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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 07/25/2007

MEMORANDUM

SUBJECT: Bifenthrin: PP#6E7125, PP#6E7126, PP#6E7127, PP#6E7128; Human-Health Risk Assessment for Proposed Uses on Mayhaw, Root Vegetables, (Except Sugar Beets, Crop Subgroup 1B), Peanut, Pistachio, Soybean, and Fruiting Vegetables (Crop Group 8).
Regulatory Action: Section 3 Registration Action
Risk Assessment Type: Single Chemical Aggregate

Petition Nos.	6E7125, 6E7126, 6E7127, 6E7128	Decision Nos:	371449, 371450, 371452
DP Numbers:	334154, 334165, 334168	40 CFR:	§180.442
Chemical No.:	128825	Class:	Synthetic Pyrethroid
Trade Name:	Capture 2EC, Capture 1.15G, Brigade WSB	EPA Reg. No.:	279-3069; 279-3244; 279-3108
MRIDs:	None		

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To: Daniel Rosenblatt/Shaja Brothers (RM 05)
Registration Division (7505P)

The Interregional Research Project Number 4 (IR-4) has submitted requests for Section 3 registrations for the application of bifenthrin to mayhaw, root vegetables, (except sugar beets, crop subgroup 1b), peanut, pistachio, soybean, and fruiting vegetables (crop group 8). In conjunction with this request, the petitioner has proposed the establishment

of tolerances for bifenthrin (2-methyl[1,1′-biphenyl]-3-yl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate] *per se* in/on:

Mayhaw	1.4 ppm
Vegetable, root, except sugar beet and garden beet, subgroup 1B	0.07 ppm
Beet, garden, root	0.45 ppm
Beet, garden, top	15 ppm
Radish, top	4.5 ppm
Soybean	0.2 ppm
Soybean, hulls	0.7 ppm
Soybean, refined oil	0.4 ppm
Vegetable, fruiting, group 8	0.5 ppm
Peanut	0.05 ppm
Pistachio	0.05 ppm

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human-health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human-health that will result from the proposed uses of bifenthrin.

A summary of the findings and an assessment of human-health risk resulting from the proposed and registered uses of bifenthrin are provided in this document. The hazard characterization was provided by PV Shah, Ph.D., (RAB1); the residue chemistry review was provided by William Wassell (RAB1); the dietary exposure assessment was provided by Sheila Piper (CEB) and William Wassell; the occupational/residential exposure assessment was provided by Mark Dow (RD); the drinking water assessment was provided by Jose Melendez of the Environmental Fate and Effects Division (EFED); and the aggregate exposure and risk assessment were provided by William Wassell (RAB1).

1.0 Executive Summary

References:

- Revised Preliminary HED Chapter for the Bifenthrin Tolerance Reassessment Eligibility Decision (TRED). DP Barcode: D283796. J. Liccione. 12/04/2002.
- Bifenthrin: Human-health Risk Assessment for Proposed Uses on Cilantro, Leafy Brassica Greens (subgroup 5b), Tuberous and Corm Vegetables (Subgroup 1c), Dried Shelled Peas and Beans (except Soybean) (Subgroup 6c) and Tobacco. DP Barcode: D310088. M. Rust-Clock, *et. al.* 4/6/2006.

Background

Bifenthrin is a neurotoxic insecticide acting through direct contact and ingestion, having a slight repellent effect. The primary biological effects of bifenthrin and other pyrethroids on insects and vertebrates are inhibition of the voltage-gated Ca^{2+} channels coupled with a stimulatory effect on the voltage-gated Na^{+} channels. All pyrethroids act as axonic poisons, affecting both the peripheral and central nervous systems, and share similar modes of action. Pyrethroids, including bifenthrin, stimulate repetitive action in the nervous system by binding to voltage-gated sodium channels, prolonging the sodium ion permeability during the excitatory phase of the action potential**.** This action leads to spontaneous depolarizations, augmented neurotransmitter secretion rate and neuromuscular block, which ultimately results in paralysis of the insect.

Bifenthrin is formulated as an emulsifiable concentrate (EC), wettable powder (WP), or granular (G) product and has registered uses on a variety of commodities . Current tolerances (ranging from 0.05 to 10 ppm) are established in 40 CFR §180.442 for residues of bifenthrin in/on various plant and livestock commodities. Time-limited tolerances for orchard grass and sweet potato roots (0.05 ppm) have been established in conjunction with Section 18 Emergency Exemptions [40 CFR §180.442(2b)]. A tolerance of 0.05 ppm is established for residues of bifenthrin in food and feeds as a result of uses in food/feed handling establishments [40 CFR §180.442(2)]. Residential uses are registered for bifenthrin; however, no new residential uses are proposed in the subject actions.

A Tolerance Reassessment Eligibility Decision (TRED) was issued for bifenthrin in 2002 (reference above) and a human-heath risk assessment was completed on 4/6/2006. The TRED examined all registered uses of bifenthrin. The background information and conclusions reported in the 2002 TRED (including exposure from dietary, occupational and residential uses) and previous risk assessment have been summarized and incorporated into this risk assessment. For more details, see the 2002 TRED or the 2006 risk assessment.

Hazard Characterization

Bifenthrin has a moderate order of acute toxicity via the oral route (Category II) and a low order of acute toxicity via the dermal route (Category III) of exposure. There are no acute inhalation studies on bifenthrin technical; however, acceptable studies on the end-

use products are available. Bifenthrin has a low vapor pressure. It is neither an eye nor skin irritant, nor is it a dermal sensitizer.

Bifenthrin produces characteristic pyrethroid neurotoxicity. Tremors have been observed in developmental toxicity studies in the rat and rabbit, a 2-generation rat reproduction toxicity study, subchronic toxicity studies in the rat and dog, acute and subchronic neurotoxicity rat studies, a 21-day toxicity dermal rat study, chronic oral toxicity studies in the rat and dog, and a mouse oncogenicity study. The subchronic and chronic oral toxicity studies in dogs and rats demonstrate neurotoxicological responses of similar magnitude. Staggered gait and exaggerated hindlimb flexion were noted in a 21-day dermal toxicity study in the rat. The neurotoxicity of bifenthrin has been supported by the results of acute and subchronic neurotoxicity studies in the rat. Functional observation battery (FOB) findings were observed in these neurotoxicity studies. FOB findings consisted of tremors, abnormal posture, splayed hindlimbs, staggered gait, altered activity, altered landing foot-splay, twitching, uncoordinated movement/ataxia, and convulsions.

Bifenthrin is neither a developmental nor a reproductive toxicant. Bifenthrin has been evaluated for potential developmental effects in the rat (following gavage or dietary administration) and in the rabbit (gavage administration). Maternal toxicity included neurological effects (tremors in rats and rabbits; head and forelimb twitching in rabbits). There were no developmental effects of biological significance in either species.

The potential reproductive toxicity of bifenthrin was examined in a two-generation reproduction study in the rat. Tremors were noted only in females of both generations with one parental generation rat observed to have clonic convulsions. Administration of bifenthrin did not result in reproductive or offspring toxicity.

A developmental neurotoxicity (DNT) study on bifenthrin with rats has been submitted. In this study, maternal and offspring toxicity was observed at the same dose levels. The maternal toxicity was primarily manifested as tremors, clonic convulsions, and increased grooming counts. The offspring toxicity was manifested as increased grooming counts. This study does not show any evidence of increased susceptibility of offspring following exposure to bifenthrin.

Bifenthrin was negative in most tests for mutagenicity. It was marginally mutagenic with and without S9 activation in the mouse lymphoma forward gene mutation assay. This finding has not been confirmed in a repeat test. There is also inconclusive, but presumptive, evidence that bifenthrin was mutagenic in the S9-activated phase of the Chinese hamster ovary (CHO) cell gene mutation assay; however, this study was classified as unacceptable.

There was no conclusive evidence of carcinogenic potential of bifenthrin in the rat. A mouse oncogenicity study provided some evidence for carcinogenic potential in this species. In the mouse oncogenicity study, high-dose (81.3 mg/kg/day) males showed a highly significant increased incidence of urinary bladder tumors. Other findings in the mouse study included a dose-related trend of increased combined incidences of adenoma and adenocarcinoma of the liver (males only), and increased incidences of bronchioalveolar adenomas and adenocarcinomas of the lung in females at some, but not all dose levels relative to their controls. HED's Carcinogenicity Peer Review Committee (CPRC) has characterized bifenthrin as Category C (possible human carcinogen) primarily on the basis of a mouse study in which the Cancer Assessment Review Committee (CARC) (1992) recommended that, for the purpose of risk characterization, the reference-dose (RfD) approach should be used for quantification of human cancer risk.

Several dermal-absorption studies on bifenthrin are available; each study was considered acceptable for regulatory purposes when taken in conjunction with the other studies. The Hazard Identification and Review Committee (HIARC) recommended a dermal absorption rate of 25% based on the weight-of the-evidence available for structurally related pyrethroids.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision
The HED HIARC met on June 25, 2002 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to bifenthrin. Since the last HIARC meeting, the registrant submitted the DNT study in rats. This study is classified as **Acceptable/Non-guideline** and may be used for regulatory purposes. This study did not impact endpoints selected by the HIARC for various exposure scenarios. The database uncertainty factor due to lack of a DNT study is now removed. No appropriate acute dietary endpoints were available to quantify risk to females 13-50 years of age from a single-dose administration of bifenthrin. However, an acute reference dose (aRFD) of 0.33 mg/kg/day, relevant to the general population including infants and children, and based on observation of mortality (females only), clinical and FOB findings, and differences in motor activity, was selected from an acute neurotoxicity study in rats for acute risk assessment. The aRfD is based on the no observed adverse-effect level (NOAEL) of 32.8 mg/kg/day divided by an uncertainty factor (UF) of 100 (10x for inter-species extrapolation and 10x for intra-species variations).

The short- and intermediate-term incidental oral and inhalation endpoints are based on observations of an increased incidence of tremors in male and female dogs in a 90-day oral toxicity study. A cRfD of 0.013 mg/kg/day was determined from the 1-year oral dog study that demonstrated increased incidence of tremors in both sexes. The cRfD is based on the NOAEL of 1.3 mg/kg/day divided by an UF of 100 (10x for inter-species extrapolation and 10x for intra-species variations). The results of the 1-year dog toxicity study were also the basis for the determination of the short-, intermediate-, and long-term

inhalation endpoint. An inhalation-absorption default factor of 100% was used for risk assessment purposes, since the endpoint was derived from an oral study. The 21-day rat dermal toxicity study was used to select short-, intermediate- and long-term dermal endpoints; clinical signs included staggered gait and exaggerated hindlimb flexion.

The FQPA requires the Agency to consider potential special sensitivity to infants and children from exposure to bifenthrin. The HED FQPA Safety Factor Committee (SFC) met on July 15 and 22, 2002 to evaluate the hazard and exposure data for bifenthrin with regard to making a decision on the additional safety factor for the protection of infants and children. Acceptable developmental studies in the rat and rabbit revealed no increased susceptibility of rat or rabbit fetuses following *in utero* exposure to bifenthrin. In addition, there was no evidence of increased susceptibility of young rats in the reproduction study with bifenthrin. Since the last HIARC meeting, a developmental toxicity study in rats has been submitted. There was no evidence of increased susceptibility of offspring in the DNT study in rats conducted with bifenthrin.

The 1x FQPA safety factor has been applied to all dietary and residential non-dietary exposure scenarios. The acute and chronic RfD modified by the FQPA Safety Factor is referred to as a population-adjusted dose (PAD). Therefore, the acute PAD (aPAD) for bifenthrin is 0.33 mg/kg/day, and the chronic PAD (cPAD) for bifenthrin is 0.013 mg/kg/day.

The FQPA Committee noted that there were no residual uncertainties in the exposure databases. The dietary food exposure assessment was refined using percent crop treated (CT) information, and anticipated residue (AR) values calculated from the available monitoring data and field trial results. Dietary drinking water exposure is based on conservative modeling estimates, and the HED residential standard operating procedures (SOPs), in conjunction with some chemical specific data, were used to assess residential handler and post-application exposure to adults and children. These assessments will not underestimate the exposure and risks posed by bifenthrin.

Dietary Exposure Assessment
Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

Acute Dietary Exposure and Risk
A Tier 3, acute probabilistic dietary exposure and risk assessment was conducted for all registered (and pending) food uses and drinking water. Anticipated residues (ARs) were developed based on the latest U.S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data 1998-2005, Food and Drug Administration (FDA) data, or field

trial data for bifenthrin. Anticipated residues were further refined using the latest percent crop treated (%CT) data and processing factors where appropriate.

EFED calculated the ground and surface drinking water Tier 1 estimated drinking water concentrations (EDWCs) for bifenthrin using the screening concentration in ground water (SCI-GROW) and FQPA Index Reservoir Screening Tool (FIRST) models. EDWCs in ground water were estimated as 0.003 ppb and 0.014 ppb in surface water. The acute drinking water concentration of bifenthrin in surface water (0.014 ppb) is based on the application of bifenthrin to lettuce at the highest application rate (0.5 lb ai/A/season).

The acute dietary exposure estimates for food and drinking water are below HED's level of concern (<100% aPAD) at the 99.9th percentile of exposure. Bifenthrin dietary exposure at the 99.9th percentile for food and drinking water for the U.S. population is 10% of the aPAD and 25% of the aPAD for all infants, the most highly exposed population subgroup. These estimates include drinking water.

Chronic Dietary Exposure and Risk
An chronic population-adjusted-dose (cPAD) is established based upon the one-year oral toxicity study in dogs. In this study, the lowest observed adverse-effect level (LOAEL) of 2.7 mg /kg/day is based on observations of increased incidence of tremors in both sexes. A UF of 100x was used to calculate the cPAD.

A refined chronic dietary exposure assessment was also conducted for the supported food uses of bifenthrin and drinking water using single point estimates of anticipated bifenthrin residues for food and drinking water. The estimated surface water concentration of 0.014 ppb, based on application to lettuce at the highest application rate, was also used for the chronic dietary assessment.

The chronic dietary exposure estimates for food and drinking water are below HED's level of concern (<100% cPAD) for the U.S. population and all population subgroups. Bifenthrin dietary exposure for food and drinking water is 20% of the cPAD for the U.S. population and 53% of the cPAD for children 3-5 years old, the most highly exposed population subgroup.

Cancer Dietary Risk
The CARC (1992) recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human risk. The chronic exposure analysis exhibited exposures that were less than 100% RfD, and it is assumed that the chronic dietary endpoint is protective for cancer dietary exposure.

Residential Exposure and Risk
Bifenthrin has both indoor and outdoor residential uses. Adults are potentially exposed to bifenthrin residues during residential application of bifenthrin. Adults and children are potentially exposed to bifenthrin residues after application (post-application) of

bifenthrin products in residential settings. Risk estimates were generated for residential handler exposures, and potential post-application contact with lawn, soil, and treated indoor surfaces using HED's Draft SOPs for Residential Exposure Assessment, and dissipation data from a turf transferable residue (TTR) study. These estimates are considered conservative, but appropriate, since the study data were generated at maximum application rates.

Residential Handler Risk Estimates
Short- to intermediate-term dermal and inhalation exposures may occur for residential handlers of bifenthrin products. Residential handler risks from inhalation exposures to bifenthrin gas/vapor are considered unlikely, since the vapor pressure of bifenthrin is low. Inhalation exposure was assessed for aerosols/particulates during residential mixing, loading, and application of granular products. Short- and intermediate-term handler MOEs estimated for combined dermal and inhalation exposures were > 100, and therefore, are not of concern to HED.

Residential Post-Application Risk Estimates
Adults and children may be potentially exposed to bifenthrin residues after application of bifenthrin products in residential settings. Short- and intermediate-term post-application dermal exposures for adults, and short- and intermediate-term post-application dermal and incidental oral exposures for children are anticipated. Risk estimates were generated for potential contact with lawn, soil, and treated indoor surfaces. Short- and intermediate-term risks estimated for post-application exposure for adults and children are not of concern to HED. Combined oral and dermal short-term exposures for children are not of concern to HED. Combined adult handler and post-application risk estimates (inhalation and dermal) associated with homeowner applied formulations are not of concern to HED.

Aggregate Risk
Because there is the potential for short- and intermediate-term, non-dietary post-application exposure of children and adults to bifenthrin when used as a residential treatment, aggregate risk was assessed. Short- and intermediate-term aggregate (dietary + residential) MOEs for the general U.S. population and any subpopulation of the general U.S. population are at least 150. This value does not exceed HED's level of concern (MOE ≤100). Chronic (>6 months) non-dietary post-application exposure to bifenthrin as a residential treatment is considered unlikely; therefore, chronic aggregate risk assessments were not performed.

Occupational Handler Risk
Based upon the proposed use pattern, HED expects the most highly exposed occupational pesticide handlers (mixers, loaders, applicators) to be 1) mixer/loader using open pour loading of liquids; 2) mixer/loader using open pour loading of granules; 3) an aerial applicator and 4) an applicator using open-cab, ground-boom spray equipment. Estimates for short- and intermediate-term occupational risks were calculated. Provided

that mixer/loaders wear protective gloves, all MOEs are above 100, and, therefore, are not of concern to HED.

Occupational Post-Application Risk
Based on the proposed use pattern, HED has calculated post-application exposure and risk for workers exposed to bifenthrin residues following treatment. Workers engaging in activities such as hand harvesting, topping, stripping and irrigation activities were assessed. Standard assumptions were incorporated into the assessment to reflect conservative risk estimates. The MOE for the theoretically most highly exposed post-application agricultural activity is 410, and is not of concern to HED. All other identified post-application activities are expected to have lower exposures and greater MOEs.

Based on the acute toxicity category classification for bifenthrin, the interim worker protection standard (WPS) restricted-entry interval (REI) of 12 hours is adequate to protect agricultural workers from post-application exposures. The proposed end-use product labels list an REI of 12 hours.

HED Recommendations
The tolerances proposed by the registrants in the current petitions are listed below, along with HED's recommended tolerance levels.

Provided revised Sections B and F are submitted, the residue chemistry and toxicology databases support conditional registration and permanent tolerances for the following:

Tolerance Summary for Bifenthrin.			
Proposed		Recommended	
Commodity Definition	Tolerance (ppm)	Commodity Definition	Tolerance (ppm)
Mayhaw	1.4	Same	Same
Vegetable, root, except sugar beet and garden beet, subgroup 1B	0.07	Same	**0.10**
beet, garden, root	0.45	Same	Same
beet, garden, top	15	Same	Same
Radish, top	4.5	Same	Same
Soybean	0.2	Same	Same
Soybean, hulls	0.7	Same	**0.50**
Soybean, refined oil	0.4	Same	**0.30**
Vegetable, fruiting, group 8	0.5	**Delete request for fruiting vegetables**	
		Groundcherry	**0.5**
		Pepino	**0.5**
Peanut	0.05	Same	Same
Pistachio	0.05	Same	Same
None	None	**Aspirated Grain Fractions**	**70**

The registration may be made permanent once additional data concerning aspirated grain fractions are submitted. Revised Sections F with the correct tolerance levels and commodity definitions should be submitted where appropriate.

2.0 Ingredient Profile

2.1 Summary of Proposed Uses

The petitioner has proposed the use of Brigade WSB, Capture 2EC, and/or Capture 1.15G (EPA Reg. Nos. 279-3069, 279-3244, and 279-3108, respectively) for use on mayhaw, root vegetables, (except sugar beets, crop subgroup 1B), peanut, pistachio, soybean, and fruiting vegetables (crop group 8). Table 2.1 is a summary of the proposed application scenarios.

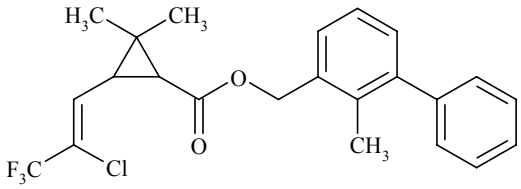
The submitted labels adequately describe the proposed application scenarios. As the petitioner has not requested the establishment of tolerances for residues in/on peanut hay, the following restriction must be added to the label: **Do not feed green immature plants and peanut hay to livestock**. Based on the current rotational crop data, **HED concludes that a 30-day rotational crop restriction is appropriate for all non-labeled crops (labeled crops may be planted at anytime; see section OPPTS 860.1850). A revised Section B is requested.**

Table 2.1. Proposed Application Scenarios.

Formulation	Crop	App. Rate (lb ai/acre)[1]	PHI[2] (days)	Comments[3]
Brigade WSB Capture 2EC	Mayhaw	0.08 to 0.10	30	Apply in at least 28 gallons per acre. Apply no more than once every 7 days. Do not apply more than 0.2 lb ai/A per season.
Brigade WSB Capture 2EC Capture 1.15G	Root Crops (edible burdock, carrot, celeriac, chevil, chicory, ginseng, horseradish, parsley, parsnip, radish, oriental radish, rutabaga, salsify, black salsify, Spanish salsify, skirret, turnip)	0.08 to 0.10 (0.006 lb ai per 1000 linear ft)[3]	21	Apply in at least 25 gallons per acre. Apply no more than once every 7 days. Do not apply more than 0.5 lb ai/A per season (including soil application). (Make one in-furrow application of Capture 1.15G at planting.)
Brigade WSB Capture 2EC Capture 1.15G	Garden beet	0.08 to 0.10 (0.006 lb ai per 1000 linear ft)	1	Apply in at least 25 gallons per acre. Apply no more than once every 7 days. Do not apply more than 0.4 lb ai/A per season (including soil application). (Make one in-furrow application of Capture 1.15G at planting.)
Brigade WSB Capture 2EC	Peanut	0.033 to 0.10	14	Apply in at least 10 gallons per acre. Apply no more than once every 14 days. Do not apply more than 0.5 lb ai/A per season.
Brigade WSB Capture 2EC	Pistachio	0.05 to 0.20	21	Apply in at least 50 gallons per acre by ground and at least 10 gallons per acre by air. Apply no more than once every 15 days. Do not apply more than 0.2 lb ai/A per application and do not exceed 0.50 lb ai/A per season.
Brigade WSB Capture 2EC	Soybean	0.033 to 0.10	18	Apply in at least 10 gallons per acre. Apply no more than once every 30 days. Do not apply more than 0.3 lb ai/A per season.
Brigade WSB Capture 2EC Capture 1.15G	Eggplant, bell and non-bell pepper, groundcherry, pepino	0.033 to 0.08 (0.04 to 0.10)	7	Apply in at least 2 gallons per acre by air or 10 gallons per acre by ground. Apply no more than once every 7 days. Do not apply more than 0.2 lb ai/A per season. (Make application of Capture 1.15G as soon as pest are present.)
Brigade WSB Capture 2EC Capture 1.15G	Tomato, tomatillo	0.033 to 0.08 (0.04 to 0.10)	1	Apply in at least 15 gallons per acre. Apply no more than once every 10 days. A maximum of 4 applications may be applied per season. (Make application of Capture 1.15G as soon as pest are present.)

[1] The rates list in parentheses are for Capture 1.156 G; ai = active ingredient.
[2] PHI = pre-harvest interval.
[3] The comments in parentheses and application rates are specific to Capture 1.15 G.

2.2 Structure and Nomenclature

Table 2.2. Nomenclature of Bifenthrin.	
Compound	
Common name	Bifenthrin
Company experimental names	Capture® Insecticide/Miticide
IUPAC name	2-methylbiphenyl-3-ylmethyl (1*RS*,3*RS*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate or 2-methylbiphenyl-3-ylmethyl (1*RS*)-*cis*-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate
CAS name	(2-methyl[1,1′-biphenyl]-3-yl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate
CAS #	82657-04-03
End-use products/EPs	2.0 lb ai/gal emulsifiable concentrate formulation (Capture 2EC; EPA Reg. No. 279-3069) 1.15% granular formulation (Capture 1.15G; EPA Reg. No. 279-3244) 10% wettable-powder formulation (Brigade WSB, EPA Reg. No. 279-3108)

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of the Technical Grade Bifenthrin.		
Parameter	**Value**	**Reference**
Melting range	68-70.6°C	Product Chemistry Chapter of the TRED
pH	NA[1]	
Density at 24°C	1.26 g/mL	
Water solubility	<0.1 µg/L	
Solvent solubility (g/100 mL)	8.9 in heptane and methanol 125 in acetone, chloroform, ether, methylene chloride, and toluene	
Vapor pressure (Pa) at 25°C	2.41×10^{-5}	
Dissociation constant (pK_a)	Not applicable	
Octanol/water partition coefficient (Kow)	$>1 \times 10^{6}$	
UV/visible absorption spectrum	NA	

[1] NA = information not available.

Hazard Characterization/Assessment

References:

- *BIFENTHRIN - 3rd Report of the Hazard Identification Assessment Review Committee*. TXR No. 0051570. B. Tarplee. 2/19/2003.

- *Revised Preliminary HED Chapter for the Bifenthrin Tolerance Reassessment Eligibility Decision (TRED)*. PC Code: 128825 DP Barcode: D283796. J. Liccione. 12/04/2002.

Bifenthrin is a non-systemic insecticide/miticide in the class of synthetic pyrethroids. It is registered for use on a variety of crops for the control of insect pests.

Bifenthrin is classified as Category II for acute oral toxicity, and Category III for acute dermal toxicity. There are no acute inhalation studies on bifenthrin technical. It is not an eye or skin irritant, or a dermal sensitizer.

Bifenthrin produces characteristic pyrethroid neurotoxicity. Tremors have been observed in developmental toxicity studies in the rat and rabbit, a 2-generation rat reproduction study, subchronic toxicity studies in the rat and dog, acute and subchronic neurotoxicity rat studies, a 21-day dermal rat study, chronic oral studies in the rat and dog, and oncogenicity rat and mouse studies. FOB findings were observed in the acute and subchronic neurotoxicity studies in the rat.

There is no evidence of increased susceptibility of rats or rabbits to *in utero* and/or post-natal exposure to bifenthrin. A DNT study on bifenthrin was conducted in rats. In this study maternal and offspring toxicity was observed at the same dose levels. The maternal toxicity was primarily manifested as tremors, clonic convulsions, and increased grooming counts. The offspring toxicity was manifested as increased grooming counts. This study does not show any evidence of increased susceptibility of offspring following exposure to bifenthrin.

Bifenthrin was negative in most tests for mutagenicity. It was marginally mutagenic with and without S9 activation in the mouse lymphoma forward gene mutation assay. This finding has not been confirmed in a repeat test. There is also inconclusive, but presumptive evidence that bifenthrin was mutagenic in the S9-activated phase of the CHO gene mutation assay (unacceptable study).

The CPRC (1992) has characterized bifenthrin as Category C (possible human carcinogen) and recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human cancer risk. This decision was based in part on the statistically significant increased trend for hemangiopericytomas in the urinary bladders' of Swiss Webster mice. The incidence of these lesions was double at the highest dose tested (HDT; 600 ppm) as compared to controls. The male mice also had significant dose-related trends with respect to hepatocellular carcinomas and combined hepatocellular adenomas and carcinomas, and increased incidences of bronchioalveolar adenomas and adenocarcinomas of the lung in females at 50, 200 and

600 ppm (but not 500 ppm) relative to their controls. No compound related tumors were noted in rats. The mutagenicity evidence presents low concern for bifenthrin.

3.1 Hazard and Dose-Response Characterization

The acute toxicity profile for bifenthrin is presented below in Table 3.1. The full toxicological profile is presented in Attachment 1 to this memo. A summary of the toxicology of bifenthrin is discussed below.

Subchronic Toxicity
The database for subchronic toxicity is considered complete. The available subchronic oral toxicity studies in rats and dogs demonstrated the neurotoxicity of bifenthrin. Tremors were observed in rats fed doses equal to or greater than 100 ppm (7.5 mg/kg/day for males; 8.5 mg/kg/day for females) bifenthrin for 90 days. Male and female dogs were administered (via gelatin capsule) bifenthrin at doses equal to or greater than 4.42 mg/kg/day for up to 13 weeks exhibited tremors. Ataxia was noted in male dogs at 8.84 and 17.7 mg/kg/day, and in female dogs at 4.42 mg/kg/day. Languidness occurred primarily at 17.7 mg/kg/day in both sexes, but also occasionally at 8.84 mg/kg/day. All of these symptoms occurred more frequently during the last 3 weeks of the study. Other dose-related clinical signs included blinking, mydriasis, nystagmus, lacrimation, and polypnea (increased rate of respiration) in the two highest dose groups. One high-dose female appeared thin and/or dehydrated during the final weeks of the study. A non-statistically significant, but possibly treatment-related, reduction in mean body-weight gain was noted in females at 17.7 mg /kg/day (0.6 kg) relative to the controls (1.3 kg).

Neurotoxicity
Bifenthrin produces characteristic pyrethroid neurotoxicity. Tremors have been observed in developmental toxicity studies in the rat and rabbit, a 2-generation rat reproduction study, subchronic toxicity studies in the rat and dog, acute and subchronic neurotoxicity rat studies, a 21-day dermal rat study, chronic oral studies in the rat and dog, and oncogenicity rat and mouse studies. Staggered gait and exaggerated hindlimb flexion were noted in a 21-day dermal toxicity study in the rat. The neurotoxicity of bifenthrin has been supported by the results of acute and subchronic neurotoxicity studies in the rat. FOB findings were observed in these neurotoxicity studies. FOB findings consisted of tremors, abnormal posture, splayed hindlimbs, staggered gait, altered activity, altered landing foot-splay, twitching, uncoordinated movement/ataxia, and convulsions.

Chronic Toxicity
The database for chronic toxicity is considered complete. No additional data are required at this time. The results of chronic toxicity studies support the finding of neurotoxicity for bifenthrin. Tremors were observed in both a 1-year feeding study in the dog (LOAEL = 2.7 mg/kg/day for both sexes; NOAEL = 1.3 mg/kg/day for both sexes), in a combined chronic toxicity/oncogenicity dietary study in the rat (LOAEL = 6.1 mg/kg/day for females; NOAEL = 3.0 mg/kg/day for males), and in a combined chronic

toxicity/oncogenicity dietary study in the mouse (LOAEL = 25.6 mg/kg/day in males; NOAEL = 6.7 mg/kg/day in males).

Developmental Toxicity
A complete developmental toxicity database exists for bifenthrin. The available data provided no indication of increased susceptibility (quantitative or qualitative) of rats or rabbits to *in utero* and/or post-natal exposure to bifenthrin. In the prenatal developmental (gavage) toxicity study in rats, a slight increase in the incidence of "hydroureter without hydronephrosis" was observed in fetuses at the highest dose tested (2 mg/kg/day); maternal toxicity (tremors) was also observed at this dose level, and the maternal and developmental NOAELs were equivalent at 1 mg/kg/day. This effect was not observed in the prenatal developmental (dietary) toxicity study in rats; maternal toxicity was evident at 15.5 mg/kg/day as tremors and decreased food consumption, body-weight gains, and adjusted (for gravid uterine weight) body-weight gains. In the prenatal developmental toxicity study in rabbits, there was no evidence of developmental toxicity at the highest dose tested (8 mg/kg/day). Head and forelimb twitching was observed at the maternal LOAEL of 4 mg/kg/day; the maternal NOAEL was established at 2.67 mg/kg/day.

A DNT study on bifenthrin was conducted in rats. In this study maternal and offspring toxicity was observed at the same dose levels. The maternal toxicity was primarily manifested as tremors, clonic convulsions, and increased grooming counts. The offspring toxicity was manifested as increased grooming counts. This study does not show any evidence of increased susceptibility of offspring following exposure to bifenthrin.

Reproductive Toxicity
Bifenthrin is not a reproductive toxicant and there is no evidence of increased susceptibility of offspring. In an acceptable two-generation reproduction study in rats, no evidence of toxicity was noted in the offspring at dietary levels up to 100 ppm (5 mg/kg/day). Parental toxicity (tremors and decreased body-weights) was observed at 100 ppm (5 mg/kg/day), with a NOAEL of 60 ppm (3.0 mg/kg/day).

Carcinogenicity
The CPRC (1992) has characterized bifenthrin as Category C (possible human carcinogen) and recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human cancer risk. This decision was based in part on the statistically significant increased trend for hemangiopericytomas in the urinary bladders of Swiss Webster mice. The incidence of these lesions was double at the highest dose tested (HDT; 600 ppm) as compared to controls. The male mice also had significant dose-related trends with respect to hepatocellular carcinomas and combined hepatocellular adenomas and carcinomas, and increased incidences of bronchioalveolar adenomas and adenocarcinomas of the lung in females at 50, 200 and 600 ppm (but not 500 ppm) relative to their controls. No compound related tumors were noted in rats. The mutagenicity evidence presents low concern for bifenthrin.

Mutagenicity
Bifenthrin was negative in most tests for mutagenicity. It was marginally mutagenic with and without S9 activation in the mouse lymphoma forward gene mutation assay. This finding has not been confirmed in a repeat test. There is also inconclusive, but presumptive, evidence that bifenthrin was mutagenic in the S9-activated phase of the CHO gene mutation assay; however, this was an unacceptable study.

Metabolism
Bifenthrin is absorbed by the oral route and eliminated primarily in the feces (about 70% within 48 hours). Approximately 10% of the administered doses were excreted in the urine. Nearly all the administered dose was eliminated in urine and feces within 7 days indicating no retention in the body. Very little of the administered radioactive dose is expired as ^{14}C-CO_2. The major metabolic route of radiolabeled bifenthrin is hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Protein binding of radioactive components or metabolites increases with time.

Dermal Absorption
Several dermal-absorption studies on bifenthrin are available; each study is considered acceptable for regulatory purposes when taken in conjunction with the other studies. The HIARC recommended a dermal absorption rate of 25% based on the weight-of the-evidence available for structurally related pyrethroids.

Table 3.1. Acute Toxicity Profile – Bifenthrin

Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100/Acute oral toxicity	0013519	LD_{50} = 70.1 mg/kg (♂); 53.8 mg/kg (♀)	II
870.1200/Acute dermal toxicity	00132520	LD_{50} > 2,000 mg/kg	III
870.1300/Acute inhalation toxicity	46029703	Data waived. Acceptable atmosphere could not be generated with product.	IV
870.2400/Primary eye irritation	00132522	Non-irritant	IV
870.2500/Primary dermal irritation	00132521	Non-irritant	IV
870.2600/Dermal sensitization	00132523	Not a sensitizer	N/A

3.2 FQPA Considerations

3.2.1 Adequacy of the Toxicity Database

The HIARC concluded that the toxicology database for bifenthrin is complete.

3.2.2 Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to bifenthrin. This is based on the observation of neurotoxicity (clinical signs) in the acute neurotoxicity, subchronic neurotoxicity, 2-generation reproduction, developmental toxicity, dermal toxicity, subchronic toxicity and chronic toxicity studies. In addition, FOB findings were observed in the acute and subchronic neurotoxicity studies.

3.2.2.1 Acute Neurotoxicity Study

In an acute oral neurotoxicity study (MRID 44862102), bifenthrin (FMC 54800 technical, 93.7% ai; FMC Ref. No. PL97-592) was administered by a single gavage dose to 10 Sprague-Dawley rats/sex/dose at doses of 0, 10, 35 or 75 mg/kg, or 0, 9.4, 32.8, or 70.3 mg/kg/day (2 control males and 2 control females were removed from the study due to an unspecified dosing error, leaving 8/sex). The FOB assessment and motor activity testing were performed during the pretest interval, and on days 0, 7 and 14. Five animals/sex/group were perfused *in situ* for neurohistological examination at day 14 and brain, central and peripheral nervous system tissues from control and high dose animals were examined microscopically.

At 75 mg/kg, two females died on day 0, shortly after dosing. The following clinical signs were observed in males after dosing (# incidences): decreased feces (1 vs. 0 control); staggered gait (1 vs. 0 control); tremors (1 vs. 0 control); and twitching (3 vs. 0 control). Females displayed the following clinical signs following dosing (# incidences): abdominogenital staining (2 /2 died vs. 0 control); clonic convulsions (1 treated/died vs. 0 control); chromorhinorrhea (2 /2 died vs. 0 control); and tremors (3 [2 died] vs. 0 control). All clinical signs of toxicity were resolved in survivors by study day 2.

The following FOB home cage observations were noted on day 0 at 6-8 hrs postdosing: whole body tremors (1 male, 1 female/died vs. 0 control); abnormal mobile posture (1 male vs. 1 control); uncoordinated movement/ataxia (1 male vs. 0 control); splayed hindlimbs (1 male vs. 0 control); convulsions (2 females/2 died vs. 0 control); tense/rigid during handling (1 male, 4 females/2 died vs. 0 controls); and unusual posture (immobile; 1 female/died vs. 0 control). Day 0 FOB open field observations included the following: localized spasms/twitching (2 males vs. 0 control); whole body tremors (2 males, 2 females/ 1 died treated vs. 0 control); staggered gait (1 male vs. 0 control); abnormal posture (mobile; 1 male vs. 0 control); uncoordinated movement/ataxia (1 male vs. 0 control); splayed hindlimbs (1 male vs. 0 control); increased activity (1 female vs. 0

control); decreased activity (1 female/died vs. 0 control); convulsions (2 females/1 died vs. 0 control); walking on toes (1 female vs. 0 controls); and unusual immobile posture (1 female/died vs. 0 control). Landing foot-splay values were decreased in males during the day 0 FOB (↓15%, $p \leq 0.05$). No treatment-related differences from controls were observed in the FOB assessment in survivors on study days 7 and 14. Mean motor activity was decreased in males on day 0 (↓36%, not statistically significant), while motor activity in the females was increased on days 0 and 14 (↑23% and ↑18%, respectively; not statistically significant), although the day 14 increase was not considered biologically significant. No treatment-related differences were observed in body-weights, body-weight gains, gross observations or neuropathological examinations in any treated group (the latter only examined in control and high dose groups). No treatment-related findings were observed at 10 or 35 mg/kg.

The LOAEL for this study is 75 mg/kg (70.3 mg/kg/day) based on mortality (females only), clinical and FOB findings and differences in motor activity. The NOAEL for this study is 35 mg/kg (32.8 mg/kg/day).

3.2.2.2 Subchronic Neurotoxicity Study

In this subchronic oral neurotoxicity study (MRID 44862103), FMC 54800 technical (Bifenthrin, 93.7% ai, batch PL97-592) was administered continuously in the diet for 13 weeks to 10 Sprague-Dawley rats/sex/dose at doses of 50, 100 or 200 ppm (equivalent to [M/F] 0/0, 2.9/3.7, 6.0/7.2 or 11.8/14.6 mg/kg).

At 100 ppm, tremors were observed during clinical examinations in 8 (28 incidences) males and 10 (119 incidences) females. Twitching was observed in 4 (4 incidences) males and 2 (5 incidences) females. During the open field portion of the FOB, tremors were observed in all females following 4 weeks of treatment. In addition, females displayed decreased ($p \leq 0.05$) hindlimb grip strength during weeks 8 and 13 (↓22-25%). One female died on day 52 as a result of kidney inflammation; however, this death was not considered treatment related.

At 200 ppm, tremors were observed during clinical examinations in 10 (311 incidences) males and 10 (336 incidences) females. Twitching was also observed in 10 (76 incidences) males and 10 (96 incidences) females. During the open field FOB, tremors were observed in all males and females following 4 weeks of treatment. In addition, females displayed increased arousal when compared to concurrent controls (3 treated vs. 1 control). Females displayed decreased ($p \leq 0.05$ or 0.01) forelimb grip strength (↓20-31%) and hindlimb grip strength (↓18-36%), and increased landing foot-splay values (↑21-28%) during weeks 4, 8 and 13. In addition, decreased forelimb grip strength was observed in males at week 4 (↓27%, not statistically significant), but not at later times.

No treatment-related differences were observed at any dose level in body-weights, body-weight gains, food consumption, home cage FOB examination, motor activity measurements, or gross or neuropathological examinations.

The LOAEL for this study is 100 ppm (equivalent to 6.0 mg/kg/day in males and 7.2 mg/kg/day in females) based on neuromuscular findings (tremors, changes in grip strength and landing foot-splay). The NOAEL is 50 ppm (equivalent to 2.9 mg/kg/day in males and 3.7 mg/kg/day in females).

3.2.3 Developmental Toxicity Studies

3.2.3.1 Rat

Developmental Rat Studies
In a **pilot developmental study** (MRID 00154482), bifenthrin (88.35% ai) in corn oil was administered via gavage to mated female Sprague-Dawley rats (10/sex/dose) at dose levels of 0, 0.5, 1.0, 2.0, or 2.5 mg/kg/day FMC 54800 during days 6-15 of gestation. These doses are equivalent to 0, 0.44, 0.88, 1.77, and 2.2 mg/kg/day. Three of 10 rats at 2.5 mg/kg/day died on days 14-15. Tremors were noted in all 10 rats at 2.5 mg/kg/day (days 6-15) and in 9/10 at 2.0 mg/kg/day (days 7 through 18). Two of the rats administered 2.5 mg/kg/day also exhibited clonic convulsions. Mean body-weight gains were depressed at 2.5 mg/kg/day throughout the study, and food consumption was lower (↓20%) at this dose level during days 6-13. There were no differences in mean body-weight gains or food consumption in the lower dose groups with respect to the controls. There were no treatment-related differences from controls in the number of implantations or litter size. The mean number of resorptions was similar in the lower dose groups; at 2.5 mg/kg/day it was somewhat higher, but this was attributable to an excessive number of resorptions in a single rat.

The maternal LOAEL is 1.77 mg/kg/day (2.0 mg/kg/day) based on sporadic tremors (gestation days 7-18) and 30% mortality at 2.2 mg/kg/day (2.5 mg/kg/day). The maternal NOAEL is 0.88 mg/kg/day (1.0 mg/kg/day). The developmental LOAEL and NOAEL were not determined; fetuses were not examined.

In a **second developmental study** in rats (MRID 00141201), bifenthrin (88.35% ai) (as FMC 54800 technical) in corn oil was administered via gavage to pregnant female Sprague-Dawley rats (25/dose) at dose levels of 0, 0.5, 1.0, or 2.0 mg/kg/day, which is equivalent to 0, 0.44, 0.88, and 1.77 mg/kg/day, or with 250 mg/kg/day aspirin (positive control) in 2% carboxymethylcellulose during days 6-15 of gestation.

Maternal toxicity was characterized as tremors in 18/25 dams at 1.77 mg/kg/day (2.0 mg/kg/day) during days 10-19. There were no deaths during the study, and no significant differences between groups or dose-related trends with respect to mean maternal body-weight gains or food consumption were noted.

The maternal LOAEL is 1.77 mg/kg/day (2.0 mg/kg/day) based on the incidence of tremors. The maternal NOAEL is 0.88 mg/kg/day (1.0 mg/kg/day).

Slight developmental toxicity was noted at 1.77 mg/kg/day (2.0 mg/kg/day) and was characterized as an increased fetal and litter incidence of "hydroureter without hydronephrosis." Although not statistically significant, the incidence of hydroureter was double that of the vehicle control and the lower dose groups (3.55% versus 0% in controls and low dose groups). Also, 5 fetuses from dams at 1.77 mg/kg/day (2.0 mg/kg/day) (from five different litters) had "hydroureter without hydronephrosis," a finding that was not present in controls or any of the other exposure groups. There were no other treatment-related malformations or variations noted at any dose level. There were no group differences or dose-related trends with respect to pregnancy rates, numbers of corpora lutea, implantation sites and resorptions, litter sizes, sex ratios, fetal body-weights, or viability. The positive control gave the appropriate responses of increased early resorptions, depressed fetal body-weights, external, visceral, and skeletal malformations and variations.

The developmental LOAEL is 1.77 mg/kg/day (2.0 mg/kg/day) based on the increased fetal and litter incidence of hydroureter without hydronephrosis. The developmental NOAEL is 0.88 mg/kg/day (1.0 mg/kg/day).

This developmental toxicity study in the rat is classified as acceptable-guideline and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700) in the rat.

Comments: The original DER presented fetal incidence data for hydroureter (with hydronephrosis and without hydronephrosis separated). Litter incidence data were not provided. The reviewer notes that litter incidence of "hydroureter without hydronephrosis" is 0/23, 0/24, 0/25, and 5/23; the litter incidence of "hydroureter with hydronephrosis" is 3/23, 2/24, 2/24 and 2/23. The original DER concluded based on fetal incidence data, "the increased incidence of hydroureter without associated hydronephrosis is equivocal, but without further information it is being interpreted as indicating a slight fetotoxic effect at 2 mg/kg/day." The reviewer notes that the litter incidence of hydroureter without hydronephrosis was also slightly increased. A pilot rat developmental study (MRID 00154482) did not include gross necropsies, soft tissue or skeletal examination on fetuses. Hydroureter was not reported in the rabbit developmental study, or in the prenatal developmental toxicity (dietary) study in rats (MRID 45352301). No historical control data were presented.

In **another developmental toxicity study** (MRID 45352301), bifenthrin (95.3% ai; Lot/Batch #PL99-0108) was administered orally in the diet to 25 female Sprague-Dawley CD rats/group at dose levels of 0, 30, 60, 90, or 200 ppm (equivalent to 0, 2.5, 5.0, 7.4, and 16.3 mg/kg/day or 0, 2.4, 4.8, 7.1 or 15.5 mg/kg/day when adjusted for purity) on

gestation days (GD) 6 through 20. All dams were sacrificed on GD 20 and their fetuses were removed by cesarean and examined.

No animals died during the study. When compared to concurrent controls, no treatment-related changes were observed in gross pathology, the number of corpora lutea, number of implantations, number of live and dead fetuses, number of resorptions, fetal weights, sex ratios, or post-implantation losses.

At 200 ppm, clinical signs, indicative of neurotoxicity, were observed. These signs included tremors (22/25), observed from days 9-20; hypersensitivity to sound (5/25), observed from days 18-20; splayed hindlimbs (1/25), observed from days 15-20; and piloerection (1/25) observed at day 19. None of these findings was observed in any control animal. A negative trend ($p \leq 0.05$) in body-weight gains was observed during GDs 6-9, 15-18, and 18-20 with a decrease of 44, 17, and 14%, respectively, at 200 ppm relative to controls. In addition, a negative trend ($p \leq 0.001$) was observed in adjusted (for gravid uterine weight) body-weight gain with a 22% decrease at 200 ppm when compared to controls. Food consumption was decreased at 200 ppm at the beginning (GD 6-9) and end (GD 18-20) of treatment (↓11-12%, relative to controls). In addition, a negative trend ($p \leq 0.05$) was observed during GDs 6-9, 9-12, 18-20, and for the overall treatment interval (GD 6-20).

Dose-dependent ($p \leq 0.05$ for negative trend) decreases in food consumption were observed; however, the decreases that were noted at doses below 200 ppm did not result in decreased body-weight gains and were considered not to be toxicologically important.

The maternal LOAEL is 200 ppm (equivalent to 16.3 mg/kg/day or 15.5 mg/kg/day) based on clinical signs and decreased food consumption, body-weight gains, and adjusted (for gravid uterine weight) body-weight gains. The maternal NOAEL is 90 ppm (equivalent to 7.4 mg/kg/day or 7.1 mg/kg/day).

No treatment-related developmental findings were noted at any dose tested.

The developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 200 ppm.

3.2.3.2 Rabbit

Developmental Rabbit Study
In a developmental study (MRID 00145997), bifenthrin (88.35% ai) in corn oil was administered via gavage to pregnant female New Zealand White rabbits (20/dose) at dose levels of 0, 2.67, 4.0, or 8.0 mg/kg/day FMC 54800 technical (equivalent to 0, 2.36, 3.5, and 7.1 mg/kg/day) or with 3.0 g/kg/day 6-aminonicotinamide (positive control) in 2% carboxymethylcellulose via IP injection during days 7-19 of gestation. Maternal toxicity was characterized at 7.1 mg/kg/day (8.0 mg/kg/day) as tremors in 17/20 rabbits (observed during days 12-23) and twitching of the head and forelimb in 14/20 rabbits (observed during days 13-20). In addition, one rabbit in the 7.1 mg/kg/day group displayed clonic convulsions and loss of muscle control during days 17 and 18. At 3.5 mg/kg/day (4.0 mg/kg/day) head and forelimb twitching was noted in 4/20 rabbits (observed during days 8-16). There were no treatment-related deaths in the does; however, 10 rabbits died during the study and 9 of these deaths (including 3 vehicle control animals) were attributed to *Pasteurella multocida*. There were no apparent treatment-related differences in mean body-weight gains in the does or pregnancy rates; data excluded those with infection. There were no gross or microscopic findings attributable to exposure to the test material.

The maternal LOAEL is 3.5 mg/kg/day (4.0 mg/kg/day) based on the treatment-related incidence of head and forelimb twitching. The maternal NOAEL is 2.36 mg/kg/day (2.67 mg/kg/day). There was no developmental toxicity demonstrated at any dose level.

There were no treatment-related effects on the number of live fetuses, fetal weights, implantations, resorptions, external, visceral or skeletal malformations and variations. The positive control gave the appropriate responses of increased early resorptions, reduced number of live fetuses, increased external, visceral, and skeletal malformations and variations.

A developmental LOAEL was not observed. The developmental NOAEL is ≥7.1 mg/kg/day (8.0 mg/kg/day).

3.2.3.3 Developmental Neurotoxicity Study (Rat)

In a DNT study (MRID 46750501) Bifenthrin (94.8% ai, lot PL02-0477) was administered in the diet to 25 female Crl:CD®(SD) rats per dose at dose levels of 0, 50, 100 and 125 ppm (0, 3.6, 7.2 and 9.0 mg/kg/day, respectively, during gestation; 0, 8.3, 16.2 and 20.7 mg/kg/day, respectively, during lactation) from gestation day (GD) 6 through lactation day (LD) 21. Dietary concentrations were selected on the basis of a range-finding study (MRID 46750502). A FOB was performed on all dams on GDs 10 and 15 and on LDs 10 and 21. On post-natal day (PND) 4, litters were culled to yield four males and four females (as closely as possible). Offspring were allocated for detailed clinical observations (FOB) and assessment of motor activity, auditory startle

reflex habituation, learning and memory (water maze testing) and neuropathology at termination (PND 72). On PND 21, the whole brain was collected from 10 pups/sex/group for micropathologic examination and morphometric analysis. Pup physical development was evaluated by body-weight. The age of sexual maturation (vaginal opening in females and preputial separation in males) was assessed.

No dams died during the study. Maternal body-weight, body-weight gain and food consumption were unaffected by treatment. Tremors were observed during the daily examinations in 8/23 females at 100 ppm beginning on LD 14 and in 23/25 females in the 125 ppm group beginning on LD 4. In the 100 ppm group, the tremors were graded as slight and resolved in 4/8 females after one occurrence; slight tremors were observed in the remaining 4/8 females 3-7 times. In the 125 ppm group, the tremors were graded slight to moderate and continued on multiple occasions (2-18 consecutive days) during lactation. Piloerection was observed once or twice in 6/25 females at 125 ppm, primarily during LDs 14-17. During the FOB, the mean number of grooming counts was significantly increased in females at 100 and 125 ppm during gestation and lactation. At 125 ppm, slight piloerection was observed in 4/25 females on GD 15 and in 1/25 or 2/25 females on LDs 10 and 21. Clonic convulsions (limb tremors) and tremors were noted in 2/25 and 7/25 females, respectively, in the 125 ppm group on LD 10. On LD 21, the number of females with these findings was 10/25 and 13/25, respectively. Clonic convulsions (limb tremors) and tremors were noted in 2/23 and 3/23 females in the 100 ppm group, respectively, on LD 21. Reproductive performance was unaffected by treatment.

The maternal LOAEL for bifenthrin in rats was 100 ppm (7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation) based on clinical signs of neurotoxicity (tremors, clonic convulsions, and increased grooming counts). The maternal NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation).

The mean number of delivered pups per dam, percentage of liveborn and stillborn pups and sex ratio on the day of birth were not affected by treatment. There was no treatment-related effect on offspring body-weight or body-weight gain. The mean day for reaching sexual maturation (vaginal opening in females and balanopreputial separation in males) was not affected by treatment. Two of 20 females in the 125 ppm group had tremors during the detailed physical examinations on PND 28. During the FOB, an increase in the incidence of tremors and clonic convulsions (limb tremors) was observed in males at 125 ppm on PND 21. A significant increase in mean grooming counts was noted in females at 100 and 125 ppm on PND 21. No treatment-related effects on motor activity, acoustic startle response, or learning and memory testing were observed. Brain weight, length, and width and macroscopic findings were not affected by treatment. Historical control data were not provided for several microscopic findings and are therefore requested. In brain morphometry, a slight increase (3.5%) in the height of the hemisphere (Level 1) that was observed at 125 ppm was not considered toxicologically significant.

The offspring LOAEL for bifenthrin in rats is 100 ppm (7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation; maternal dose) based on clinical signs of neurotoxicity (increased grooming counts). The offspring NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation). Direct dosing to pups was not performed.

3.2.4 Reproductive Toxicity Study (Rat)

In a 2-generation study (MRID 00157225), liquified bifenthrin (88.35% ai) mixed with acetone was administered in the diet to TAC(SD)fBR rats (25/sex/dose) at dose levels of 0, 30, 60, or 100 ppm as FMC 54800 technical (approximately equivalent to 0, 1.5, 3.0 and 5.0 mg/kg/day). P-generation females at 100 ppm had lower mean body-weights (↓4%, $p<0.05$) at week 17 (after gestation and lactation), significantly lower body-weights during the first lactation (days 7 and 14) period; and lower body-weight gains during the second gestation and lactation periods (statistically significant only on lactation day 14, ↓5% body-weight and ↓34% for body-weight gain, $p<0.01$). There was no correlation between lower body-weight and frequency of tremors. Lower body-weights in females at 60 ppm (although not statistically significant) frequently paralleled body-weight depression at 100 ppm. There were no clinical signs or effects on body-weight at 30 ppm. There were no significant differences in mean body-weights between treated F1animals and controls. In the high-dose P generation females, there was a statistically significant increase in absolute and relative brain weights. Mean absolute ovary weights were slightly decreased (↓9%, $p<0.05$ or ↓12%, $p<0.01$) at 60 and 100 ppm, respectively, in the F1 parental generation; however, ovary-to-body-weight ratios were unaffected. In the 100 ppm group F1b female progeny, absolute adrenal and heart weights were statistically elevated compared to control values. Significantly elevated absolute ovary and ovary/brain weights were also observed in these animals. There were no treatment-related gross or microscopic findings in either adults or progeny. In either the P or F1 generations, there were no treatment-related effects on reproductive parameters (mating, male fertility, female fertility and gestation indices), and there were no treatment-related gross or microscopic findings in either sex.

The parental LOAEL is 100 ppm (5.0 mg/kg/day) based on the incidence of tremors and marginally lower body-weights in P and F1 generation females during gestation and lactation. The parental NOAEL is 60 ppm (3.0 mg/kg/day). A reproductive and offspring LOAEL was not observed. The reproductive and offspring NOAEL is 100 ppm (5.0 mg/kg/day).

Comments: The original DER identified the 60 ppm dose as a LOAEL based on decreased absolute ovarian weight; however, the DER also indicated that the decreased F1 absolute ovarian weight is “equivocal as it was only observed in F1 adult females and not in F1b or F2b weanlings),” and “when ovary-to-body-weight ratios for F1 females are examined, none of the FMC 54800 exposed groups are statistically different from

controls for this parameter." The reviewer agrees, and notes the lack of histopathology effects. The reviewer considers the 60 ppm dose level as a NOAEL.

A range-finding study summarized in the DER indicates that excessive fetotoxicity occurred at 10 mg/kg/day (all pups from 2 of the 4 litters at 10 mg/kg/day died within 14 days of birth) and body-weight gains were decreased during lactation at 2.5, 5, and 10 mg/kg/day.

3.2.5 Additional Information from Literature Sources

None.

3.2.6 Pre-and/or Post-natal Toxicity

The HIARC concluded that there is not a concern for pre- and/or post-natal toxicity resulting from exposure to bifenthrin.

3.2.6.1 Determination of Susceptibility

Based on the results in a developmental toxicity studies in rats and rabbits, there is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to bifenthrin. In the prenatal developmental (gavage) toxicity study in rats, a slight increase in the incidence of "hydroureter without hydronephrosis" was observed in fetuses at the highest dose tested (2 mg/kg/day); maternal toxicity (tremors) was also observed at this dose level, and the maternal and developmental NOAELs were equivalent at 1 mg/kg/day. This effect was not observed in the prenatal developmental (dietary) toxicity study in rats. In the prenatal developmental toxicity study in rabbits, there was no evidence of developmental toxicity at the highest dose tested.

Based on the results in a 2-generation reproduction study in rats, there was no quantitative or qualitative evidence of increased susceptibility of neonates (as compared to adults) to bifenthrin.

Based on the results of the DNT study in rats, there was no quantitative or qualitative evidence of increased susceptibility of neonates (as compared to adults) to bifenthrin. In this study the maternal and offspring toxicity NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation) based on clinical signs of neurotoxicity.

3.2.6.2 Degree-of-Concern Analysis

There are no concerns or residual uncertainties for pre- and/or post-natal toxicity following exposure to bifenthrin.

3.2.7 Recommendation for a DNT Study

A DNT study with bifenthrin is available.

3.2.8 FQPA Safety Factor (SF) for Infants and Children

The bifenthrin risk assessment team recommends that the 10X FQPA SF for increased susceptibility be reduced to 1X for all exposure scenarios. This recommendation is based on the following considerations:

- The toxicology database is complete.
- There are no residual uncertainties concerning pre- and postnatal toxicity.

- The dietary food exposure assessment utilizes field trial data and 100% crop treated (CT) information for all proposed commodities. Anticipated residue values and percent crop treated were used for some commodities. By using these assumptions, the acute and chronic exposures/risks will not be underestimated.
- The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

The FQPA Safety Factor recommended by the bifenthrin review team **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

Based upon the above-described data, no FQPA safety factor is needed (*i.e.* 1X) since there are no residual uncertainties for pre and/or post-natal toxicity.

3.3 Hazard Identification and Toxicity Endpoint Selection

The strengths and weaknesses of the bifenthrin toxicology database were considered during the process of toxicity endpoint and dose selection. The selected toxicity endpoints are summarized in Table 3.

Table 3.3. Summary of Toxicological Doses and Endpoints for Bifenthrin.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF[1] and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary-general population, including infants and children	NOAEL = 32.8 mg/kg UF = 100 Acute RfD = 0.33 mg/kg/day	FQPA SF = 1X aPAD = acute RfD / FQPA SF = 0.33 mg/kg/day	Acute neurotoxicity study in rats. LOAEL = 70.3 mg/kg/day based on observations of mortality (females only), clinical and FOB findings and differences in motor activity.
Chronic Dietary-general population, including infants and children	NOAEL = 1.3 mg/kg/day UF = 100 Chronic RfD = 0.013 mg/kg/day	FQPA SF = 1X cPAD = cRfD / FQPA SF = 0.013 mg/kg/day	1-year oral toxicity in dogs. LOAEL = 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Short-Term (1-30 days) Incidental Oral	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100	90-day oral toxicity study in dogs. LOAEL = 4.42 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Intermediate-Term (1-6 months) Incidental Oral	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100	90-day oral toxicity study in dogs. LOAEL = 4.42 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Short-Term (1-30 days) Dermal	Dermal NOAEL = 47 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	21-day dermal study in rats. LOAEL = 93 mg/kg/day based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex).
Intermediate-Term (1-6 months) Dermal	Dermal NOAEL = 47 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	21-day dermal study in rats. LOAEL = 93 mg/kg/day based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex).

Long-Term (>6 months) Dermal	Dermal NOAEL = 47 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	21-day dermal study in rats. LOAEL = 93 mg/kg/day based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex).
Short-Term (1-30 days) Inhalation	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 Occupational MOE = 100	1-year oral toxicity in dogs. LOAEL = 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Intermediate-Term (1-6 months) Inhalation	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 Occupational MOE = 100	1-year oral toxicity in dogs. LOAEL = 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Long-Term (>6 months) Inhalation	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 Occupational MOE = 100	1-year oral toxicity in dogs. LOAEL = 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Cancer (oral, dermal, inhalation)	**Classification: Category C** (possible human carcinogen). No Q_1* has been derived. RfD approach recommended for cancer assessment.		

UF = uncertainty factor, FQPA SF = Special FQPA Safety Factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose (a = acute, c = chronic), PAD = population adjusted dose, MOE = margin of exposure, LOC = level of concern, N/A = Not Applicable.
[1]Refer to Section 3.4

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

HIARC determined that no appropriate acute dietary endpoint was available to quantify risk to females 13-50 years of age from a single-dose administration of bifenthrin.

A developmental toxicity study in rats (gavage) with a developmental NOAEL of 0.88 mg/kg/day (1.0 mg/kg/day) based on the increased fetal and litter incidence of hydroureter without hydronephrosis seen at the LOAEL of 1.77 mg/kg/day (2.0 mg/kg/day) was considered as an endpoint for aRfD for females age 13-49. However, this evidence was considered as equivocal since the litter incidence of "hydroureter without hydronephrosis" is 0/23, 0/24, 0/25, and 5/23; the litter incidence of "hydroureter with hydronephrosis" is 3/23, 2/24, 2/24 and 2/23. In addition, this effect was not observed in a dietary developmental toxicity study in rats using the same strain of rats. Therefore, HIARC concluded that the endpoint (hydroureter/hydronephrosis) is not appropriate for this risk assessment.

3.3.2 Acute Reference Dose (aRfD) - General Population

Acute dietary endpoints were available to quantify risk to the general population, including infants and children. For this scenario, an aRFD of 0.33 mg/kg/day was determined on the basis of an acute neurotoxicity study in rats and the application of an UF of 100 (10x for inter-species extrapolation and 10x for intra-species variation). The NOAEL in this study was 32.8 mg/kg/day and the LOAEL was 70.3 mg/kg/day based on mortality (females), clinical and FOB findings and differences in motor activity. Although a lower NOAEL for an effect (*i.e.*, tremors in dams) associated with a single dose exposure was observed in a developmental gavage study, the vehicle (corn oil) used in this study enhanced the toxicity of bifenthrin. There is evidence that, in the case for bifenthrin, corn oil can enhance its toxicity. This evidence is based on the results of comparative studies of the acute oral LD50 of bifenthrin following oral gavage as either a corn oil vehicle or as an undiluted technical material to rats. These comparative studies demonstrate increased lethality from bifenthrin exposure in a corn oil vehicle. In the acute neurotoxicity study in rats, bifenthrin was administered undiluted by gavage, making this study more suitable than the developmental gavage study (with corn oil as vehicle) for risk assessment purposes. Clinical signs of neurotoxicity (tremors, clonic convulsions, and increased grooming counts) were seen in maternal animals during gestation and lactation and increased grooming counts in offspring during lactation in the DNT study. The DNT NOAEL for maternal and offspring toxicity was NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation). Since the clinical signs were seen during gestations, it was not considered as a single dose effect. Therefore, the acute neurotoxicity study was selected for the acute reference dose, and the aRfD is 0.33 mg/kg/day.

3.3.3 Chronic Reference Dose (cRfD)

A cRfD of 0.013 mg/kg/day was determined on the basis of the one-year oral study in dogs and the application of an UF of 100 (10x for inter-species extrapolation and 10x for intra-species variation). The NOAEL in this study was 1.3 mg/kg/day and the LOAEL was 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.

3.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

A NOAEL of 2.21 mg/kg/day was selected from the 90-day oral study in dogs, and used for short- and intermediate-term incidental oral and inhalation risk assessments. This NOAEL was based on observations of increased incidence of tremors in males and females at the LOAEL of 4.42 mg/kg/day. The HIARC concluded that the selected dose/endpoint is appropriate for the population and durations of concern.

3.3.5 Dermal Absorption

Several dermal-absorption studies on bifenthrin were available; each study was considered acceptable for regulatory purposes when taken in conjunction with the other studies. The HIARC recommended a dermal-absorption rate of 25% based on the weight-of-the-evidence available for structurally related pyrethroids. However, since a dermal toxicity study was used for the assessment of short- and intermediate-term dermal risk, the dermal-absorption factor was not used.

3.3.6 Dermal Exposure (Short- and Intermediate-Term)

A NOAEL of 47 mg/kg/day was selected from the 21-day dermal study in rats. The LOAEL of 93 mg/kg/day was based on observations of clinical signs (staggered gait and exaggerated hindlimb flexion). The HIARC determined that the dermal toxicity study is appropriate for short-, intermediate- and long-term dermal exposures and durations because, besides route specificity, the subchronic and chronic oral toxicity studies in dogs and rats demonstrate neurotoxicity of similar magnitude. Since a dermal toxicity study is selected for dermal risk assessment, a dermal-absorption factor is not required.

3.3.7 Inhalation Exposure (Short- and Intermediate-Term)

A NOAEL of 2.21 mg/kg/day was selected from the 90-day oral study in dogs, and used for short- and intermediate-term inhalation risk assessments. This NOAEL was based on observations of increased incidence of tremors in males and females at the LOAEL of 4.42 mg/kg/day. The HIARC concluded that the selected dose/endpoint is appropriate for the population and durations of concern. An inhalation-absorption factor of 100% (default value assuming equivalent inhalation and oral absorption) was used for route-to-route extrapolation.

The results of the one-year oral dog study were selected for the long-term inhalation risk assessment. The NOAEL in this study was 1.3 mg/kg/day and the LOAEL was 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes. An inhalation absorption factor of 100% (default value assuming equivalent inhalation and oral absorption) was used for route-to-route extrapolation.

3.3.8 Levels of Concern for Margin of Exposure

The target MOEs for occupational and residential exposure risk assessments are as follows:

Route	Duration		
	Short-Term (1-30 days)	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	100[a]	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	100
Dermal	100	100	100
Inhalation	100	100	100

[a] Based on the conventional UF of 100X (10X for inter-species extrapolation and 10X for intra-species variation).

3.3.9 Recommendation for Aggregate Exposure Risk Assessments

The toxicity endpoints selected for these routes of exposure may be aggregated as follows: for short-, intermediate- and long-term aggregate exposure risk assessments, the oral, dermal and inhalation (oral equivalent) routes can be combined because of the common toxicity endpoints (clinical signs of neurotoxicity) via these routes.

3.3.10 Classification of Carcinogenic Potential

The CPRC (1992) has characterized bifenthrin as Category C (possible human carcinogen) and recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human cancer risk. This decision was based in part on the statistically significant increased trend for hemangiopericytomas in the urinary bladders of Swiss Webster mice. The incidence of these lesions was double at the highest dose tested (HDT; 600 ppm) as compared to controls. The male mice also had significant dose-related trends with respect to hepatocellular carcinomas and combined hepatocellular adenomas and carcinomas, and increased incidences of bronchioalveolar adenomas and adenocarcinomas of the lung in females at 50, 200 and 600 ppm (but not 500 ppm) relative to their controls. No compound related tumors were noted in rats. The mutagenicity evidence presents low concern for bifenthrin.

3.4 Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (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 the Federal Insecticide, Fungicide, and Rodenticide Act (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). Bifenthrin database did not indicate any endocrine mediated effects. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, bifenthrin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Dietary Exposure/Risk Characterization

4.1 Pesticide Metabolism and Environmental Degradation

4.1.1 Metabolism in Primary Crops and Livestock

4.1.1.1 Metabolism in Primary Crops

References:

- Bifenthrin TRED, S. Levy, 21-AUG-2002; DP# 283808
- Bifenthrin: Human-health Risk Assessment for Proposed Uses on Cilantro, Leafy Brassica Greens (subgroup 5b), Tuberous and Corm Vegetables (Subgroup 1c), Dried Shelled Peas and Beans (except Soybean) (Subgroup 6c) and Tobacco. M. Rust-Clock, et. al. 4/6/2006
- 45794202.der
- Bifenthrin; PP#6E7125, PP#6E7126, PP#6E7127, PP#6E7128; Section 3 Registration for Application of Bifenthrin to Mayhaw, Root Vegetables, (Except Sugar Beets, Crop Subgroup 1B), Peanut, Pistachio, Soybean, and Fruiting Vegetables (Crop Group 8). Summary of Residue Chemistry Data. Pending, W. Wassell, DP#: 334164
- Memo, M. Flood, 07/30/93, PP#7F3456

The nature of bifenthrin residues in plants is adequately understood based on the available metabolism studies with corn, cotton, and apple. HED previously determined that for purposes of tolerance expression and risk assessment, the residue of concern in cotton and apple commodities is bifenthrin *per se* (Memoranda, M. Flood, 12/24/87 and N. Dodd, 7/02/87). After re-examining the cotton and apple metabolism data and additional corn metabolism data, the HED Metabolism Committee (Memo, M. Flood, 7/23/93) reaffirmed that the residue of concern in plant commodities is bifenthrin *per se*.

In conjunction with the previous risk assessment for use on tuberous and corm vegetables, IR-4 submitted a metabolism study on potatoes reflecting both soil and foliar

applications of [^{14}C] bifenthrin. The potato study is adequate and the results from the metabolism study support HED's previous determination that the residue of concern is bifenthrin *per se*. The bifenthrin review team agrees with these decisions.

4.1.1.2 Metabolism in Livestock

Adequate studies are available depicting the metabolism of [^{14}C]bifenthrin in ruminants and poultry. The nature of the residue in livestock is adequately understood based on goat and hen metabolism studies. The HED Metabolism Committee determined that for purposes of tolerance expression and risk assessment, the residue of concern in livestock is bifenthrin *per se* (Memo, M. Flood, 7/23/93). The bifenthrin review team agrees with this decision.

4.1.2 Metabolism in Rotational Crops

Adequate confined and field rotational crop studies are available. Based on the confined study, HED has concluded that the residue of concern in rotational crops is the parent compound only. The bifenthrin review team agrees with this decision.

4.1.3 Analytical Methodology

Adequate gas chromatography (GC)/electron-capture detection (ECD) methods are available for enforcing tolerances of bifenthrin in plant and livestock commodities. The available methods for plant commodities generally involve extraction of the sample with acetone, partitioning with hexane, purification using a Florisil column, and analysis of residues by GC/ECD. The limit of quantitation (LOQ) for these methods is 0.05 ppm. Samples from the current field trials and the potato processing study were analyzed using methods that are modifications to one of the current enforcement methods (P-2550 M), with variations in extraction solvents and detection methods. Residues of bifenthrin in/on mustard greens and cilantro (leaves and seeds) were determined using a GC/ECD method (FMC Report P-2132). For this method, residues are extracted with hexane, concentrated, and cleaned up using a Florisil column, then analyzed by GC/ECD. Residues in/on potato fractions and dried beans and peas were determined using a GC/mass-selective detection (MSD) method (FMC Report P-3426). For this method, residues are extracted with acetone, concentrated, and purified by silica-gel solid-phase extraction (SPE). The residues are then analyzed by GC/MSD, using the m/z 181 ion for quantitation. Residues in/on green tobacco were determined using a related GC/MSD method (FMC Report P-3457). For this method, residues are extracted with acetone/water, partitioned into hexane, and cleaned up with a SPE column, and analyzed by GC/MSD. For each of the above methods, the LOQ for bifenthrin is 0.05 ppm, and the reported limit of detection (LOD) is 0.01 ppm. Each of these methods was adequately validated in conjunction with analysis of samples from the field trials or processing study.

4.1.4 Environmental Degradation

References:

- Tier I Estimated Environmental Concentrations of Bifenthrin for the Use in the Human-Health Risk Assessment. 02/07/2006. J. Melendez
- Memo, 6/21/2002, S. Knizer, TXR# 0050887

The environmental fate database for bifenthrin is complete enough to characterize drinking water exposure. The submitted data indicate that bifenthrin is relatively persistent under both laboratory and field conditions. Bifenthrin is relatively immobile in four soils tested. Due to its low mobility, bifenthrin is not likely to reach subsurface soil environments (lower microbial activity) or ground waters. Various terrestrial field dissipation studies confirm that bifenthrin remains mostly in the upper soil level. Due to its low solubility and high level of binding it appears that bifenthrin would remain bound to the soils during run-off events and it may reach surface waters if the run-off event is accompanied by erosion.

The HED Metabolism Assessment Review Committee (MARC) concluded that the parent compound, bifenthrin *per se*, should be the residue of concern for drinking water risk assessment based on its persistence and the absence of major degradates in laboratory studies (Memo, 6/21/2002, S. Knizer, TXR# 0050887). The bifenthrin review team agrees with this decision.

4.1.5 Food Residue Profile

The field trials with bifenthrin on mayhaw, radish, garden beet, carrot, peanut, and soybeans are adequate. An adequate number of trials were conducted reflecting the proposed use patterns in the appropriate geographic regions, and the appropriate commodities were collected at the proposed pre-harvest intervals (PHIs). Samples were analyzed using adequate analytical methods, and the sample storage intervals are supported by the available storage stability data. Tolerance levels for residues in/on mayhaw, root vegetables (subgroup 1B), radish tops, and garden beets were determined using the NAFTA MRL/Tolerance Harmonization Spreadsheet.

Although tolerances are proposed for bifenthrin *per se* in/on pistachios at 0.05 ppm and the fruiting vegetables crop group (group 14) at 0.5 ppm, residue data for these crops were not included in the current submissions. A tolerance is established for residues of bifenthrin *per se* in/on the tree nut crop group (group 14) at 0.05 ppm. For pistachios, HED policy is to translate data and tolerances from almonds to pistachios (Reviewer's Guide & Summary of HED ChemSAC Approvals for Amending Crop Group/Subgroups [40 CFR §180.41] & Commodity Definitions [40 CFR 180.1(h)], 6/14/2006, B Schneider). **Thus, a tolerance for residues of bifenthrin *per se* should be established in/on pistachios at 0.05 ppm.** For fruiting vegetables, tolerances are established for

residues of bifenthrin *per se* at 0.05 ppm in/on eggplant, at 0.15 ppm in/on tomato, and at 0.5 ppm in/on bell and non-bell pepper. HED has determined that a fruiting vegetables crop group tolerance for residues of bifenthrin *per se* is not appropriate for the following reasons: maximum residues in eggplant are more than a factor of five lower than the tolerance for tomatoes and the use pattern for tomato and tomatillo are different from the other members of the crop group in terms of the PHI, maximum seasonal use rate, number of applications, and interval between applications. **However, HED could recommend for tolerances for residues in/on groundcherry and pepino at 0.50 ppm.** A revised Section F would be required. **As 40 CFR §180.1 indicates that a tolerance for residues in/on tomato applies to tomatillo, a tolerance for residues in/on tomatillo is not required.**

Mayhaw: Residues of bifenthrin ranged from 0.24 to 0.78 ppm in/on mayhaw harvested 28 to 29 days following two broadcast foliar applications of Capture 2EC for a total rate of approximately 0.2 pounds active ingredient per acre (lb ai/A). **HED concludes a tolerance for residues of bifenthrin *per se* in/on mayhaw at 1.4 ppm is appropriate.**

Radish: Residues of bifenthrin ranged from <0.05 to 0.07 ppm in radish roots and ranged from 0.56 to 2.26 ppm in radish tops harvested 6 to 8 days following an in-furrow application of Capture 1.15G at planting and two broadcast foliar applications of Capture 2EC for a total foliar rate of approximately 0.20 lb ai/A. **Based upon the submitted data, HED concludes a tolerance for residues of bifenthrin *per se* in/on radish tops at 4.5 ppm is appropriate. For radish roots, see the discussion below concerning the tolerances for residues in/on subgroup 1B.**

Garden Beet: Residues of bifenthrin ranged from <0.05 ppm to 0.28 ppm in garden beet roots and ranged from 4.8 ppm to 12.2 ppm in garden beet tops harvested 1 day following four broadcast foliar applications of Capture 2EC for a total rate of approximately 0.40 lb ai/A. **Based upon the submitted data, HED concludes tolerances for residues of bifenthrin *per se* in/on garden beet tops and roots at 15 ppm and 0.45 ppm, respectively, are appropriate.**

Carrot: Residues of bifenthrin were less than the method LOQ (<0.05 ppm) in/on carrots harvested 7, 14, and 20 to 22 days following a three broadcast foliar applications of Capture 2EC for a total rate of 0.49 to 0.51 lb ai/A.

Carrot and radish are the representative commodities of the root vegetables, except sugar beet, crop subgroup (1B). The petitioner has proposed tolerances for residues of bifenthrin in/on root vegetables, except sugar beet, crop subgroup (1B) at 0.07 ppm. Residues of bifenthrin ranged from <0.05 to 0.07 ppm in radish roots with 4 of 6 trials showing residues levels less than the LOQ (<0.05 ppm). Residues of bifenthrin were less than the LOQ (<0.05 ppm) in/on carrots from all of the submitted trials (10 trials). **Based upon the submitted data, HED concludes a tolerance for residues of bifenthrin *per***

***se* in/on root vegetables, except sugar beet and garden beet, crop subgroup (1B) at 0.10 ppm is appropriate.**

Peanut: For the treated peanut nutmeat samples, residues of bifenthrin were not detected (<LOD, <0.01 ppm) in all samples except one which had apparent residue levels estimated at 0.01 ppm. Apparent residues of bifenthrin were not detected (<LOD, <0.01 ppm) in/on 9 samples of untreated peanut nutmeats. **HED concludes a tolerance for residues of bifenthrin *per se* in/on peanut at 0.05 ppm is appropriate.**

Soybean: Residues of bifenthrin ranged from <0.05 to 0.18 ppm in soybean seed harvested 17 to 21 days following the last of three broadcast foliar applications of Capture 2EC for a total foliar rate of approximately 0.30 lb ai/A. In 12 of 15 trials, residues of bifenthrin were less than the LOQ (<0.05 ppm). **HED concludes a tolerance for residues of bifenthrin *per se* in/on soybean at 0.20 ppm is appropriate.**

Processed Food and Feed:

Peanut: The petitioner has submitted processing data for the use of bifenthrin on peanuts and subsequent processing of the peanuts to peanut meal and refined oil. The total foliar application rate was 0.9 lb ai/A per season (9.0x exaggerated rate). The harvested peanuts were dried, shelled, and processed into meal and refined oil using simulated commercial practices.

The results show that residues of bifenthrin were below the method LOQs (<0.05 ppm) but above the method limit of detection (LOD, 0.01 ppm) in/on peanut nutmeat treated at a seasonal rate of 0.9 lb ai/A. Apparent residue levels of bifenthrin were estimated at 0.02 ppm in/on treated peanut nutmeats. Following processing of the treated nutmeat, the residues were not detected (<0.01 ppm) in peanut meal and were below the method LOQ but above the method LOD in/on all treated peanut refined oil samples except one which had bifenthrin residues at the LOQ (0.05 ppm). Apparent residue levels of bifenthrin in peanut refined oil were estimated at 0.04 ppm. As residues decreased when peanut nutmeats are processed to meal, a processing factor for this process was not calculated and tolerances for residues in/on peanut meal are not required. The processing factors for the processing of peanut nutmeats to refined oil were estimated to be 2.2x. The highest-average field trial (HAFT) value for residues of bifenthrin in/on peanut nutmeats is 0.01 ppm (residues were non-detectable). The processing factor for nutmeats to oil multiplied by the HAFT is 0.022ppm (2.2 x 0.01 ppm). As this value is below the LOQ (0.05 ppm) and recommended tolerance level for bifenthrin in/on peanuts, **a tolerance for residues in/on peanut oil is not required.**

Soybean: The petitioner has submitted a processing study with bifenthrin on soybeans. In one trial conducted in Iowa during the 2001 growing season, soybean seed was harvested 18 days following the last of three foliar broadcast applications of Capture 2EC for a total rate of 0.7 lb ai/A (7.0x). Soybean seed samples were processed into meal, hulls, and refined oil. Additionally, aspirated grain fractions (AFGs) were generated.

The average total residues of bifenthrin were the LOQ of 0.05 ppm (0.025 ppm) in/on the raw agricultural commodity (RAC) soybean seed treated at a total rate of 0.7 lb ai/A. Following processing of the treated RAC, total residues did not concentrate in meal, but concentrated slightly in hulls (2.6x) and refined oil (1.6x). Additionally, residues significantly concentrated in AFGs (9.51 ppm, 380x). The observed processing factors are less than the theoretical concentration factors for soybean commodities.

The AGF samples were collected and classified via sieve. After classification, the fractions were recombined to produce the AGF samples. The study report indicates that the AFGs were recombined as per the specifications of the Study Director; however, the report does not indicate the final makeup of the AGF samples in terms of percent composition based upon particle size. This information should be submitted prior to granting of a permanent registration for soybeans. Once these data are submitted, HED will make a determination as to whether additional data or an altered tolerance level are needed.

The HAFT value for residues of bifenthrin in/on soybean is 0.18 ppm. The processing factors for soybeans to hulls, meal, refined oil, and AGF is as follows:

Soybean hulls: 0.18 ppm x 2.6 = 0.47 ppm.
Soybean meal: no concentration of residues.
Soybean refined oil: 0.18 ppm x 1.6 = 0.29 ppm
Soybean aspirated grain fractions: 0.18 ppm x 380 = 68.4 ppm

HED concludes tolerances for residues of bifenthrin in/on soybean hulls at 0.50 ppm, soybean refined oil at 0.30 ppm and aspirated grain fractions at 70 ppm are appropriate.

4.1.5.1 Tolerance Summary

The tolerances proposed by the registrants in the current vegetable petitions are listed below in Table 5.1.5.1, along with HED's recommended tolerance levels. Tolerance levels for residues in/on mayhaw, root vegetables (subgroup 1B), radish tops, garden beets were determined using the NAFTA MRL/Tolerance Harmonization Spreadsheet. Tolerances for residues in other commodities were determined by rounding up the appropriate field trial residue value.

Table 5.1.5.1. Tolerance Summary for Bifenthrin.			
Proposed		Recommended	
Commodity Definition	Tolerance (ppm)	Commodity Definition	Tolerance (ppm)
Mayhaw	1.4	Same	Same
Vegetable, root, except sugar beet and garden beet, subgroup 1B	0.07	Same	**0.10**
beet, garden, root	0.45	Same	Same
beet, garden, top	15	Same	Same
Radish, top	4.5	Same	Same
Soybean	0.2	Same	Same
Soybean, hulls	0.7	Same	**0.50**
Soybean, refined oil	0.4	Same	**0.30**
Vegetable, fruiting, group 8	0.5	**Delete request for fruiting vegetables**	
		Groundcherry	**0.5**
		Pepino	**0.5**
Peanut	0.05	Same	Same
Pistachio	0.05	Same	Same
None	None	**Aspirated Grain Fractions**	**70**

4.1.6 International Residue Limits

The Codex Alimentarius Commission has established maximum residue limits (MRLs) for residues of bifenthrin in/on various commodities. Codex MRLs are expressed in terms of bifenthrin *per se*, as are U.S. tolerances. There are no equivalent Canadian or Mexican MRLs for the tolerances being requested in the current petition.

4.1.7 Drinking Water Residue Profile

Residues of Concern in Drinking Water
The HED MARC concluded that the parent compound, bifenthrin *per se*, should be the residue of concern for drinking water risk assessment based on its persistence and the absence of major degradates in laboratory studies (HED Doc. No. 0050887).

Drinking Water Estimates
The EDWCs for bifenthrin were calculated based on a maximum application rate of 0.5 lb ai/A/season to lettuce. The acute drinking water concentration in surface water is 0.0140 ppb of bifenthrin, based on aerial applications to lettuce. The cancer/chronic drinking water concentration is 0.0140 ppb (based on applications of lettuce, highest application rate). The SCI-GROW generated EDWC is 0.003 ppb of bifenthrin, which is recommended for use, both for acute and chronic exposures. Because of the very low

solubility of bifenthrin, the EDWCs did not exceed 0.0140 ppb (the solubility of bifenthrin).

Table 4.1.7. Tier 1 Estimated Drinking Water Concentrations for Bifenthrin

DRINKING WATER SOURCE (MODEL USED)	USE (rate modeled)	MAXIMUM ESTIMATED DRINKING WATER CONCENTRATION (EDWC) (ppb)	
Groundwater (SCI-GROW)	Lettuce (0.5 lb. ai/A/season)	Acute and Chronic	0.00300
Surface water (FIRST)	Lettuce (0.5 lb. ai/A/season)	Acute	0.0140
	Lettuce (0.5 lb. ai/A/season)	Chronic	0.0140

4.2 Dietary Exposure and Risk

Acute and chronic dietary exposure and risk assessments were conducted using the DEEM-FCID™, Version 2.03, which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed as part of a registration action; (1) to support a Section 3 Registration on root vegetables (except sugar beets, Crop Group 1B), peanuts, pistachio, soybean, and fruiting vegetables (Crop Group 8); (2) to include drinking water estimates reflecting the new uses; and (3) to support a new evaluation of the acute and chronic toxicological endpoints.

4.2.1 Acute Dietary Exposure and Risk

A Tier 3, acute probabilistic dietary exposure and risk assessment was conducted for all supported (and pending) food uses and drinking water. AR were developed based on the latest U.S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data 1998-2005, Food and Drug Administration (FDA) data, or field trial data for bifenthrin. Anticipated residues were further refined using the latest percent crop treated (%CT) data and processing factors where appropriate.

EFED calculated the ground and surface drinking water Tier 1 EDWCs for bifenthrin new uses using the screening concentration in ground water (SCI-GROW) and FQPA Index Reservoir Screening Tool (FIRST) models. It was found that lettuce is still the use with the major exposure and the highest PCA, and, therefore, the drinking water assessment results do not change from the previous ones. The EDWCs for bifenthrin were calculated based on a maximum application rate of 0.5 lb ai/A/season and the EDWCs in ground water were estimated as 0.003 ppb and 0.014 ppb in surface water.

The acute dietary exposure estimates for food and drinking water are below HED's level of concern (<100% aPAD) at the 99.9th percentile of exposure. Bifenthrin dietary exposure at the 99.9th percentile for food and drinking water is 10% of the aPAD for the

U.S. population and 25% of the aPAD for all infants(<1 year old), the most highly exposed population subgroup.

Table 4.2.1. Results of Bifenthrin Acute Dietary (Food + Drinking Water) Exposure Analysis Using DEEM FCID.

Population Subgroup	aPAD (mg/kg/day)	99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.328	0.033389	10
All Infants (< 1 year old)	**0.328**	**0.083293**	**25**
Children 1-2 years old	0.328	0.058377	18
Children 3-5 years old	0.328	0.051553	16
Children 6-12 years old	0.328	0.043915	13
Youth 13-19 years old	0.328	0.026013	8
Adults 20-49 years old	0.328	0.018021	5
Adults 50+ years old	0.328	0.014262	4
Females 13-49 years old	0.328	0.017374	5

4.2.2 Chronic Dietary Exposure and Risk

A refined chronic dietary exposure assessment was also conducted for the supported food uses of bifenthrin and drinking water using single point estimates of anticipated bifenthrin residues for food and drinking water. The EDWC of 0.014 ppb, based on application to lettuce at the highest application rate, was also used for the chronic dietary assessment.

The chronic dietary exposure estimates for food and drinking water are below HED's level of concern (<100% cPAD) for the U.S. population and all population subgroups. Bifenthrin dietary exposure for food and drinking water is 20% of the cPAD for the U.S. population and 53% of the cPAD for children 3-5 years old, the most highly exposed population subgroup.

Table 4.2.2. Results of Chronic Dietary (Food + Drinking Water) Exposure and Risk for Bifenthrin.		
Population Subgroup	**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD**
General U.S. Population	0.002620	20
All Infants (< 1 year old)	0.002748	21
Children 1-2 years old	0.006366	49
Children 3-5 years old	**0.006912**	**53**
Children 6-12 years old	0.005109	39
Youth 13-19 years old	0.002621	20
Adults 20-49 years old	0.001882	15
Adults 50+ years old	0.001650	13
Females 13-49 years old	0.001914	15

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

- ***Bifenthrin: REVISED Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Eligibility Decision (TRED) Document.*** **S. Weiss. D286358. 10/25/2002.**

Bifenthrin products are available to homeowners for indoor and outdoor application to residential premises. Adults and children may be potentially exposed to bifenthrin residues resulting from application.

Potential exposure and risk to residents (or "homeowners") have been assessed previously by HED. Information for this section was adapted from previous residential assessment for bifenthrin performed in 2002 (see reference above). Since completion of the last residential assessment, no product cancellations have occurred that would alter the conclusions. A summary of the exposure and risk resulting from residential uses of bifenthrin is provided below. These exposure estimates were used in the aggregate risk assessment which appears in Section 7.0 of this document.

5.1 Residential Handler Exposure

End-use products containing bifenthrin are formulated as ready-to-use-sprays, emulsified concentrates, wettable powders, granulars, pelletized tablets, and pressurized liquids.

The current maximum application rates of granulars and liquids by lawn care operators (LCOs) are 0.4 and 0.3 lb ai/acre, respectively. For liquid and granular formulations applied by homeowners, the maximum rate is 0.2 lb ai/acre. In a letter to the Agency dated September 16, 2002, FMC agreed to lower the maximum rate for all turf uses to 0.2 lb ai/acre. Bifenthrin products may be applied by pest control operators (PCOs) and homeowners in and around homes as a spray in concentrations of up to 0.06%. The majority of residential labels do not specify frequency of application.

On October 25, 2002, HED performed a residential exposure and risk assessment for the use of bifenthrin (see reference above). A summary of the uses and the results of the assessment are summarized below. For more details and for the results of all exposure scenarios, please see the original residential exposure assessment.

Short- and intermediate-term exposures may occur for residents applying bifenthrin products. Chronic exposures are not anticipated for residential handlers. The exposure and risk for residential handlers were assessed using the revised draft SOPs for Residential Exposure Assessment, and includes surrogate data from the Pesticide Handlers Exposure Database (PHED) Outdoor Residential Exposure Task Force (ORETF). Since PHED and ORETF do not include data for ready-to-use spray bottle application, data from a proprietary study were used to estimate exposure (MRID 447393-01).

The major exposure scenarios for non-occupational (residential) handler exposures are as follows:

* Mixing/loading/applying Liquids for Low-Pressure Handwand Application
* Mixing/loading/applying Liquids for Hose-end Sprayer Application
* Mixing/loading/applying Liquids for Backpack Sprayer Application
* Paintbrush Application
* Loading/applying Granulars for Belly-Grinder Application
* Loading/applying Granulars for Push-type Spreader Application
* Applying Granulars with Bare Hands
* RTU Spray Bottle Application

The most likely residential handler exposure scenario resulting in the highest exposure and risk is for loading/applying granular formulation by belly-grinder application. The short- and intermediate-term MOEs are 300 for dermal and 25,000 for inhalation, resulting in a combined MOE of 300. The exposure for this use is not of concern to HED.

5.2 Residential Post-application Exposure

Adults and children may be potentially exposed to bifenthrin residues after application of bifenthrin products in residential settings. Short- and intermediate-term post-application dermal exposures for adults, and short- and intermediate-term post-application dermal and incidental oral exposures for children are anticipated. Long-term exposure is not expected. Risk estimates were generated for potential contact with lawn, soil, and treated indoor surfaces using HED's Draft SOPs for Residential Exposure Assessment, and for the lawn scenarios, dissipation data from a chemical specific TTR study. Indoor surface residues in homes were based on crack and crevice data collected for bifenthrin and malathion. These estimates are considered conservative screening level estimates, but appropriate, since the study data were adjusted to reflect maximum application rates. Only the scenarios that result in the highest exposure are summarized in Table 5.2.

Table 5.2. Summary of Residential Post-Application Risk for Bifenthrin.

Exposure Scenario	Population	Route of Exposure	Short-Term MOE	Intermediate-Term MOE
Indoor: High-Contact Activity	Adults	Dermal	3100	3100
	Toddlers	Derma Orall	1800 2600	1800 5500
Outdoor: High-Contact Activity on Turfgrass	Adults	Dermal	2300	4500
	Toddler	Oral and Dermal	740 Oral 1400 Dermal	1600 Oral 2700 Dermal

5.3 Other (Spray Drift)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for bifenthrin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

6.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from dietary and residential sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Short-term aggregate risk assessment is required for bifenthrin due to the potential for residential exposure. The common toxicological effect observed across the oral and dermal routes of exposure is clinical signs of neurotoxicity. An aggregate MOE was calculated by taking the inverse of the sum of inverse MOEs for dietary and non-dietary (incidental oral and dermal) exposure pathways.

6.1 Acute Aggregate Risk

No acute residential/recreational exposures are expected. Since the dietary assessment included food and water, the exposures in Table 5.2.1 represent aggregate exposures. The acute aggregate risk levels are not of concern to HED.

6.2 Short- and Intermediate-term Aggregate Risk

Because there is the potential for short- and intermediate-term, non-dietary exposure of children and adults to bifenthrin as a residential treatment (indoors and outdoors), it is appropriate to aggregate these exposures with dietary (food and water) exposure. Adults can be exposed through the residential application of bifenthrin via dermal and inhalation routes and through post-application exposure via the dermal route (treated turf). Children might be exposed following application in residential settings via dermal and oral routes. HED believes that if a toddler were to be exposed to bifenthrin granules, it would most likely be episodic, that is, a one-time occurrence and not likely to be repeated. Therefore, this episodic scenario was not aggregated with dietary exposure.

Residential exposure and risk have been summarized based on HED residential risk assessments for the existing uses of bifenthrin. Those scenarios resulting in the highest exposure and risk for adults and children have been summarized in Table 6.2.1. These exposures were used to calculated short- and intermediate-term aggregate risk by combining residential exposure with that from dietary sources.

Table 6.2.1. Summary of Residential Risk Resulting in Highest Exposure and Risk for Bifenthrin.

Population	Exposure Scenario		Route of Exposure	Short-Term MOE
Adults	Loading/applying granulars with a belly-grinder	Handler	Dermal and Inhalation	300 Dermal 25,000 Inhalation
	Hose-end Sprayer Application	Handler	Dermal and Inhalation	97,000 Inhalation 3000 Dermal
		Post-Application	Dermal	2300
	Liquid Structural Wood Treatment with Paintbrush	Handler	Dermal and Inhalation	23,000 Inhalation 600 Dermal
		Post-Application	No exposure expected due to low accessibility to treated areas (termite control).	
	Indoor: Liquid Crack and Crevice Spray	Handler	Dermal and Inhalation	210,000 Inhalation 14,000 Dermal
		Post-Application	Dermal	3100
Toddler	Outdoor: High Contact Activity on Turfgrass	Post-Application	Hand-to-Mouth/Oral	740
			Mouthing Treated Turf	3000
			Soil Ingestion	220,000
			Dermal	1400

[1] Combined MOE for handlers since dermal and inhalation endpoints (clinical signs of same [1/(1/MOE-dermal)+(1/MOE-inhalation)].

The short- and intermediate-term NOAEL for non-dietary **oral** exposure is based on the 90-day oral toxicity study in dogs (NOAEL = 2.21 mg/kg/day). The short- and intermediate-term NOAEL **dermal** exposure is based on the 21-day dermal toxicity study in the rat (NOAEL = 47 mg/kg/day). The common toxicological effect observed across the oral and dermal routes of exposure is clinical signs of neurotoxicity. The aggregate LOC (MOE) is 100.

The results of the short- and intermediate-term aggregate risk assessment for various subpopulations based on age are reported in Table 6.2.2. Short- and intermediate-term aggregate (dietary + residential) MOEs for the general U.S. population and any subpopulation of the general U.S. population are greater than 150 and therefore are not of concern to HED.

Table 6.2.2. Short- and Intermediate-Term Aggregate Risk for Bifenthrin.

Population	Dietary MOE[1]	Non-dietary Oral MOE[2]	Dermal MOE[3]	Inhalation MOE[4]	Aggregate MOE[5]
General U.S. population	850	N/A	300	25,000	220
All infants (<1 yr old)	800	590	1400	N/A[6]	270
Children 1-2 yrs. Old	350	590	1400		190
Children 3-5 yrs. Old	320	590	1400		150
Children 6-12 yrs. Old	430	N/A	1400		330
Youth 13-19 yrs. Old	760		1400		490
Adults 20-49 yrs. Old	1200		300	25,000	240
Adults 50+ yrs. Old	1300		300	25,000	240
Females 13-49 yrs. Old	1200		260	25,000	210

[1] Dietary MOE = [(short- or intermediate-term oral NOAEL)÷(chronic dietary exposure)]; NOAEL = 2.21 mg/kg/day; chronic dietary (food + water) exposures (see Table 5.2.2) were utilized as surrogates for short- and intermediate-term exposures.
[2] Non-dietary oral MOE = [(short- or intermediate-term oral NOAEL)÷(sum of all high-end incidental oral residential exposure)]; NOAEL=2.21 mg/kg/day; chronic dietary (food + water) exposures (see Table 4.2.2) were utilized as surrogates for short- and intermediate-term exposures.
[3] Dermal MOE = [(short- or intermediate-term dermal NOAEL)÷(high-end dermal residential exposure)]; NOAEL=47 mg/kg/day; structural wood treatment (paintbrush application) used for adult estimates
[4] Inhalation MOE = [(short- or intermediate-term inhalation NOAEL)÷(high-end dermal residential exposure)]; NOAEL=2.21 mg/kg/day.
[5] Aggregate MOE (dietary and residential) = 1÷[(1÷dietary MOE) + (1÷non-dietary oral MOE) + (1÷dermal MOE) + (1÷inhalation MOE)]; values expressed to 2 significant figures; Inhalation MOE based on adult residential handler exposure.
[6] N/A = not applicable.

6.3 Long-term (Chronic) Aggregate Risk

A chronic (non-cancer) aggregate risk assessment was not performed, because chronic residential exposure to bifenthrin (*i.e.*, >6 months) is not considered likely to occur.

6.4 Cancer Risk

The CARC (1992) recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human risk. The chronic exposure analysis revealed <100% RfD, and it is assumed that the chronic dietary endpoint is protective for cancer dietary exposure.

7.0 Cumulative Risk Characterization/Assessment

Bifenthrin is a member of the pyrethroid class of pesticides. EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the pyrethroids. Although all pyrethroids alter nerve function by modifying the normal biochemistry and physiology of nerve membrane sodium channels, available data show that there are multiple types of sodium channels and it is currently unknown whether the pyrethroids as a class have similar effects on all channels or whether modifications of different types of sodium channels would have a cumulative effect. Nor do we have a clear understanding of effects on key downstream neuronal function, e.g., nerve excitability, or how these key events interact to produce their compound specific patterns of neurotoxicity. Without such understanding, there is no basis to make a common mechanism of toxicity finding. There is ongoing research by the EPA's Office of Research and Development and pyrethroid registrants to evaluate the differential biochemical and physiological actions of pyrethroids in mammals. This research is expected to be completed by 2007. When available, the Agency will consider this research and make a determination of common mechanism as a basis for assessing cumulative risk. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure/Risk Pathway

8.1 Short-/Intermediate-Term Handler Risk

Based upon the proposed use pattern, HED expects the most highly exposed occupational pesticide handlers (mixers, loaders, applicators) to be 1) mixer/loader using open pour loading of liquids; 2) mixer/loader using open pour loading of granules; 3) an aerial applicator and 4) an applicator using open-cab, ground-boom spray equipment. HED believes most exposure durations will be short-term (1 - 30 days). However, the Science Policy Council for Exposure (ExpoSAC) maintains that it is possible for commercial applicators to be exposed to intermediate-term exposure durations (1 - 6 months). Therefore estimates for short- and intermediate-term risks are presented.

It is expected that some private applicators may perform all tasks, that is, mix, load and apply the material. However, HED ExpoSAC draft SOP (29 March 2000) directs that although the same individual may perform all tasks, in some cases they shall be assessed separately.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, air-blast sprayers, or high-pressure handwand sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of PPE for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data were available with which to assess potential exposure to occupational pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline"; that is, for workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" and the use of protective gloves or other PPE as might be necessary. The proposed product label involved in this assessment directs applicators and other handlers who may be exposed to the dilute through application or other tasks must wear: long-sleeved shirt and long pants, chemical resistant gloves, such as barrier laminate, nitrile, neoprene or viton rubber and shoes plus socks. Handlers who may be exposed to the concentrate through mixing, loading, application or other tasks must wear; long-sleeved shirt and long pants, chemical resistant gloves such as barrier laminate, nitrile, neoprene or viton rubber, shoes plus socks and protective eye wear.

Since single application rates for the proposed uses range from 0.1 lb ai/acre to 0.3 lb ai/acre, those uses with the higher application rate were assessed in the table below (potatoes). Since the dermal effects are derived from a 21-day dermal study, there are no adjustments made for dermal absorption. HED asssumes 100% inhalation absorption.

See Table 9.1 for a summary of estimated exposures and risks. In this case, the toxicological effects are similar (*i.e.*, neurological) for the dermal and inhalation routes although they were identified from different studies. Therefore, MOEs are expressed as Combined MOEs.

Table 8.1 Occupational Exposure and Risk Estimates for Proposed Uses of Bifenthrin

Unit Exposure[1] (mg/lb ai handled)	Application rate and Acres Treated[2]	Average Daily Dose[3] (mg/kg bw/day)	MOE[4]	Combined MOE[5]
Mixer/Loader – Liquids – Open Pour – Supporting Aerial Applications				
Dermal: SLNG: 2.9 HC SLWG: 0.023 HC	0.3 lb ai/A 350 Acres/Day	Dermal: NG: 4.35 WG: 0.0345	NG: 11 WG: 1400	NG: 11 WG: 650
Inhal: 0.0012		Inhal: 0.0018	Inhal: 1200	
Mixer/Loader – Granules – Open Pour				
Dermal: SLNG: 0.0084 LC SLWG: 0.0069 MC	0.3 lb ai/A 350 Acres/Day	Dermal: NG: 0.0126 WG: 0.0104	NG: 3700 WG:4500	NG: 700 WG: 730
Inhal: 0.0017		Inhal: 0.00255	Inhal: 870	
Aerial Applicator[6]				
Dermal: SLNG: 0.0050	0.3 lb ai/A 350 Acres/Day	Dermal: NG: 0.0075	NG: 6300	NG: 4900
Inhal: 0.000068		Inhal: 0.00010	Inhal: 22,000	
Applicator – Open Cab – Ground Boom				
Dermal: SLNG: 0.014 SLWG: 0.014	0.3 lb ai/A 200 Acres/Day	Dermal: SLNG: 0.012 SLWG: 0.012	NG: 3900 WG: 3900	NG: 1800 WG: 1800
Inhal: 0.00074		Inhal: 0.00063	Inhal: 3500	

1. Unit exposure = mg/lb ai handled; taken from PHED Surrogate Exposure Guide (v. 1.1, 8/1998) SLNG=single layer PPE, no gloves; SLWG=single layer PPE with gloves. HC=high confidence data; MC=medium confidence data; LC=low confidence data.
2. Application rates are the maximum recommended rates from the product labels and acres treated are derived from ExpoSAC Policy No. 9.1, revised 9/25/2001.
3. Average Daily Dose (ADD) = Unit Exposure*Application Rate*Acres Treated ÷ 70 kg body-weight.
4. MOE=Margin of Exposure (MOE) = NOAEL ÷ ADD.
5. Margins of Exposure may be combined when the dermal and inhalation toxicological effect is the same but derived from different studies. The convention used to combine is: 1 ÷ [(1/MOE-DERMAL) + (1/MOE-INHALATION)]
6. Pilots are not required to wear protective gloves.

A MOE of 100 is adequate to protect occupational pesticide handlers. Provided that mixer/loaders wear protective gloves, all MOEs are > 100 and are not of concern to HED.

8.3 Short-/Intermediate-Term Post-application Risk

There is typically the possibility for agricultural workers to experience post-application exposure to dislodgeable pesticide residues. In conjunction with the Agricultural Re-Entry Task Force (ARTF), HED has identified a number of agricultural work activities that may result in post-application, re-entry exposure to pesticides. In addition, HED has identified surrogate Transfer Coefficients (TCs) in units of cm^2/hr derived from exposure studies relative to "standard" agricultural work activities but which were conducted to assess exposure to other compounds.

Not all of the identified post-application work activities are listed here. However, the activities associated with the highest TCs are summarized in Table 9.2.

Table 8.2. Transfer Coefficients Associated With Proposed Uses of Bifenthrin.

Crop	Activity	Transfer Coefficient (cm^2/hr)
Leafy green vegetables (cilantro)	Hand Harvesting	2500
Brassica leafy greens		2500
Beans, Peas - dried, shelled		2500
Tobacco	Hand Harvesting, Topping, Stripping	2000
Roots and tuber (potatoes)	Irrigation activities, Scouting	1500

Since there are no chemical-specific data with which to assess post-application exposures to agricultural workers, HED uses TCs identified from surrogate studies in conjunction with the assumption that 20% of the rate of application is available as dislodgeable foliar residue (DFR) on day zero after application. Although hand harvesting (cilantro, leafy greens and peas and beans) has a TC of 2,500, the rate of application is 0.1 lb ai/A. The rate of application for potato is 0.3 lb ai/A which results in a higher exposure despite a slightly lower TC. Therefore, as a "worse case" screening-level assessment, a TC of 1500 cm²/hr is used in conjunction with an application rate of 0.3 lb ai/A.

The TCs used in this assessment are from an interim TC policy developed by HED's ExpoSAC using proprietary data from the ARTF database (policy # 3.1 Revised 7 AUG 2000). It is the intention of HED's ExpoSAC that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature. The following convention may be used to estimate post-application exposure to agricultural workers.

Surrogate DFR:
DFR = application rate * 20% available as dislodgeable residue * 4.54 x 108µg/lb * 2.47 x 10-8 A/cm2 or 1.08 x 10-3 ft2/cm²

and the Average Daily Dose
ADD = DFR (µg/cm2) * TC (cm2/hr) * hr/day * 0.001 mg/µg * 1/70 kg bw

∴ 0.3 b ai/A * 0.20 * 4.548 µg/lb * 2.47-8 A/cm² = 0.673 g/cm2 and

0.673 µg/cm^2 * 1500 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.12 mg/kg bw/day

Since MOE = NOAEL ÷ ADD then 47 mg/kg bw/day ÷ 0.12 mg/kg bw/day = 410

The MOE for the theoretically most highly exposed post-application agricultural activity is

410 (>100), and is not of concern. All other identified post-application activities are expected to have lower exposures therefore greater MOEs.

RESTRICTED ENTRY INTERVAL (REI)

Bifenthrin is classified in Acute Toxicity Category II for acute oral toxicity; Category III for acute dermal toxicity; and Category IV for acute inhalation, primary eye irritation, and dermal irritation. It is not a dermal sensitizer. Therefore, the interim WPS REI of 12 hours is adequate to protect agricultural workers from post-application exposures. The proposed end-use product labels list a REI of 12 hours.

9.0 Data Needs and Label Requirements

9.1 Toxicology

- None.

9.2 Residue Chemistry

- Revised Section F – see Table 4.1.5.1
- Revised Section B – see Section 2.1
- Additional information concerning aspirated grain fractions.

9.3 Occupational and Residential Exposure

None.

RDI: RAB1: 07/18/2007
PP#6E7125, PP#6E7126, PP#6E7127, PP#6E7128
EPA Registration Numbers: 279-3069; 279-3244; 279-310808
DP Numbers: 334154, 334165, 334168
PC Code: 128825
WDWassell:S10316:Potomac Yard:703-305-6135:7509P:RAB1

Appendix 1: Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	00141199 (1984) Acceptable/guideline M: 0, 0.88, 3.8, 7.5, 15 mg/kg/day F: 0, 1.04, 4.3, 8.5, 17.2 mg/kg/day	NOAEL=M/F: 3.8/4.3 mg/kg/day LOAEL=M/F: 7.5/8.5 mg/kg/day based on increased incidence of tremors.
870.3150	90-Day oral toxicity (dog)	00141200 (1984) Acceptable/guideline 0, 2.21, 4.42, 8.84, 17.7 mg/kg/day	NOAEL =M/F: 2.21 mg/kg/day LOAEL = M/F: 4.42 mg/kg/day based on based on increased incidence of tremors.
870.3200	21/28-Day dermal toxicity (rat)	45280501 (2000) Acceptable/guideline 0, 23, 47, 93, 932 mg/kg/day	NOAEL = 47 LOAEL = 93 mg/kg/day based on staggered gait and exaggerated hindlimb flexion.
870.3200	21/28-Day dermal toxicity (rabbit)	00141198 (1984) Acceptable/guideline 0, 22, 44, 88 442 mg/kg/day	NOAEL = 88 mg/kg/day LOAEL = 442 mg/kg/day based on loss of muscle coordination and increased incidence of tremors.
870.3700a	Prenatal developmental in rat (gavage)	00154482 (1983) Acceptable/non-guideline 0, 0.44, 0.88, 1.77, 2.2 mg/kg/day	**Maternal** NOAEL = 0.88 mg/kg/day LOAEL = 1.77 mg/kg/day based on tremors during gestation. **Developmental** NOAEL and LOAEL were not established (fetuses were not examined).
870.3700a	Prenatal developmental in rat (gavage)	00141201 (1984) Acceptable/guideline 0, 0.44, 0.88, 1.77 mg/kg/day	**Maternal** NOAEL = 0.88 mg/kg/day LOAEL = 1.77 mg/kg/day based on tremors. **Developmental** NOAEL = 0.88 mg/kg/day LOAEL = 1.77 mg/kg/day based on increased fetal and litter incidence of hydroureter without nephrosis.
870.3700a	Prenatal developmental in rat (diet)	45352301 (2001) Acceptable/guideline 0, 2.4, 4.8, 7.1, 15.5 mg/kg/day	**Maternal** NOAEL = 7.1 mg/kg/day LOAEL = 15.5 mg/kg/day based on clinical signs and decreased food consumption, body weight gains, and body weight gains (adjusted for gravid uterine weight). **Developmental** NOAEL = 15.5 mg/kg/day LOAEL was not established.
870.3700b	Prenatal developmental in rabbit (gavage)	00145997 (1984) Acceptable/guideline 0, 2.36, 3.5, 7 mg/kg/day	**Maternal** NOAEL = 2.36 mg/kg/day, LOAEL = 3.5 mg/kg/day based on treatment-related head and forelimb twitching. **Developmental** NOAEL =7 mg/kg/day, LOAEL was not established.

Appendix 1: Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	00157225 (1986) Acceptable/guideline 0, 1.5, 3.0, 5.0 mg/kg/day	**Parental/Systemic** NOAEL = M/F: 5.0/3.0 mg/kg/day, LOAEL was not established in males. In females, LOAEL= 5.0 mg/kg/day based on tremors and decreased body weights. **Reproductive/ Offspring** NOAEL = 5.0 mg/kg/day, **Reproductive/ Offspring** LOAEL was not established.
870.4100b	Chronic toxicity (dog)	00163065 (1985) Acceptable/guideline 0, 0.66, 1.3, 2.7, 4.4 mg/kg/day	NOAEL = 1.3 mg/kg/day, LOAEL= 2.7 mg/kg/day based on increased incidence of tremors.
870.4300	Chronic/ Carcinogenicity (rat)	00157226 (1986) Acceptable/guideline M: 0, 0.6, 2.3, 4.7, 9.7 mg/kg/day F: 0, 0.7, 3.0, 6.1, 12.7 mg/kg/day	NOAEL = M/F: 4.7/3.0 mg/kg/day, LOAEL =M/F: 9.7/6.1 mg/kg/day based on increased incidence of tremors. **No conclusive evidence of carcinogenicity**
870.4300	Chronic/ Carcinogenicity (mouse)	00157227 (1986) Acceptable/guideline M: 0, 6.7, 25.6, 65.4, 81.3 mg/kg/day F: 0, 8.8, 32.7, 82.2, 97.2 mg/kg/day	NOAEL =M/F: 6.7/8.8 mg/kg/day, LOAEL = M/F: 25.6/32.7 mg/kg/day based on based on increased incidence of tremors. **Carcinogenic** potential was evidenced by a dose-related increase in the incidence of leiomyosarcomas in the urinary bladder, a significant dose-related trend for combined hepatocellular adenomas and carcinomas in males, and a significantly higher incidence of combined lung adenomas and carcinomas in females.
870.6200a	Acute neurotoxicity-rat (gavage)	44862102(1998) Acceptable/Guideline 0, 9.4, 32.8, 70.3 mg/kg/day	NOAEL = 32.8 mg/kg/day, LOAEL=70.3 mg/kg/day based on clinical signs of toxicity, FOB findings, altered motor activity, and mortality (females only).
870.6200b	Subchronic neurotoxicity screening battery (rat)	44862103 (1998) Acceptable/Guideline M: 0, 2.7, 5.6, 11.1 mg/kg/day F: 0, 3.5, 6.7, 13.7 mg/kg/day	NOAEL= M/F: 2.7/3.5 mg/kg/day, LOAEL= M/F: 5.6/6.7 mg/kg/day based on neuromuscular findings (tremors, changes in grip strength and landing foot-splay).

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Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6300	Developmental Neurotoxicity (rat)	46750501 (2006) Acceptable/non-guideline 0, 3.6, 7.2 and 9.0 mg/kg/day (gestation) 0, 8.3, 16.2 and 20.7 mg/kg/day (lactation)	**Maternal** NOAEL = 3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation, LOAEL = 7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation based on clinical signs of neurotoxicity (tremors, clonic convulsions, and increased grooming counts). **Developmental** NOAEL =3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation. **Developmental** LOAEL = 7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation based on clinical signs of neurotoxicity (increased grooming counts).