxicity studies. The acute dietary reference dose (aRfD) for females 13- 49 years of age is based on a NOAEL of 15 mg/kg/day from the rabbit developmental study. The LOAEL was 30 mg/kg/day based on cleft palate 4/116 fetuses (2/20 litters), 0 in control. The Agency considers the observation of cleft palate to be the result of a single dose exposure.

There was no appropriate endpoint attributable to a single exposure identified for the general population.

In the 2-generation reproduction study in rats, the NOAELs for parental, reproduction and offspring toxicity were the highest dose tested (for males and females, 2.04 and 2.79 mg/kg/day). Thus, the LOAELs were not attained (animals not dosed high enough, doses based on 3-month study).

A rat metabolism/pharmacokinetics study was submitted to the Agency. Within 96 hours of dosing, 96-110% of the radioactivity was recovered. High levels were found in feces of intravenous dosed rats (45-49%), indicating biliary excretion was a major route of elimination. In bile-duct cannulated rats, most of the dose was recovered in the bile. After oral dosing, high levels were recovered in the urine and bile, indicating absorption from the gastrointestinal (GI) tract. No parent compound was found in the urine, feces or bile, indicating fenpropimorph was completely metabolized. Metabolism appears to involve oxidation of the *tert*-butyl group on the phenyl ring to form acid metabolite BF 421-2, which is hydroxylated to yield the major metabolite BF 421-3. Most of radioactivity in bile (56-69%) was made up of many unknown components. The presence of unknowns indicated metabolites initially excreted undergo further metabolism and reabsorption prior to final elimination in urine and feces. Several major metabolites (>5% dose) were detected in urine and feces.

FQPA and Uncertainty Factors

The toxicological database for fenpropimorph is adequate for Food Quality Protection Act (FQPA) assessment. There are developmental toxicity studies in two species, the rat and the rabbit. In addition, there is a multigeneration study in the rat. The most severe parameter of fetal toxicity in the developmental studies (both species), was the increased incidence of cleft palate. The severity of the developmental effects relative to maternal toxicity is evidence of qualitative susceptibility; however, because maternal and developmental effects occurred at similar doses, there is no evidence of quantitative susceptibility.

Treatment-related toxicological signs of neurotoxicity were observed in some studies. Nervous system effects were noted in the acute neurotoxicity battery in rats where the NOAELs for males and females were 500 mg/kg and the LOAELs were 1500 mg/kg (close to the limit dose). In this acute study, the males showed piloerection plus one rat had dilation of the ventricles of the brain and females were observed to have dilation of the brain (one rat), piloerection and an overall decrease in motor activity.

A developmental neurotoxicity study is not required because neurotoxic parameters were affected only at very high doses, considerably higher than the NOAELS observed for liver related changes (500 times higher) and developmental effects (100 times higher).

In addition to these toxicological considerations, the dietary assessment will not underestimate exposure due to the assumption of tolerance level residues and 100% crop treated. Therefore, the Fenpropimorph Risk Assessment Team concludes that the FQPA safety factor be removed (i.e., reduced to 1X) and that no additional uncertainty factors are needed.

Rationale for Not Including Metabolites and Degradates in Tolerance Expression

Parent compound and [^{14}C]-labeled natural constituents (sugars from starch) were identified in the metabolism study in bananas. No metabolites were identified with the phenyl ring degraded. Therefore, the Fenpropimorph Risk Assessment Team concluded that the residue of concern in the raw agricultural commodity bananas be designated as the parent compound only.

In a series of rat metabolism studies ([phenyl-^{14}C]-fenpropimorph and [morpholine-^{14}C]-morpholine-fenpropimorph) analyses of urine, fecal extracts, and bile did not detect any parent compound, indicating that fenpropimorph is completely metabolized by rats. Based upon the metabolites identified in urine and feces, the metabolism of fenpropimorph in rats appears to involve the successive oxidation of the tert-butyl group on the phenyl ring to form the acid metabolite, BF 421-2, which is then hydroxylated on one of methyl groups of the morpholine ring to yield the major metabolite BF 421-3. Several major (more than 5% of dose) unknowns were also detected in urine and feces.

Although the rat metabolism study failed to identify detected unknown metabolites in urine and feces that accounted for more than 5% of the administered dose, HED believes that any risks of concerns which may result from the unknown metabolites are addressed in the toxicology database and hazard characterization section of this risk assesssment.

Residue Chemistry

Based on the banana metabolism study, the residue of concern, for both tolerance expression and risk assessment purposes, is designated as the parent compound only. There are no significant livestock feed items associated with this petition; therefore, the nature of residue in livestock does not need to be addressed. There are no established Mexican or Canadian maximum residue limits (MRL) for fenpropimorph residues. There are Codex MRLs established for fenpropimorph residues in various commodities, including an MRL of 2 mg/kg in bananas; refer to the International Residue Limit Status form appended to this document (Appendix 6).

HED recommends that the proposed tolerance (without U.S. registration) for residues of fenpropimorph in imported bananas be granted, but established at the level of 2.0 ppm (in order to harmonize with the existing Codex MRL of 2 mg/kg), provided that acceptable method validation recovery data for fenpropimorph from bananas are submitted by the petitioner (as detailed in Section 6.1.1). The petitioner should submit a revised Section F to reflect this increase in the proposed tolerance level.

Dietary Exposure

HED performed Tier 1 acute and chronic dietary exposure and risk analyses for fenpropimorph using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03)). The DEEM-FCID™ assessment was based on tolerance-level residues in/on bananas commodities, processing factors of 3.9 for dried banana commodities, and 100% crop treated (100% CT) assumptions.

An acute dietary dose and an endpoint attributable to a single dose were only identified for one subpopulation, females ages 13 through 49. The acute exposure estimate of approximately 0.004 mg/kg/day corresponds to 2.6 % of the aPAD. An appropriate endpoint attributable to a single exposure was not identified for the general population or any of the other population subgroups. For chronic dietary risk , the most highly exposed population subgroup was children 1-2 years old. The chronic exposure estimate of approximately 0.004 mg/kg/day corresponds to 11 % of the cPAD. Risks for the general U.S. population and all other population subgroups were lower. Fenpropimorph has been classified as not likely to be carcinogenic to humans; therefore, a dietary assessment for cancer risk was not conducted.

Drinking Water Exposure/ Residential (Non-occupational) Exposure/ Occupational Exposure

Since this action is for a tolerance on imported bananas only, there are no registered uses in the United States. There is no expectation that exposure to fenpropimorph residues would occur via water consumption, residential or occupational exposure. Therefore, assessment of drinking water, residential, or occupational exposure and risk is not required.

Aggregate Risk Estimates

Since there are no registered (agricultural, occupational nor residential) uses associated with fenpropimorph, the only route of exposure is through food (bananas). No additional exposure

from residential or drinking water exposure pathways is expected; therefore, an aggregate risk assessment not required.

Recommendation

HED recommends that the proposed tolerance (without U.S. registration) for residues of fenpropimorph in imported bananas be granted, but established at the level of 2.0 ppm (in order to harmonize with the existing Codex MRL of 2 mg/kg), provided that acceptable method validation recovery data for fenpropimorph from bananas are submitted by the petitioner (as detailed in Section 6.1.1). The petitioner should submit a revised Section F to reflect this increase in the proposed tolerance level.

For purposes of the proposed tolerance on imported bananas, additional radiovalidation data for the method eventually selected for enforcement will not be required, provided acceptable recovery data for fresh fortifications in bananas are submitted. However, for any future tolerance requests on additional crops, that method selected for tolerance enforcement should be radiovalidated using appropriate samples from a plant metabolism study.

Table 1: Tolerance Summary for Fenpropimorph

Commodity	Proposed Tolerance	Recommended Tolerance	Comments
Bananas	1.5 ppm	2.0 ppm	The available residue data would support a tolerance of 3.0 ppm on bananas. (However, a tolerance of 2.0 ppm is being recommended in order to harmonize with the existing Codex MRL of 2 mg/kg). The CFR entry should also state that there are no U.S. registrations for use on bananas.

2.0 Ingredient Profile

Fenpropimorph, an inhibitor of ergosterol biosynthesis, is a systemic morpholine fungicide with protectant and eradicant activity. Its intended use is for the control of Sigatoka diseases in bananas and plantains.

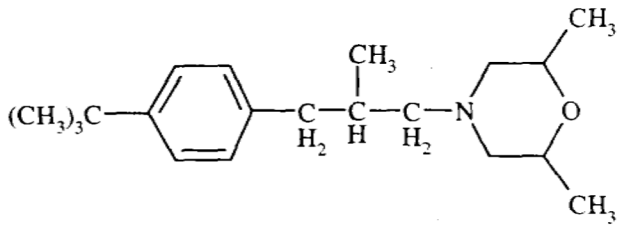
2.1 Summary of Proposed Uses

BASF Corporation's Agricultural Products Division has submitted a petition (PP#7E4874) proposing the establishment of a permanent tolerance for residues of the fungicide fenpropimorph in/on imported bananas at 1.5 ppm. The petitioner proposes the use of VOLLEY™ 88OL Fungicide, an OL formulation of fenpropimorph with 880 g/L a.i., for the control of Sigatoka diseases (*Mycosphaerella spp.*) in bananas and plantains imported into the US. Registration is proposed for Mexico, Guatemala, Belize, El Salvador, Honduras, Columbia, Nicaragua, Costa Rica, and Panama. There are currently no U.S. tolerances established for residues of fenpropimorph in/on plant or animal commodities and BASF is not proposing any uses for fenpropimorph on bananas grown in the U.S.

TABLE 2.1 Summary of Current Use Directions for Fenpropimorph on Imported Bananas[1].							
End-Use Product (EUP)	**Applications**						
	Type	**Timing[2] [Application Sequence]**	**Maximum Single Rate (kg ai/ha)**	**Maximum Number per Season[2]**	**Maximum Seasonal Rate[2] (kg ai/ha)**	**RTI[3] (Days)**	**PHI[4] (Days)**
VOLLEY™ 88OL	Foliar broadcast spray to underside of leaves (ground equipment) or to foliage canopy (aerial equipment)	[1] Raceme formation	0.44	4	1.76	NA[5]	0
		[2] Raceme development				12	
		[3] Raceme development				44	
		[4] Mature mats				12	

1. There are no current uses for fenpropimorph in the US.
2. Not specified in the current use directions, but supported by the field trials.
3. RTI = Re-Treatment Interval; not specified in the current use directions, but supported by the field trials.
4. PHI = Pre-Harvest Interval.
5. NA = Not Applicable.

2.2 Structure and Nomenclature

TABLE 2.2 Nomenclature of Fenpropimorph.	
Chemical Structure	
Empirical Formula	$C_{20}H_{33}NO$
Common Name	Fenpropimorph
Company Experimental Name	BAS 421 F
IUPAC Name	(*RS*)-*cis*-4-[3-(4-*tert*-butylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine
CAS Name	*rel*-(2*R*,6*S*)-4-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]-2,6-dimethylmorpholine
CAS Number	67564-91-4
Chemical Class	Antimicrobial morpholine fungicide
Known Impurities of Concern	None
EUP	VOLLEY™ 88OL

2.3 Physical and Chemical Properties

TABLE 2.3 Physicochemical Properties.*	
Parameter	**Value**
Melting Point/Range (°C)	Liquid at STP
pH	Not available
Density at 20°C (g/cm^3)	0.933 [technical material]
Water Solubility at 20°C, pH 7 (mg/L)	4.32
Solvent Solubility at 20°C (g/100 ml)	Acetone 760.35 Ethyl Acetate 777.95 Toluene 764.60 Dichloromethane (DCM) 774.20 n-Heptane 725.35 ACN 772.70 Methanol 789.15 Iso-propanol 816.70 Octanol 770.50
Vapor Pressure at 20°C (Pa)	3.5×10^{-3}
Dissociation Constant (pK_a)	Does not dissociate
Octanol/Water Partition Coefficient at 22°C, pH 7 (Log [K_{ow}])	4.1
UV/Visible Absorption	Not available

* References: PP#7E4874 administrative materials (MRIDs #44323902, 45857201, 46097501).

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

In a series of rat metabolism studies (MRID #44323920), [phenyl-^{14}C]-fenpropimorph and [morpholine-^{14}C]-morpholine-fenpropimorph were administered to Wistar rats. Within 96 hours of dosing with [^{14}C]-fenpropimorph, 96 to 109% of the dosed radioactivity was recovered in excreta, bile, exhaled air, cage washes, and tissues. Excretion of radioactivity was similar between the sexes and dose groups, although there were minor differences in the pattern of excretion. The high levels of radioactivity recovered in the urine and bile following oral dosing indicate that fenpropimorph was readily absorbed from the gastrointestinal tract of rats. Radioactivity remaining in the carcass and tissues 96 hours after [^{14}C]-dosing was also similar between the sexes and between the dose groups. Following either a single low or high dose, the concentration of radioactivity in blood and plasma reached maximum levels by 8 hours post-dose in both sexes and declined thereafter. Analyses of urine, fecal extracts, and bile did not detect any parent compound, indicating that fenpropimorph is completely metabolized by rats. Based upon the metabolites identified in urine and feces, the metabolism of fenpropimorph in rats appears to involve the successive oxidation of the *tert*-butyl group on the phenyl ring to form the acid metabolite, BF 421-2, which is then hydroxylated on one of methyl groups of the morpholine ring to yield the major metabolite BF 421-3. Metabolite BF 421-3 is then either conjugated with unspecified components, or undergoes degradation of the morpholine ring to form BF 421-17. The other phenyl-specific acid metabolite, BF 421-16, results from the further degradation of the 2-methylpropanoic acid group remaining on BF 421-17. Several major (more than 5% of dose) unknowns were also detected in urine and feces. **This study is classified unacceptable and does not satisfy the requirement for a metabolism study in rats**, but can be upgraded by submission of data further characterizing and/or identifying the major unknown metabolites in urine and feces that accounted for more than 5% of the administered dose.

Parent compound and [^{14}C]-labeled natural constituents (sugars from starch) were identified in bananas. The petitioner proposes that carbon fragments derived from breakdown of the morpholine ring are incorporated into reducing sugars in the leaves, and to some degree in the photosynthetically active green peel, and are then transported into the fruit and stored as starch. The degradation products formed in the leaves, the source of the [$^{14}C_1$]-fragments used for sugar biosynthesis, are depicted in Figure 3.4. No metabolites were identified with the phenyl ring degraded; the tendency for morpholine ring-opening may explain the higher TRR observed in [morpholine-^{14}C]-treated fruit.

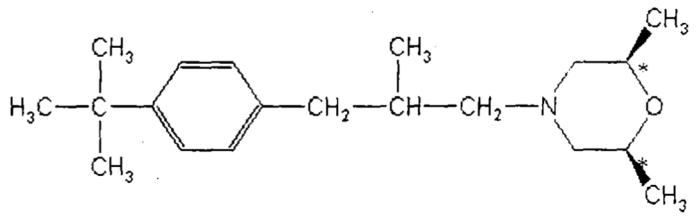
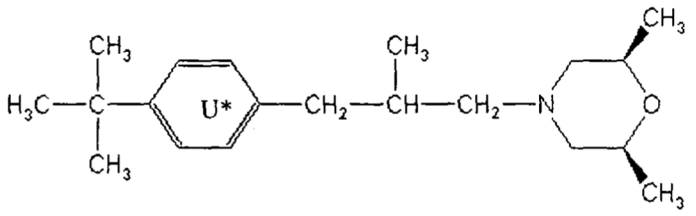
Since there are no significant livestock feed items associated with this petition, there is no concern for livestock metabolites and or pathways.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

Based on the banana metabolism study mentioned above, the petitioner proposes that carbon fragments derived from breakdown of the morpholine ring are incorporated into reducing sugars

in the leaves, and to some degree in the photosynthetically active green peel, and are then transported into the fruit and stored as starch.

TABLE 3.2.1 Characteristics of Test Materials Used in the Metabolism Study.	
Chemical Structure	
Common Name	[Morpholine-^{14}C]-fenpropimorph
Radiolabel Position (*)	Two methyl-substituted carbons (2,6) in morpholine ring
Chemical Structure	
Common Name	[Phenyl-^{14}C]-fenpropimorph
Radiolabel Position (*)	All carbons in phenyl ring

3.2.2 Description of Livestock Metabolism

There are no significant livestock feed items associated with this petition; therefore, the nature of the residue in livestock does not need to be addressed.

3.2.3 Description of Rotational Crop Metabolism

Per the NAFTA Guidance Document on Data Requirements for Tolerances on Imported Commodities (dated April 2003), rotational crop data are not required to support the proposed tolerance on imported bananas. Furthermore, because bananas are a perennial crop, confined and field rotational crop studies are not required to establish a tolerance for residues in bananas.

3.3 Environmental Degradation

Because fenpropimorph is proposed for use only on imported bananas, with neither existing nor proposed U.S. registration, there is no expectation that fenpropimorph residues would occur in surface or ground water sources of drinking water.

3.4 Toxicity Profile of Major Metabolites and Degradates

Parent compound and [^{14}C]-labeled natural constituents (sugars from starch) were identified in the metabolism study in bananas. No metabolites were identified with the phenyl ring degraded. No toxicity data were provided for the metabolites of fenpropimorph that were observed in

bananas.

In a series of rat metabolism studies ([phenyl-^{14}C]-fenpropimorph and [morpholine-^{14}C]-morpholine-fenpropimorph) analyses of urine, fecal extracts, and bile did not detect any parent compound, indicating that fenpropimorph is completely metabolized by rats. Based upon the metabolites identified in urine and feces, the metabolism of fenpropimorph in rats appears to involve the successive oxidation of the *tert*-butyl group on the phenyl ring to form the acid metabolite, BF 421-2, which is then hydroxylated on one of methyl groups of the morpholine ring to yield the major metabolite BF 421-3. Metabolite BF 421-3 is then either conjugated with unspecified components, or undergoes degradation of the morpholine ring to form BF 421-17. The other phenyl-specific acid metabolite, BF 421-16, results from the further degradation of the 2-methylpropanoic acid group remaining on BF 421-17. Several major (more than 5% of dose) unknowns were also detected in urine and feces.

Although the rat metabolism study failed to identify detected unknown metabolites in urine and feces that accounted for more than 5% of the administered dose, HED believes that any risks which may result from the unknown metabolites are addressed through endpoint selection for risk assessment, as described in the toxicology database and hazard characterization section of this risk assessment.

FIGURE 3.4 Tabular Summary of Fenpropimorph Metabolites and Degradates.*

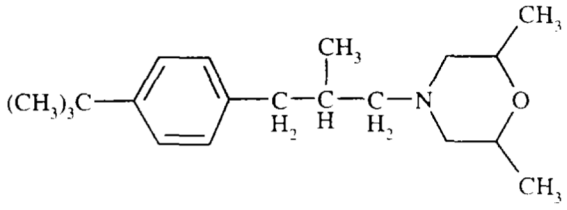
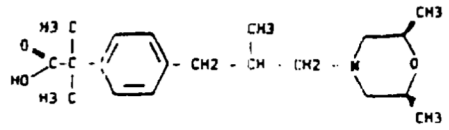
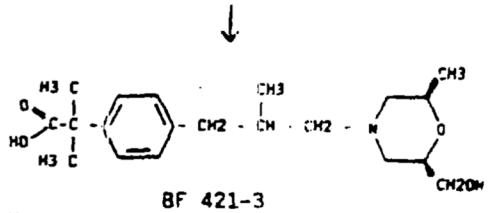
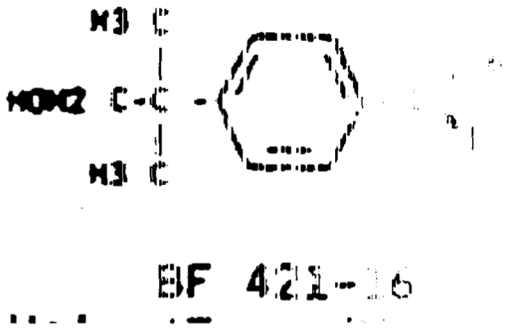
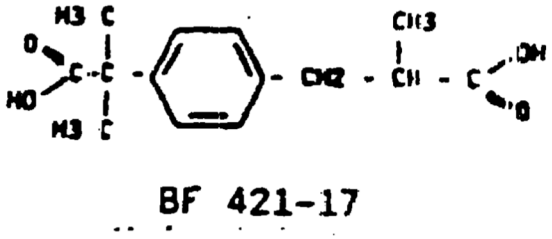
Common [Code] Name *% Total Radioactive Residues*	**Structure**
Fenpropimorph [BAS 421 F] *Rat* *Essentially 0% TRR* *Banana (Fruit)* *6 to 61% TRR*	
[BF 421-2-] Rat - % TRR	 BF 421-2 Urine/Feces/Bile/Liver/Kidney/Plasma ↓

FIGURE 3.4 Tabular Summary of Fenpropimorph Metabolites and Degradates.*

Common [Code] Name *% Total Radioactive Residues*	Structure
BF 421-3 - Rat -32 - 49%TRR	 BF 421-3 Urine/Feces/Liver/Kidney/Plasma
BF 421-16- Rat - 6.2 - 23.4%TRR (combined levels of BF 421-16 and BF 421-17	
BF 421-17- Rat - 6.2 - 23.4%TRR (combined levels of BF 421-16 and BF 421-17	 BF 421-17
Banana metabolism (MRID #44380110). Four foliar broadcast applications of [^{14}C]-fenpropimorph to banana plants, each at 0.90 kg ai/ha (roughly 2X the proposed maximum single application rate); fruit and foliage harvested at a PHI of 1 day. Rat metabolism (MRID #44323920). Either a single oral (gavage) dose at 1.25 or 100 mg/kg, a single intravenous (iv) dose at 1.25 mg/kg, a single oral dose at 1.25 mg/kg following a 14-day pretreatment with fenpropimorph at 1.25 mg/kg/day, or as a repeated dose at 1.25 mg/kg/day for 7 consecutive days. In addition, 5 rats/sex were administered a single oral dose of [morpholine-^{14}C]-fenpropimorph at 100 mg/kg and 3 bile-duct cannulated rats/sex were administered a single oral dose of [phenyl-^{14}C]-fenpropimorph at 1.25 mg/kg.	

* Fenpropimorph *per se* was identified in banana fruit; the other metabolites depicted in this table were identified in leaf extracts only. The petitioner proposed that the morpholine-ring-opened metabolites are the precursors to [^{14}C]-sugars found in fruit extracts. The [$^{14}C_1$] fragments are incorporated into sugars which are transported from the leaves into the fruit and assimilated into starch.

3.4.1 Rationale for Not Including Metabolites and Degradates in Tolerance Expression.

Parent compound and [^{14}C]-labeled natural constituents (sugars from starch) were identified in the metabolism study in bananas. No metabolites were identified with the phenyl ring degraded. Therefore, the Fenpropimorph Risk Assessment Team concluded that the residue of concern in raw agricultural commodities (bananas) be designated as the parent compound only.

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

TABLE 3.6 Residues of Concern (ROC) Included in the Risk Assessment and Tolerance Expression.		
Crop [Matrix]	**Residue in Risk Assessment**	**Residue in Tolerance Expression**
Banana [Fruit]	Parent compound only (fenpropimorph *per se*)	Parent compound only (fenpropimorph *per se*)

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

The toxicology data base for fenpropimorph is adequate to support the proposed tolerance on imported bananas, and there are no data gaps at this time. The scientific quality of the database for fenpropimorph is high, and the toxicity profile can be characterized for all effects, including potential developmental, reproductive and neurotoxic effects.

A complete battery of acute studies for both the active ingredient (91%) and end-use product (5.4% WOLSIN LP 13762, 5.85% of technical containing 93% active) was submitted to the EPA. Fenpropimorph has low acute toxicity via the oral and dermal routes of exposure (Toxicity Category III). Fenpropimorph also has low acute toxicity via the inhalation route of exposure (Toxicity Category III), and the end use product acute inhalation toxicity was lower (Category IV). Acute eye irritation with the active ingredient was classified as Toxicity Category II; however, the end-use product was classified as Toxicity Category I (severely irritating). The acute dermal irritation studies in rabbits with both the active ingredient and end-use product, showed severe irritation after one hour exposure (Toxicity Category I). Dermal sensitization studies (guinea pig) were not provided. There is no evidence of delayed neurotoxicity following exposure to fenpropimorph.

Effects of administration of fenpropimorph were on a variety of measured nervous system parameters. In two 90-day rat studies, there were decreases in serum/plasma cholinesterase levels. However, these serum/plasma values are not considered relative for risk assessment purposes. In addition, there were decreases in brain cholinesterase levels at 2.1 mg/kg/day in both sexes. Regarding a mouse carcinogenicity study, in females only, the NOAEL for RBC cholinesterase was 0.5 mg/kg/day with the LOAEL being 3.5 mg/kg/day. These cholinesterase affects were not considered in choosing NOAELs or LOAELs because of the inconsistency of the results among studies, species and controls. No apparent affect on any cholinesterase levels was

noted in dogs. Additional nervous system effects were reported in the acute neurotoxicity battery in rats where the NOAELs for males and females were 500 mg/kg and the LOAELs were 1500 mg/kg. In this study, in males, piloerection plus dilation of the ventricles of the brain (one male) were observed; in females, one rat had dilation of the ventricles of the brain, and there was piloerection as well as overall decrease in motor activity.

The liver was affected by the administration of fenpropimorph. In one 90-day rat study, the LOAELs were 7.1 and 8.5 mg/kg/day for males and females, respectively, based upon decreases in body weights and body weight gains in both sexes as well as an increase in absolute and relative liver weights in males and increases in only relative weights in females. In this study, the NOAELs were 0.7 and 0.8 mg/kg/day for males and females, respectively. In the other 90-day rat study, liver weights increased and were reported at doses of 1.54 mg/kg/day in males or 1.80 mg/kg/day in females (HDT); however, no other effects in liver were noted. In the chronic rat study, the LOAELs for liver findings were 1.7 and 2.1 mg/kg/day for males and females, respectively. No liver effects were noted in the 90-day dog study (doses up to 11.63 mg/kg/day for males and 14.64 mg/kg/day for females). However, in the 12-month dog study, the NOAEL was 3.2 mg/kg/day (both sexes) with the LOAELs being 12.3 and 13.2 mg/kg/day for males and females, respectively, based on $\geq$ 200% increase in alanine aminotransferase (ALT). No liver changes were reported for any of the other studies.

In a rat developmental toxicity study (gavage), the maternal NOAEL was 40 mg/kg/day with the LOAEL being 160 mg/kg/day based on vaginal bleeding and decreased body weight as well as body weight gain. The same NOAEL and LOAEL were noted for the developmental aspect with the following being observed: decreased number of live fetuses/dam, increased resorptions, increased % postimplantation loss and increased incidence of cleft palate. In a second rat developmental toxicity study (gavage) in which dosing was during gestation and lactation through PND 21 (no visceral or skeletal examinations of fetuses/pups), the maternal NOAEL was 10 mg/kg/day with the LOAEL being 40 mg/kg/day based on decreased body weight gain. For the developmental portion of the study, the NOAEL was 10 mg/kg/day with the LOAEL being 40 mg/kg/day based on a decrease in live fetuses/dam and survival indices as well as an increase in postimplantation loss. In addition, there was a decrease in grip strength in females.

There were two developmental rabbit studies (gavage). In the more recent study, the maternal NOAEL was 15 mg/kg/day with the LOAEL being 30 mg/kg/day based on 9/20 showing swelling of the anus GD 15-29. The developmental NOAEL was 15 mg/kg/day with the LOAEL being 30 mg/kg/day based on increased incidence of cleft palate (4/116 fetuses; 2/20 litters; 0 in control). In the earlier study, the maternal NOAEL was 12 mg/kg/day and the LOAEL was 36 mg/kg/day based on mortality, abortions and clinical signs of toxicity. The developmental NOAEL was 12 mg/kg/day and the LOAEL was 36 based on increased incidences of resorptions, external anomalies and skeletal variations/retardations.

In the 2-generation reproduction study in rats, the NOAELs for parental, reproduction and offspring toxicity were the highest dose tested (for males and females, 2.04 and 2.79 mg/kg/day, respectively). Thus, the LOAELs were not attained (animals not dosed high enough; doses based on 3-month study).

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), fenpropimorph was classified as, "not likely to be carcinogenic to humans." There were no increased incidences of benign or malignant tumors in either a rat chronic/carcinogenicity or a mouse carcinogenicity study.

A complete battery of mutagenicity studies was negative.

A rat metabolism/pharmacokinetics study was submitted to the Agency. Within 96 hours of dosing, 96-110% of the radioactivity was recovered. High levels were found in feces of intravenous dosed rats (45-49%), indicating biliary excretion was a major route of elimination. In bile-duct cannulated rats, most of the dose was recovered in the bile. After oral dosing, high levels were recovered in the urine and bile, indicating absorption from the GI tract. No parent compound was found in the urine, feces or bile, indicating fenpropimorph was completely metabolized. Metabolism appears to involve oxidation of the *tert*-butyl group on the phenyl ring to form acid metabolite BF-421-2, which is hydroxylated to yield the major metabolite BF-421-3. Most radioactivity in the bile (56-69%) was made up of many unknown components. Presence of unknowns indicated metabolites initially excreted undergo further metabolism and reabsorption prior to final elimination in urine and feces. Several major metabolites (>5% dose) were detected in urine and feces.

Tables 4.1a and 4.1b provide a summary of the acute toxicity profile of the technical and end-use product. Table 4.1c provides a summary of the subchronic, and chronic toxicity profile of technical fenpropimorph.

Table 4.1a: Acute Toxicity for Fenpropimorph Technical (91%)

GDLN	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral - rat	45857208	LD_{50}: M = 2830 mg/kg F = 1670 mg/kg combined = 2230 mg/kg	III
870.1100	Acute Oral - rat	45857209	LD_{50}: M = 3650 mg/kg F = 3425 mg/kg combined = 3515 mg/kg	III
870.1200	Acute Dermal - rat	45857210	LD_{50}: M = >4000 mg/kg F = > 4000 mg/kg combined = > 4000 mg/kg	III
870.1300	Acute Inhalation - rat	45857211	LC_{50}: M = 3.7 mg/L F = >2.2,<2.4 mg/L combined = 2.9 mg/L	IV
870.2400	Acute Eye Irritation - rabbit	45857212	Redness (no observations between 72 hr and day 8)	IIa
870.2500	Acute Dermal Irritation - rabbit	45857213	Severely irritating after 1-hr exposure	I
870.2600	Dermal Sensitization - guinea pig	b	b	N/A

a = no worse than Category II N/A = not applicable
b = study not provided

Table 4.1b: Acute Toxicity for End-Use Product (5.4%) WOLSIN LP 13762

GDLN	Study Type	MRID	Results	Toxicity Category
870.1100	Acute Oral - rat	45857203	LD_{50}: M = >2000 mg/kg F = > 2000 mg/kg combined = > 2000 mg/kg	III
870.1200	Acute Dermal - rat	45857204	LD_{50}: M = > 2000 mg/kg F = > 2000 mg/kg combined = > 2000 mg/kg	III
870.1300	Acute Inhalation - rat	45857205	LC_{50}: M = 3.62 mg/L F = 1.52 mg/L combined not reported	III
870.2400	Acute Eye Irritation - rabbit	45857206	severely irritating	I
870.2500	Acute Dermal Irritation - rabbit	45857207	severely irritating and irreversible damage	I
870.2600	Dermal Sensitization - guinea pig	a	a	N/A

a = study not provided N/A = not applicable

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	RESULTS
870.1100 870.6100 Acute oral toxicity and acute delayed neurotoxicity of organophosphorus - Hens (gavage) 92.5%	44323909 (1980) Acceptable/guideline Acute oral study single dose: 250, 500, 1000, 2000, or 4000 mg/kg (with or without pretreatment with atropine sulfate and PAM) Acute delayed study single dose: 425, 850 or 1700 mg/kg (pretreated with atropine sulfate and PAM) 10 hens treated with fenpropimorph at 1700 mg/kg	**ACUTE ORAL STUDY** Oral LD_{50}: Unprotected = 1,600 mg/kg Protected = 1,700 mg/kg Toxicity Category = III **ACUTE DELAYED STUDY** NOAEL = ≥1700 mg/kg (HDT) LOAEL = not observed for delayed neurotoxicity
870.3100 90-Day dietary toxicity - Rat 91.1%	44380103 (1979) Acceptable/guideline ppm=0, 6.25, 12.5 or 25 M= 0, 0.382, 0.768 or 1.54 mg/kg/day F=0, 0.465, 0.915 or 1.80 mg/kg/day	NOAEL= M: 0.768 mg/kg/day F: 0.915 mg/kg/day LOAEL= M: 1.54 mg/kg/day based on increase relative liver weights and increase incidence of liver single cell necrosis F: 1.80 mg/kg/day based on increase absolute and relative liver weights and increase incidence of liver single cell necrosis
870.3100 870.6200 90-Day dietary toxicity and neurotoxicity - Rat 94.3%	44380105 (1997) Acceptable/guideline ppm=0, 1, 10, 100 or 1000 M=0, 0.1, 0.7, 7.1 or 71.0 mg/kg/day F= 0, 0.1, 0.8, 8.5 or 77.7 mg/kg/day [FOB & motor activity days -7, 22, 50, 85; 5/sex/group profused neurohistology exams]	**SYSTEMIC** NOAEL=M: 0.7 mg/kg/day F: 0.8 mg/kg/day LOAEL=M: 7.1 mg/kg/day based on ↓ BW & BWG, ↑absol & rel liver wt F: 8.5 mg/kg/day based on ↓BW & BWG, ↑relliver wt **NEUROTOX** NOAEL=M: 7.1 mg/kg/day F: 8.5 mg/kg/day LOAEL=M: 71.0 mg/kg/day based on differences in landing foot splay values F:77.0 mg/kg/day based on differences in landing foot splay values

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**RESULTS**
870.3150 90-Day dietary toxicity - Dog 91.1%	44380104 (1980) Acceptable/guideline ppm=0, 50, 100, 200 or 400 M=0, 1.46, 2.96, 6.40 or 11.63 mg/kg/day F=0, 1.77, 3.69, 7.92 or 14.64 mg/kg/day	NOAEL= M: 11.63 mg/kg/day F: 14.64 mg/kg/day LOAEL= M: not established F: not established
870.3200 28-Day dermal toxicity - Rat 96.6%	45868902 (2001) Acceptable/guideline M= 0, 0.2, 0.6 or 2.0 mg/kg/day F= 0, 0.2, 0.6 or 2.0 mg/kg/day	NOAEL = M: 2.0 mg/kg/day F: 2.0 mg/kg/day LOAEL = M: not established F: not established **NOTE:** from a range-finding study, the material was tested at the maximum dose that would not produce severe skin irritation
870.3700 Developmental toxicity - Rat (gavage) 92.5%	44380108 (1978) Acceptable/guideline (PRE-GLP) 2000 - Supplemental submission of data concerning test article preparation, solubility & stability (no MRID #) mg/kg/day=0, 2.5, 10, 40 or 160	**MATERNAL** NOAEL=40 mg/kg/day LOAEL=160 mg/kg/day based on clinical signs of toxicity (vaginal bleeding) and ↓BW & BWG **DEVELOPMENTAL** NOAEL=40mg/kg/day LOAEL=160 mg/kg/day based on ↓# live fetuses/dam, ↑ resorptions, ↑% postimplantation loss,↑incidence of cleft palate 14/274 fetuses (7/24 litters) with 0 in controls
870.3700 Developmental toxicity - Rat (gavage) 92.5%	44323912 (1979) Acceptable/non-guideline (dosing during gestation & lactation; partial developmental neurotox thru PND 21) 2000 - Supplemental submission of data concerning test article preparation, solubility & stability (no MRID #) mg/kg/day=0, 2.5, 10, 40 or 160	**MATERNAL** NOAEL=10 mg/kg/day LOAEL=40 mg/kg/day based on ↓BWG **DEVELOPMENTAL** NOAEL=10 mg/kg/day LOAEL= 40 mg/kg/day based on ↓# live fetuses/dam, ↑% postimplantation loss, ↓mean litter size & # live pups, ↓ survival indices **NEUROTOXICITY** NOAEL=10 mg/kg/day LOAEL= 40 mg/kg/day based on ↓F grip strength **NOTE:** no visceral or skeletal examinations of fetuses/pups

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**RESULTS**
870.3700 Prenatal Developmental - Rabbit (gavage) 95.6%	44323914 (1993) Acceptable/guideline mg/kg/day=0, 7.5, 15 or 30	**MATERNAL** NOAEL = 15 mg/kg/day LOAEL = 30mg/kg/day based on clinical signs (9/20 swelling of anus GD 15-29) **DEVELOPMENTAL** NOAEL = 15 mg/kg/day LOAEL = 30 mg/kg/day based on cleft palate 4/116 fetuses (2/20 litters), 0 in control; anomalies
870.3700 Prenatal Developmental - Rabbit (gavage) 92.5%	44323913 (1980) Acceptable/guideline mg/kg/day=0, 2.4, 12 or 60 (mortality at 60) supplementary: mg/kg/day=0 or 36	**MATERNAL** NOAEL = 12 mg/kg/day LOAEL = 36 mg/kg/day based on mortality, abortions and clinical signs of toxicity **DEVELOPMENTAL** NOAEL = 12 mg/kg/day LOAEL = 36 mg/kg/day based on increased incidence of resorptions, external anomalies and skeletal variations/retardations.
870.3800 2-Generation reproduction study - Rat, diet 92.5%	44323915 (1982) Acceptable/non-guideline ppm=0, 6.25, 12.5 or 25 M=0, 0.51, 1.03 or 2.04 mg/kg/day F=0, 0.71, 1.46 or 2.79 mg/kg/day	**PARENTAL** NOAEL=M: 2.04 mg/kg/day F: 2.79 mg/kg/day LOAEL=M: not attained F: not attained **REPRODUCTION** NOAEL=M:2.04 mg/kg/day F: 2.79 mg/kg/day LOAEL=M: not attained F: not attained **OFFSPRING** NOAEL=M: 2.04 mg/kg/day F: 2.79 mg/kg/day LOAEL=M: not attained F: not attained **NOTE:** animals not dosed high enough; 25 ppm based on ↑rel liver wts in 3-month rat study
870.4300 114-Week chronic/carcino-genicity dietary study -Rat 92.5%	44380106 (1982) Acceptable/guideline ppm=0, 5, 10, 50 or 250 M=0, 0.2, 0.3, 1.7 or 8.8 mg/kg/day F=0, 0.2, 0.4, 2.1 or 11.2 mg/kg/day	NOAEL =M: 1.7 mg/kg/day F: 2.1 mg/kg/day LOAEL =M: 8.8 mg/kg/day based on histopathological liver findings F: 11.2 mg/kg/day based on histopathological liver findings NO EVIDENCE OF CARCINOGENICITY

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**RESULTS**
870.4100 12-Month dietary toxicity - Dog, diet ≥94.7%	44323911 (1990) Acceptable/guideline ppm=0, 25, 100 or 400 M= 0, 0.8, 3.2 or 12.3 mg/kg/day F=0, 0.8, 3.2 or 13.2 mg/kg/day	NOAEL=M: 3.2 mg/kg/day F: 3.2 mg/kg/day LOAEL=M: 12.3 mg/kg/day based on ↑ blood enzyme activity ≥200% (ALT, liver) F: 13.2 mg/kg/day based on ↑ blood enzyme activity ≥200% (ALT, liver)
870.4200 Carcinogenicity study - Mouse, diet 92.5%	44380107 (1982) Acceptable/guideline ppm=0, 5, 30, 150 or 1000 M=0, 0.5, 3.0, 16 or 106 mg/kg/day F=0, 0.5, 3.5, 17 or 118 mg/kg/day treatment=95 wks; 10/sex/group terminated wk 52 & wk 95; survivors untreated until wk 103/104	NOAEL=M: 16 mg/kg/day F: 118 mg/kg/day LOAEL=M: 106 mg/kg/day based on ↓ BWG F: not attained NO EVIDENCE OF CARCINOGENICITY
870.5100 Reverse Gene Mutation Assay (*Salmonella typhimurium*) 95.6%	44323917 (1994) Acceptable/guideline	No evidence of induced mutant colonies over background.
870.5375 *In vitro* Chinese hamster lung cells 95.6%	44323919 (1995) Acceptable/guideline	There were no treatment-related increases in total aberration frequency at any dose level with or without metabolic activation.
870.5395 *In vivo* mammalian cytogenetics - micronucleus assay in mice 95.6%	44323918 (1994) Acceptable/guideline	No significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at any dose at any sampling time.
870.5550 Unscheduled DNA synthesis in primary rat hepatocytes 94.7%	44323916 (1988) Acceptable/guideline	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures, was induced.

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**RESULTS**
870.6200 Acute neurotoxicity screening battery - rat 94.3%	44323910 (1997) Acceptable/guideline M=0, 100, 500 or 1500 mg/kg (single gavage dose)	NOAEL=M: 500 mg/kg F: 500 mg/kg LOAEL=M: 1500 mg/kg based on piloerection observations during the clinical examinations and FOB and neuropathy (one had slight dilation of ventricles in the frontal lobe, parietal lobe and the midbrain) F: 1500 mg/kg based on piloerection observations during the clinical examinations and FOB and decreased overall motor activity
870.6200 Subchronic toxicity and neurotoxicity - Rat, diet [See 870.3100]	44380105 (1997) Acceptable/guideline **NOTE:** for doses, see 870.3100	**NOTE:** for results, see 870.3100

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**RESULTS**
870.7485 Metabolism and pharmacokinetics - Rat ≥98.4% (radiochemical)	44323920 Unacceptable/non-guideline mg/kg/day (radioactive) 1.25: single gavage 1.25: single intravenous 1.25: single gavage after 14 days of 1.25 non-radio active; or as repeated dose for 7 consecutive days 100: single gavage	REASON FOR UNACCEPTABLE/NON-GUIDELINE: Can be upgraded: needs data characterizing and/or identifying major unknown metabolites in urine and feces that were >5% of administered dose. Within 96 hrs of dosing at 1.25 or 100 mg/kg/day, 96-110 % recovered in excreta, bile, exhaled air, cage washes and tissues. Excretion similar between sexes and dose groups. Renal excretion higher (1.1-1.3x) in males and fecal excretion higher (1.1-1.5x) in females regarding ^{14}C-phenyl fenpropimorph. ^{14}C-morpholine fenpropimorph treated rats, no sex difference in excretion. Males excreted about equal amounts in urine and feces; females, more in feces than urine. High levels of radioactivity in feces of i.v. dosed rats (45-49%) indicated biliary excretion was a major route of elimination. In bile-duct cannulated rats, the majority of the dose was recovered in the bile. High levels recovered in urine and bile after oral dosing indicated absorption from the GI tract. Changing ^{14}C position from phenyl to morpholine ring had little effect on excretion. Radioactivity in the carcass and tissues after 96 hours was similar regarding sexes and doses (3.2-6.0%); i.v. dosing, 7.9-10.1%. Residues highest in liver, GI tract and fat; lowest in muscle, bone and brain. Single low or high dose, maximum activity in blood and plasma was by 8 hours. No parent compound in urine, feces or bile; indicating fenpropimorph is completely metabolized. Metabolism appears to involve oxidation of *tert*-butyl group on phenyl ring to form acid metabolite, BF 421-2, which is hydroxylated to yield the major metabolite BF 421-3. This is conjugated with unspecified components, or undergoes degradation of the morpholine ring to BF 421-17. The other phenyl-specific acid metabolite, BF 421-16, is from degradation of the 2-methylpropanoic acid group on BF 421-17. BF 421-3, -17, -16 and -2 accounted for 54-77% of the dose in each group (except bile-duct cannulated rats). Metabolite profile in urine and feces similar for sexes and dosed groups. Major metabolite in urine and feces was BF 421-3 (32-49%). Acid metabolite, BF 421-2, in urine and/or feces of males and females in both dose groups. Phenyl specific BF 421-16 and -17 were similar for males and females in each dose group. Only components in bile were BF 421-2 (3.3-7.4%) and conjugated 421-3 (4.8%, females only). Most of radioactivity in bile (56-69%) made up of many unknown components. Presence of unknowns indicates metabolites initially excreted undergo further metabolism and reabsorption prior to final elimination in urine and feces. Several major metabolites (>5% dose) were detected in urine and feces:U2.3, U3.1, F1.2 and F3.

Table 4.1c Acute, Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**RESULTS**
Special Study: Cholinesterase inhibition in rats after a single intra-peritoneal dose 99.1%	44380109 (1980) Unacceptable/non-guideline F only: 0, 200, 650 or 2000 mg/kg (single dose) intraperitoneally Unacceptable: stated objects of the study not achieved	OBJECTIVES: 1. Would single dose result in ↓ plasma cholinesterase. 2. Was ↓ in enzyme activity the result of direct inhibition of the enzyme by test material (or metabolite) or was decrease due to liver dysfunction. SUMMARY: 1. ↓ plasma cholinesterase activity at 200 and 650 mg/kg/day at 72-hr post dose 2. clin. chemistry and liver wt effects were confounded by peritonitis (irritation by test chemical by route of adminisration). CONCLUSION: Study inconclusive: periotonitis and systemic toxicity may have contributed to observed effects.
Special Study: Hepatic drug-metabolizing enzyme activity - rat, diet (purity not reported)	44323921 Acceptable/non-guideline ppm=0, 50, 25 or 1600	Administered for 14 days to males; phenobarbitone was pos. control; microsomal and cytosolic xenobiotic metabolizing enzyme activities were measured and hepatocyte ultrastructure investigated. No differences from control in urinary excretion of ascorbic acid which differed from pentobarbitone sleeping times. No differences from control in P-450 or in plasma cholinesterase. Increase in aniline hydroxylase, ethylmorphine-N-demethylase, glucuronyltransferase and gluthithione S-transferase. Relative liver wts ↑ at 250 and 1600 ppm; no changes in hepatic morphology.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The toxicological database for fenpropimorph is adequate for FQPA assessment. There are developmental toxicity studies in two species, the rat (two studies) and the rabbit (two studies), a multi-generation study in the rat as well as acute and subchronic neurotoxicity rat studies. In the 2-generation reproduction study, the highest doses tested were 2.04 and 2.79 mg/kg/day in males and females, respectively. No effects were reported at these doses. Although the 2-generation reproduction study was not conducted according to current guidelines (LOAEL was not attained) a new study will not impact the current risk assessment for fenpropimorph.

4.2.2 Evidence of Neurotoxicity

There is evidence of neurotoxicity in the hazard database. Decreases in plasma/ RBC/brain cholinesterase levels were observed. These changes in cholinesterase activity were considered to

be of questionable toxicological significance because there was no clear dose response relationship and because the effects were inconsistent across time points and different studies/studies. In an acute neurotoxicity screening battery in rats, the neurotoxicity NOAELs were 500 mg/kg/day with the LOAELs being 1500 mg/kg/day based on: piloerection during the clinical examinations and battery (FOB) in both sexes; neuropathy (one male had slight dilation of the ventricles in the frontal lobe, parietal lobe and the midbrain); and decreased overall motor activity in females. None of the above findings were noted in a 90-day combined dietary toxicity/neurotoxicity study in rats (HDT was 78 mg/kg/day).

4.2.2.1 Acute Neurotoxicity - Rats OPPTS 870.6200 [§81-8];. 1997):

EXECUTIVE SUMMARY: In this acute oral neurotoxicity study (MRID 44323910), fenpropimorph was administered in a single dose by gavage to 10 Wistar rats/sex/group at levels of 0, 100, 500, and 1500 mg/kg body weight. Five animals/sex/group were perfused for neurohistological examination. FOB and motor activity were evaluated on study days -7, 0, 7, and 14.

At 1500 mg/kg, piloerection was observed in 4 males on day 1 and in one male on days 1, 6 through 8, and 9 through 11. One female displayed piloerection on day 1, and one female displayed piloerection on days 1 through 6 and 8 through 10. Piloerection was also observed during the sinsorimotor tests of the FOB in 7 males and 7 females on day 0. Females displayed decreased overall motor activity (↓40%, $p \leq 0.02$) on day 0. In addition, evaluation of the interval data revealed decreases (↓38-71%, $p \leq 0.05$-0.01) in females during intervals 1, 3 and 4 on day 0. Males displayed decreased mean body weight (↓7%, $p \leq 0.05$) and body weight gain (↓50%, $p \leq 0.01$) on day 7. Females also showed decreased body weight gain (↓48%, p=not statistically significant) on day 7. During necropsy, one male was found to have a slight dilation of ventricles in the frontal lobe, parietal lobe, and the midbrain.

At 500 mg/kg, one male and two females displayed piloerection during the sensorimotor tests of the FOB on day 0. In addition, a moderate dilation of ventricles was observed in the frontal and parietal lobe regions of the brain of one female during necropsy. No adverse effects were observed in the 100 mg/kg group. No animals died during the study.

The LOAEL for this study is 1500 mg/kg body based on piloerection observations during the clinical examinations and FOB, decreased overall motor activity in females, and signs of neuropathy in males. The NOAEL for this study is 500 mg/kg body weight.

This acute oral neurotoxicity study is classified as **acceptable (870.6200, 81-8)** and satisfies the guideline requirements for an acute neurotoxicity screening battery in rats.

4.2.2.2 Sub-chronic Neurotoxicity - Rats OPPTS 870.6200 (thirteen-week administration in the diet - 1997).

EXECUTIVE SUMMARY: In this subchronic oral toxicity and neurotoxicity study (MRID 44380105), fenpropimorph (94.3% a.i.) was administered for 90 days to 10-15 Wistar rats/sex/dose at dietary concentrations of 0, 1, 100, or 1000 ppm (equivalent to [M/F] 0/0, 0.1/0.1, 0.7/0.8, 7.1/8.5, or 71.0/77.7 mg/kg/day). In the controls, 10, 100, and 1000 ppm animals, functional observation battery (FOB) and motor activity observations were performed on study days -7, 22, 50, and 85. Five animals/sex/group were perfused for neurohistological examination.

No treatment related findings were observed in the 1 ppm dose group. No animals died during the study. Clinical observations, ophthalmoscopic observations, hematological parameters, urinalysis parameters, and gross and histopathological findings were unaffected by the test substance.

In the 100 ppm group, females displayed decreased body weight (↓7-8%, $p \leq 0.05$) on days 21, 35, 42, 49, and 77, and decreased body weight gains (↓14-24%, $p \leq 0.05$ or 0.01) throughout the study. Overall (days 0-90) body weight gains were decreased (↓15%, $p \leq 0.05$) in females. The females showed increased relative liver weights (↑13%, $p \leq 0.01$), and the males displayed increased relative and absolute liver weights (↑18% each, $p \leq 0.01$).

In the 1000 ppm group, both sexes exhibited reduced ($p \leq 0.01$) food consumption (↓9-31%), body weight (↓8-15%), and body weight gains (↓24-85%) throughout the study. Increased ($p \leq 0.01$) alanine aminotransferase was observed in both males and females (↑34-46%), as well as increased total bilirubin (↑26%) in females. Increased relative liver weights were also observed in females (↑21%, $p \leq 0.01$). There were no treatment-related findings in brain weights, the motor activity evaluations or during the homecage and open field observations of the FOB. Erythrocyte and brain cholinesterase activities in all animals were similar to controls; however, clinical chemistry findings indicated a decrease in serum cholinesterase in both sexes. Females displayed decreased serum cholinesterase at 10 ppm, 100 ppm, and 1000 ppm (↓29, ↓54, and ↓69%, respectively; $p \leq 0.01$), while males showed decreased serum cholinesterase in the 100 ppm and 1000 ppm groups (↓32 and ↓31%, respectively; $p \leq 0.01$). Foot-splay values were decreased in the 100 ppm females on day 22 (↓10%, $p \leq 0.02$) compared to controls. High-dose animals displayed differences in landing foot-splay values (↓10%-21%, $p \leq 0.02$ or 0.002) and retarded pupillary reflex (1 female, day 22; 8 males/5 females, day 50; 8 males/5 females, day 85).

In the animals selected for perfusion, minimal axonal degeneration was found in the proximal sciatic nerve of one high-dose female and in the sural nerve of a different high-dose female. Minimal axonal degeneration was also found in one lumbar dorsal root of one male control, in the tibial nerve of one male control, and in the proximal sciatic nerve of another male control.

The systemic oral toxicity LOAEL is 100 ppm (equivalent to 7.1 mg/kg/day in males, 8.5 mg/kg/day in females) based on decreased body weight and body weight gain, as well as increased relative liver weight in females in addition to increased absolute and relative liver weights in males. The systemic oral toxicity NOAEL is 10 ppm (equivalent to 0.7 mg/kg/day in males, 0.8 mg/kg/day in females).

The neurotoxicity LOAEL is 10 ppm (equivalent to 0.7 mg/kg/day) for females and 100 ppm (equivalent to 7.1 mg/kg/day) in males based on decreases in serum cholinesterase activity. The neurotoxicity NOAEL is 10 ppm (equivalent to 0.7 mg/kg/day) for males. The neurotoxicity NOAEL was not established for females.

The submitted study is classified as **acceptable (870.3100, 82-1 and 870.6200, 82-7)** and satisfies the guideline requirements for a subchronic oral toxicity and neurotoxicity study in rats.

4.2.3 Developmental Toxicity Studies

There are two (gavage) developmental toxicity studies in the rat and two (gavage) in the rabbit. In a rat study, the maternal NOAEL was 40 mg/kg/day with the LOAEL being 160 mg/kg/day based on vaginal bleeding and decreased body weight as well as body weight gain. The same NOAEL and LOAEL were noted for the developmental aspect with the following being observed: decreased number of live fetuses/dam, increased resorptions, increased % postimplantation loss and increased incidence of cleft palate. In a second rat developmental toxicity study in which dosing was during gestation and lactation through PND 21 (no visceral or skeletal examinations of fetuses/pups), the maternal NOAEL was 10 mg/kg/day with the LOAEL being 40 mg/kg/day based on decreased body weight gain. For the developmental portion of the study, the NOAEL was 10 mg/kg/day with the LOAEL being 40 mg/kg/day based on decreased live fetuses/dam, increased % postimplantation loss and decreased mean litter size as well as number of live pups and survival indices. In the neurotoxicity portion of this study, the NOAEL was 10 mg/kg/day with the LOAEL being 40 mg/kg/day based on a decrease in grip strength in females.

In the more recent rabbit developmental study (1993), the maternal NOAEL was 15 mg/kg/day with the LOAEL being 30 mg/kg/day based on 9/20 showing swelling of the anus GD 15-29. The developmental NOAEL was 15 mg/kg/day with the LOAEL being 30 mg/kg/day based on increased incidence of cleft palate (4/116 fetuses; 2/20 litters; 0 in control). In the earlier study (1980), the maternal NOAEL was 12 mg/kg/day and the LOAEL was 36 mg/kg/day based on mortality, abortions and clinical signs of toxicity. The developmental NOAEL was 12 mg/kg/day and the LOAEL was 36 mg/kg/day based on increased incidences of resorptions, external anomalies and skeletal variations/retardations.

4.2.3.1 Executive Summary for Developmental Toxicity Studies in Rats OPPTS 870.3700 [83-3]

First Rat Study (1978)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44380108), fenpropimorph (92.5% a.i., Lot/Batch #: 78/164-1) in olive oil was administered to pregnant Sprague-Dawley rats (35-36/dose) at dose levels of 0, 2.5, 10, 40, or 160 mg/kg/day by gavage on gestation days (GDs) 6 through 15. Dams were sacrificed on GD 20. No premature deaths occurred during the study. It was stated that at 160 mg/kg/day, 16 animals exhibited vaginal bleeding during GDs 10-19; no data were provided.

At 160 mg/kg/day, decreases ($p \leq 0.01$) in body weight were noted on GDs 11, 15, and 20 (↓10-

19%) when compared to concurrent controls. Body weight gains were reduced ($p \leq 0.01$) for the GDs 0-11 interval (↓90%, $p \leq 0.01$), and the overall study interval (↓41%, GDs 0-20).

Food consumption was not measured and no gross pathology data were provided. The number of implantations/dam and preimplantation losses were similar between control and treated groups and percent male was not provided.

The maternal LOAEL is 160 mg/kg/day, based on vaginal bleeding during GDs 10-19 as well as decreased body weight and body weight gain.
The maternal NOAEL is 40 mg/kg/day.

At 160 mg/kg/day, the following Cesarean section findings were noted: decreased number of live fetuses/dam (↓10%, $p \leq 0.01$); increased total number of resorptions (NS); increased number of resorptions/dam (about double); increased early (by Salewski) resporptions/dam (1.6 at high-dose vs 0 controls); increased intermediate resorptions/dam (↑43%, calculated by reviewers); increased late resorptions/dam (0.08 at high-dose vs 0 controls); increased totally resorbed litters (7 at high-dose vs 0 controls); and increased percent postimplantation loss (calculated by reviewers). All endpoints calculated by reviewers were not analyzed for statistical significance. Additionally, cleft palate, a skeletal anomaly, was observed at an increased incidence (fetal, 5.1%; litter, 29.2%) vs 0 controls.

The developmental LOAEL is 160 mg/kg/day, based on decreased number of live fetuses/dam, increased resorptions and percent postimplantation losses, as well as increased incidence of skeletal anomalies. The developmental NOAEL is 40 mg/kg/day.

This developmental toxicity study is classified **acceptable/guideline (870.3700, 83-3)** and does satisfy the guideline requirement for a developmental toxicity study in the rat.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, and Flagging statements were provided. No Quality Assurance statement was provided.

Second Rat Study (1979)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44323912), fenpropimorph (92.5% a.i., Lot/Batch #: 78/164-1) in olive oil was administered to Sprague-Dawley rats (17-18/dose) at dose levels of 0, 2.5, 10, 40, or 160 mg/kg/day by gavage on gestation day (GD) 15 through postnatal day (PND) 21. Dams were sacrificed on PND 22 or 23. Food consumption was not measured. The following data were not provided: postnatal maternal mortality; maternal, fetal, or pup clinical signs; maternal, fetal, or pup gross pathology; and visceral or skeletal examination. No maternal or developmental treatment-related findings were noted at 2.5 or 10 mg/kg/day.

No premature deaths occurred during the gestation period; it was stated that four 160 mg/kg/day animals died, one on the day after giving birth, two on PND 2, and one on PND 6. At 40 mg/kg/day, body weight gains were reduced ($p \leq 0.05$) for the GDs 0-20 interval, the PNDs 0-7 interval, the PNDs 0-14 interval (↓11-45%), the overall treatment (GD 15-PND 21) interval, and

the overall (GD 0-PND 21) study interval (↓21%, calculated by reviewers and not analyzed statistically).

At 160 mg/kg/day, it was stated that during treatment the animals displayed diarrhea, isolated cases of salivation and trembling, severe reddening of the urogenital area, and urine with a penetrating odor. Vaginal bleeding was observed in the female that died on PND 6; no clinical signs data were provided. Decreases ($p \leq 0.01$) in body weight were noted beginning on GD 20 and continuing until PND 21 (↓9-21%). Body weight gains were reduced (≤ 0.01) for the GDs 0-20 interval, the PNDs 0-7 interval, the PNDs 0-14 interval (↓35-97%), the overall treatment (GD 15-PND 21) interval (↓excessive), calculated by reviewers and not analyzed statistically), and the overall (GDs 0-PND 21) study interval (↓36%, calculated by reviewers and not analyzed statistically). It was stated that upon necropsy, three of the four animals that died prematurely had bulging stomachs full of food; whereas, their intestinal tracts were empty of food; no gross pathology data were provided. Terminal body weights were reduced (↓8%, $p \leq 0.01$), as were absolute heart, spleen, liver and kidney weights (↓14-19%, $p \leq 0.05$ or 0.01). Relative (to body) heart and kidney weights were reduced (↓8 and 13 %, respectively, $p \leq 0.01$). It was stated that delivery behavior was characterized by unsatisfactory care of the pups and in some cases the completely retained placentae were connected to the umbilical cord and the pup. Further, the dams failed to clean the pups they delivered. No delivery data were provided.

The maternal LOAEL is 40 mg/kg/day, based on decreased body weight gain. The maternal NOAEL is 10 mg/kg/day.

At 40 mg/kg/day, the following findings were noted when compared to concurrent controls: decreased number of live fetuses/dam (↓ 18%, $p \leq 0.05$); increased total number of dead implantations/dam (↑49%); and increased percent postimplantation loss (↑56%, calculated by reviewers and not analyzed statistically). Decreases (calculated by reviewers and not analyzed statistically) in mean litter size and number of live pups were noted on days 0, 7, 14, and 21 (↓18-28%). Decreases ($p \leq 0.05$ or 0.01) in day 14 and day 21 survival indices (↓11-12%) were observed. No clinical signs data were provided; it was stated that one fetus displayed anophthalmia bilaterally. Decreased (≤ 0.05) grip strength was observed in the females on PND 15 (44.44% treated vs 22.22% controls).

At 160 mg/kg/day, the following findings were noted: decreased number of live fetuses/dam (↓86%, $p \leq 0.01$); increased number of dead fetuses (155 at high-dose vs 5 in controls); increased total number of dead implantations/dam (↑24%); and increased percent postimplantation loss (↑not applicable, calculated by reviewers and not analyzed statistically). Decreases in mean litter size and number of live pups were noted on days 0, 7, 14, and 21 (↓60-92%). Additionally, increased number of deaths during PNDs 0-7 (↑100%), decreased livebirth index (↓83%), and an increased stillborn index (↑not applicable) were observed; these were calculated by reviewers and not analyzed statistically. Decreases ($p \leq 0.01$) in survival indices were observed on days 7, 14, and 21 (↓37-45%). No clinical signs data were provided. Decreased male and female day 0 fetal weights (↓11-13%, $p \leq 0.01$) were observed when compared to concurrent controls. Additionally, male and female pup body weights were reduced ($p \leq 0.05$ or 0.01) throughout the study (↓11-31%; days 0-21), as were pup body weight gains ($p \leq 0.05$ or 0.01) on days 0-7, days 0-14, and days 0-21 (↓4-41%). Delays ($p \leq 0.01$) in development were noted in male and female fetuses as follows:

delay in erect auricles on PND 3 (18.75% treated vs 7.21% controls); delay in fur development on PND 10 (18.75% treated vs 3.87% controls); and delay in eye opening on PND 16 (46.67% vs 0.56% controls).

The developmental LOAEL is 40 mg/kg/day, based on decreased number of live fetuses/dam, increased total number of resorptions/dam, increased percent postimplantation loss, decreased mean litter size and number live pups, decreased survival indices, and decreased grip strength in the females. The developmental NOAEL is 10 mg/kg/day.

This developmental toxicity is classified **acceptable/non-guideline (870.3700, 83-3)** and is not a required guideline study.

4.2.3.2 Executive Summary for Developmental Toxicity Study in Rabbits 870.3700 [83-3]

First Rabbit Study (1993)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44323914), fenpropimorph (95.6% a.i.) in 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose was administered to pregnant Russian Chbb:HM rabbits (20/dose) at dose levels of 0, 7.5, 15, or 30 mg/kg/day by gavage of gestation days (GDs) 7 through 19. Does were sacrificed on GD 29.

No premature deaths occurred during the study. No treatment-related clinical signs, changes in body weight, or reductions in food consumption were observed in the low- or mid-dose animals. At the high-dose level, 9/20 animals displayed swelling of the anus beginning on GD 15 and continuing until GD 29 (2-12 occurrences during the 29 day study period); at necropsy, only a single high-dose female exhibited macroscopic swelling of the anus.

No treatment-related changes were observed in body weight, body weight gain, food consumption, Cesarean section, or gross pathological findings at any dose level tested.

The maternal LOAEL is 30 mg/kg/day, based on clinical signs (swelling of the anus). The maternal NOAEL is 15 mg/kg/day.

Regarding developmental toxicity at the high-dose level, numerous external, visceral, and skeletal malformations were noted. i) The only external malformation which occurred in more than one fetus was cleft palate (4/116 fetuses, 2/20 litters; 3.4% fetuses, 10.0% litters; historical control % 0.0-0.9 for fetuses and 0.0-5.3% for litters). None of these external malformations were observed in the controls. ii) Visceral malformations observed when compared to concurrent controls included [% fetal incidence (% litter incidence)]: cleft palate, 1.7 (5.0) with historical control ranges of 0.0-0.9 (0.0-5.3). iii) Skeletal malformations: shortened scapula, humerus, radius, ulna, femur, tibia, and fibula, each 17.2 (15.0). All observations of shortened limbs were different ($p<0.01$) from controls and all twenty fetuses with shortened limbs were found in three high-dose litters. Of 20 fetuses with shortened limbs, one showed the malformations of the cranial bones, while another displayed the reduced parietal bones; both of these fetuses showed absent ossification of the pubis.

At the high-dose level, several external anomalies were noted and included position anomaly of the forelimb (fetal, 21.6%; litter, 35.0%; p<0.01) with a historical control fetal incidence of 0.0-3.7% and litter incidence of 0.0-20.0%; and position anomaly of the hindlimb (fetal, 6.9%; litter, 15.0%; p< 0.01). None of these external anomalies were observed in the controls. Of the skeletal anomalies, an increased incidence of fragmented sternebra-1 was observed (fetal, 2.6%; litter, 15.0%) vs 0 concurrent controls and a historical control incidence (fetal, 0.0-1.0%; litter, 0.0-6.3%).

Also at the high-dose, skeletal variations included [% fetal incidence (% litter incidence)]: i) slot in the parietal bone, 4.3 (20.0) vs concurrent control incidences of 1.6 (11.1) and historical control incidences of 0.0-1.0 (0.0-6.3) and ii) absent ossification of caudal vertebral centers, 44.0 (85.0) vs concurrent control incidences of 26.2 (77.8) and historical control ranges of 10.6-21.7 (29.4-68.4).

The developmental LOAEL is 30 mg/kg/day, based on increased incidence of external, visceral, and skeletal malformations (cleft palate), increased incidence of external and skeletal anomalies, and increased incidence of skeletal variations. The developmental NOAEL is 15 mg/kg/day.

This developmental toxicity study is calssified **acceptable (870.3700, 83-3[b]** and does satisfy the guideline requirement for a developmental toxicity study in the rabbit.

Second Rabbit Study (1980)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44323913), fenpropimorph (92.5% a.i.) in carboxymethyl cellulose was administered to pregnant Himalayan Chbb:HM rabbits (15/dose) at dose levels of 0, 2.4, 12, or 60 mg/kg/day by gavage on gestation days (GDs) 6 through 18. Due to severe mortality at 60 mg/kg/day, additional rabbits (10 or 15/dose) were administered a dose of 36 mg/kg/day in a supplementary study that included a vehicle control group (control-2). All does were sacrificed on GD 29. At 2.4 or 12 mg/kg/day, no treatment-related changes in body weight, body weight gain, food consumption, Cesarean section, or gross pathological findings were observed.

At 2.4 mg/kg/day, one animal died on GD 20 after showing signs of severe emaciation and diarrhea; upon necropsy, it was stated this animal showed pronounced cachexia, dilatation of the right heart, congestive hyperemia, and an empty gastrointestinal tract; however, no gross pathological data were provided. One 12 mg/kg/day animal was sacrificed on GD 6 due to injury; no further information was provided. At 36 mg/kg/day, 3 animals were sacrificed *in extremis* and 2 abortions occurred; it was stated that the animals sacrificed displayed a round, necrobiotic, and very distinct area that extended into the parenchyma on the parietal surface of the liver, but no gross pathological data were provided. At 60 mg/kg/day, 11 animals (9 pregnant, 2 nonpregnant) died as follows: one each on GDs 10, 11, 19, and 21 and two each on GDs 12, 17, and 20 (day of death for one 60 mg/kg/day doe was not provided). It was stated that 3 of the eleven 60 mg/kg/day animals that died exhibited dilatation of the right heart and congestive hyperemia; no gross pathological data were provided.

At 36 mg/kg/day, it was stated the following clinical signs were noted, each observed in a single animal: i) mucous feces and greenish saliva beginning on GD 16, followed by severe emaciation and sacrifice *in extremis* on GD 22; ii) inflammation of the vaginal region on GD 14, salivation and abortion on GD 18, and sacrifice on GD 20; iii) diarrhea beginning on GD 16 and abortion on GD 21; iv) diarrhea and considerable weight loss on GD 16 and sacrifice on GD 22; and v) severe diarrhea, considerable weight loss, and a mouth lesion and sacrifice on GD 22. No clinical signs data were provided.

At 60 mg/kg/day, it was stated the animals displayed severe diarrhea, salivation, apathy, greenish and mucous discharge from the nose, mucous and gelatinous feces, convulsions shortly before death, local alopecia on the snout, and encrustation in the vaginal region and snout. No clinical signs data were provided. Decreases ($p \leq 0.05$ or 0.01) were noted in body weight from GD 12 to termination (↓7-27%), in body weight gain beginning at the GDs 6-9 interval and continuing to the GDs 19-21 interval, and in gravid uterine weight (↓92%). Body weight gains increased ($p \leq 0.05$ or 0.01) during the post-treatment intervals of GDs 21-23, 23-26, and 26-29; additionally, an increase in overall corrected (for gravid uterine weight) body weight gain, was noted. Decreases ($p \leq 0.05$ or 0.01) in absolute (g/day) food consumption were observed at the GDs 7-12 interval and continuing through the GDs 20-29 post-treatment interval (↓22-93%); overall food consumption was also reduced (↓29%, $p \leq 0.01$, GDs 1-29).

The maternal LOAEL is 36 mg/kg/day, based on mortality, abortions, and stated clinical signs of toxicity. The maternal NOAEL is 12 mg/kg/day.

At 36 mg/kg/day, the number of resorptions/doe was increased (not statistically significant) from the control-2 group as follows: i) an increased number of total resorptions; an increased number of early resorptions; an increased number of resorptions/dam; an increased number of early resorptions/dam; and an increased percent postimplantation loss. Bilateral pseudoancylosis, an external anomaly, was observed (fetal incidence, 9.4%; litter incidence, 22.2%) vs 0 fetuses in control-2. Asymmetrical sternebrae, a skeletal variation/retardation, was observed at an increased incidence (fetal incidence, 3.8%; litter incidence, 22.2%) when compared to the control-2 group.

At 60 mg/kg/day, the following observations were noted (not statistically significant): a decrease in the number of live fetuses/doe; increased total number of resorptions and number of early resorptions; increased total number of resorptions/dam and early resorptions/dam; and increased percent postimplantation loss. Due to severe maternal mortality, only one fetus was examined for developmental abnormalities; fused sternebrae, a skeletal anomaly, was observed in this fetus vs 0 controls.

The developmental LOAEL is 36 mg/kg/day, based on increased incidence of resorptions, external anomalies, and skeletal variations/retardations. The developmental NOAEL is 12 mg/kg/day.

This developmental toxicity study is classified **acceptable (870.3700, 83-3[b])** and does satisfy the guideline requirement for a developmental toxicity study in the rabbit.

4.2.4 Reproductive Toxicity Study OPPTS 870.3800 [83-4]; (1982)

In the 2-generation reproduction study, the rats were given the following doses by dietary admix: males = 0, 0.51, 1.03 or 2.04 mg/kg/day; females = 0, 0.71, 1.46 or 2.79 mg/kg/day. These doses were based on an increase in relative liver weights in a 90-day dietary rat study at 25 ppm (approximately 1.25 mg/kg/day). The NOAELs for parental, reproduction and offspring parameters were 2.04 and 2.79 mg/kg/day for males and females, respectively (highest dose tested). Therefore, LOAELs were not attained.

Since this study was performed prior to the adoption of the Pesticide Assessment Guidelines (Subdivision F), the animals were not dosed with a sufficient concentration of the test substance to cause toxicity in the parental animals. Therefore there could be concern that the study was not conducted sufficiently to adequately address post-natal toxicity concerns. Upon review of the study, HED concluded that although the study is non-guideline (higher doses should have been administered), all other aspects of the study were conducted correctly and therefore the degree of uncertainty of the reported NOAELs is minimal. Furthermore, the highest dose tested in the multigeneration study (2.04 and 2.79 mg/kg/day for males and females, respectively) is similar to the dose selected for chronic dietary exposure assessment (3.2 mg/kg/day)) which is not only protective for the NOAELs from the multi-generation study, and already incorporates a 100 fold uncertainty factor for inter-species extrapolation and intraspecies variations. A conservative dietary exposure estimate is 10x lower than exposures that would be of concern (i.e. 100% of the cPAD). Finally, in the rat developmental toxicity study (MRID 44323912) dosing occurred during gestation, lactation and through post-natal day 21 up to 160 mg/kg/day which resulted in a developmental NOAEL of 10 mg/kg/day. The lowest developmental adverse effects were not observed until 40 mg/kg/day (LOAEL). This rat developmental study with post-natal dosing, further justifies that post-natal toxicity is occurring at levels higher than those observed in the multigeneration study. Therefore, repeating another 2-generation reproduction study would only result in testing at higher doses which would result in a NOAEL higher than the NOAEL (3.2 mg/kg/day) currently used to assess chronic risk. Therefore, there is no residual uncertainty for the lack of the LOAEL in the 2-generation reproduction study. In summary, there is no residual uncertainty for pre- and/or post natal toxicity.

4.2.4.1 Executive Summary for 2-Generation Reproduction Study in Rats

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 44323915), Fenpropimorph (Batch/Lot # 79/4; 92.5% a.i.) was administered in the diet to 12 male/24 female Sprague Dawley (Mura: SPF 78 Han.) rats/dose at dose levels of 0, 6.25, 12.5, or 25.0 ppm (equivalent to 0/0, 0.51/0.71, 1.03/1.46, and 2.04/2.79 mg/kg bw/day males/females). The P generation parents were dosed for at least 100 days before they were mated to produce the F_1 litters; the F_1 parents were dosed for at least 120 days before they were mated to produce the F_2 litters. The F_1 pups were weaned on postnatal day (PND) 21, and 12 male/24 female rats/dose were selected as parents of the F_2 generation.

In the parental animals, no treatment-related effects were observed on mortality, clinical signs, body weights. body weight gains, food consumption, organ weights, or gross/microscopic pathology.

The LOAEL for parental toxicity was not observed. The NOAEL is 25.0 ppm (equivalent to 2.04/2.79 mg/kg bw/day).

In the offspring, no treatment-related effects were observed on the following parameters: survival, viability, lactation indices, clinical signs, body weights, body weight gains, developmental landmarks, behavioral criteria, organ weights, or gross/microscopic pathology.

The LOAEL for offspring toxicity was not observed. The NOAEL is 25.0 ppm (equivalent to 2.04/2.79 mg/kg bw/day).

No treatment-related effects were observed regarding gestation, fertility or pregnancy.

The LOAEL for reproductive performance was not observed. The NOAEL for reproductive performance is 25.0 ppm (equivalent to 2.04/2.79 mg/kg bw/day).

This study is classified as **acceptable/non-guideline** and does not satisfy the guideline requirements (OPPTS 870.3800, 83-4) for a two-generation reproduction study in the rat. Although this study was performed prior to the adoption of the Pesticide Assessment Guideline (Subdivision F), the animals were not dosed with a sufficient concentration of the test substance to cause toxicity in the parental animals, and the reasoning for the selection of the doses used in this study was unacceptable.

4.2.5 Additional Information from Literature Sources

A literature search was conducted, but no additional toxicity information was found.

4.2.6 Pre-and/or Postnatal Toxicity

It is concluded that there is pre-natal toxicity resulting from the exposure to fenpropimorph. The primary findings are the increased incidences of cleft palate in a rat and a rabbit developmental study. In addition, in the two rat studies, there were decreases in the number of live fetuses/dam and the number of live pups as well as increases in resorptions and postimplantation loss. In the rat study, with a developmental NOAEL of 40 mg/kg/day and a LOAEL of 160 mg/kg/day, the incidences of this finding are 14/274 fetuses and 7/24 litters compared with no fetuses with cleft palate in the control or lower dose groups. Regarding the rabbit study, in which the developmental NOAEL was 15 mg/kg/day and a LOAEL of 30 mg/kg/day, the incidences are 4/116 fetuses and 2/20 litters compared with no fetuses in the control or lower dose groups. Another rat developmental study was performed where dosing was during gestation and lactation (through PND 21) with no visceral or skeletal examinations of the fetuses/pups. In a second rabbit developmental study, the NOAEL was 12 mg/kg/day with the LOAEL being 36 mg/kg/day based on increased incidences of resorptions, external anomalies and skeletal variations/retardations (no cleft palates).

There was no mention of cleft palate in the multigeneration study. However, the highest dose administered in that study (2.79 mg/kg/day) was lower than the NOAELs in the rat and rabbit developmental studies (10 or 15 mg/kg/day).

4.2.6.1 Determination of Susceptibility

The NOAELs for maternal and fetal aspects in the two rat and two rabbit developmental studies are the same so that there is no apparent increase in quantitative susceptibility. Regarding qualitative susceptibility, the LOAEL doses for both species are the same for maternal and fetal effects, but the fetal effects (cleft palate and postimplantation loss with fetal deaths) appear to be more severe than the maternal effects (vaginal bleeding and decreases in body weight as well as body weight gain in rats; swelling of the anus, mortality and abortions in rabbits). In the one developmental rat study where fetuses were examined, there was a decrease in the number of live fetuses/dam, an increase in resorptions and an increase in the % postimplantation loss. In the rabbit study in which the NOAEL was 12 mg/kg/day and the LOAEL was 36 mg/kg/day, the maternal effects were primarily maternal mortality and abortions; whereas, there were no cleft palates reported.

In an acute neurotoxicity screening battery in rats, the neurotoxicity NOAELs were 500 mg/kg/day with the LOAELs being 1500 mg/kg/day based on: piloerection during the clinical examinations and FOB in both sexes; neuropathy (one male had slight dilation of the ventricles in the frontal lobe, parietal lobe and the midbrain); and decreased overall motor activity in females. None of the above findings were noted in a 90-day combined dietary toxicity/neurotoxicity study in rats (HDT was 78 mg/kg/day).

Based upon the above findings, it is determined that there is no increase in quantitative susceptibility regarding fetuses (NOAELs for systemic and developmental parameters were the same). There was an increase in qualitative susceptibility due to the severity of the fetal findings (increased incidence of cleft palate in rats and rabbits and fetal loss in the rat studies).

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

Although there is evidence for increased qualitative susceptibility in the developmental rat and rabbit studies, the fenpropimorph Risk Assessment Team concluded that there is a low degree of concern (and no residual uncertainty) because: 1) the increased susceptibility was seen at LOAELs of 160 mg/kg/day in the rat study and at 30 mg/kg/day in the rabbit study (NOAELs were 40 and 15 mg/kg/day for the rat and rabbit studies, respectively); 2) cleft palate was not reported in a second rabbit developmental study with doses up to 36 mg/kg/day; 3) no mention was made of cleft palate in another developmental rat study at doses up to 160 mg/kg/day (however, there were no visceral or skeletal examinations of fetuses/pups); 4) at doses up to 2.79 mg/kg/day in a 2-generation reproduction study in rats, cleft palate was not reported; 5) developmental effects were observed only in the presence of maternal toxicity; and 6) the doses selected for acute and chronic dietary exposure and risk assessment were considerably lower than the doses at which developmental effects were observed.

The Fenpropimorph Risk Assessment Team concluded that the data indicate there are no (residual) concerns for pre- and/or postnatal toxicity following exposure to fenpropimorph and therefore no additional safety factors are necessary to protect the safety of infants and children.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports not requiring a Developmental Neurotoxicity study

Treatment-related toxicological signs of neurotoxicity were observed in some studies. Nervous system effects were noted in the acute neurotoxicity battery in rats where the NOAELs for males and females were 500 mg/kg and the LOAELs were 1500 mg/kg (close to the limit dose). In this acute study, the males showed piloerection plus one rat had dilation of the ventricles of the brain and females were observed to have dilation of the brain (one rat), piloerection and an overall decrease in motor activity.

It is considered that there is little or no evidence to support requiring a developmental neurotoxicity study at this time because neurotoxic parameters were affected only at very high doses, considerably higher than the NOAELS observed for liver related changes (500 times higher) and developmental effects (100 times higher).

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

Executive Summaries: see Sections 4.2.3.1 (rat developmental), 4.2.3.2 (rabbit developmental) and 4.2.4.1 (2-generation reproduction)

Dose and Endpoint for Establishing RfD: NOAEL of 15 mg/kg/day in a rabbit developmental study with a LOAEL of 30 mg/kg/day based on an increased incidence of cleft palate. A rat developmental study also had cleft palates, the NOAEL was 40 mg/kg/day and the LOAEL was 160 mg/kg/day. In addition, in rat developmental studies, there was fetal mortality as evidenced by a decrease in the number of live fetuses/dam as well as an increase in resorptions and postimplantation loss. The NOAEL of 15 mg/kg/day (LOAEL was 30 mg/kg/day) was chosen because of the distance between the NOAEL and LOAEL in the developmental rat study (NOAEL = 10 mg/kg/day, LOAEL = 40 mg/kg/day) and the developmental rabbit study (NOAEL = 12 mg/kg/day, LOAEL = 36 mg/kg/day). In addition, in the developmental rat study (NOAEL of 10 mg/kg/day), fetuses/pups were not examined.

Uncertainty Factor(s): 100, based on 10 for intraspecies variation and 10 for interspecies extrapolation.

$$\textbf{Acute RfD (females 13=49)} = \frac{15 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.15 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): Cleft palate is considered to possibly be caused by a single dose. There were no reported cleft palate findings in a second rat developmental study at doses up to 160 mg/kg/day; however, the dosing was during gestation and lactation, and the fetuses/pups were not examined for visceral or skeletal changes. In a 2-generation rat reproduction study, the highest doses tested were 2.04 and 2.79 mg/kg/day for

males and females, respectively; there was no indication in the study that cleft palates were observed.

4.4.2 Chronic Reference Dose (cRfD)

EXECUTIVE SUMMARY RATS

EXECUTIVE SUMMARY: In a combined chronic/oncogenicity study (MRID 44380106), fenpropimorph (92.5% a.i.) was administered in the diet for up to 114 weeks to 60 Sprague-Dawley rats/sex/group at levels of 0, 5, 10, 50, or 250 ppm (achieved doses of 0, 0.2/0.2, 0.3/0.4, 1.7/2.1, or 8.8/11.2 mg/kg/day [M/F]. Ten rats/sex/dose were terminated at 52 weeks; the remaining rats were sacrificed at 108 (females) or 115 weeks (males). A satellite group (15 rats/sex/dose) was used for interim blood and urinalyses determinations and was terminated at 104 weeks.

There were no differences of toxicological concern observed in survival rates, food consumption, water consumption, ophthalmological parameters, hematological parameters, clinical chemistry, urinalysis, RBC cholinesterease activity, gross pathology, and non-neoplastic histopathology when compared to concurrent controls.

At 5 ppm, plasma cholinesterase activity was reduced in males at 114 weeks (↓18%, $p<0.05$) and in females at 104 weeks (↓21%, $p<0.05$) with respect to concurrent controls. Brain cholinesterase activity was decreased in males at the final (115 week) sacrifice (↓23%, $p<001$).

In females, an increased incidence of foci of eosinophilic hepatocytes (10/50 treated vs 5/50 controls) was observed at 108 weeks. This finding was not dose-dependent, but was increased in all treated females.

At 10 ppm, plasma cholinesterase activity was reduced in females at 52 and 104 weeks (↓23-25%, $p<0.01$). Brain cholinesterase activity was decreased in males at the final (115 week) sacrifice (↓24%, $p<0.001$). At 52 weeks, covariate-adjusted (to body weight) liver weights were increased ($p<0.05$) in the males (↑15%). Additionally, females exhibited a non-dose-dependent increase in the incidence of foci of eosinophilic hepatocytes (12/50 vs 5/50).

At 50 ppm, plasma cholinesterase activity was reduced ($p< 0.05$ or 0.001) in the males at 78 and 114 weeks (↓18-29%) and in females at 52, 78, and 104 weeks (↓18-27%). Brain cholinesterase activity was decreased ($p<0.01$ or 0.001) in males (↓30%) and females (↓13%) at the final sacrifice. At the interim and terminal necropsy, covariate-adjusted (to body weight) liver weights were increased in the males (↑13-17%, $p<0.05$ or 0.01). At 52 weeks, slight enlargement of centrilobular hepatocytes was observed in males (2/10 treated vs 0/10 controls). When considering all remaining animals from the main study group, foci of ballooned hepatocytes were observed in males (21/50 treated vs 10/50 controls) and enlarged periportal hepatocytes were observed in females (15/50 treated vs 1/50 controls). Females also exhibited a non-dose-dependent increase in the incidence of foci of eosinophilic hepatocytes (11/50, treated vs 5/50 controls).

At 250 ppm, differences in body weights, as calculated by the reviewers, but not analyzed statistically, occurred in the males from week 2 to termination (↓1-15%) and in the females from week 1 to termination (↓2-25%). Body weight gains for weeks 0-92 were reduced ($p<0.001$) in males and females (↓9-19%) for weeks 1-26. Plasma cholinesterase activity was reduced (p=not significant, <0.05, 0.01 or 0.001 in the males from week 26 to termination (↓18-29%) and in females from week 6 to termination (↓23-41%). Brain cholinesterase activity was decreased ($p<0.05$, 0.01, or 0.001) in males at the final sacrifice (↓40%) and in females at the interim and final sacrifice (↓12%). Covariate-adjusted (to body weight) liver weights were increased ($p<0.05$ or 0.001) in males at 52 (↑31%), 104 (↑19%), and 115 weeks (↑13%), and in females at 52 weeks (↑14%). At the interim necropsy, enlargement of centrilobular hepatocytes was observed in males, ranging from minimal (5/10 treated vs 0/10 controls) to slight (2/10 treated vs 0/10). Minimal enlargement of midzonal hepatocytes was also observed in males (2/10 treated vs 0/10 controls). In the females, vacuolation of hepatocytes was observed (1/10 treated vs 0/10 controls). Other alterations of the liver, such as ballooned hepatocytes, focal fibrosis, and lipid deposition, were observed, but the incidences were low (1/10 treated vs 0/10 controls). Increases in hepatic alterations were also observed in the remaining main group animals: foci of eosinophilic hepatocytes (20/50 treated vs 4/50 controls), foci of ballooned hepatocytes (22/50 treated vs 10/50 controls), enlarged centrilobular hepatocytes (16/50 treated vs 0/50 controls), and multinucleated hepatocytes 5/50 treated vs 0/50 controls) were observed in males. In the females, enlarged periportal hepatocytes (16/50 treated vs 1/50 controls) and an increased incidence of foci of eosinophilic hepatocytes (14/50 treated vs 5/50 controls) were observed.

The chronic LOAEL for males and females is 250 ppm (equivalent to 8.8 and 11.2 mg/kg/day respectively) based on liver findings. The chronic NOAEL was 50 ppm (1.7 and 2.1 mg/kg/day for males and females respectively).

There were no treatment-related increases in neoplasms between the treated and concurrent control groups in the interim necropsy group or in the main group. A leiomyosarcoma was observed in one deceased male from the main study group. This rare tumor has been previously reported in female mice in an oncogenicity study of fenpropimorph (MRID 44380107), but the incidences were within historical control ranges and considered not of toxicological concern.

The submitted study is classified as **acceptable (870.4300, 83-5)** and does satisfy the guideline requirements for a chronic toxicity study (83-1) and a carcinogenicity study (83-2) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. No Flagging statement was provided.

EXECUTIVE SUMMARY DOG

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 44323911), fenpropimorph (≥94.7% a.i.) was administered to beagle dogs (6/sex/group) at concentrations of 0, 25, 100 or 400 ppm in the diet (achieved doses M/F 0/0, 0.8/0.8, 3.2/3.2 or 12.3/13.2 mg/kg/day) for 12 months. No deaths occurred during the study.

At 400 ppm, several changes ($p<0.05$ or 0.02) in clinical chemistry were noted as follows: in males, increased alkaline phosphatase activity on days 93, 186 and 361 (↑36%, $p<0.05$; ↑21%, not significant; ↑67%, $p<0.02$; respectively) and increased serum cholinesterase activity on days 29, 57, 93, 186 and 361 (↑25-37%; $p<0.02$ on day 93 only); in females, increased alanine aminotransferease on day 361 (↑204%, $p<0.02$). One high-dose male exhibited increased alanine aminotransferase activities (↑340-799%) compared to the controls; the difference became more exaggerated as the study progressed.

When compared to concurrent controls, no treatment-related differences in body weight or body weight gains, food consumption, hematological parameters, urinalysis parameters, ophthalmoscopic abnormalities or gross as well as microscopic pathology were observed.

The LOAEL is 400 ppm (equivalent to 12.3/13.2 mg/kg/day [M/F] based on increases in blood enzyme activities. The NOAEL is 100 ppm (equivalent to 3.2 mg/kg/day).

This toxicity study is classified **acceptable (83-1[b])** and satisfies the guideline requirement for a chronic toxicity study in the dog.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Dose and Endpoint for Establishing RfD: The NOAEL was 3.2 mg/kg/day (males and females), with the LOAELs of 8.8/11.2 mg/kg/day (males and females) based on histopathological liver findings (eosinophilic, enlarged centrilobular, multinucleated and foci of ballooned hepatocytes).

Uncertainty Factor(s): 100, based on 10 for intraspecies variation and 10 for interspecies extrapolation.

$$\textbf{Chronic RfD} = \frac{3.2 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.032 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): The one-year dog and the chronic/carcinogenicity rat studies were considered co-critical in establishing the chronic reference dose (cRfD), based on liver effects observed in both studies following dosing with fenpropimorph. In the one-year dog study, the NOAEL was 3.2 mg/kg/day with LOAELs of 12.3/13.2 mg/kg/day (M/F), based on increased levels of the liver enzyme alanine aminotransferase (ALT) equal to 204% in females and to 304-799% (increasing severity with time) in males. Additionally, increased alkaline phosphatase levels were seen in males throughout the study. No accompanying changes in liver weights or histopathology were seen in the one-year dog study. In the chronic/carcinogenicity rat study, the NOAELs were 1.7/2.1 mg/kg/day (M/F) with LOAELs of 8.8/11.2 mg/kg/day (M/F), based on multiple types of histopathological changes observed in the liver of both interim and main group animals. Furthermore, increased relative (to body weight) liver weights were seen in both males and females.

A weight of the evidence approach can be used to determine whether adverse liver effects are

considered critical. A combination of treatment-related changes in liver enzymes, weights, and histopathology is considered stronger evidence than when effects are seen in only one or two of these parameters. In the case of fenpropimorph, liver effects were across species, in both the rat and dog, at doses ≥8.8 mg/kg/day; however, the liver enzyme changes were noted in dogs only, and the liver weight and histopathological changes were seen only in the rat. Although the lowest dose to produce liver toxicity in the dog (12.3/13.2 mg/kg/day) was greater than in the rat (8.8/11.2), the severity of the liver enzymes increases (up to 799%) makes it likely that increased liver enzyme levels would be seen at lower doses, such as the rat LOAEL. Therefore, the combination of liver changes, beginning at 8.8 mg/kg/day with the histopathological changes in the rat, which are supported by the liver enzyme changes in the dog, forms the basis for the cRfD.

The doses chosen for the chronic rat and dog studies were spaced such that they overlap. Because of this, the NOAELs and LOAELs for these studies, while similar, are not exactly the same. However, the target organ in both the chronic rat and dog fenpropimorph studies is the liver, and the adverse effects indicating liver changes in both of these studies are seen at approximately the same doses; therefore, the team chose the NOAEL of 3.2 mg/kg/day to be protective of potential liver toxicity in the human.

The team also reviewed the 90-day dietary rat study (MRID 44380103) as a possible selection for the chronic endpoint and dose with a lower NOAEL (0.768 mg/kg/day for males and 0.915 mg/kg/day for females) and LOAEL of 1.54 mg/kg/day in males and 1.8 mg/kg/day in females based on increased relative and absolute (females only) liver weights and incidence of liver single cell necrosis. However, upon detailed review of the data, it was determined that single cell necrosis was not an effective/significant endpoint selection since there was no evidence of a dose response, and cell necrosis and changes in liver weights did not occur in the 90-day dog or 2 year reproduction study in the rat.

4.4.3 Incidental Oral Exposure, Dermal and Inhalation Exposure

Since this action is for an import tolerance on bananas, no proposed uses would result in either occupational and residential exposure in the U.S. and, therefore, no oral, dermal or inhalation risk assessments are required. Such endpoints were not selected.

4.4.4 Recommendation for Aggregate Exposure Risk Assessments

Since fenpropimorph is not registered in the United States there are no residential uses or drinking water levels to aggregate and therefore, no reason to perform an aggregate exposure assessment.

4.4.5 Classification of Carcinogenic Potential

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the Cancer Assessment Review Committee (CARC) classified fenpropimorph as **" not likely to be carcinogenic to humans"**. There were no increased incidences of benign or malignant tumors in either a rat chronic/carcinogenicity or a mouse carcinogenicity study.

4.4.5.1 Two-Year Dietary Toxicity/Carcinogenicity Study in Rats

(See Executive Summary in section 4.4.3)

4.4.5.2 95-Week Dietary Carcinogenicity Study in Mice

(See Executive Summary in section 4.4.3)

Fenpropimorph Toxicological Endpoints

Table 4.4. Fenpropimorph - Summary of Toxicological Doses and Endpoints for Chemical for Use in Human Health Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	NOAEL = 15 mg/kg/day Total UF = 100X Acute RfD = 0.15 mg/kg/day	FQPA SF = 1X aPAD = Acute RfD / FQPA SF aPAD = 0.15 mg/kg/day	Rabbit Developmental Study Developmental LOAEL = 30 mg/kg/day based on cleft palates
Acute Dietary (general population)	No toxicological endpoint attributable to a single exposure was identified in the available toxicity studies		
Chronic Dietary (all populations)	NOAEL = 3.2 mg/kg/day Total UF = 100 X Chronic RfD = 0.032 mg/kg/day	FQPA SF = 1X cPAD = Chronic RfD / FQPA SF cPAD = 0.032 mg/kg/day	One-Year Dog and Chronic/Carcinogenicity Rat Studies [Co-critical studies for endpoint selection]. LOAEL of 9-11 mg/kg/day, based on liver histopathology
Incidental Oral (All durations)	Endpoints were not selected for occupational/residential exposure risk assessments since this petition is for an import tolerance.		
Dermal (All durations)			
Inhalation (All durations)			
Cancer (oral, dermal, inhalation)	**Classification: "Not likely to be carcinogenic to humans."** No increased incidences in tumors in a chronic/carcinogenicity rat study or a carcinogenicity mouse study.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level. PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* Refer to Section 4.5

4.5 Special FQPA Safety Factor

Based on the review of the toxicology database, the Fenpropimorph Risk Assessment Team recommends that the Special FQPA Safety Factor (10x) should be removed (reduce to 1x). This recommendation is applicable to all population subgroups for all exposure routes and durations.

It is recommended that the Special FQPA Safety Factor can be removed (i.e., reduced to 1X) because: 1) there is a low degree of concern for the qualitative susceptibility in developmental rat and rabbit studies, because the fetal effects were observed only in the presence of maternal toxicity; and 2) there is no concern for pre/post natal toxicity since no off-spring toxicity was seen in the 2 generation reproduction study; 3) the endpoints of concern are addressed in this risk assessment; and 4.) the dietary exposure assessment assumed tolerance level residues and 100% crop treated.

4.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on fenpropimorph there was no estrogen, androgen, and/or thyroid mediated toxicity. However, when additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fenpropimorph may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

5.1 Incident Reports

No incidents report was prepared for this use since it is an import tolerance and there are no uses in the United States.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

(Tolerance Petition Requesting Food Use of Fenpropimorph on Imported Bananas. Summary of Analytical Chemistry and Residue Data. Petition No 7E7874. William Drew, DP Barcode D309994, 10/19/2005)

The geographic representation and number of banana field trials performed are sufficient to support a tolerance for residues of fenpropimorph in/on imported bananas. The petitioner provided data from 12 locations (15 trials) in banana-producing countries accounting for approximately 93% of the bananas imported into the U.S. (1993). The study conforms adequately to the requirements set forth in the Draft Import Tolerance Guidelines (4/25/1997) with respect to trial number and distribution.

The submitted banana field trial data are adequate.

Residues of fenpropimorph were <0.050 to 0.37 and <0.050 to 1.4 ppm in 15 samples each of bagged and unbagged whole fruit (respectively) harvested on the day of the last of four foliar applications of fenpropimorph (880 g/L OL) at 0.44 to 0.64 kg ai/ha per application (1X to roughly 1.5X the proposed maximum single application rate), totaling 2.11 to 2.80 kg ai/ha per season. Utilization of the USEPA/PMRA Tolerance Spreadsheet indicates that these data support a tolerance for residues of fenpropimorph in imported bananas of 3.0 ppm. However, in order to harmonize with the existing Codex MRL for fenpropimorph in bananas of 2 mg/kg, HED recommends that the tolerance be established at 2.0 ppm (without U.S. registration).

The proposed tolerance enforcement method utilizing gas chromatography with nitrogen-phosphorus detection (GC/NPD), BASF Method 241/1, is adequate for collecting data on residues of fenpropimorph in/on bananas. Adequate method validation data were submitted. The method has been adequately radiovalidated, and has undergone a marginally successful independent laboratory validation (ILV) trial. The validated limit of quantitation (LOQ) for residues of fenpropimorph is 0.050 ppm. However, the Analytical Chemistry Laboratory of the Biological and Economic Analysis Division (ACL/BEAD) has determined that the extractor specified in the method (Bleidner apparatus) is not readily available enough to serve in a suitable tolerance enforcement method. An unpublished study prepared by the petitioner (BASF Document ID 2001/1000985, Study Code 64311, Angelika Benz and Christiane Mackenroth, 4/2/2001) reports method validation data for an LC/MS/MS method, BASF Method 456/0, regarding the recovery of fenpropimorph from various plant matrices (wheat forage, grain, and straw; oranges; sunflower seeds). Currently, there are also Dutch & German Multiresidue Methods (MRMs) available, both of which utilize LC/MS/MS analysis, that have likewise been successfully used to quantitate fenpropimorph in plant matrices, but neither of these have recovery data listed for bananas. ACL has reviewed these methods and deemed any of them sufficient as a potential tolerance enforcement method, provided that the petitioner submits data on acceptable recovery of fenpropimorph from bananas. Therefore, HED requests that the petitioner provide recovery data on fenpropimorph from bananas using either BASF Method 456/0, the Dutch MRM, or the German MRM.

For purposes of the proposed tolerance on imported bananas, additional radiovalidation data for the method eventually selected for enforcement will not be required, provided acceptable recovery data for fresh fortifications in bananas are submitted. However, for any future tolerance requests on additional crops, that method selected for tolerance enforcement should be radiovalidated using appropriate samples from a plant metabolism study.

6.1.2 Acute and Chronic Dietary Exposure and Risk

(Fenpropimorph: Acute and Chronic Dietary Exposure Assessment to Support Proposed Section 3 Registration Import Tolerance on Bananas. William Drew, DP Barcode D317314; 10/19/2005)

HED performed a Tier 1 acute and chronic dietary exposure and risk analysis for fenpropimorph using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03)), which uses the most recent food consumption data from USDA (CSFII, 1994-1996 and 1998). The Dietary Exposure Evaluation Model (DEEM-FCID™) assessment was based on tolerance-level residues in banana commodities, processing factors of 3.9 for dried banana commodities, and 100% crop treated (100% CT) assumptions.

The results of the acute and chronic dietary exposure analyses are summarized in Table 6.1. An acute dietary dose and an endpoint attributable to a single dose were identified for only one subpopulation, females ages 13 through 49. The acute exposure estimate of approximately 0.004 mg/kg/day corresponds to 2.6 % of the aPAD. An appropriate endpoint attributable to a single exposure was not identified for the general population nor any of the other population subgroups. The chronic exposure estimate for the most highly exposed population subgroup (children 1-2 years old) was approximately 0.004 mg/kg/day, or 11 % of the cPAD. Risks for the general U.S. population and all other population subgroups were lower. Typically, HED has concerns regarding dietary risk when the exposure estimates exceed 100% of the aPAD or cPAD. Based on the dietary exposure analyses conducted, there are not dietary risk concerns for fenpropimorph. Fenpropimorph has been classified as not likely to be carcinogenic to humans; therefore, a dietary assessment for cancer risk was not conducted.

Table 6.1. Result of Acute and Chronic Dietary Exposure and Risk Estimates for Fenpropimorph.

Population Subgroup	aPAD, mg/kg/day	DEEM-FCID		cPAD mg/kg/day	DEEM-FCID	
		95% ile Exposure, mg/kg/day	% aPAD		95% ile Exposure, mg/kg/day	% cPAD
Chronic Dietary Estimates						
U.S. Population	NA			0.032	0.00072	2.2
All infants (< 1 yr)				0.032	0.00291	9.1
Children 1-2 yrs				0.032	**0.00366**	**11**
Children 3-5 yrs				0.032	0.00187	5.8
Children 6-12 yrs				0.032	0.00077	2.4
Youth 13-19 yrs				0.032	0.00026	< 1
Adults 20-49 yrs				0.032	0.00042	1.3
Adults 50+ yrs				0.032	0.00071	2.2

Females 13-49 yrs	**0.15**	**0.00386**	**2.6**	0.032	0.00042	1.3

Note: The values for the population with the highest risk for each type of risk assessment are bolded.

7.0 Aggregate Risk Assessments and Risk Characterization

Fenpropimorph is proposed for use only on imported bananas. Since there are no registered (neither agricultural, occupational nor residential) uses associated with fenpropimorph in the U.S., the only route of exposure is dietary (food only). Dietary exposure will be limited to residues from imported bananas. With no proposed U.S. registrations, there is no expectation that fenpropimorph residues would occur via water consumption or residential use. Therefore, neither a residential, water or aggregate exposure is expected and no aggregate risk assessment was required.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fenpropimorph and any other substances and fenpropimorph does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fenpropimorph has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

There are no proposed occupational uses associated with fenpropimorph. Therefore, an occupational exposure and risk assessment is not required.

10.0 Data Needs and Label Requirements

10.1 Toxicology

None

10.2 Residue Chemistry

The available banana field trial data are adequate and utilization of the USEPA/PMRA Tolerance Spreadsheet indicates that these data support a tolerance for residues of fenpropimorph in imported bananas of 3.0 ppm. However, in order to harmonize with the existing Codex MRL for

fenpropimorph in bananas of 2 mg/kg, HED recommends that the tolerance be established at 2.0 ppm.

Therefore, HED recommends that the proposed tolerance (without U.S. registration) for residues of fenpropimorph in imported bananas be granted and established at the level of 2.0 ppm, provided that acceptable method validation recovery data for fenpropimorph from bananas are submitted by the petitioner (as detailed in Section 6.1.1). The petitioner should submit a revised Section F to reflect this increase in the proposed tolerance level.

TABLE 10.2 Tolerance Summary for Fenpropimorph.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Banana	1.5	2.0	The available residue data would support a tolerance of 3.0 ppm on bananas. (However, a tolerance of 2.0 ppm is being recommended, in order to harmonize with the existing Codex MRL of 2 mg/kg). The CFR entry should also state that there are no U.S. registrations for use on bananas.

10.3 Occupational and Residential Exposure

None

References:

Fenpropimorph. Tolerance Petition Requesting Food Use of the Fungicide Fenpropimorph on Imported Bananas. Summary of Analytical Chemistry and Residue Data. William Drew, DP Barcode 309994 , 10/19/2005

Fenpropimorph . Acute and Chronic Dietary Exposure Assessment for Tolerances on Imported Bananas . William Drew, DP Barcode D321866 , 10/19/2005

Appendices

A-1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for food use (tolerances on imported commodities only) of fenpropimorph are in Appendix Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

APPENDIX TABLE 1 Toxicology Data Requirements.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	no	no
870.3250	90-Day Dermal	no	no
870.3465	90-Day Inhalation	no	no
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	yes
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	no	yes*
870.6200b	90 Day Neuro. Screening Battery (rat)	no	yes*
870.6300	Develop. Neuro	no	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	no

*Acute and 90 day neurotoxicity studies were not required but were submitted

A-2.0 NON-CRITICAL TOXICOLOGY STUDIES

Only the executive summaries of studies not already discussed in the hazard assessment and the endpoint selection sections are presented.

2.1 Subchronic Studies

2.1.1 90-Day Subchronic Toxicity [Feeding] - Rat

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 44380103), fenpropimorph (91.1% a.i.) was administered to 30 Sprague-Dawley rats/sex/dose at dietary concentrations of 0, 6.25, 12.5, or 25.0 ppm (equivalent to 0/0, 0.382/0.465, 0.768/0.915, or 1.54/1.80 mg/kg/day [M/F]) for 13 consecutive weeks. To monitor the reversal of effects, ten animals/sex/group were maintained for a 6-week post-treatment period.

Treatment-related decreases ($p<0.05$ or 0.01) in mean plasma cholinesterase (↓11-34%) were observed in the 6.25-ppm males and 12.5- and 25.0-ppm males and females, and decreases in mean erythrocyte cholinesterase activity (↓26-56%; $p<0.01$) were observed in females from all dose groups (male data were too variable to ascertain a possible treatment-related effect). In addition, treatment-related increases in triglyceride levels (↑31-58%, $p<0.05$) were observed in 25.0-ppm males. Increases ($p<0.01$) in absolute liver weight (↑10%) were observed in 25.0-ppm females, and increases ($p<0.05$ or 0.01) in relative liver weights (↑5-10%) were observed in 12.5- and 25.0-ppm males and females. Histopathological examination revealed nearly a twofold increase in the incidence of single cell necrosis with perifocal cellular reaction in the livers of 25.0-ppm animals of both sexes compared to controls at the end of the 13 week treatment period (24/40 treated vs 13/40 controls) and 6 week recovery period (7/20 treated vs 0/20 controls). The association of increased liver weights and histopathology indicates the liver as a target organ.

No treatment-related effects on mortality, clinical signs, body weight, food consumption, hematology, urinalysis, or gross pathology were observed. Ophthalmoscopic examinations were not conducted. No neoplastic tissue was observed in the treated or control rats.

Oral toxicity LOAEL = 25 ppm (equivalent to 1.54/1.80 mg/kg/day [M/F]), based on increased relative liver weights [M] and increased relative and absolute liver weights [F] as well as increased incidence of liver single cell necrosis [M/F]. Oral toxicity NOAEL was 12.5 ppm (equivalent to 0.768/0.915 mg/kg/day [M/F]

2.1.2 Oncogenicity Study in Mice

EXECUTIVE SUMMARY: In a mouse oncogenicity study (MRID 44380107), fenpropimorph (92.5% a.i.) was administered to CD-1 mice (60/sex/group) for up to 95 weeks at 0, 5, 30, 150, or 1000 ppm (equivalent to 0/0, 0.5/0.5, 3.0/3.5, 16/17, and 106/118 mg/kg/day [M/F], respectively). Ten animals/sex/group were terminated at 52 weeks and at 95 weeks. At 95 weeks, all surviving animals were fed an untreated diet and sacrificed at 103/104 weeks [M/F], thus constituting a withdrawal period.

There were no changes of toxicological concern in clinical signs, mortality, body weights, food consumption, organ weights, gross pathology, non-neoplastic or neoplastic histopathology, or brain cholinesterase activity. Changes observed in hematology parameters and plasma cholinesterase were of equivocal toxicological concern.

At 30 ppm, RBC cholinesterase activity was decreased (↓22%, $p<0.001$) at week 95 in females, but not at week 51 (↓2%). At the end of the withdrawal period (week 101), RBC cholinesterase activity was similar to control values (110% of controls). The rebound in cholinesterase activity after withdrawal supports the conclusion that the decrease in RBC cholinesterase activity seen at week 95 was treatment-related.

At 1000 ppm, body weight gains were reduced ($p<0.05$) relative to concurrent controls in the males (↓16%) for the overall (week 0-95) treatment period. Body weight gain for females for the same period was also reduced (↓15%), although not significantly. A decrease in food efficiency was noted in the males during weeks 1-13 (↓12%), although the difference was not significant. In males at week 95, hemoglobin concentration (↓12%), MCHC (↓10%), WBC (↓41%), and lymphocytes (↓47%) were decreased ($p<0.05$, 0.01, or 0.001). Because these findings occurred only at 95 weeks, only in males, and there was no associated histopathological evidence, their toxicological significance is uncertain. RBC cholinesterase activity was decreased (↓29%, $p<0.001$) in females at week 95, but not at week 51 (↑5%). At the end of the withdrawal period (week 101), RBC cholinesterase activity was similar to control values (105% of controls). Plasma cholinesterase activity was increased ($p<0.05$) at week 95 in the 1000 ppm males (↑34%) and at week 101 in the 150 ppm males (↑31%), but the biological significance of the increased enzyme activity is not known.

At 150 ppm, RBC cholinesterase activity was decreased (↓26%, $p<0.001$) in the females at week 95, but not at week 51 (↓1%). At the end of the withdrawal period (week 101), RBC cholinesterase activity was similar to control values (92% of controls).

Dosing was considered adequate based on decreased body weight gains.

The LOAEL for chronic toxicity is 1000 ppm in males (equivalent to 106 mg/kg/day) based on decreased body weight gains. The LOAEL was not attained in females. The chronic NOAEL is 150 ppm in males (equivalent to 16 mg/kg/day) and 1000 ppm in females (equivalent to 118 mg/kg/day).

Under the conditions of this study, there was no evidence of an increased incidence of carcinogenesis.

2.1.3 90-Day Subchronic Toxicity [Feeding] - Dog

EXECUTIVE SUMMARY: In a subchronic toxicity study (MRID 44380104), fenpropimorph (91.1% a.i.) was fed to four beagle dogs/sex/dose at dietary concentrations of 50, 100, 200, or 400 ppm (equivalent to approximately 1.46/1.77, 2.96/3.69, 6.40/7.92, or 11.63/14.64 mg/kg/day [M/F], respectively) for 3 consecutive months. An additional four dogs/sex were maintained as a control group.

No dogs died during the study and no treatment-related differences in body weights, body weight gains, food consumption, hematology, clinical chemistry (including plasma cholinesterase activity), urinalysis, organ weight, histopathology, and gross pathology were observed in any of the test groups. It was stated that no clinical signs of toxicity were observed. No neoplastic tissue was observed.

The oral (feeding) NOAEL is ≥400 ppm (11.63/14.64 mg/kg/day [M/F]), the highest dose tested, in males and females. A LOAEL was not established.

2.1.4 Special Mechanistic - Rat

EXECUTIVE SUMMARY: In a special mechanistic study (MRID 44323921), fenpropimorph (purity not reported) was administered for 14 days via the diet to male CD-Sprague-Dawley rats (16/dose) at levels of 0, 50, 250, or 1600 ppm. In a separate study, phenobarbitone (50 mg/kg/day), as a positive control, was administered orally by gastric intubation to 16 male rats for 14 days; the control group (8 rats) received distilled water. Microsomal and cytosolic xenobiotic metabolizing enzyme activities were measured and hepatocyte ultrastructure was investigated in both studies. The study was initiated to determine the effect of the test compound on hepatic drug-metabolizing enzyme activity.

There were no statistically significant differences from controls in urinary excretion of ascorbic acid, which was at variance with dose related decreases ($p<0.01$) in mean pentobarbitone sleeping times in the 50 (↓20%), 250 (↓41%), and the 1600 (↓58%) ppm rats. There were no statistically significant differences compared to controls in microsomal P 450 levels or in plasma cholinesterase activity levels in the fenpropimorph treated rats. However, increased ($p<0.05$ or 0.01) hepatic microsomal enzyme activity was observed as follows: (i) aniline hydroxylase in the 250 (↑69-70%) and 1600 (↑111-115%) ppm rats; (ii) ethylmorphine-N-demethylase in the 50 (↑36-41%), 250 (↑100-103%), and 1600 (↑105-114%) ppm rats; and (iii) glucuronlytransferase in the 250 (↑66-67%) and 1600 (↑97-106%) ppm rats. In addition, glutathione S-transferase activity was increased ($p<0.05$) in the 250 (↑15-21% and the 1600 (↑22-32%) ppm rats. Except for the slight increase in ethylmorphine-N-demethylase activity, dosing at 50 ppm with fenpropimorph did not produce a general induction of hepatic microsomal xenobiotic metabolizing enzymes.

Relative liver weights were increased ($p<0.01$) in the 250 (↑24%) and 1600 (↑32%) ppm rats, but no ultrastructural changes in hepatocyte morphology were observed.

2.1.5 28-Day Dermal Toxicity - Rat

EXECUTIVE SUMMARY - In a 28-day dermal toxicity study (MRID 45868902), Fenpropimorph (96.6% a.i.; Batch #: N103) in 0.05% (w/v) aqueous Cremophor EL was applied (4 mL/kg) to the shaved intact skin of 10 Wistar rats/sex/dose at dose levels of 0, 0.2, 0.6, or 2.0 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The method for dermal irritation scoring was not reported.

No treatment-related effects were observed in mortality, clinical signs, dermal effects, body weight, body weight gain, food consumption, food efficiency, ophthalmoscopy, hematology,

clinical chemistry, organ weights, gross lesions, or microscopic pathology at any dose in either sex.

The LOAEL was not observed. The NOAEL is 2 mg/kg/day.

Although a LOAEL was not observed and the test material was not tested to the limit dose, this study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3200; OECD 410) for a 28-day dermal toxicity study in rats because, based on the results of the range-finding study (BASF Project No.: 15C0235/99107), the test material was tested at the maximum dose that would not produce severe skin irritation.

2.1.6 Metabolism - Rat

EXECUTIVE SUMMARY:

In a series of rat metabolism studies (MRID 44323920), [^{14}C-U-phenyl]fenpropimorph (≥98.4 % radiochemical purity) was administered to Wistar rats (5/sex/dose) as either a single oral (gavage) dose at 1.25 or 100 mg/kg, a single intravenous (iv) dose at 1.25 mg/kg, a single oral dose at 1.25 mg/kg following a 14-day pretreatment with fenpropimorph at 1.25 mg/kg/day, or as a repeated dose at 1.25 mg/kg/day for 7 consecutive days. In addition, 5 rats/sex were administered a single oral dose of [^{14}C-mopholine]fenpropimorph (≥99 % radiochemical purity) at 100 mg/kg and 3 bile-duct cannulated rats/sex were administered a single oral dose of [^{14}C-phenyl]fenpropimorph at 1.25 mg/kg.

Within 96 hours of dosing with [^{14}C]fenpropimorph at 1.25 or 100 mg/kg, 96.0-109.4% of the dosed radioactivity was recovered in excreta, bile, exhaled air, cage washes, and tissues. Excretion of radioactivity was similar between the sexes and dose groups, although there were minor differences in the pattern of excretion. Excluding bile-duct cannulated rats, renal excretion of radioactivity in [^{14}C-phenyl]-dosed rats was slightly higher (1.1-1.3x) in males, whereas fecal excretion was slightly higher (1.1-1.5x) in females. [^{14}C-morpholine]fenpropimorph-treated rats showed no differences in the pattern of excretion between the sexes.

Only minor differences in the pattern of excretion were noted between the various dose groups. Following a single oral dose of [^{14}C-phenyl]fenpropimorph at 100 mg/kg or 1.25 mg/kg (with or without pretreatment), male rats excreted approximately equal amounts of the dose in the urine (40.0-49.6% dose) and feces (39.7-47.3% dose); whereas females excreted more of the dose in the feces (54.4-58.8% dose) than in the urine (36.7-37.3% dose). The overall pattern of excretion was the same for rats dosed intravenously at 1.25 mg/kg, although radioactivity in urine of the iv-dosed males (51.7% dose) and females (43.8% dose) was somewhat higher (1.2-1.3x) than in urine of orally dosed rats, and iv-dosed females had slightly lower (0.8x) levels of radioactivity in feces (49.0% dose) than orally dosed females. The high levels of radioactivity in feces of iv-dosed animals (43.5-49.0% dose) indicated that biliary excretion was a major route of elimination.

Oral dosing of bile-duct cannulated rats at 1.25 mg/kg confirmed the importance of biliary excretion in the elimination of fenpropimorph residues. For both sexes, the majority of the administered dose was recovered in the bile, with biliary excretion being slightly higher (1.2x) in

females (79.2% dose) than in males (66.6% dose). Radioactivity in the feces accounted for 7.0 and 1.3% of the dose in males and females, respectively. Renal excretion of bile-duct cannulated rats was still higher (1.6x) in males (24.6% dose) than in females (15.7% dose), but was reduced (0.4-0.6x) in both sexes compared to the normal rats indicating that approximately half of the radioactivity initially excreted in the bile is reabsorbed from the intestines and excreted in the urine.

The high levels of radioactivity recovered in the urine and bile following oral dosing indicate that fenpropimorph was readily absorbed from the gastrointestinal tract of rats.

Altering the position of the ^{14}C-label within the parent molecule from the phenyl ring to the morpholine ring also had only a minor impact on the pattern of excretion in rats, with males and females excreting equivalent amounts of radioactivity in the urine (37.4-37.8% dose) and feces (45.0-45.8% dose). Compared to the [^{14}C-phenyl]dosed group, the recovery of radioactivity in [^{14}C-morpholine]dosed rats was slightly dencreased (0.8x) in the urine of males and the feces of females. The most notable difference between the [^{14}C-phenyl] and [^{14}C-morpholine] high-dose groups was the recovery of 1.5-1.8% of the dose in exhaled air from [^{14}C-morpholine]dosed rats, compared to 0.01% of the dose recovered in exhaled air from [^{14}C-phenyl]dosed males. The presence of $^{14}CO_2$ in exhaled air from [^{14}C-morpholine]dosed rats indicates that the morpholine ring of the molecule may be subject to complete degradation.

Radioactivity remaining in the carcass and tissues 96 hours after ^{14}C-dosing were also similar between the sexes and between the dose groups. Excluding bile-duct cannulated rats, residual radioactivity accounted for 3.2-6.0% of the dose in rats dosed orally with [^{14}C]fenpropimorph at 100 mg/kg or 1.25 mg/kg (with or without pretreatment). Intravenous dosing resulted in slightly higher levels of residual radioactivity (7.9-10.1% dose) after 96 hours.

By 96 hours post-dose, tissue ^{14}C-residue concentrations were similar between the sexes within each dose group. With the exception of fat, ^{14}C-residues in tissues of females averaged 0.9-1.3x the concentrations observed in tissues of males from the same dose group. In all dose groups, females had slightly higher ^{14}C-residues in fat (1.2-2.0x) than males. Although actual tissue ^{14}C-residue concentrations differed between dose groups, the relative tissue distribution of radioactivity was the same within each dose group. ^{14}C-Residues were highest in liver, digestive tract, and fat and lowest in muscle, bone and brains.

In single oral low-dose rats, ^{14}C-residues were highest in liver (0.196-0.278 µg/g), digestive tract (0.109-0.153 µg/g), fat (0.055-0.104 µg/g) and lowest in muscle and bone (0.007-0.009 µg/g). Increasing the dose level from 1.25 to 100 mg/kg increased the concentration of radioactivity in tissues by 57.9x on average for both sexes, with the greatest increases occurring in fat (95-116x) and the digestive tract (80-108x). These increases approximated the 80-fold increase in the dose level between the low- and high-dose groups. Repeated dosing at 1.25 mg/kg/day for 14 days prior to treatment with [^{14}C]fenpropimorph had little or no effect on accumulation of ^{14}C-residues in tissues, increasing ^{14}C-residues only in males by an average of 1.5x vs the single low-dose group. Intravenous dosing increased the concentration of ^{14}C-residues in all tissues for both sexes by an average of 2.4x vs the single low-dose group, except in fat, where the increases ranged from 7.0-7.3x. Altering the position of the ^{14}C-label in the parent molecule from the phenyl ring to the

morpholine ring also resulted in a minor increases (means: 1.7-2.3x) in tissue ^{14}C-residues of [^{14}C-morpholine]fenpropimorph dosed rats. However, the greatest relative increases occurred in the tissues with the lowest absolute levels of radioactivity - bone and muscle (males, 3.2-4.6x; females, 2.2-2.7x). Tissues containing the highest levels of ^{14}C-residues (liver, digestive tract, and fat) had only minor increases ($\leq$1.6x).

Following either a single low or high dose, the concentration of radioactivity in blood and plasma reached maximum levels by 8 hours post-dose in both sexes and declined thereafter. The maximum blood radioactivity concentrations and the AUC values were similar between sexes and were dose-dependent - 60.5-119x higher in high-dose than in low-dose rats, approximating the 80x increase in the dose level. However, the half-life for elimination of radioactivity from plasma was similar between the sexes and dose levels, ranging from 16.1-23.9 hours; indicating that elimination was not saturated at the higher dose. Similar kinetics for the elimination of radioactivity were observed in blood and tissues of rats following repeated dosing with [^{14}C]fenpropimorph. Maximum concentrations of radioactivity in blood and tissues were attained within 4-8 hours of administering the last of 7 consecutive daily doses of [^{14}C-phenyl]fenpropimorph at 1.25 mg/kg/day. Half-lives for the elimination of radioactivity from liver, kidney, testes/ovaries, blood and plasma in these rats were 19.3-26.7 hours for males and 22.4-28.9 hours for females, indicating that ^{14}C-residues from fenpropimorph are not retained in tissues. However, elimination of radioactivity from fat was appreciably slower ($T_{1/2}$ = 40.8-57.8 hours).

Analyses of urine, fecal extracts, and bile did not detect any parent compound, indicating that fenpropimorph is completely metabolized by rats. Based upon the metabolites identified in urine and feces, the metabolism of fenpropimorph in rats appears to involve the successive oxidation of the *tert*-butyl group on the phenyl ring to form the acid metabolite, BF 421-2, which is then hydroxylated on one of methyl groups of the morpholine ring to yield the major metabolite BF 421-3. Metabolite BF 421-3 is then either conjugated with unspecified components, or undergoes degradation of the morpholine ring to form BF 421-17. The other phenyl-specific, acid metabolite, BF 421-16, results from the further degradation of the 2-methylpropanoic acid group remaining on BF 421-17. Metabolites BF 421-3 (free and conjugated), BF 421-17, BF 421-16, and BF 421-2 together these metabolites accounted for 53.5-76.8% of the dose in each group except the bile-duct cannulated rats.

The metabolite profile in urine and feces was qualitatively similar between the sexes and between the [^{14}C-phenyl]-dosed groups. Free and conjugated BF 421-3 was the major metabolite identified in urine and feces, accounting for 32.3-48.7% of the dose in excreta from each group, except bile-duct cannulated rats. Levels of free BF 421-3 were highest in excreta of high-dose rats (22.7-32.8% dose); whereas levels of conjugated BF 421-3 were highest in single oral and iv low dose rats (conjugated, 23.6-35.2% dose). The relative levels of conjugated BF 421-3 excreted by males and females varied depending on the dose group, but in each dose group males extracted more free BF 421-3 than females (males, 17.9-32.8% dose; females 6.2-24.5% dose).

The acid metabolite, BF 421-2, was also identified in urine and/or feces of males and females from each dose group, with males generally excreting higher amounts than females. The levels of BF 421-2 found in excreta were lowest for the single oral low-dose rats treated with [^{14}C-

phenyl]fenpropimorph (≤4.5% dose) and highest for the single oral high-dose rats treated with [^{14}C-morpholine]fenpropimorph (14.8-20.6% dose).

The phenyl specific metabolites, BF 421-16 and BF 421-17, were detected in all dose groups except the [^{14}C-morpholine]fenpropimorph-dosed group, as the morpholine moiety was lost or degraded in both these metabolites. The combined levels of BF 421-16/BF 421-17 were similar between males and females in each dose group, although males (6.2-23.4% dose) generally excreted more of these metabolites than females (6.5-16.3% dose). Among the different dose groups, levels of BF 421-16/BF 421-17 were lowest in excreta of the single oral low-dose group (6.2-6.5% dose) and highest in excreta of the repeated oral dose group (16.3-23.4% dose), indicating that repeated dosing may induce changes in the metabolism of fenpropimorph.

The only components identified in bile were BF 421-2 (3.3-7.4% dose) and conjugated BF 421-3 (4.8% dose, females only). The majority of radioactivity in the bile (55.9-69.3% dose) was comprised of multiple unknown components. The predominant biliary unknowns were B2 (8.8% dose) and B3.1 (31.6% dose) in males, and unknowns B1 (6.3% dose), B3.1 (21.8% dose), B4.1 (7.4% dose), and B4.2 (21.1% dose) in females. The high level of unknowns present in the bile compared to urine and feces indicates that metabolites initially excreted in the bile undergo further metabolism and reabsorption prior to final elimination in the feces or urine.

Several major (>5% dose) unknowns were also detected in urine and feces. Urinary unknown U2.3 was detected in all [^{14}C-phenyl]fenpropimorph-dosed groups and accounted 4.7-8.7% of the dose in oral and iv low-dose rats. Based on its absence in urine of [^{14}C-morpholine]fenpropimorph-dosed rats, U2.3 may be a metabolite in which the morpholine ring has been degraded or lost. Another major urinary unknown, U3.1, was detected at 2.8-8.1% of the dose in bile-cannulated rats and [^{14}C-morpholine]fenpropimorph-dosed rats. Fecal unknown F1.2, which was characterized as a conjugate, and fecal unknown F3 each accounted for 6.0-10.9% of the dose in females from each dose group. Unknown F3 was shown to be identical to the bile unknown B4.2, which accounted for 21.1% of the dose in bile of females.

This study is classified **unacceptable (§870.7485, 85-1)** and does not satisfy the requirement for a metabolism study in rats, but can be upgraded by submission of data further characterizing and/or identifying the major unknown metabolites in urine (U3.2 and U3.1) and feces (F1.2 and F3) that accounted for >5% of the administered dose.

2.1.7 Acute Oral Toxicity and Acute Delayed Neurotoxicity of Organophosphorus Substances - Hen

EXECUTIVE SUMMARY: In a combined acute oral toxicity and acute delayed neurotoxicity study (MRID 44323909), fasted domestic hens at least 12 months old were either protected or not protected against acute cholinergic effects and given a single oral dose of fenpropimorph (92.5% a.i.) in olive oil by gavage and observed for 14 (acute oral toxicity studies) or 21 days (acute delayed neurotoxicity study). In the acute oral toxicity substudy, 5 hens/dose were fasted overnight and either pre-treated or not pre-treated with intramuscular atropine sulphate and pyridine-2-aldoxime methane sulphonate (PAM), given a single oral dose of fenpropimorph at 250, 500, 1000, 2000, or 4000 mg/kg by gavage, and observed for 14 days. In the acute delayed

neurotoxicity substudy, 10 hens/dose were fasted overnight, pre-treated with atropine and PAM, given a single oral dose of fenpropimorph at 425, 850, or 1700 mg/kg by gavage, and observed for 21 days. An additional 10 birds were treated with fenpropimorph at 1700 mg/kg and maintained as a separate group.

Oral LD_{50} Unprotected = 1,600 mg/kg (95% C.I. = 1032 to 2480 mg/kg)
Protected = 1,700 mg/kg (95% C.I. = 885 to 3264 mg/kg)

Fenpropimorph is classified as **TOXICITY CATEGORY III** based on the observed LD_{50} values.

In the unprotected LD_{50} substudy, 5/5 animals from the 4000 mg/kg dose group and 2/5 from each of the 2000 and 1000 mg/kg dose groups died from 2 to 6 days after dosing. In the protected LD_{50} substudy, 3/5 animals from the 4000 mg/kg dose group, 4/5 from the 2000 mg/kg dose group, and 2/5 from the 1000 mg/kg dose group died from days 2 to 5 after dosing. Clinical signs observed included unsteadiness in all surviving birds in all treatment groups on day 4 in both the protected and unprotected LD_{50} substudy. All animals from both substudies appeared to have returned to good health on or after day 6 post-dosing. No treatment-related effect on body weights was observed in surviving animals. Gross necropsies were not performed.

In the acute delayed neurotoxicity study, 1 control animal died on day 3 after dosing. In the two 1700 mg/kg dose groups, 4/10 animals died in each group from days 2-7 after dosing. In the 850 mg/kg dose group, 2/10 animals died from days 2 to 4 after dosing. All birds in the 850 and 1700 mg/kg groups showed slight unsteadiness and all birds in the 425 mg/kg group showed slight leg weakness on day 1 after dosing. On day 3, all birds in the 1700 mg/kg dose groups were very weak. Surviving birds appeared to have recovered from the unsteadiness by day 5, although one bird in the 1700 mg/kg dose groups was unable to stand on day 7 and found dead at the end of the day. No signs of ataxia were observed in any of the birds treated with fenpropimorph. There was an apparent treatment-related decrease in body weights for all fenpropimorph-treated animals over days 0 to 3 post-dosing that was associated with clinical signs and reduced feed consumption. Food consumption was decreased with respect to controls in one or both 1700 mg/kg groups for the day 1-3, 4-7, and 8-10 period. The food consumption in the 850 mg/kg group was decreased for the day 1 to 3 period. There were no gross necropsy or histopathological findings considered to be treatment-related. The positive control animals demonstrated neurotoxicity (ataxia), decreased body weights and food consumption, and neuropathological changes in the spinal cord.

The LOAEL for delayed neurotoxicity was not observed. The NOAEL is ≥1700 ppm, the highest dose tested.

2.1.8 Cholinesterase Inhibition - Rat

EXECUTIVE SUMMARY: In a cholinesterase inhibition study (MRID 44380109), fenpropimorph (99.1% a.i.) was administered as a single intraperitoneal injection to female Sprague-Dawley rats (20/group) at levels of 0, 200, 650, or 2000 mg/kg. Because high mortality was expected at 2000 mg/kg, two groups each containing 20 animals were used at this dose level. The animals were observed for 3 days post-dosing. Blood samples in the controls, low- and mid-dose were obtained at 2, 6, 24, and 72 hours post-dosing to determine plasma cholinesterase

activity and other clinical chemistry parameters. Blood samples from the high-dose were obtained at 2, 6, and 30 or 50 hours. Because of poor general health and increased mortality, data for blood parameters at the 30 and 50 hour samplings at the high-dose were not considered reliable.

This study had the following two objectives: (i) to determine if a single administration of the test chemical would result in lowering of plasma cholinesterase activity and (ii) to determine whether the decrease in enzyme activity was the result of a direct inhibition of the enzyme by the test material (or a metabolite) or whether the decrease was due to liver dysfunction.

In the 200 mg/kg group, piloerection was observed and body weights compared to controls were decreased. Mean absolute liver weights were increased (not statistically significant [NS]) compared to controls, but no histopathological findings were observed. The following differences ($p \leq 0.05$ or 0.01) from controls were observed in this group: (i) increased bilirubin at 6 hours; (ii) increased globulin levels at 72 hours; (iii) decreased albumin levels at 24 and 72 hours; and (iv) a lower albumin/globulin ratio at 72 hours.

In the 650 mg/kg group, piloerection was observed followed by dyspnea, slightly indrawn flanks, and staggering, and a squatting position. From the second day onward, the general condition of these animals was impaired with signs of peritoneal irritation. The following parameters were increased ($p \leq 0.05$ or 0.01) relative to controls: (i) coagulation time at 6 and 24 hours; (ii) total bilirubin at 2, 6, and 24 hours; and (iii) globulin levels at 6 and 72 hours. The following parameters were decreased ($p \leq 0.05$ or 0.01) relative to controls: (i) total protein level at 24 and 72 hours; (ii) albumin level at 24 and 72 hours; and (iii) albumin/globulin ratio at 6, 24, and 72 hours. At necropsy, mean absolute liver weight was increased (NS) and a bloody icteric peritoneal effusion was found.

In the 2000 mg/kg group, piloerection, dyspnea, slightly indrawn flanks, staggering, apathy and hypothermia were exhibited within 20 minutes after dosing. Immediately after the first blood sampling (20 animals each at the 2 and 6 hour samplings), the animals became comatose with hypothermia, abdominal position with flaccid extremities, urine-soiled coat, and absence of pain reflexes. Because of their moribund condition, the surviving animals were sacrificed 30 or 50 hours after dosing. The following parameters were increased ($p \leq 0.05$ or 0.01) relative to controls: (i) coagulation time at 6 hours; (ii) total bilirubin at 2 and 6 hours ; and (iii) globulin levels at 6 hours. A decreased ($p \leq 0.05$) albumin/globulin ratio was observed at the 6 hour sampling. At necropsy, mean absolute liver weight was decreased (NS) and bloody icteric ascites and deposits of the test substance on the peritoneum and on the liver capsule with local peritonitis were observed. These gross and microscopic findings detected at the mid- and high-dose may have been due to local irritation and accompanying inflammation as a result of the intraperitoneal route of administration:

Plasma cholinesterase activity (PCE) was decreased ($p \leq 0.01$) compared to concurrent controls in the 200 and 650 mg/kg groups rats at the 72 hour postdosing sampling. For the first 24 hours post-dosing, there was a dose-dependent increase ($p \leq 0.05$ or 0.01) over controls in the activity of glutamic oxalacetic transaminase (GOT). Increases in lactate dehydrogenase (LDH) levels were not dose-dependent and conflicting data were presented for the levels of glutamic pyruvic transaminase (GPT). Alkaline phosphatase (ALP) levels decreased instead of increasing as

expected with some liver diseases.

In summary, a single intraperitoneal injection of fenpropimorph in female rats at levels of 0, 200, 650, or 2000 mg/kg resulted in a decrease in plasma cholinesterase activity in the 200 and 650 mg/kg animals at 72 hours post-dosing. Signs of possible systemic effects on the liver, including some clinical chemistry parameters and liver weights, were observed in the treated animals; these findings, however, were confounded by the presence of peritonitis that was probably a result of direct irritation by the test chemical caused by the route of administration. Since both the peritonitis and systemic toxicity may have contributed to the observed effects, the study is inconclusive.

This cholinesterase inhibition study is classified **unacceptable (nonguideline)** It is unacceptable because the stated objectives of this special study were not achieved.

2.1.9 *In vivo* mammalian cytogenetics - micronucleus assay in mice

EXECUTIVE SUMMARY:

In two independent experiments of a bone marrow micronucleus assay (MRID 44323918), 10 NMRI mice/sex/dose were treated by intraperitoneal injection with fenpropimorph (95.6% a.i.) in 0.5% carboxymethylcellulose at single doses of 250, 500, or 1,000 mg/kg (Experiment 1) or 1,000 mg/kg (Experiment 2). In both experiments, bone marrow cells were harvested at 24 and 48 hours post-treatment and scored for micronucleated polychromatic erythrocytes (MPCEs). In Experiment 1, 10 additional mice/sex received vehicle alone, 2 male and 3 female mice received a single intraperitoneal injection of cyclophosphamide (20 mg/kg), and 3 male and 2 female mice received a single intraperitoneal injection of vincristine (0.15 mg/kg). In Experiment 2, 2 or 3 mice/sex received vehicle alone, and 5 mice/sex received a single intraperitoneal injection of cyclophosphamide (20 mg/kg). In both experiments, bone marrow from mice treated with cyclophosphamide or vincristine was harvested at 24 hours post-treatment as the positive controls. The high dose, 1,000 mg/kg, was selected based on a preliminary test that showed deaths occurring at ≥ 1,250 mg/kg.

One 1,000 mg/kg animal died the day after treatment (Experiment 1). Poor general health and clinical signs that included apathy, abdominal position, and piloerection were observed at all dose levels about 30-60 minutes after dosing. Some of these clinical signs persisted in the 1,000 mg/kg animals on the days following dosing. The positive controls induced the appropriate response. Fenpropimorph was not toxic to the bone marrow (PCE:NCE ratio), and **there was not a significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at any dose level of fenpropimorph at any sampling time.**

2.1.10 *Salmonella typhimurium* mammalian activation reverse gene mutation assay

EXECUTIVE SUMMARY:
In a microbial mutagenicity assay (MRID 44323917), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed to fenpropimorph (95.6% a.i.) in dimethylsulfoxide, with and without metabolic activation at concentrations of 5-5,000 µg/plate in three trials of the

standard plate assay and at 4-1,000 µg/plate in one trial of the standard plate assay that included a preincubation step. S9 homogenates for metabolic activation were made from Aroclor-induced rat livers.

Fenpropimorph was tested to cytotoxic concentrations and the limit of solubility. In the standard plate test, cytotoxicity (inhibition of growth, decrease in the number of revertant colonies/plate) was apparent at 50-500 µg/plate and higher with TA100, TA1535, and TA1537 and at ≥1,000 µg/plate with TA98, depending on test conditions. There were no reproducible, dose-related differences in the number of revertant colonies in any tester strain at any dose level/condition compared to the vehicle controls. The positive control substances induced marked increases in revertant colonies in their respective strains.

2.1.11 In vitro mammalian chromosome aberrations in Chinese hamster lung cells

EXECUTIVE SUMMARY:

In an *in vitro* mammalian cell chromosome aberration assay (MRID 44323919), Chinese hamster lung (V79) cell cultures were exposed to ethanol alone or to fenpropimorph (95.6% a.i.) in ethanol at concentrations ranging from 0.5-30 µg/mL. Cultures were treated for 4 hours with and without metabolic (S9) activation and harvested 18 or 28 hours after treatment. Cyclophosphamide and ethyl-methane-sulfonate served as positive controls for clastogenicity for the S9-activation and nonactivation cultures, respectively.

Fenpropimorph was tested to cytotoxic concentrations and the limit of solubility. There were no treatment-related increases in total aberration frequency at any dose level with or without metabolic activation. Slight increases (4.5-5.0%) in exchanges were observed in cells treated with fenpropimorph at ≥20 µg/mL with metabolic activation. The increases were not statistically significant, but exceeded the historical control range (0-2.5%). The positive controls induced the appropriate responses.

2.1.12 Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell Cultures

EXECUTIVE SUMMARY:

In a single unscheduled DNA synthesis (UDS) assay (MRID 44323916), primary rat hepatocyte cultures were exposed to fenpropimorph (94.7% a.i.) in ethanol at 15 concentrations of 0.025-1,000 µg/mL for 20 hours. The criterion for a positive mutagenic response, as measured by unscheduled DNA synthesis, was a substantial increase in the net nuclear grain count (≥6 grains), a substantial increase (≥10%) in the percent of nuclei having ≥6 grains, or in the percent of nuclei (≥2%) having ≥20 grains at any concentration as compared to concurrent vehicle control values. 2-Acetylaminofluorene (2-AAF), a known inducer of UDS in rat hepatocyte primary cell cultures, served as the positive control.

Fenpropimorph was analyzed for UDS at concentrations of 0.1, 0.25, 0.5, 1, 2.5, and 5 μg/mL with viability reduced to 78.3% at the high dose. The positive control induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.**

A-3.0 METABOLISM CONSIDERATIONS

A-3.1 Team Proposal

Parent compound and [^{14}C]-labeled natural constituents (sugars from starch) were identified in bananas. The petitioner proposes that carbon fragments derived from breakdown of the morpholine ring are incorporated into reducing sugars in the leaves, and to some degree in the photosynthetically active green peel, and are transported into the fruit and stored as starch. Therefore, the risk assessment team has concluded that the residue of concern, for both tolerance expression and risk assessment purposes, be designated as the parent compound only, fenpropimorph *per se*.

A-3.2 Nature of the Residue Studies in Plants

Executive Summary of Banana Metabolism Study

Parent compound and [^{14}C]-labeled natural constituents (sugars from starch) were identified in bananas. The petitioner proposes that carbon fragments derived from breakdown of the morpholine ring are incorporated into reducing sugars in the leaves, and to some degree in the photosynthetically active green peel, and are then transported into the fruit and stored as starch. The degradation products formed in the leaves, the source of the [$^{14}C_1$]-fragments used for sugar biosynthesis, are depicted in Appendix 2 (Figure A.2). No metabolites were identified with the phenyl ring degraded; the tendency for morpholine ring-opening may explain the higher TRR observed in [morpholine-^{14}C]-treated fruit.

The submitted banana metabolism study is adequate. One day following the last of four foliar applications of [phenyl-^{14}C]- or [morpholine-^{14}C]-fenpropimorph at 0.90 kg ai/ha (roughly 2X the maximum single application rate) totaling 3.6 kg ai/ha, TRR were 0.317-0.669 ppm in [morpholine-^{14}C]-treated fruit, and 0.025-0.105 ppm in [phenyl-^{14}C]-treated fruit. The roughly 6X to 12X difference in TRR levels between the two radiolabels indicates differential degradation of the respective rings. The petitioner suggests that [^{14}C]-assimilates, produced in leaves/unripe fruit exclusively from morpholine ring-opening, are transported and incorporated into starch in the growing fruit. Solvent extraction released 78-83% of the [^{14}C]-activity in fruit (unbagged) with the exception of [morpholine-^{14}C]-labeled unripe fruit, of which only 21% of the TRR was released. A lower extractability in unripe samples may be due to the insolubility of [^{14}C]-activity incorporated into starch which is readily extractable as [^{14}C]-sugars after ripening.

In the unripe whole fruit (RAC), fenpropimorph accounted for 32-61% of the TRR (0.008-0.064 ppm) from [phenyl-^{14}C]-labeled samples and 6-10.5% of the TRR (0.022-0.070 ppm) from

[morpholine-^{14}C]-labeled samples. A total of 4 to 7 unknown metabolites, each accounting for a maximum of 0.008 ppm were also formed in [phenyl-^{14}C]- and [morpholine-^{14}C]-labeled unripe fruit. A single polar peak (P_1) found in [morpholine-^{14}C]-labeled fruit, accounting for 8.8% of the TRR (0.059 ppm), was identified as natural constituents (sugars). Unextracted residues in [phenyl-^{14}C]-labeled unripe bananas were relatively low (<0.023 ppm); however, unextractable residues in [morpholine-^{14}C]-labeled unripe pulp comprised 66.2% (0.443 ppm) of the [^{14}C]-activity on a whole fruit basis, most of which (approximately 50% TRR) was identified as being incorporated into starch. Although fenpropimorph accounted for a lower percentage of the TRR in [morpholine-^{14}C]-treated fruit, the actual levels (ppm) of parent were similar in fruit treated with either the [phenyl-^{14}C] or [morpholine-^{14}C] radiolabels. The higher levels of [^{14}C]-residues in [morpholine-^{14}C]-labeled fruit are apparently due to the complete breakdown of the [morpholine-^{14}C] ring, the assimilation of released [$^{14}C_1$] fragments into natural constituents, and their preferential transport to the growing fruit.

TRR were 17.4-168 and 70-142 ppm, respectively, in [phenyl-^{14}C]- and [morpholine-^{14}C]-labeled leaves (1st to 7th position). Although varying by leaf number, the range of TRR in leaves from both radiolabels was similar indicating that the test substance was applied consistently to the two treated trees. The details of extraction of leaves were not provided; however, several metabolites were isolated and identified in leaves (Appendix 2, Figure A.2).

Tabular Summary of Banana Metabolism Study

APPENDIX TABLE 3.2.1	**Summary of [^{14}C]-Residues Characterized/Identified in Bananas Treated with [Morpholine-2-6-^{14}C]-Fenpropimorph.**							
Metabolite/Fraction	**Unbagged fruits**				**Bagged fruits**			
	Unripe (0.669 ppm)		**Ripe (0.610 ppm)**		**Unripe (0.345 ppm)**		**Ripe (0.317 ppm)**	
	% TRR [1]	**ppm [2]**	**% TRR**	**ppm**	**% TRR**	**ppm**	**% TRR**	**ppm**
Fenpropimorph	10.5	0.07	2.8	0.017	6.4	0.022	3.8	0.012
Unknown Polar HPLC Peak P_1 [3]	8.8	0.059	77.2 [4]	0.471	12.2	0.042	64	0.203
Other Unknown HPLC Peaks [5]	1.9	0.013	2.9	0.017	1.2	0	3.5	0.011
Starch [6]	51.9	0.347	NR [7]	--	NR	--	NR	--
Total Characterized or Identified	**22.2**	**2.129**	**82.9**	**0.505**	**19.8**	**0.064**	**71.3**	**0.226**
Unextracted	9.1	0.061	15.9	0.097	75.9	0.262	31.9	0.101

1. Not corrected for recovery; calculated on a whole fruit basis.
2. Expressed in fenpropimorph equivalents.
3. Retention time of 7.65-9.81 minutes. Most radioactivity associated with P_1 could be partitioned into water.
4. Further HPLC analysis indicated that carbohydrates (glucose, fructose, and saccharose) comprise a substantial portion of the radioactivity associated with P_1.
5. A total of 3 to 7 unknown peaks, each accounting for ≤1.7% TRR (≤0.010 ppm).
6. [^{14}C]-Sugars released by amyloglucosidase digestion of pulp non-extractables, 66.2% TRR (0.443 ppm).
7. NR = Not Reported.

APPENDIX TABLE 3.2.2	**Summary of [^{14}C]-Residues Characterized/Identified in Bananas Treated with [Phenyl-U-^{14}C]-Fenpropimorph.**							
Metabolite/Fraction	**Unbagged fruit**				**Bagged fruit**			
	Unripe (0.105 ppm)		**Ripe (0.094 ppm)**		**Unripe (0.025 ppm)**		**Ripe (0.026 ppm)**	
	% TRR [1]	**ppm [2]**	**% TRR**	**ppm**	**% TRR**	**ppm**	**% TRR**	**ppm**
Fenpropimorph	61	0.064	40.4	0.038	32	0.01	19.2	0.01
Unknown HPLC Peaks [3]	17.1	0.018	44.7	0.042	20	0.01	69.2	0.018
Total Characterized or Identified	**78.1**	**0.082**	**85.1**	**0.08**	**52**	**0.013**	**88.4**	**0.023**
Unextracted	21.9	0.023	14.9	0.014	44	0.011	19.2	0.01

1. Not corrected for recovery.
2. Expressed in fenpropimorph equivalents.
3. A total of 4 to 9 unknown peaks, each at ≤0.008 ppm except one peak at 12.8% TRR (0.012 ppm) from peel (ripe/unbagged) with a retention time of 41.3-42.0 minutes.

A-4.0 ANALYTICAL METHODOLOGY

APPENDIX TABLE 4 Summary of Parameters for the Proposed Tolerance Enforcement Method for Fenpropimorph Residues in Banana Matrices.	
Method Name	BASF Method 241/1
Applicable Commodities	Banana (fruit, peel, and pulp)
Analyte	Fenpropimorph
Extraction Solvents	Homogenized banana samples (50 g) are slurried with water (600 mL), distilled for 2 hours using a Bleidner apparatus, and collected into chloroform. (Clean-up steps are described below.) The cleaned-up residues in methanol are diluted with water, acidified with 1 M HCl, partitioned into DCM, and concentrated to dryness. The residues are re-dissolved in a final volume of iso-octane/acetone (9:1 vol/vol) and quantified by GC/NPD.
Clean-Up Steps	Residues collected in chloroform (during the distillation/extraction) are partitioned with 0.5 M HCl, filtered and dried through a cotton wool plug, and evaporated to dryness. The residues are re-dissolved in methanol, and cleaned up using a cation-exchange (sulfonic acid form) SPE column eluted with 1 M NaOH followed by methanol.
Determinative Step	Analysis is by GC, utilizing an FSCC (SE-54, 18m x 0.27mm x 0.5μm) with NP detection, helium carrier gas, and a 10:1 split injection ratio. The injector and detector are held at 280°C; the column oven program is 150°C for 1 minute, then a rate of 20°C/minute to 250°C, held for 5 minutes.
LOQ (ppm)	0.050 ppm
LOD (ppm)	Not reported

A-5.0 SUMMARY OF MAGNITUDE OF THE RESIDUE STUDIES FOR FENPROPIMORPH ON BANANA

Crop field trials are conducted to determine the maximum residue which may be expected in/on a raw agricultural commodity as a result of the legal use of the pesticide. The trials should reflect label directions which would be expected to result in the maximum residue levels; ergo, the trials should employ maximum label rates, maximum number of applications, minimum retreatment interval(s), and minimum pre-harvest interval.

APPENDIX TABLE 5 Residues of Fenpropimorph in/on Bananas.								
Location	Application Data				Fenpropimorph Residues (ppm)			
	Type of Application	Total Rate (kg ai/ha)	RTI [1]	PHI [2]	Bagged		Unbagged	
					Whole Fruit	Pulp	Whole Fruit	Pulp
Costa Rica 1	Ground	2.11	13, 43, 12	0	0.13	0.081	1.2	0.3
				5	0.16	<0.05	0.72	0.17
	Aerial	2.27	12, 42, 13	0	<0.05	<0.05	0.11	<0.05
				5	<0.05	<0.05	0.086	<0.05
Costa Rica 2	Ground	2.23	13, 44, 12	0	0.37	0.2	0.75	0.22
				5	0.38	0.19	0.38	0.18
				10	0.4	0.19	0.5	0.29
				15	0.31	0.11	0.32	0.13
				25	<0.05	<0.05	<0.05	<0.05
Costa Rica 3	Ground	2.24	13, 44, 12	0	0.13	<0.05	1.4	0.29
				5	0.33	0.074	0.66	0.43
Ecuador 1	Ground	2.80 [3]	13, 45, 12	0	<0.05	<0.05	0.26	0.058
				5	<0.05	<0.05	0.2	0.059
	Aerial	2.21	11, 46, 10	0	<0.05	<0.05	<0.05	<0.05
				5	<0.05	<0.05	<0.05	<0.05
Ecuador 2	Ground	2.34	13, 45, 12	0	<0.05	<0.05	0.21	<0.05
				5	<0.05	<0.05	0.36	<0.05
Ecuador 3	Ground	2.16	12, 43, 12	0	0.17	0.066	0.099	<0.05
				5	0.17	0.059	0.06	<0.05
Columbia 1	Ground	2.09	12, 44, 12	0	<0.05	<0.05	0.16	<0.05
				5	<0.05	<0.05	0.078	<0.05
				10	<0.05	<0.05	0.092	<0.05
				15	0.13, 0.12	<0.05	0.11	<0.05

APPENDIX TABLE 5 Residues of Fenpropimorph in/on Bananas.								
Location	Application Data				Fenpropimorph Residues (ppm)			
	Type of Application	Total Rate (kg ai/ha)	RTI [1]	PHI [2]	Bagged		Unbagged	
					Whole Fruit	Pulp	Whole Fruit	Pulp
				25	<0.05	<0.05	0.068	<0.05
	Aerial	2.24	12, 44, 12	0	<0.05	<0.05	<0.05	<0.05
				5	<0.05	<0.05	<0.05	<0.05
Columbia 2	Ground	2.18	12, 44, 12	0	<0.05	<0.05	0.12	<0.05
				5	<0.05	<0.05	0.069	<0.05
Honduras 1	Ground	2.07	12, 45, 12	0	<0.05	<0.05	0.47	0.19
				5	<0.05	<0.05	0.65	0.28
Honduras 2	Ground	2.09	12, 43, 13	0	<0.05	<0.05	0.3	0.14
				5	<0.05	<0.05	0.43	0.12
Guatemala	Ground	2.3	12, 44, 11	0	<0.05	<0.05	0.7	0.18
				5	<0.05	<0.05	0.45	0.12
Mexico	Ground	2.17	12, 44, 11	0	<0.05	<0.05	0.32	0.069
				5	<0.05	<0.05	0.18	0.083

1. RTI = Re-Treatment Interval.
2. PTI = Pre-Harvest Interval.
3. The first application was made on two consecutive days at 0.53 kg ai/ha each, for a total of 1.05 kg ai/ha.

A-6.0 INTERNATIONAL CONSIDERATIONS

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: *rel*-(2*R*,6*S*)-4-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]-2,6-dimethylmorpholine	**Common Name:** Fenpropimorph	**X Proposed tolerance** ☐ Reevaluated tolerance ☐ Other	**Date:** 1/26/2005
Codex Status (Maximum Residue Limits)		US Tolerances	
☐ No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested		Petition Number: 7E4874 DP Barcode: D309994 Other Identifier: PC Code 121402	
Residue definition (step 8/CXL): Fenpropimorph		Reviewer/Branch: William T. Drew/RAB2	
		Residue definition: Fenpropimorph	
Crops	MRL (mg/kg)	Crop	Tolerance (ppm)
Banana	2	**Banana (recommended)**	**2.0**
Barley/oats/rye/wheat	0.5		
Barley/oats/rye (dry straw/fodder)	5		
Beet, sugar or fodder (leaves/tops)	1		
Sugar beet*	0.05		
Eggs*/land-mammal fats/milks	0.01		
Kidney (cattle/goats/pigs/sheep)	0.05		
Liver (cattle/goats/pigs/sheep)	0.3		
Meat (land-mammal)	0.02		
Poultry (fats/meat/edible offal)*	0.01		
Limits for Canada		Limits for Mexico	
X No Limits ☐ No Limits for the crops requested		X No Limits ☐ No Limits for the crops requested	
Residue definition: Not applicable		Residue definition: Not applicable	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
NOTES: Per Steven Funk, 1/26/2005. * Not expected at the LOQ of the analytical method.			

13544

R116369

Chemical:	**Fenpropimorph**
PC Code:	**121402**
HED File Code	**14000 Risk Reviews**
Memo Date:	**10/19/2005**
File ID:	**DPD309498**
Accession Number:	**412-06-0007**

HED Records Reference Center
10/24/2005