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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

MEMORANDUM

Date: **July 18, 2007**

Subject: **Lambda-Cyhalothrin. Human Health Risk Assessment for the Proposed Food/Feed Uses of the Insecticide on Cucurbit Vegetables (Group 9), Tuberous and Corm Vegetables (Subgroup 1C), Grass Forage, Fodder, and Hay (Group 17), Barley, Buckwheat, Oat, Rye, Wild Rice, and Pistachios. Petition Numbers 5F6994, 3E6593, and 6E7077.**

PC Code:	**128897**
DP Numbers:	**313315, 324219, 330542**
Regulatory Citation:	**40CFR §180.438**
Chemical Class:	**Synthetic Pyrethroid Insecticide**
Trade Names:	**Warrior®, Karate®**

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1.0 EXECUTIVE SUMMARY

Lambda-cyhalothrin is a synthetic pyrethroid insecticide used to control a wide range of pests on food/feed crops and livestock, as well as in and around buildings and structures. Lambda-cyhalothrin is an enriched isomer of cyhalothrin. It is currently used on a wide range of pests (including aphids, adult Japanese beetles, grasshoppers, and butterfly larvae) in a variety of applications. It may also be used for structural pest management (termiticide), and in public health applications to control insects (such as mosquitoes, cockroaches, ticks, and flies) which may act as disease vectors. Another use is as a pour-on insecticide, which is applied down the backline of beef cattle for control of lice and horn flies. There are existing residential uses for lambda-cyhalothrin.

Syngenta Crop Protection (Syngenta) and Interregional Research Project #4 (IR-4) have submitted petitions supporting new uses for lambda-cyhalothrin as a microencapsulated formulation (capsule suspension, CS) containing either 1.0 or 2.08 pounds of active ingredient per gallon (lb ai/gal). The proposed new uses of lambda-cyhalothrin are on barley, buckwheat, oats, rye, cucurbit vegetables, grasses, tuberous and corm vegetables, wild rice, and pistachios. The formulations being proposed for these uses include a 1.0 lb ai/gal CS and a 2.08 lb ai/gal CS. These formulations are currently registered to Syngenta for use on a wide variety of food and feed crops at seasonal rates of 0.06-0.48 lb ai per acre (lb ai/A). Tolerances are established for the combined residues of lambda-cyhalothrin and its epimer (R157836) in/on plant and animal commodities under 40CFR §180.438.

Human Health Risk Assessment

Toxicology/Hazard

The main target organ for lambda-cyhalothrin is the neuromuscular system. Lambda-cyhalothrin produces neurotoxicity in three species (rats, mice, and dogs); neurotoxicity is evident in rats after oral, dermal, and inhalation exposure. As with other pyrethroids, inhalation exposure appears to be the most toxic route of exposure. The observed neurotoxic effects are classic pyrethroid effects, and they are toxicologically significant. The observed liver effects in some studies strongly suggest an adaptive response. Lambda-cyhalothrin is classified as "not likely to be carcinogenic to humans," based on the lack of evidence of carcinogenicity in mice and rats. This classification was determined at the HIARC meeting of 3/1/2004.

Developmental studies in rats and rabbits exposed to cyhalothrin demonstrated no indication of increased quantitative or qualitative sensitivity of rats or rabbits to *in utero* exposure to cyhalothrin. No developmental toxicity was observed in either of the developmental toxicity studies in rats and rabbits. Maternal toxicity was observed in the form of clinical signs of neurotoxicity in the rat study; additionally, reduced body weight gain and food consumption were observed in both the rat and the rabbit studies.

A 3-generation reproduction study exposing rats to cyhalothrin demonstrated no indication of increased quantitative or qualitative sensitivity of rats to post-natal exposure to cyhalothrin. In the 3-generation reproduction study in rats, the parental/offspring No Observed Adverse Effect Levels (NOAELs) are the same, based on decreased parental and pup body weight and body weight gain.

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The endpoint selected for assessment of acute dietary risk is appropriate because it is based on effects that were observed within the first 2 days of exposure in an oral study in dogs. The NOAEL used for the acute dietary dose is 0.5 mg/kg, with a Lowest Observed Adverse Effect Level (LOAEL) of 3.5 mg/kg. The endpoint selected for assessment of chronic dietary risk is appropriate because it is based on a chronic oral study in dogs. This NOAEL (0.1 mg/kg/day) is somewhat lower than those seen in dog studies with other pyrethroids; however, transient effects were observed in several dogs at the LOAEL of 0.5 mg/kg/day. The short- and intermediate-term incidental oral NOAELs are 0.1 mg/kg/day, based on clinical signs of neurotoxicity in the chronic dog study at the LOAEL of 0.5 mg/kg/day. The NOAEL for dermal exposure is 10 mg/kg/day from a dermal toxicity study in rats, and is based on clinical signs of neurotoxicity at the LOAEL of 50 mg/kg/day. The NOAEL for inhalation exposure is 0.08 mg/kg/day in an inhalation study in rats, and is based on clinical signs of neurotoxicity at the LOAEL of 0.90 mg/kg/day.

No additional uncertainty factors (UFs) have been retained, so HED's level of concern (LOC) is a margin of exposure (MOE) of less than 100.

FQPA Safety Factor

The toxicology database is considered complete for the purposes of an FQPA risk assessment. Based on the developmental studies in rats and rabbits, and the 3-generation and neurodevelopmental studies in rats, there is no evidence of increased susceptibility. The neurotoxicity observed in adult animal studies raised a concern for potential neurodevelopmental effects. A rat neurodevelopmental toxicity (DNT) study is available. In this study, the lowest dose showing neurotoxicity in the offspring (effects on mortality, body weights, body weight gains, learning, learning and memory, and brain morphometry) is 10 mg/kg bw/day, with a NOAEL of 4 mg/kg bw/day. Effects in offspring and adult animals are found at a similar dose based on body weight decreases. It should be noted that some of the parameters evaluated in this DNT study were regarded as acceptable but several others were not, leading to a study classification of "unacceptable." The study deficiencies which, taken together, led to the unacceptable classification include: 1) statistical analyses that adjusted for body weights after treatment had begun, 2) an inadequate assessment of motor activity, 3) an inadequate assessment of auditory startle in PND 61 females, and 4) missing low- and mid-dose morphometry data. However, it is not likely that these limitations will impact the risk assessment for the following reasons. The slight changes in brain morphometry were seen at the highest dose tested. Because these changes were slight, it is uncertain whether toxicologically significant differences would be seen at the mid dose, and it is unlikely that significant changes would be seen at the lowest dose tested. The auditory startle response is considered adequate for assessment in PND 23 males/females and PND 61 males where no treatment-related effects were seen in auditory startle response. Only the auditory response data for PND 61 females is inadequate. Motor activity was examined and there did not appear to be any differences between treated and control animals other than decreases for multiple subsessions in PND 18 males/females at the high dose only, but due to the high variability and the lack of habituation, these data are considered equivocal. If a 10-fold factor is applied to the NOAEL in the study (i.e., 4 mg/kg bw/day) to account for the scientific limitations of the study, the resulting value is 0.4 mg/kg bw/day. The estimate of 0.4 mg/kg/day is similar to the doses from the chronic dog study used for risk assessment (i.e., 0.5 mg/kg/day for acute dietary exposure scenarios and 0.1 mg/kg/day for chronic dietary exposure

scenarios). In the exposure databases, there are also no residual uncertainties. The exposure assessments are based on reliable data and reasonable worst-case assumptions, and will not likely underestimate risks. There was no published literature found that would indicate a neurodevelopmental concern for lambda-cyhalothrin.

Based on all of the considerations above, there is not a need to retain the additional 10X safety factor for children. Application of the 10X intraspecies uncertainty factor (which accounts for the possibility that a subpopulation may be 10 times more sensitive than the average individual) and a 10X interspecies factor (which accounts for the possibility that humans may be 10 times more sensitive than animals) to the dog NOAEL (i.e., the most sensitive species) should assure protection of human health including children.

Dietary Exposure (Food/Water)

The nature of the residue in plants is sufficiently understood. The residues to be regulated are lambda-cyhalothrin and its epimer R157836.

An adequate confined rotational crop study is available indicating that significant residues (greater than 0.01 ppm) will not be present in crops rotated 30 days after application of lambda-cyhalothrin (EFED review; 4/6/1988).

Studies of lambda-cyhalothrin metabolism in ruminants and poultry have been reviewed. As with plants, HED has determined that the residues to be regulated are lambda-cyhalothrin and its epimer R157836. The other minor animal metabolites do not need to appear in the tolerance expression.

Adequate gas chromatographic/electron capture detection (GC/ECD) methods are available for enforcing tolerances on both plant (Method PRAM 81) and animal (Method PRAM 86) commodities. For both methods, residues are extracted with acetone/hexane (1:1, v/v), then cleaned up using liquid-liquid chromatography and Florisil column chromatography. Residues are determined by GC/ECD; the method limit of quantitation (LOQ) is 0.01 ppm for each analyte.

The available field trial data on potatoes, cucumbers, muskmelons, summer squash, and grasses are adequate, and support the proposed use patterns for lambda-cyhalothrin (CS) on tuberous and corm vegetables, cucurbit vegetables, and grasses. The number and geographic distribution of the field trials are adequate, and the appropriate samples were collected at the proposed pre-harvest intervals (PHIs). In addition to the new field trial data, adequate field trial data are available on rice, wheat, almonds, and pecans from previously reviewed petitions. The data on rice will be translated to support an identical use on wild rice; the data on almonds and pecans will be translated to support an identical use on pistachios; and the data on wheat will be translated to support identical uses on barley, buckwheat, oats, and rye.

Adequate storage stability data are available indicating that both lambda-cyhalothrin and R157836 are stable under frozen storage in a wide variety of raw and processed commodities for intervals of 26-36 months. These data support the storage durations (2.9-8.5 months) and conditions for samples from the field trials and processing studies submitted with the current petitions.

Adequate processing studies are available for potato and wheat grain; processing data are not required for cucurbit vegetables, grass, nor wild rice. Separate tolerances are not required for potato processed fractions. However, based on the available wheat grain processing data, separate tolerances are required for both barley and rye bran.

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The Codex Alimentarius Commission, Mexico, and Canada have all established maximum residue limits (MRLs) for residues of lambda-cyhalothrin in/on a variety of raw agricultural commodities. Each of these regulatory bodies expresses residues in terms of only cyhalothrin; however, the US tolerance expression includes both lambda-cyhalothrin and its epimer R157836. For the crop uses currently under consideration, only potatoes have existing international tolerances, and the recommended US tolerance of 0.02 ppm will be in harmony with the existing 0.02 mg/kg MRLs for Codex and Mexico.

Acute and chronic dietary (food + drinking water) exposure analyses were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03). The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED), and incorporated directly into the dietary assessment.

Acute Dietary Exposure Results and Characterization

A refined acute probabilistic dietary exposure assessment was performed for lambda-cyhalothrin to support all existing and proposed food uses, and included drinking water exposure. The acute dietary exposure assessment incorporated processing factors and percent crop treated (%CT) estimates provided by the Biological and Economic Analysis Division (BEAD). Acute anticipated residues were derived from PDP monitoring data, field trial studies, and a market basket survey for beef-fat.

The acute drinking water concentration in surface water of 5.35 ppb was based on the FIRST (FQPA Index Reservoir Screening Tool) estimated peak concentration resulting from applications to orchards.

The acute dietary exposure estimates for food and drinking water are below HED's LOC, 100% of the acute population adjusted dose (aPAD) for the general US population and all population subgroups. Lambda-cyhalothrin acute dietary exposure at the 99.9th percentile for food and drinking water is 46% of the aPAD for the general US population, and 61% of the aPAD for all infants (<1 year old), the most highly-exposed population subgroup.

Chronic Dietary Exposure Results and Characterization

A refined chronic dietary exposure assessment was also conducted for lambda-cyhalothrin to support all existing and proposed food uses, and included drinking water exposure, utilizing point estimates of anticipated residues for food and drinking water. The chronic dietary exposure assessment incorporated processing factors and %CT estimates provided by BEAD. Chronic anticipated residues were derived from PDP monitoring data, field trial studies, and a market basket survey for beef-fat.

The chronic drinking water concentration in surface water of 0.130 ppb was based on the FIRST estimated mean concentration resulting from applications to orchards.

The chronic dietary exposure estimates for food and drinking water are below HED's LOC, 100% of the chronic population adjusted dose (cPAD), for the general US population and all population subgroups. Lambda-cyhalothrin chronic dietary exposure for food and drinking water is 17% of the cPAD for the general US population, and 50% of the cPAD for children (1-2 yrs old), the most highly-exposed population subgroup.

Residential Exposure/Risks

The residential risk assessment evaluated existing uses for lambda-cyhalothrin. Existing uses on turf, in gardens, on golf courses, and for structural pest control were qualitatively assessed, but a quantitative calculation was only completed for post-application exposure on

treated turf because this scenario is expected to have the highest associated exposures. This would be protective for all residential exposures, even the handler scenarios, because the anticipated dose levels for children playing on treated lawns exceed those expected for all other scenarios.

For post-application exposure, all residential MOES were well above the Agency target MOE of 100 for the inhalation, dermal, and oral routes (ranging from 700 to 15,000), and therefore do not exceed HED's LOC. Additionally, when the MOEs for the three routes were aggregated, MOEs were still not of concern (MOEs for children were 460 to 500, and the MOE for adults was 3000).

Aggregate Exposure/Risks

Aggregate risk assessments (including both dietary and residential exposure routes) for short- and intermediate-term durations were conducted. For these exposure durations, aggregate MOEs were greater than the Agency target MOE of 100 (ranging from 140 to 490), and there are thus no concerns for aggregate exposure. For the acute and chronic durations, the aggregate exposure and risk estimates are equivalent to the dietary estimates, and are also not of concern.

Occupational Exposure/Risks

Handlers

An MOE of 100 or more is adequate to protect occupational pesticide handlers from exposures to lambda-cyhalothrin. Provided mixer/loaders wear personal protective equipment (PPE) as directed by the labels, all MOEs are greater than 100 (ranging from 110 to 1700), except for mixer/loaders supporting aerial applications to wild rice at a rate of 0.04 lb ai per acre (lb ai/A), and 1200 acres treated per day (A/day). Their exposure can be mitigated by reducing the amount of ai handled per day, or by the use of a dust-mist respirator. Baseline MOEs for applicators and flaggers range from 820 to 4900.

Post-application

An MOE of 100 or more is adequate to protect persons from post-application exposures to lambda-cyhalothrin, as described in the proposed use patterns. Because the estimated MOEs are all greater than 100 (ranging from 520 to 13,000), post-application exposures arising from the proposed uses do not exceed HED's LOC.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered for this human health risk assessment, in accordance with US Executive Order 12898, *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations*, http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by USDA under the CSFII, and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, non-dietary exposures

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based on home use of pesticide products, associated risks for adult applicators, and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix C) have been determined to require a review of their ethical conduct, and they have received that review.

Additional Data Needs

Toxicology

Although several parameters were unacceptable in this study, as explained in Sections 3.1.3 and 3.3.2, a repeat of this study is unlikely to yield a lower regulatory endpoint. Thus, the database is complete for purposes of this risk assessment. There are no data gaps that would quantitatively impact the risk assessment.

Regulatory Recommendations and Residue Chemistry

No major deficiencies were noted in the subject petitions that would preclude the establishment of permanent tolerances for lambda-cyhalothrin on the proposed commodities. Only minor deficiencies were noted pertaining to the proposed label directions and recommended tolerance levels (listed below). HED recommends in favor of establishing permanent tolerances for lambda-cyhalothrin residues at the levels listed in Table 1.0, below.

(1) Use directions for grasses should be clarified to specify that the restriction of 0.03 lb ai/A per cutting includes pastures and rangeland in addition to grasses grown for seed. A minimum RTI of 30 days should be specified for pastures and rangeland which are not cut between applications. In addition, the PHI for forage should be changed to 0 days, as PHIs for forage are not practical for rangeland applications.

(2) A tolerance was not proposed in rye bran. Based on the available wheat residue data, a separate tolerance is required at 0.2 ppm in rye, bran.

(3) Based on the calculated theoretical dietary burdens (TDBs) for livestock, and the available livestock residue studies, the current tolerance for lambda-cyhalothrin in milk fat is too low. An increased tolerance should be proposed in milk fat (10 ppm). The data also indicate that the current tolerances in hog commodities could be lowered to 0.2 ppm in fat, 0.01 ppm in meat, and 0.02 ppm in meat-byproducts.

Regulatory Recommendations and Occupational and Residential Exposure

The labels for Warrior® Insecticide (EPA Registration #100-1112) and Karate® Insecticide (EPA Registration #100-1097) should state that mixer/loaders supporting aerial applications to wild rice at a rate of 0.04 lb ai/A, and treating 1200 acres (or more) per day, are required to use a dust-mist respirator.

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Table 1. 0 Tolerance Summary for Lambda-Cyhalothrin.			
Commodity	**Established/Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
Barley, bran	0.2	0.2	Tolerances are based on the existing residue data and tolerances in similar wheat commodities.
Barley, grain	0.05	0.05	
Barley, hay	2.0	2.0	
Barley, straw	2.0	2.0	
Buckwheat, grain	0.05	0.05	
Cucurbit vegetables	0.05	0.05	*Vegetable, cucurbits, group 9*
Grass forage, fodder, and hay	9.0	7.0	A crop group tolerance is appropriate. *Grass forage, fodder, and hay, group 17*
Hog, fat	3.0	0.2	Based on a TDB* of 0.9 ppm for swine, the maximum expected residues are 0.16 ppm in hog fat, 0.006 ppm in hog meat, and 0.011 ppm in hog meat-byproducts.
Hog, meat	0.2	0.01	
Hog, meat-byproducts	0.2	0.02	
Milk, fat (reflecting 0.4 ppm in whole milk)	5.0	10	Based on a TDB of 10.4 ppm for dairy cattle, the maximum expected residues in milk are 0.35 ppm, equivalent to 8.8 ppm in milk fat.
Oat, grain	0.05	0.05	Tolerances are based on the existing residue data and tolerances in similar wheat commodities.
Oat, forage	2.0	2.0	
Oat, hay	2.0	2.0	
Oat, straw	2.0	2.0	
Pistachio	0.05	0.05	Tolerance is based on existing almond and pecan residue data, and the tolerance in the tree nut group.
Rice, wild, grain	1.0	1.0	Tolerance is based on the existing tolerance and residue data in rice.
Rye, bran	None	0.2	Tolerances are based on the existing residue data and tolerances in similar wheat commodities.
Rye, grain	0.05	0.05	
Rye, forage	2.0	2.0	
Rye, straw	2.0	2.0	
Tuberous and corm vegetables	0.05	0.02	Combined residues were <0.02 ppm in/on all potato samples from all field trials conducted at 1x rate, and from the field trial conducted at a 5x rate. *Vegetable, tuberous and corm, subgroup 1C*

* TDB = Theoretical Dietary Burden.

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2.0 INGREDIENT PROFILE

Lambda-cyhalothrin is a synthetic pyrethroid insecticide used to control a wide range of pests on food/feed crops and livestock, as well as in and around buildings and structures. Lambda-cyhalothrin is an enriched isomer of cyhalothrin, and is classified as a Type II pyrethroid compound.

Syngenta Crop Protection has submitted a petition (PP#5F6994) proposing the use of 1.0 and 2.08 lb ai/gal CS formulations of lambda-cyhalothrin on tuberous and corm vegetables (subgroup 1C), cucurbit vegetables (group 9), and grasses (group 17). In addition, IR-4 submitted two petitions (PPs#3E6593 and 6E7077) proposing to expand the use of lambda-cyhalothrin (CS) to include barley, buckwheat, oats, rye, wild rice, and pistachios, based on the existing residue data and tolerances on wheat, rice, and tree nuts.

2.1 Summary of Registered/Proposed Uses

Table 2.1, below, summarizes the proposed use patterns and formulations specified for the two end-use products containing lambda-cyhalothrin.

Table 2.1 Summary of Directions for Use of Lambda-Cyhalothrin.

Application Timing, Type, and Equipment	Formulation [EPA Reg. #]	Use Rate (lb ai/A)	Max. # Applic. per Season	Max. Seasonal Use Rate (lb ai/A)	PHI (Days)	Use Directions and Limitations
Cereal Grains (including Wheat, Wheat Hay, Triticale, Barley, Buckwheat, Oats, and Rye)						
Broadcast foliar applications using ground or aerial equipment	1.0 lb ai/gal CS [100-1112] 2.08 lb ai/gal CS [100-1097]	0.03	2	0.06	7 [forage, hay] 30 [grain, straw]	The minimum RTI is 3 days. Do not allow livestock to graze within 7 days of treatment. Use a minimum of 2 and 10 gal/A for aerial and ground applications, respectively.
Cucurbit Vegetables						
Broadcast foliar applications using ground or aerial equipment	1.0 lb ai/gal CS [100-1112]	0.03	6	0.18	1	The minimum RTI is 5 days. Use a minimum of 2 and 10 gal/A for aerial and ground applications, respectively.
Grass Forage, Fodder and Hay						
Broadcast foliar applications using ground or aerial equipment	1.0 lb ai/gal CS [100-1112] 2.08 lb ai/gal CS [100-1097]	0.03	3	0.09	1 [forage] 7 [hay, straw, and seed screenings]	Do not apply more than 0.03 lb ai/A per cutting. Following application to grasses grown for seed, regrowth may be cut for forage or hay 30 days after harvest of seed. Use a minimum of 2 and 7 gal/A for aerial and ground applications, respectively.
Tuberous and Corm Vegetables						
Broadcast foliar applications using ground or aerial equipment	1.0 lb ai/gal CS [100-1112]	0.03	4	0.12	7	The minimum RTI is 7 days. Use a minimum of 2 and 10 gal/A for aerial and ground applications, respectively.

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Table 2.1 Summary of Directions for Use of Lambda-Cyhalothrin.						
Application Timing, Type, and Equipment	**Formulation [EPA Reg. #]**	**Use Rate (lb ai/A)**	**Max. # Applic. per Season**	**Max. Seasonal Use Rate (lb ai/A)**	**PHI (Days)**	**Use Directions and Limitations**
Rice and Wild Rice						
Broadcast foliar applications using ground or aerial equipment	1.0 lb ai/gal CS [100-1112] 2.08 lb ai/gal CS [100-1097]	0.04	3	0.12	21	Do not apply more than 0.08 lb ai/A within 28 days of harvest, or more than 0.04 lb ai/A within 21 days of harvest. The minimum RTI is 5 days. Do not release flood water within 7 days of application. Do not use treated rice fields for the aquaculture of edible fish and crustacaea. Do not apply as an ULV spray. Use a minimum of 2 gal/A for aerial applications.
Tree Nuts (including Pistachio)						
Broadcast foliar applications during growing season using ground or aerial equipment	1.0 lb ai/gal CS [100-1112]	0.04	4	0.16	14	Do not apply more than 0.12 lb ai/A/year post-bloom. The minimum RTI is 5 days. Use a minimum of 5 gal/A for aerial applications.

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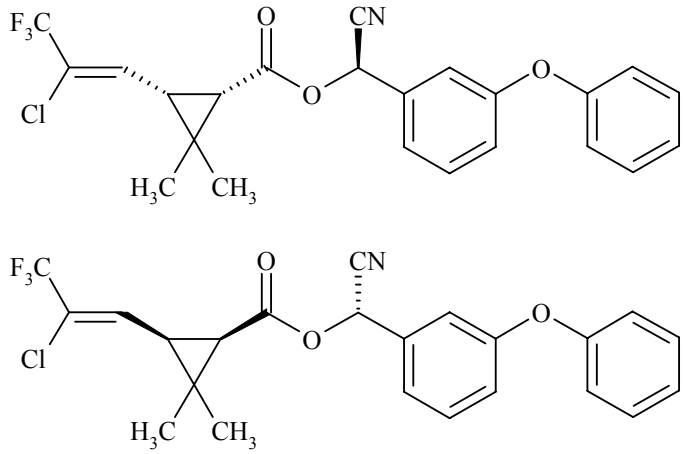
2.2 Structure and Nomenclature

Table 2.2 Lambda-Cyhalothrin Nomenclature.	
Compound	1:1 mixture of (Z)-(1R,3R), S-ester: (Z)-(1S,3S), R-ester 
Common Name	Lambda-Cyhalothrin
Company Experimental Name	ICIA0321
Molecular Formula	$C_{23}H_{19}ClF_3NO_3$
Molecular Weight	449.9
IUPAC Name	(*R*)-α-cyano-3-phenoxybenzyl (1*S*)-*cis*-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate and (*S*)-α-cyano-3-phenoxybenzyl (1*R*)-*cis*-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Name	*rel*-(*R*)-cyano(3-phenoxyphenyl)methyl (1*S*,3*S*)-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number	91465-08-6
End-use Products (EPs)	1.0 lb ai/gal CS (Warrior® Insecticide with Zeon™ Technology; EPA Registration #100-1112) 2.08 lb ai/gal CS (Karate® Insecticide with Zeon™ Technology; EPA Registration #100-1097)

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Lambda-Cyhalothrin.		
Parameter	**Value**	**Reference**
Melting Point/Range (°C)	49.2	D284860 [1]
pH	NA [2]	
Density (g/cm^3 at 25°C)	1.33	
Water Solubility (mg/L at 20ºC, pH 6.5)	0.005	
Solvent Solubility (g/L)	NA	
Vapor Pressure (mm Hg at 20°C)	1.5×10^{-9}	
Dissociation Constant (pK_a at 20°C)	>9	
Octanol/water Partition Coefficient (Log[K_{OW}])	7.00	
UV/visible Absorption Spectrum	NA	

1. Kit Farwell, 8/15/2002.
2. NA = Not Available.

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3.0 HAZARD CHARACTERIZATION/ASSESSMENT

Lambda-cyhalothrin is moderately acutely toxic via the oral, dermal, and inhalation routes (Category II). It is also a moderate eye irritant (Category II). It is neither irritating to the skin nor is it a sensitizer in the guinea pig. Acute toxicity studies conducted with cyhalothrin indicate that it is also Category II via the oral, dermal (rat), and inhalation routes. It is a moderate eye irritant without irrigation, and a mild eye irritant with irrigation (Category III). It is a mild skin irritant in rats, but not an irritant in rabbits (Category IV). Cyhalothrin is a skin sensitizer in guinea pigs.

3.1 Hazard and Dose-Response Characterization

The toxicological database for lambda-cyhalothrin, when bridged with that for cyhalothrin, indicates one major target for this chemical: the neuromuscular system. The neuromuscular effects are typical of chemicals in the pyrethroid class of insecticides. The neuromuscular effects are consistently characterized by gait abnormalities and salivation; these effects are observed across species, and across routes of administration (oral, dermal, and inhalation). A comparison of the 90-day oral study in rats with the chronic feeding study in rats indicates that toxicity is not induced at lower dose levels when rats are exposed over a longer period of time. As with other pyrethroids, the dog appears to be the most sensitive species, exhibiting gait abnormalities at doses as low as 0.5 mg/kg/day, starting at week 2. Neither sex appears to be more sensitive. In studies where the liver is affected, it appears to be an adaptive response.

3.1.1 Database Summary

3.1.1.1 Studies Available and Considered

Through the use of bridging data, the toxicology database for lambda-cyhalothrin has been completed using developmental, reproduction, chronic (rodent), and oncogenicity studies conducted with cyhalothrin. The toxicology database for lambda-cyhalothrin, when bridged with cyhalothrin, is complete for the purposes of this risk assessment; there are no data gaps that would quantitatively impact the risk assessment. The scientific quality is relatively high, and the toxicity profile of lambda-cyhalothrin can be characterized for all effects, including potential developmental, reproductive, and neurotoxic effects. The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or post-natal exposure to cyhalothrin.

3.1.1.2 Mode of Action, Metabolism, Toxicokinetic Data

G.W. Ware (*The Pesticide Book*; 4th Edition; 1994; pages 62-64, 171-172) states that, "Pyrethroids initially stimulate nerve cells to produce repetitive discharges, and eventually cause paralysis in the insect. Such effects are caused by their action on the sodium channel, a tiny hole through which sodium ions are permitted to enter the axon to cause excitation. These effects are produced in insect nerve cord, which contains ganglia and synapses, as well as in giant nerve fiber axons. The stimulating effect of pyrethroids is much more pronounced than that of DDT. The exact sites of action of pyrethroids at synapses are not known. It is probable that the toxic action of pyrethroids is primarily due to its blocking action on the nerve axon since this action shows a negative temperature coefficient. But because the cockroach ganglion is affected by

pyrethroid concentrations many fold less than are required to block conduction in giant fibers, it also seems likely that pyrethroids act on some aspect of synaptic function. The fast knockdown of flying insects could be the result of rapid muscular paralysis, suggesting that the ganglia of the insect central nervous system are affected." Pyrethroid neurotoxicity in mammalian species is also believed to be related to their effects on the sodium conductance channel.

3.1.2 Toxicological Effects

The main target organ for lambda-cyhalothrin is the neuromuscular system. Lambda-cyhalothrin produces neurotoxicity in three species (rats, mice, and dogs); neurotoxicity is evident in rats after oral, dermal, and inhalation exposure. As with other pyrethroids, inhalation exposure appears to be the most toxic route of exposure. The observed neurotoxic effects are classic pyrethroid effects, and they are toxicologically significant. The observed liver effects in some studies appear to be an adaptive response.

In an acute neurotoxicity study in the rats exposed to λ-cyhalothrin, clinical signs of neurotoxicity and changes in the FOB parameters were observed; however, no treatment-related neuropathology was evident. Clinical signs of neurotoxicity were observed in the chronic and subchronic dog study (gait abnormalities, muscle tremors and convulsions, subdued behavior, head shaking, excessive salivation); developmental rat study (gait abnormalities); subchronic mouse study (gait abnormalities, hunched posture); 21-day dermal rat study (reduced splay reflex, gait abnormalities, reduced stability); 21-day inhalation rat study (gait abnormalities, salivation, paw flicking, tail erections, lachrymation, reduced foot withdrawal, reduced righting reflex, shaking, head flicking, reduced splay reflex, decreased visual placing response); and 28-day rat feeding study (gait abnormalities, hunched posture, tail erect, salivation) studies.

Developmental studies in rats and rabbits exposed to cyhalothrin were available for consideration. The data demonstrate no indication of increased quantitative or qualitative sensitivity of rats or rabbits to *in utero* exposure to cyhalothrin. No developmental toxicity was observed in either of the developmental toxicity studies in rats and rabbits. Maternal toxicity was observed in the form of clinical signs of neurotoxicity in the rat study; additionally, reduced body weight gain and food consumption were observed in both the rat and the rabbit studies.

A 3-generation reproduction study exposing rats to cyhalothrin is part of the toxicology database. The data demonstrate no indication of increased quantitative or qualitative sensitivity of rats to post-natal exposure to cyhalothrin. In the 3-generation reproduction study in rats, the parental/offspring NOAELs are the same, based on decreased parental and pup body weight and body weight gain.

The requirements for oncogenicity studies in the rat and the mouse with lambda-cyhalothrin have been satisfied by a combined chronic/oncogenicity study in rats, and an oncogenicity study in mice, both conducted with cyhalothrin. Although mice should have been tested at a higher dose, it was determined that there was not enough toxicological concern to warrant a requirement for a new carcinogenicity study in mice. The chemical is classified as "not likely to be carcinogenic to humans," based on the lack of evidence of carcinogenicity in mice and rats.

3.1.3 FQPA

The toxicology database is considered complete for the purposes of an FQPA risk assessment. Based on the developmental studies in rats and rabbits, and the 3-generation and

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neurodevelopmental studies in rats, there is no evidence of increased susceptibility. The neurotoxicity observed in adult animal studies raised a concern for potential neurodevelopmental effects. A rat neurodevelopmental toxicity (DNT) study is available. In this study, the lowest dose showing neurotoxicity in the offspring (effects on mortality, body weights, body weight gains, learning, learning and memory, and brain morphometry) is 10 mg/kg bw/day, with a NOAEL of 4 mg/kg bw/day. Effects in offspring and adult animals are found at a similar dose based on body weight decreases. It should be noted that some of the parameters evaluated in this DNT study were regarded as acceptable but several others were not, leading to a study classification of "unacceptable." The study deficiencies which, taken together, led to the unacceptable classification include: 1) statistical analyses that adjusted for body weights after treatment had begun, 2) an inadequate assessment of motor activity, 3) an inadequate assessment of auditory startle in PND 61 females, and 4) missing low- and mid-dose morphometry data. However, it is not likely that these limitations will impact the risk assessment for the following reasons. The slight changes in brain morphometry were seen at the highest dose tested. Because these changes were slight, it is uncertain whether toxicologically significant differences would be seen at the mid dose, and it is unlikely that significant changes would be seen at the lowest dose tested. The auditory startle response is considered adequate for assessment in PND 23 males/females and PND 61 males where no treatment-related effects were seen in auditory startle response. Only the auditory response data for PND 61 females is inadequate. Motor activity was examined and there did not appear to be any differences between treated and control animals other than decreases for multiple subsessions in PND 18 males/females at the high dose only, but due to the high variability and the lack of habituation, these data are considered equivocal. If a 10-fold factor is applied to the NOAEL in the study (i.e., 4 mg/kg bw/day) to account for the scientific limitations of the study, the resulting value is 0.4 mg/kg bw/day. The estimate of 0.4 mg/kg/day is similar to the doses from the chronic dog study used for risk assessment (i.e., 0.5 mg/kg/day for acute dietary exposure scenarios and 0.1 mg/kg/day for chronic dietary exposure scenarios). In the exposure databases, there are also no residual uncertainties. The exposure assessments are based on reliable data and reasonable worst-case assumptions, and will not likely underestimate risks. There was no published literature found that would indicate a neurodevelopmental concern for lambda-cyhalothrin.

Based on all of the considerations above, there is not a need to retain the additional 10X safety factor for children. Application of the 10X intraspecies uncertainty factor (which accounts for the possibility that a subpopulation may be 10 times more sensitive than the average individual) and a 10X interspecies factor (which accounts for the possibility that humans may be 10 times more sensitive than animals) to the dog NOAEL (i.e., the most sensitive species) should assure protection of human health including children.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Metabolism studies have been conducted with cyhalothrin in both the rat and the dog, and with lambda-cyhalothrin in the rat. In the rat, approximately 55% of the oral dose is absorbed. It is extensively metabolized when absorbed. The urinary/fecal excretion ratio is 2.5:1.0 after subcutaneous administration. Over 50% of the dose remained in the carcass 7 days after a subcutaneous dose. Metabolism results in cleavage of the ester to cyclopropylcarboxylic acid and a phenoxybenzyl derivative. The distribution patterns and excretion rates in the multiple

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oral dose studies are similar to the single oral dose studies. There is accumulation of unchanged compound in the fat upon chronic administration. Otherwise, cyhalothrin is rapidly metabolized and excreted. Cyclopropyl carboxylic acid, 3-phenoxybenzoic acid, glucuronide conjugated 3-4'-hydroxyphenoxy benzoic acid, and a sulfate conjugate were identified in the urine.

Cyhalothrin is taken up slowly by the fat, and released slowly. It is rapidly released by blood, kidneys, and liver. The rates of metabolism of both enantiomer pairs are likely identical (cyhalothrin and lambda-cyhalothrin). The absorption, distribution, metabolism, and excretion patterns of lambda-cyhalothrin and cyhalothrin following a single dose of 1 mg/kg in the male rat appear to be identical.

In the dog, oral absorption of the C_{14} benzyl label was 80%, and absorption of the C_{14} cyclopropyl label was 48%. The metabolite patterns for each half of the molecule were different, indicating extensive cleavage of the ester bond. Seven metabolites in the urine were identified for the benzyl label, and 12 metabolites were identified for the cyclopropyl label. In the feces, a large proportion of the radioactivity was due to unchanged compound. Excretion in the urine and feces was rapid (nearly all in 48 hours).

Oral and dermal metabolism and pharmacokinetics studies were conducted in humans. Mild paresthesia of varying degrees was observed following dermal dosing. The minimal oral absorption was estimated to be from 50.35 to 56.71%. The minimal dermal absorption was estimated to be from 0.115 to 0.122%. The estimated dermal absorption value of 1% was determined by rounding these values up to the nearest whole number. No metabolites were found near the limit of detection in plasma from the oral dose study. Blood was not analyzed from the dermal study.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

Acceptable developmental studies conducted with cyhalothrin are available in both rats and rabbits. A 3-generation reproduction study in rats conducted with cyhalothrin is available for FQPA consideration. Neurotoxicity is evident throughout the toxicology database. A DNT study has recently been submitted, and reviewed by the Agency. The lowest dose showing neurotoxicity in the offspring (effects on mortality, body weight, body weight gains, learning and memory, and brain morphometry) is 10 mg/kg bw/day. It should be noted that some of the parameters evaluated in this study were regarded as acceptable but others were not (see Sections 3.1.3 and 3.3.2 for further details). If a 10-fold factor is applied to the NOAEL (i.e., 4 mg/kg bw/day) to account for the scientific limitations of the study, the resulting value is 0.4 mg/kg bw/day. This estimate of 0.4 mg/kg/day is similar to the doses from the chronic dog study used for risk assessment (i.e., 0.5 mg/kg/day for acute dietary exposure scenarios and 0.1 mg/kg/day for chronic dietary exposure scenarios). Therefore, HED concludes that using the NOAELs from the dog study would not underestimate risks from dietary exposure, and consequently, the FQPA safety factor can be reduced to 1X. In conclusion, the toxicology database is considered complete for the purposes of the FQPA assessment.

3.3.2 Evidence of Neurotoxicity

Neurotoxicity is evident in three species (rat, mouse, and dog), and via all three routes of exposure in rats (oral, inhalation, and dermal). The neurotoxic effects observed (gait

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abnormalities, tremors, convulsions, excess salivation) are common to the pyrethroid class of pesticides. Signs generally appear several hours after dosing, and disappear by the next day; they are transitory in nature, and stop with the removal of the test compound.

The DNT in Wistar rats was conducted and submitted to the Agency (MRID 46449102); the calculated doses were 1.8, 4.3, and 10.0 mg/kg/day during gestation and 4.0, 9.4, and 23.1 mg/kg/day during lactation. The maternal LOAEL was 10 mg/kg/day, based on decreased body weight, body weight gains, and food consumption. The maternal NOAEL was 4 mg/kg/day. At the highest dose tested, offspring had a 6% decrease in pre-cull survival, a maximum of 12% decrease in body weights, the mean time to completion of the water maze in PND 21 females was longer, the proportion of successful trials in PND 21 females was lower than controls for cut-off times ranging from 3-10 seconds, the group mean success rate at 1.5 the straight channel swim time in PND 21 females was decreased (NS), the proportion of successful trials for cut-off times from 3-9 seconds in PND24 females were still decreased, and morphometric measurement were affected up to a maximum13% difference compared to controls. Although Offspring neurotoxicity was seen with a LOAEL/NOAEL of 10/4, a definitive LOAEL/NOAEL cannot be determined due to many data insufficiencies. The study is unacceptable due to an inadequate assessment of motor activity, an inadequate assessment of auditory startle in PND 61 females, missing low- and mid-dose morphometry data, and statistical analyses that adjusted for body weights after treatment had begun.

3.3.3 Developmental Toxicity Studies

The requirements for developmental studies conducted with lambda-cyhalothrin have been satisfied by developmental studies conducted with cyhalothrin. The data demonstrate no indication of increased quantitative or qualitative sensitivity of rats or rabbits to *in utero* exposure to cyhalothrin. No developmental toxicity was observed in either of the developmental toxicity studies in rats and rabbits. Maternal toxicity was observed in the form of clinical signs of neurotoxicity in the rat study; additionally, reduced body weight gain and food consumption were observed in both the rat and the rabbit studies.

3.3.4 Reproductive Toxicity Study

The requirement for a reproduction study conducted with lambda-cyhalothrin has been satisfied by a reproduction study conducted with cyhalothrin. The data demonstrate no indication of increased quantitative or qualitative sensitivity of rats to post-natal exposure to cyhalothrin. In the 3-generation reproduction study in rats, the parental/offspring NOAELs are the same, based on decreased parental and pup body weight and body weight gain.

3.3.5 Pre- and/or Post-Natal Toxicity

3.3.5.1 Determination of Susceptibility

Based on the available developmental toxicity studies in rats and rabbits, and the 3-generation reproduction study in rats using cyhalothrin, there is no increased quantitative or qualitative susceptibility to fetuses exposed *in utero*.

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3.3.5.2 Degree of Concern Analysis and Residual Uncertainties

Although the developmental and reproduction studies were conducted with cyhalothrin, and while lambda-cyhalothrin is more refined, the degree of concern for pre- and/or post-natal susceptibility is low. Comparing the LOAELs from all the toxicity studies (across four species - rat, mouse, rabbit, dog), the LOAELs from the subchronic and chronic dog studies, based on clinical signs of neurotoxicity, are the lowest/most conservative doses and endpoints available. The LOAEL from the subchronic dog study (using cyhalothrin as the test compound) is 2.5 mg/kg/day, based on clinical signs of neurotoxicity (NOAEL = 1.0 mg/kg/day). Studies of similar duration (subchronic, developmental, and reproduction studies) via the oral route, show that rats were adversely affected by cyhalothrin/lambda-cyhalothrin at doses between 5.0 – 15.0 mg/kg/day, based primarily on decreased body weights and body weight gains. In the subchronic mouse study, mice had decreased body weight gain and food consumption, changes in hematology and organ weights, and minimal centrilobular hepatocyte enlargement at a dose level of 309/294 mg/kg/day M/F, respectively. Rabbits in the developmental study using cyhalothrin had a LOAEL of 30 mg/kg/day, based on decreased body weight gains and food consumption. Over a longer duration, dogs exposed to lambda-cyhalothrin showed clinical signs at the LOAEL of 0.5 mg/kg/day (NOAEL = 0.1 mg/kg/day), compared to the chronic rat study which showed decreases in body weights at 12.5 mg/kg/day and the chronic mouse study which showed clinical signs and decreased body weight at 75 mg/kg/day. Lambda-cyhalothrin is an enriched isomer of cyhalothrin, and many of the cyhalothrin studies have been used to bridge the toxicology database between the two chemicals. Therefore, by selecting endpoints based upon the effect of concern (neurotoxicity) in the most sensitive species (dog) using the active ingredient lambda-cyhalothrin, the doses/endpoints selected for risk assessment are appropriate and protective of potential effects seen in the other species at higher dose levels, including developmental and reproductive effects. Since there are no signs of increased susceptibility in rats or rabbits, the Agency is confident that the risk to infants and children will not be underestimated.

3.3.6 Recommendation for a Developmental Neurotoxicity Study

HED has received a developmental neurotoxicity study (DNT) for lambda-cyhalothrin (MRID 46449102), which was classified as unacceptable/guideline due to inadequacies in some of the developmental parameters tested (see DER for more details). If a 10-fold factor is applied to this study's NOAEL, (i.e., 4 mg/kg bw/day) to account for the scientific limitations of the study, the resulting value is 0.4 mg/kg bw/day. This estimate of 0.4 mg/kg/day is similar to the doses from the chronic dog study used for risk assessment (i.e., 0.5 mg/kg/day for acute dietary exposure scenarios and 0.1 mg/kg/day for chronic dietary exposure scenarios). Therefore, HED concludes that using the NOAELs from the dog study would not underestimate risks to infants and children from dietary exposure, and consequently, a repeat rat DNT study is not required.

3.3.7 Rationale for the UF_{DB}

As discussed in section 3.3.6, HED is confident that using the NOAELs from the chronic dog study as the basis for the acute and chronic dietary endpoints would not underestimate risks to infants and children, and consequently, the FQPA safety factor can be reduced to 1X. Thus, the toxicology database is considered complete for the purposes of this risk assessment, and a database uncertainty factor (UF_{DB}) is not required.

3.4 FQPA Safety Factor for Infants and Children

The toxicology database is considered complete for the purposes of an FQPA risk assessment. Based on the developmental studies in rats and rabbits, and the 3-generation study in rats, there is no evidence of increased quantitative or qualitative susceptibility. Using the NOAELs from the chronic dog study would not underestimate risks to infants and children.

There are no residual uncertainties identified in the exposure databases. The acute and chronic dietary food exposure assessments utilize anticipated residues based on USDA PDP monitoring data, field trial data, and a beef-fat market basket survey. Percent crop treated data were used for many commodities in the analysis, although 100%CT was assumed for new uses, and for existing uses where no further information was available. Although refined, the assessments are based on reliable data, and will not underestimate exposure/risk. The drinking water exposure is based on conservative modeling estimates. The residential exposure assessment utilizes residential SOPs for the adult handler and post-application scenarios, and to assess post-application exposure to children, as well as incidental oral ingestion by toddlers. The residential SOPs are based on reasonable worst-case assumptions, and will not likely underestimate exposure/risk.

Based on the above hazard and exposure considerations, the FQPA safety factor can be reduced to 1X for the current lambda-cyhalothrin risk assessment.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – General Population

Study Selected: Chronic Dog Study (λ-cyhalothrin)

MRID Number: 40027902

Executive Summary: In a chronic toxicity study, beagle dogs (6 sex\dose) were given oral administration of gelatin capsules containing lambda-cyhalothrin (96.5%) at 0, 0.1, 0.5, or 3.5 mg/kg/day, 7 days a week for 12 months. The test chemical had been dissolved in corn oil prior to placement in the capsules. The following parameters were measured and/or recorded: daily clinical observations, body weights, food consumption, ophthalmological examinations, clinical biochemistry, urinalysis, gross necropsy, and microscopic examinations.

No treatment-related toxicity was observed at 0.1 mg/kg/day. At 0.5 mg/kg/day, 1 male and 1 female dog exhibited gait abnormalities, with the effects seen in the male 7 hours post-dosing during week 2, and again 2 days later (immediately after dosing), and in the female 4 times during week 9. Convulsions were seen in two other dogs (both males); the convulsions appeared to be precipitated by the stress of handling or noise. At 3.5 mg/kg/day, the principal neurological clinical signs following dosing were ataxia (all dogs, apparent from day 2 in 2 dogs, observed 3-7 hours post-dosing), muscle tremors and convulsions, occasional subdued behavior; worn or bleeding claws, regurgitation of food during first 2 weeks, and fluid feces in all dogs. Treatment had no effect on body weights, hematology, clinical chemistry, urinalysis, nor gross or histopathology. The NOAEL is 0.1 mg/kg/day, and the LOAEL is 0.5 mg/kg/day, based on clinical signs of neurotoxicity.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a study (83-1) in the dog.

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Dose and Endpoint for Risk Assessment: NOAEL = 0.5 mg/kg/day, based on clinical signs of neurotoxicity (ataxia) observed from Day 2, 3-7 hours post-dosing, seen at LOAEL = 3.5 mg/kg/day.

Comments on Study/Endpoint/Uncertainty Factors: The endpoint selected for assessment of acute dietary risk is appropriate because it is based on effects that were observed within the first 2 days of exposure in an oral study in dogs. Based on structure-activity relationships, it is likely that this NOAEL could be higher. The NOAEL used for the acute dietary endpoint is 0.5 mg/kg, with a LOAEL of 3.5 mg/kg. With other pyrethroids, NOAELs were closer to 1.0 mg/kg, and LOAELs were around 2.0-3.0 mg/kg.

3.5.2 Chronic Reference Dose (cRfD) – General Population

Study Selected: Chronic Dog Study (lambda-cyhalothrin)

MRID Number: 40027902

Executive Summary: See Section 3.5.1.

Dose and Endpoint for Risk Assessment: NOAEL = 0.1 mg/kg/day, based on clinical signs of neurotoxicity (abnormal gait) in 2 dogs observed at the LOAEL = 0.5 mg/kg/day.

Comments on Study/Endpoint/Uncertainty Factors: The endpoint selected for assessment of chronic dietary risk is appropriate because it is based on a chronic oral study in dogs. This NOAEL (0.1 mg/kg/day) is somewhat lower than those seen in dog studies with other pyrethroids; however, transient effects were observed in several dogs at 0.5 mg/kg/day.

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

Study Selected: Chronic Dog Study (lambda-cyhalothrin)

MRID Number: 40027902

Executive Summary: See Section 3.5.1.

Dose and Endpoint for Risk Assessment: NOAEL = 0.1 mg/kg/day, based on clinical signs of neurotoxicity (abnormal gait) in 2 dogs observed at the LOAEL = 0.5 mg/kg/day.

Comments on Study/Endpoint/Uncertainty Factors: This endpoint is based on the same chronic dog study that was selected for the acute and chronic dietary endpoints. It is considered appropriate for both short- and intermediate-term exposure durations because the transient effects were observed during weeks 2 and 9.

3.5.4 Dermal Absorption

Several dermal penetration studies are available for lambda-cyhalothrin, one in humans, and one in rats. The human study indicates a dermal absorption estimate of 1%. The rat study indicates a dermal absorption estimate of 16%. In the rat study, absorption ranged from 0.24 to 15.89%. The study authors believed that paresthesia at the high dose caused the protective cover over the dosing site to loosen and resulted in spreading of test material over the skin. Thus, a relatively high percentage of the dose was found in the carcass (16% at 24 hours exposure).

3.5.5 Dermal Exposure (All Durations)

Study Selected: 21-Day Dermal Toxicity Study in Rats (lambda-cyhalothrin)

MRID Number: 44333802

Executive Summary: In a repeated-dose dermal toxicity study (MRID #44333802), lambda-cyhalothrin (96.6% ai) was applied to the clipped skin of five albino rats/sex/dose at

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dose levels of 1 or 10 mg/kg/day for 6 hours/day on 21 consecutive days. Five rats/sex were similarly treated with two or three applications at 100 mg/kg/day, reduced to 50 mg/kg/day for 21 consecutive days.

Two males which were found dead after three applications of 100 mg/kg/day had reduced, moderately-atrophied seminal vesicles, and slightly atrophied spleens. Clinical signs indicative of neurotoxicity were observed in the 100/50 mg/kg/day treatment groups. Males exhibited reduced splay reflex, downward curvature of the spine, splayed gait, bizarre behavior, pinched-in sides, dehydration, reduced stability, and thin appearance. Females exhibited an increased incidence of tiptoe gait, upward curvature of the spine, an increased incidence in signs of urinary incontinence, urinary incontinence, chromodacryorrhea, and reduced splay reflex. The clinical signs commenced on day 2 of dosing. Body weight gains for males were significantly reduced throughout the study; the final gain was 58% lower than the control gain. The final mean body weight was 19% lower than the mean control value. Body weight gains for females were somewhat reduced during the first half of the study only. Food consumption was somewhat reduced for males throughout the study. No dermal irritation was observed at 100/50 mg/kg/day in either sex. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related. No treatment-related differences in hematology or clinical blood chemistry parameters, organ weights, or histopathology were observed between the treatment and control groups. No neoplastic tissue was observed. The LOAEL is 50 mg/kg/day for both sexes, based on clinical signs of toxicity, and decreased body weight and body weight gain. The NOAEL is 10 mg/kg/day for both males and females.

This dermal toxicity study is classified acceptable (82-2), and satisfies the guideline requirement for a repeated-dose dermal toxicity study.

Dose and Endpoint for Risk Assessment: NOAEL = 10 mg/kg/day, based on clinical signs of neurotoxicity (observed from Day 2), and decreased body weight and body weight gain observed at the LOAEL = 50 mg/kg/day.

Comments on Study/Endpoint/Uncertainty Factors: This endpoint is based on a 21-day dermal study in the rat. This study used the most appropriate route of administration (dermal), and the effects of concern (clinical signs of neurotoxicity) were observed. Although the duration of this study is only 21 days, it is anticipated that this study will be protective of longer-term exposure because a comparison of the 90-day oral study in rats with the chronic feeding study in rats indicates that toxicity is not induced at lower dose levels when rats are exposed over a longer period of time. The NOAEL/LOAEL for the 90-day oral study are 2.5/12.5 mg/kg/day, based on decreased body weight gain, and the NOAEL/LOAEL for the chronic feeding study in rats are 2.5/12.5 mg/kg/day, based on decreases in mean body weight. No developmental effects were observed in any of the developmental studies. In addition, application of the 1% dermal absorption factor to the oral NOAEL of 0.1 mg/kg/day established in the chronic dog study yields a dermal equivalent dose of 10 mg/kg/day (0.1 ÷ 0.01 = 10.0) which is the same dermal NOAEL used for the dermal risk assessment. Thus, the NOAEL from the dermal rat study is protective of effects and doses observed in dogs. Also, as the design of the 21-day dermal study is similar to most of the oral studies, with respect to the neurotoxic effects of concern, it is expected that the dermal study would detect any effects observed in any of the oral studies.

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3.5.6 Inhalation Exposure (All Durations)

Study Selected: 21-Day Inhalation Study in Rats (lambda-cyhalothrin)

MRID Number: 41387702

Executive Summary: In a 21-day inhalation study, 10/sex/dose SPF Alpk:APfSD (Wistar-derived) albino rats were exposed nose-only 6 hours/day, 5 days/week for 21 days to lambda-cyhalothrin (81.5% pure) at 0, 0.3, 3.3, or 16.7 µg/L (estimated to be approximately 0, 0.08, 0.90, or 4.5 mg/kg/day). The MMAD ranged from 1.47 to 1.91 µm, and the GSD ranged from 1.02 to 2.24 µm.

No treatment-related effects were observed at 0.3 µg/L. At 3.3 µg/L the following were observed: salivation, lachrymation, paw flicking (males only), tail erections, splayed gait (males only), decreased body weight (94-95%, $p < 0.05$) and body weight gain (53-65%, $p < 0.01$) relative to control values, increased incidence of punctate foci on the cornea, slight reductions in cholesterol levels in females ($p < 0.05$), decreased urine volume in males, slightly raised specific gravity of the urine in both sexes, and reductions in urinary protein levels in males. At 16.7 µg/L, the following were observed: salivation, lachrymation, auditory hypoaesthesia, paw flicking, tail erection, splayed gait, decreased activity, reduced foot withdrawal (males only), head flicking, reduced righting reflex, shaking (males only), sides pinched in, reduced splay reflex, decreased visual placing response, absent puma reflex (females only), ungroomed appearance (females only), tiptoe gait (males only), respiratory noise decreased body weight (85-88%, $p <0.01$) and body weight gain (<3-14%, $p < 0.01$) relative to control values, decreased food consumption (46-91% ♂, 56-87% ♀) relative to control values, changes in selected clinical chemistry values (particularly in females), decreased urine volume, increased urine specific gravity, and decreased urinary protein. There was also a slight increase in the incidence of alveolitis in high dose females.

The NOAEL is 0.3 µg/L (0.08 mg/kg/day), and the LOAEL is 3.3 µg/L (0.90 mg/kg/day), based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females, and slight changes in selected urinalysis parameters.

This inhalation toxicity study is classified as acceptable (non-guideline), and does not satisfy any particular guideline requirement. The study is too short for a guideline study, and individual animal data were not provided.

Dose and Endpoint for Risk Assessment: NOAEL = 0.3 µg/L (0.08 mg/kg/day), based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females, and slight changes in selected urinalysis parameters observed at the LOAEL = 3.3 µg/L (0.90 mg/kg/day).

Comments on Study/Endpoint/Uncertainty Factors: This endpoint is based on a 21-day inhalation study in the rat. This study used the most appropriate route of administration (inhalation), and the effects of concern (clinical signs of neurotoxicity) were observed. No developmental effects were observed in any of the developmental studies. Therefore, since the design of the 21-day inhalation study is similar to most of the oral studies, with respect to the neurotoxic effects of concern, it is expected that the inhalation study will reflect any other effects observed in any of the oral studies. Although the duration of this study is only 21 days, it is anticipated that this study will be protective of longer-term exposure because comparison of the 90-day oral study in rats with the chronic feeding study in rats found that toxicity is not induced at lower dose levels when rats are exposed over a longer period of time.

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3.5.7 Level of Concern for Margin of Exposure

Table 3.5.7 Summary of Levels of Concern* for Lambda-Cyhalothrin Risk Assessment.			
Route	**Short-Term (1-30 Days)**	**Intermediate-Term (1-6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Incidental Oral	100	100	100

* The level of concern is based upon a 10x intra-species variability factor, and a 10x inter-species extrapolation factor.

3.5.8 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. For short-, intermediate-, and long-term aggregate risk assessments, the oral, dermal, and inhalation exposures can be combined in this case owing to a common toxicity endpoint (neurotoxicity).

3.5.9 Classification of Carcinogenic Potential

Lambda-cyhalothrin is classified as "not likely to be carcinogenic to humans," based on the lack of evidence of carcinogenicity in mice and rats.

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3.5.10 Summary of Toxicological Doses and Endpoints for Lambda-Cyhalothrin for Use in Human Risk Assessments

Table 3.5.10a Summary of Toxicological Doses and Endpoints for Lambda-Cyhalothrin to be Used in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 0.5 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Acute RfD = 0.005 mg/kg/day aPAD =0.005 mg/kg/day	Chronic Dog Study (lambda-cyhalothrin) LOAEL = 3.5 mg/kg/day, based on clinical signs of neurotoxicity (ataxia) observed from Day 2, 3-7 hours post-dosing.
Chronic Dietary (All Populations)	NOAEL = 0.1 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Chronic RfD = 0.001 mg/kg/day cPAD = 0.001 mg/kg/day	Chronic Dog Study (lambda-cyhalothrin) LOAEL = 0.5 mg/kg/day, based on clinical signs of neurotoxicity (abnormal gait) in two dogs.
Incidental Oral Short- and Intermediate-Term (1-30 days, 1-6 months)	NOAEL = 0.1 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Residential LOC for MOE < 100	Chronic Dog Study (lambda-cyhalothrin) LOAEL = 0.5 mg/kg/day, based on clinical signs of neurotoxicity (abnormal gait) in two dogs.
Dermal Short-Term (All Durations)	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Residential LOC for MOE < 100	21-Day Dermal Study in Rats (lambda-cyhalothrin) LOAEL = 50 mg/kg/day, based on clinical signs of neurotoxicity (observed from Day 2), and decreased body weight and body weight gain.
Inhalation Short-Term (All Durations)	NOAEL = 0.08 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Residential LOC for MOE < 100	21-Day Inhalation Study in Rats (lambda-cyhalothrin) LOAEL = 0.90 mg/kg/day, based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females, and slight changes in selected urinalysis parameters.
Cancer (Oral, Dermal, Inhalation)	Classification: "not likely to be carcinogenic to humans," based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data, and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = No Observed Adverse Effect Level. LOAEL = Lowest Observed Adverse Effect Level. UF = Uncertainty Factor. UF_A = extrapolation from animal to human (inter-species). UF_H = potential variation in sensitivity among members of the human population (intra-species). FQPA SF = FQPA Safety Factor. PAD = Population Adjusted Dose (a = acute, c = chronic). RfD = Reference Dose. MOE = Margin Of Exposure. LOC = Level Of Concern.

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Table 3.5.10b Summary of Toxicological Doses and Endpoints for Lambda-cyhalothrin to be Used in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (All Durations)	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Occupational LOC for MOE < 100	21-Day Dermal Study in Rats (lambda-cyhalothrin) LOAEL = 50 mg/kg/day, based on clinical signs of neurotoxicity (observed from Day 2), and decreased body weight and body weight gain.
Inhalation Short-Term (All Durations)	NOAEL = 0.08 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Occupational LOC for MOE < 100	21-Day Inhalation Study in Rats (lambda-cyhalothrin) LOAEL = 0.90 mg/kg/day, based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females, and slight changes in selected urinalysis parameters.
Cancer (Oral, Dermal, inhalation)	Classification: "not likely to be carcinogenic to humans," based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data, and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = No Observed Adverse Effect Level. LOAEL = Lowest Observed Adverse Effect Level. UF = Uncertainty Factor. UF_A = extrapolation from animal to human (inter-species). UF_H = potential variation in sensitivity among members of the human population (intra-species). FQPA SF = FQPA Safety Factor. MOE = Margin Of Exposure. LOC = Level Of Concern.

3.6 Endocrine Disruption

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

In the available toxicity studies on cyhalothrin and lambda-cyhalothrin, there was no estrogen, androgen, and/or thyroid mediated toxicity.

4.0 PUBLIC HEALTH AND PESTICIDE EPIDEMIOLOGY DATA

No public health/epidemiology data were used in developing this risk assessment.

5.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The nature of the residue in plants is adequately understood, based on adequate cotton, cabbage, soybean, and wheat metabolism studies. Lambda-cyhalothrin is metabolized by cleavage of the ester linkage to form cyclopropanecarboxylic acids and the corresponding phenoxybenzoic acids or alcohols. In most cases the parent compound is the principal constituent of the residue. However, in the cabbage metabolism study the cis- and trans-cyclopropanecarboxylic acids were the major constituents. HED has concluded that the plant metabolites need not appear in the tolerance expression at this time owing to lack of toxicological concern, and low concentrations found from residue studies (Memo; Pamela Hurley; 1/3/1992). The residues to be regulated are lambda-cyhalothrin and its epimer R157836.

5.1.2 Metabolism in Rotational Crops

An adequate confined rotational crop study is available indicating that significant residues (greater than 0.01 ppm) will not be present in crops rotated 30 days after application of lambda-cyhalothrin (EFED review; 4/6/1988). No additional rotational crop data are required, and no plant-back restrictions are required on the labels, based on the non-systemic nature of lambda-cyhalothrin, and its half-life of 10-14 days (NV920006; D185478; George Herndon; 10/8/1992).

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5.1.3 Metabolism in Livestock

Studies of lambda-cyhalothrin metabolism in ruminants and poultry have been reviewed. Lambda-cyhalothrin is the major component of the residue in animals, except in kidney and liver, where, in addition to the plant metabolites, 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropane-carboxylic acid (OH-CPA) and 4-hydroxy-3-phenoxybenzoic acid (4'-OH-3PBAcid) may be present in significant quantities. A residue transfer study, in which cows were fed dietary levels of 8, 25, or 80 ppm lambda-cyhalothrin, demonstrated that, at < 8 ppm, OH-CPA levels in tissue would not exceed 0.01 ppm (PPs#2F4109, 2F4114, 7F3560, and 1F3992; M. Flood; 8/31/1992). As with plants, HED has determined that the residues to be regulated are lambda-cyhalothrin and its epimer R157836. The animal metabolites do not need to appear in the tolerance expression.

5.1.4 Analytical Methodology

Adequate GC/ECD methods are available for enforcing tolerances for lambda-cyhalothrin residues in plant and animal commodities. ICI Method 81 (PRAM 81) is available for determining residues of lambda-cyhalothrin and its epimer in plant matrices, while ICI Method 86 (PRAM 86) is available for determining residues of lambda-cyhalothrin and its epimer in animal matrices. Both methods have been validated by EPA as adequate enforcement methods.

For Method PRAM81, residues of lambda-cyhalothrin and R157836 are extracted with acetone/hexane (1:1, v/v), and cleaned using liquid-liquid chromatography to remove lipids, followed by Florisil column chromatography. Residues are then determined by GC/ECD; the method LOQ is 0.01 ppm for both analytes.

For Method PRAM86, residues are extracted from milk or animal tissues with 50% acetone/hexane. The aqueous fraction is removed, after which the residues are then dried over sodium sulfate, and cleaned up using a Florisil column. Residues are determined by GC/ECD; the method LOQ is 0.01 ppm for both analytes.

In the field trials submitted with the current petitions, residues of lambda-cyhalothrin and R157836 were determined using GC/ECD methods, which are more recent modifications of the current tolerance enforcement method for plant commodities. For the analysis of potatoes and cucurbit vegetables, residues were extracted with acetone/hexane (1:1, v/v) and sodium sulfate, filtered, and partitioned with aqueous sodium chloride. Residues in the resulting hexane fraction were then cleaned up using Florisil columns, and analyzed by GC/ECD using external standards. The validated LOQ is 0.01 ppm for each analyte, for a combined LOQ of 0.02 ppm.

For the analysis of grass commodities, residues were extracted with acetone/hexane (1:1, v/v), filtered, and cleaned up using a silica gel solid-phase extraction (SPE) cartridge. Residues were then analyzed by GC/ECD using external standards. For each grass matrix, the validated LOQ is 0.003 ppm for lambda-cyhalothrin, and 0.007 ppm for R157836, for a combined LOQ of 0.01 ppm.

Each of these GC/ECD methods was adequately validated in conjunction with the analysis of field trial samples using fortified control samples. Recoveries of lambda-cyhalothrin averaged 89-96% (with standard deviations of 10-13%) from cucurbit vegetables, 85-93% (s.d. 14-17%) from grass commodities, and 90% (s.d. 10%) from potatoes. Recoveries of R157836 averaged 87-99% (s.d. 8-15%) from cucurbit vegetables, 80-95% (s.d. 11-18%) from grass commodities, and 91% (s.d. 11%) from potatoes. Apparent residues were less than the LOQ in

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most controls samples, and where apparent residues were above the LOQ in control samples, the residues were substantially less than the residues in the associated treated samples.

5.1.5 Environmental Degradation

The environmental fate database for lambda-cyhalothrin is substantially complete, but it contains various supplemental studies. Lambda-cyhalothrin is expected to have little mobility in soil surfaces and, therefore, leaching into groundwater is not expected to be an important environmental fate process (average K_{OC} = 354,100; n = 10). Volatilization from moist or dry surfaces is not expected to be an important transport process. Lambda-cyhalothrin has a relatively low vapor pressure and Henry's Law constant (1.5×10^{-9} mm Hg and 2.4×10^{-7} Atm-cm^3/mole, respectively). With a $pK_a > 9$, lambda-cyhalothrin is expected to be neutral in natural environments, but will be affected in alkaline environments.

Lambda-cyhalothrin is moderately persistent in the environment, and degrades slowly through a combination of biotic and abiotic mechanisms. Lambda-cyhalothrin is stable in acidic and neutral water, but hydrolyzes under alkaline conditions (half-life of 13 days at pH 9). Lambda-cyhalothrin is more stable to light than the first or second generation pyrethroids like allethrin and resmethrin, but still undergoes some photolysis in water, with half-lives of about a month or more in distilled water (half-life 25 days). On soil, the half-life is fairly stable (with little degradation on the order of ~13% in 35 days). It appears that the alpha cyano group stabilizes the molecule, and it does not undergo photolysis readily. Under both aerobic and anaerobic soil metabolism conditions, lambda-cyhalothrin biodegrades at moderate rates, with half-lives ranging from 12 to 72 days, but in aquatic metabolism conditions, it biodegrades more slowly, with half-lives on the order of about 113-142 days. Terrestrial field dissipation studies indicate that a combination of these mechanisms of dissipation take place. Half-lives of 12-64 days were observed in the field.

Indications are that, for synthetic pyrethroids with similar structure to that of lambda-cyhalothrin, dissipation from plant foliage occurs with half-lives on the order of 5-6 days, but it may be higher for the total residues. A low rate of volatilization was observed from leaves, with 88% of the compound applied remaining on the leaves after 24 hours (*European Commission Review Report for the Active Substance Lambda-Cyhalothrin*; 7572/VI/97-final; 1/25/2001). The chemical does not translocate in the plant tissue. Lambda-cyhalothrin is expected to be immobile in soil environments. Due to its low mobility, it is highly unlikely to reach ground waters. However, despite the protective imposed buffer zone and buffer strip, it could reach adjacent surface waters via spray drift or runoff events (via erosion). Once there, the chemical will partition with the sediment, and will linger for long periods of time (months). The sediment serves as a repository of the chemical after numerous applications, in dynamic equilibrium with the pore water and the surface water.

Lambda-cyhalothrin is moderately bioaccumulative (448X in the whole body), but it depurates slowly (only 10-15% depuration after 21 days). It appears that situations may occur where this chemical may persist in fish tissue for extended periods of time.

The (±) cis- or trans-3-(2-trifluoromethyl-2-chloro-ethenyl)-2,2-dimethylcyclopropane carboxylic acid and 3-phenoxybenzaldehyde are the result of the hydrolysis of the ester linkage of the pyrethroid structure. However, in general, the major degradates appear to be (±)cis- or trans-3-(2-trifluoromethyl-2-chloro-ethenyl)-2,2-dimethylcyclopropane carboxylic acid and 3-phenoxy-benzoic acid (3-PBA, or 3-PBacid, the oxidation product of 3-phenoxybenzaldehyde).

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It appears that 3-phenoxybenzaldehyde oxidizes quickly to 3-PBA. The findings in the field corroborate the laboratory predictions.

Ring-hydroxylated lambda-cyhalothrin, degradate XV (see Table B.1 in Appendix B), formed in aerobic soil microbial degradation (12% of the applied compound at 63 days post-treatment), was included in the drinking water assessment due to its potential toxicological concerns in humans. This degradate appears to degrade readily to carbon dioxide (average $t_{1/2}$ = 8.9 days; n = 3), and it appears to partition with the sediment. It has low mobility based on the estimated K_{OC} value of 770,900 mL/g_{OC} from structure activity relationship (SAR) modeling. The potential for groundwater contamination by this degradate is low. However, it is likely to reach surface water via runoff (through erosion) after a rainfall event.

5.1.6 Comparative Metabolic Profile

Metabolism studies have been conducted with cyhalothrin in both the rat and the dog, and with lambda-cyhalothrin in the rat. In the rat, approximately 55% of the oral dose is absorbed. It is extensively metabolized when absorbed. The urinary/fecal excretion ratio is 2.5:1.0 after subcutaneous administration. Over 50% of the dose remained in the carcass 7 days after a subcutaneous dose. Metabolism results in cleavage of the ester to cyclopropylcarboxylic acid and a phenoxybenzyl derivative. The distribution patterns and excretion rates in the multiple oral dose studies are similar to the single oral dose studies. There is accumulation of unchanged compound in the fat upon chronic administration. Otherwise, cyhalothrin is rapidly metabolized and excreted. Cyclopropyl carboxylic acid, 3-phenoxybenzoic acid, glucuronide conjugated 3-4'-hydroxyphenoxy benzoic acid, and a sulfate conjugate were identified in the urine.

Cyhalothrin is taken up slowly in fat, and released slowly. It is rapidly released by blood, kidneys, and liver. The rates of metabolism of both enantiomer pairs are likely identical (cyhalothrin and lambda-cyhalothrin). The absorption, distribution, metabolism, and excretion patterns of lambda-cyhalothrin and cyhalothrin following a single dose of 1 mg/kg in the male rat appear to be identical.

In the dog, oral absorption of the C_{14} benzyl label was 80%, and absorption of the C_{14} cyclopropyl label was 48%. The metabolite patterns for each half of the molecule were different, indicating extensive cleavage of the ester bond. Seven metabolites in the urine were identified for the benzyl label, and 12 metabolites were identified for the isopropyl label. In the feces, a large proportion of the radioactivity was due to unchanged compound. Excretion in the urine and feces was rapid (nearly all in 48 hours).

Metabolism in plants and livestock (ruminants and poultry) also involves cleavage of the ester, resulting in formation of cyclopropylcarboxylic acid (CPA) and phenoxybenzyl derivatives. In kidney and liver, the metabolites OH-CPA and 4-hydroxy-3-phenoxybenzoic acid may be present in significant quantities.

Oral and dermal metabolism and pharmacokinetics studies were conducted in humans. Mild paresthesia of varying degrees was observed following dermal dosing. The minimal oral absorption was estimated to be from 50.35 to 56.71%. The minimal dermal absorption was estimated to be from 0.115 to 0.122%. The estimated dermal absorption value of 1% was determined by rounding these values up to the nearest whole number. No metabolites were found near the limit of detection in plasma from the oral dose study. Blood was not analyzed from the dermal study.

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5.1.7 Drinking Water Residue Profile

Table 5.1.7 Summary of Estimated Drinking Water Concentrations (EDWCs) for Lambda-Cyhalothrin.

Drinking Water Source[Model Used [1]]	Use/Application Method[Rate Modeled]	Lambda-cyhalothrin EDWCs (ppb)	Degradate of Concern, XV EDWCs (ppb)	Total EDWCs (ppb)
Groundwater [SCI-GROW [2]] Acute and Chronic	Orchards/Ground and Aerial [0.5 lb/A]	0.00300	0.000360	0.00336
Surface Water [FIRST [3]] Acute	Orchards/Ground [0.5 lb/A]	5.00	0.350	5.35
	Orchards/Aerial [0.5 lb/A]	5.00	0.298	5.30
Surface Water [FIRST] Chronic	Orchards/Ground [0.5 lb/A]	0.122	0.00758	0.130
	Orchards/Aerial [0.5 lb/A]	0.117	0.00645	0.123

1. The estimated concentrations provided in this assessment are conservative estimates of concentrations in drinking water. If dietary risks require refinement, higher-tiered crop-specific and location-specific models and modeling scenarios can be utilized.
2. The SCI-GROW (Screening Concentration In GROund Water) concentration (ppb) represents the groundwater concentration that might be expected in shallow unconfined aquifers under sandy soils. Output is used for both acute and chronic endpoints.
3. The FIRST (FQPA Index Reservoir Screening Tool) concentrations (ppb) represent untreated surface water concentrations. The peak day concentration (over 30 years) is used for acute endpoints, and the annual average concentration (over 30 years) is used for chronic endpoints.

The drinking water residues used in the dietary risk assessment were provided by EFED in a memorandum (D324222, D330149; Jose Melendez; 10/26/2006), and incorporated directly into the dietary assessment. Water residues were incorporated into DEEM-FCID via the food categories "water, direct, all sources" and "water, indirect, all sources."

The analysis is a Tier I level drinking water analysis conducted using the FIRST model; refinements may be available should they be needed. The acute level in surface drinking water was 5.35 ppb of lambda-cyhalothrin and degradate XV; the chronic level in drinking water was 0.130 ppb of lambda-cyhalothrin and degradate XV. It was assumed that the maximum application rate was used on orchards via ground applications, with the minimum interval between applications (assumed to be seven days). The groundwater concentration of lambda-cyhalothrin and degradate XV, suitable for acute and chronic purposes is 0.00336 ppb. The results are based on applications of lambda-cyhalothrin at the maximum use rate to orchards.

Comparison of results for aerial or ground applications yielded a higher chronic concentration of lambda-cyhalothrin from the 4 ground applications, as opposed to the 5 aerial applications. It also yielded higher acute and chronic results from the ground applications for the transformation product XV. The high use rate of the ground application is more important than

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the high level of drift of the aerial applications. In both cases, the peak concentration was limited by the solubility of the chemical (s = 5 ppb).

There are weaknesses in the data base, owing to the fact that some of the studies are supplemental, and part of the data set for XV was modeled through SAR; however, this is considered a conservative (screening-level) drinking water analysis.

SCI-GROW (Screening Concentration in Ground Water) provides the following warning: estimated concentrations of chemicals with K_{OC} values greater than 9995 ml/g are beyond the scope of the regression data used in SCI-GROW development. If there are concerns for such chemicals, a higher-tier groundwater exposure assessment should be considered, regardless of the concentration returned by SCI-GROW. The K_{OC} input value for lambda-cyhalothrin was 301,500 ml/g, and for its degradate, XV, it was 770,900 ml/g. Given that the K_{OC} of both lambda-cyhalothrin and the degradate, XV, are far outside the range of the K_{OC} values used to develop SCI-GROW, there may be high uncertainty regarding the estimated ground water concentrations for drinking water consumption.

There is a problem with the material balance in this assessment. By nature, the approach taken to estimate the parent plus degradate will yield higher concentrations than the actual concentrations should there be a real material balance. This occurs because the degradate is modeled "in addition" to the parent. Nevertheless, EFED considers the approach suitable for a Tier I screening-level assessment, using Tier 1 aquatic models. Should additional refinements be required, EFED may explore a different approach.

5.1.8 Food Residue Profile

Residue chemistry issues relevant to the proposed new uses requested in the current petitions were reviewed in the *Summary of Analytical Chemistry and Residue Data* memorandum for lambda-cyhalothrin (D313315; William T. Drew; 12/27/2006).

In the field trials submitted with the current petitions, the maximum frozen storage durations were 2.9-3.6 months for muskmelons, cucumbers, and squash, 3 months for potatoes, and 8.5 months for grass forage, hay, straw, and seed screenings. The available storage stability data support the storage conditions and durations for samples from the current field trials and processing studies.

Adequate cattle and poultry feeding studies, and a cattle dermal application study are available to support the existing and proposed uses. Based on the existing and recommended tolerances for plant commodities, the calculated TDB for lambda-cyhalothrin residues is 10.6 ppm for beef cattle, 10.4 ppm for dairy cattle, 0.9 ppm for swine, and 1.0 ppm for poultry. Using these TDBs and the available livestock residue data, the maximum expected lambda-cyhalothrin residues in cattle commodities are 0.35 ppm in whole milk (reflecting 8.8 ppm in milk fat), 2.5 ppm in fat, 0.11 ppm in muscle, 0.06 ppm in liver, and 0.15 ppm in kidney. The maximum expected residues in hog commodities would be 0.16 ppm in fat, 0.006 ppm in meat, and 0.011 ppm in meat-byproducts. The maximum expected residues in poultry commodities would be 0.003 ppm in eggs, 0.022 ppm in fat, 0.002 ppm in meat, and 0.003 ppm in meat-byproducts. These residue levels indicate that the current tolerances in poultry commodities, as well as in the fat, meat, and meat by-products of cattle, goats, horses, and sheep, are all adequate. However, the tolerance should be increased in milk fat (from 5 ppm to 10 ppm). The data also indicate that the current tolerances in hog commodities could be lowered to 0.2 ppm in fat, 0.01 ppm in meat, and 0.02 ppm in meat-byproducts.

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Adequate confined rotational crop data are available indicating that rotational crop restrictions and tolerances are not required for the current or proposed uses.

The available field trial data on potatoes, cucumbers, muskmelons, summer squash, and grasses are adequate, and support the proposed use patterns for lambda-cyhalothrin (CS) on tuberous and corm vegetables, cucurbit vegetables, and grasses. The number and geographic distribution of the field trials are adequate, and the appropriate samples were collected at the proposed PHIs. Following four broadcast foliar applications of lambda-cyhalothrin (CS) to potatoes (during tuber development) at the 1x rate, combined residues of lambda-cyhalothrin and R157836 were less than the LOQ (<0.02 ppm) in all potato samples harvested at the proposed 7-day PHI. Following six broadcast foliar applications of lambda-cyhalothrin (CS) to representative cucurbit vegetables (during fruit development) at the 1x rate, combined residues at the proposed 1-day PHI were <0.02-<0.03 ppm in muskmelons and cucumbers, and <0.02-<0.04 ppm in summer squash. Following single broadcast applications of lambda-cyhalothrin (CS) to grasses at the 1x rate, combined residues were 0.13-8.04 ppm in forage harvested at 0-3 days after treatment (DAT), and <0.01-6.01 ppm in hay harvested at 5-11 DAT. Following a single application at the 1x rate to grasses grown for seed, combined residues were 0.35-7.80 ppm in straw, and 0.80-3.23 ppm in seed screenings harvested at maturity, 7-19 DAT.

In addition to the new field trial data, adequate field trial data are available on rice, wheat, almonds, and pecans from previously reviewed petitions. The data on rice will be translated to support an identical use on wild rice; the data on almonds and pecans will be translated to support an identical use on pistachios; and the data on wheat will be translated to support identical uses on barley, buckwheat, oats, and rye.

Adequate processing studies are available for potato and wheat grain; processing data are not required for cucurbit vegetables, grass, nor wild rice. Based on residues in potatoes (less than the LOQ) treated at a 5x rate, residues are unlikely to be detectable in processed commodities from potatoes treated at 1x; therefore, separate tolerances are not required for potato processed fractions. However, based on the available wheat grain processing data, in which residues concentrated by 3x in bran, separate tolerances are required for both barley and rye bran, each at 0.2 ppm.

5.1.9 International Residue Limits

The Codex Alimentarius Commission, Mexico, and Canada have all established maximum residue limits (MRLs) for residues of lambda-cyhalothrin in/on a variety of raw agricultural commodities. These regulatory bodies express residues in terms of only cyhalothrin (Codex) or of lambda-cyhalothrin (Canada, Mexico); none of these tolerances include the epimer R157836 found in the U.S. tolerance expression. EPA includes the epimer due to it being considered as toxic as the active ingredient and its presence at quantifiable levels in many crops. For the crop uses currently under consideration, only potatoes have existing international tolerances. Although the recommended 0.02 ppm U.S. tolerance agrees numerically with the Codex and Mexican MRLs, strictly speaking they are not in harmony due to the different residue definitions.

5.2 Dietary Exposure and Risk

Acute and chronic dietary (food + drinking water) exposure analyses were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food

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consumption data from USDA's CSFII from 1994-1996 and 1998. The dietary exposure analyses were explicated in the *Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment* memorandum for lambda-cyhalothrin (D324223; Anant Parmar; 3/12/07).

5.2.1 Acute Dietary Exposure/Risk

A refined acute probabilistic dietary exposure assessment was performed for lambda-cyhalothrin which included all existing and proposed food uses, and drinking water. The acute dietary exposure assessment incorporated processing factors (DEEM-FCID™ default factors or, where available, factors from processing studies) and %CT estimates provided by BEAD. The estimated maximum %CT (where available) for each commodity was used in the acute dietary risk assessment; where no further information was available, and for new uses, 100%CT was assumed. Acute anticipated residues were derived from PDP monitoring data, field trial studies, and a market basket survey for beef-fat.

The Estimated Drinking Water Concentrations (EDWCs) for lambda-cyhalothrin were derived from calculations based on a maximum application rate of 0.5 lb ai/A per season to orchards (ground application) to obtain surface water concentrations. The acute drinking water concentration in surface water of 5.35 ppb was based on the FIRST estimated peak concentration.

The acute dietary exposure estimates for food and drinking water are below HED's LOC, 100% of the aPAD, at the 99.9th percentile of exposure, for the general US population and all population subgroups. Lambda-cyhalothrin acute dietary exposure at the 99.9th percentile for food and drinking water is 46% of the aPAD for the general US population, and 61% of the aPAD for all infants (<1 year old), the most highly-exposed population subgroup.

Table 5.2.1 Lambda-Cyhalothrin Acute Dietary (Food + Drinking Water) Exposure Analysis.

Population Subgroup*	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure Estimate (mg/kg/day)	% aPAD	Exposure Estimate (mg/kg/day)	% aPAD	Exposure Estimate (mg/kg/day)	% aPAD
General US Population	0.005	0.000662	13%	0.001134	23%	0.002275	46%
All Infants <1 year old	**0.005**	**0.001308**	**26%**	**0.001855**	**37%**	**0.003031**	**61%**
Children 1-2 years old	0.005	0.001166	23%	0.001732	35%	0.002714	54%
Children 3-5 years old	0.005	0.000908	18%	0.001403	28%	0.002534	51%
Children 6-12 years old	0.005	0.000619	12%	0.000933	19%	0.001602	32%
Youth 13-19 years old	0.005	0.000431	9%	0.000792	16%	0.002009	40%
Adults 20-49 years old	0.005	0.000614	12%	0.001136	23%	0.002636	53%
Adults 50+ years old	0.005	0.000434	9%	0.000793	16%	0.001455	29%
Females 13-49 years old	0.005	0.000453	9%	0.000831	17%	0.001567	31%

***** Values for the population with the highest risk are in **bold** type.

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5.2.2 Chronic Dietary Exposure/Risk

A refined chronic dietary exposure assessment was also conducted for lambda-cyhalothrin to support all existing and proposed food uses, utilizing single point estimates of anticipated residues for food and drinking water. The chronic dietary exposure assessment incorporated processing factors (DEEM-FCID™ default factors or, where available, factors from processing studies) and %CT estimates provided by BEAD. The estimated weighted average %CT (where available) for each commodity was used in the chronic dietary risk assessment; where no further information was available, and for new uses, 100%CT was assumed. Chronic anticipated residues were derived from PDP monitoring data, field trial studies, and a market basket survey for beef-fat.

The chronic drinking water concentration in surface water of 0.130 ppb was based on the FIRST estimated mean concentration resulting from a maximum application rate of 0.5 lb ai/A per season to orchards (ground application).

The chronic dietary exposure estimates for food and drinking water are below HED's LOC, 100% of the cPAD, for the general US population and all population subgroups. Lambda-cyhalothrin chronic dietary exposure for food and drinking water is 17% of the cPAD for the general US population, and 50% of the cPAD for children (1-2 yrs old), the most highly-exposed population subgroup.

Table 5.2.2 Lambda-Cyhalothrin Chronic Dietary (Food + Drinking Water) Exposure Analysis.

Population Subgroup*	cPAD (mg/kg/day)	Exposure Estimate (mg/kg/day)	% cPAD*
General U.S. Population	0.001	0.000173	17%
All Infants <1 year old	0.001	0.000222	22%
Children 1-2 years old	0.001	**0.000503**	**50%**
Children 3-5 years old	0.001	0.000367	37%
Children 6-12 years old	0.001	0.000222	22%
Youth 13-19 years old	0.001	0.00013	13%
Adults 20-49 years old	0.001	0.000153	15%
Adults 50+ years old	0.001	0.000125	13%
Females 13-49 years old	0.001	0.000121	12%

***** Values for the population with the highest risk are in **bold** type.

5.2.3 Cancer Dietary Risk

Lambda-cyhalothrin is classified as "not likely to be carcinogenic to humans." As such, while acute and chronic dietary analyses are required, there is no cancer risk associated with the existing or proposed uses.

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5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The registrant supported new uses on barley, oats, rye, wild rice, buckwheat, cucurbit vegetables (crop group 9), grass forage and hay (crop group 17), and tuberous and corm vegetables (crop group 1C). New field trials were carried out on potatoes, cantaloupes, cucumbers, summer squash, and a variety of grasses. A market basket survey was provided by Syngenta for beef fat. Adequate PDP monitoring data are available for the following commodities: apples, broccoli, cauliflower, lettuce, onions, peaches, pears, sweet bell peppers, soybeans, wheat, sweet corn, sweet peas, and butter. Tolerance level values were used for the following commodities: okra, eggplant, poultry, tree nuts group (crop group 14) except almonds and pecans, and tuberous and corm vegetables subgroup (crop group 1C) except potatoes.

The screening-level estimates of agricultural uses for lambda-cyhalothrin were provided by BEAD in the form of a screening-level usage assessment (SLUA), based on data years 1999-2004 (SLUA; A. Halvorson; 9/17/2006). The estimated maximum %CT for each commodity was used in the acute dietary risk assessment, and the estimated weighted average %CT for each commodity was used in the chronic dietary risk assessment. Where no further information was available, and for new uses, 100%CT was assumed.

6.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION

Lambda-cyhalothrin uses currently include ornamental gardens, lawns, landscapes, turf, golf courses, and general insect control (spot treatments, and crack and crevice treatments) in, around, and on buildings, structures, and immediate surroundings. A review of current labels indicates that all products, except for one aerosol can product, are limited to use only by certified applicators. As such, this assessment addresses the single residential handler scenario for aerosol can users, and post-application scenarios associated with any use in a residential environment. It should be noted that the residential exposure/risk assessment is based on existing uses for lambda-cyhalothrin because all potential residential exposures must be considered in the calculation of aggregate risks.

A non-occupational (residential) exposure assessment for lambda-cyhalothrin was completed in 1997 (D238737; Pamela Hurley et al; 11/14/1997). In the 1997 pyrethroid assessment, owing to the wide variety of residential uses, it was agreed that flea control (simultaneous use on pets, lawns, and indoor surfaces) would serve as a screening-level scenario for all residential uses because it was anticipated to represent the highest potential for residential exposure. However, at that time, lambda-cyhalothrin uses did not include indoor surfaces or pets, so only exposure estimates pertaining to the lawn uses were used as appropriate in the 1997 assessment for lambda-cyhalothrin.

The 1997 lambda-cyhalothrin assessment served as the basis for the current risk calculations, which were taken from the most recent (D284860; Kit Farwell; 8/15/2002) lambda-cyhalothrin human health risk assessment, and detailed in the associated occupational and residential exposure (ORE) assessment (D280103; Margarita Collantes; 8/14/2002). The only modifications have been adjusting the values from the 1997 assessment for appropriate absorption factors. This represents a definitive screening-level approach because since that time the Agency has engaged in a series of revisions to its *Standard Operating Procedures (SOPs) for*

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Residential Exposure Assessments (the latest on 2/22/2001). Incorporating the revisions to the SOPs would only refine the exposure estimates (in all cases MOEs would be higher).

6.1 Handler

For the residential assessment, existing uses on turf, in gardens, on golf courses, and for structural pest control were considered, but a quantitative calculation was only completed for post-application exposure on treated turf. The Agency used a conservative screening-level approach to address the risks associated with the use of the aerosol can product of lambda-cyhalothrin that can be purchased and used by homeowners.

In this case, a screening-level quantitative calculation was only completed for post-application exposure on treated turf because this scenario is expected to have the highest associated exposures of all residential exposures (see Section 6.2, below, for more details on the post-application assessment). In other words, this is a lower tier approach, and HED believes that the selected post-application assessment on lawns for children is protective for all residential exposures (even the aerosol can handler scenario) because the dose levels for children playing on treated lawns are thought to exceed those expected for all other scenarios (lawn exposures for children represents the worst case scenario). This approach is based on the following conservative considerations:

(1) HED assumed that children contacted lawns immediately after application of lawn product and thus there was no dissipation of residues from the treated lawn,

(2) HED estimated dermal exposure based on a high duration of exposure on the lawn and an intensity of activity that results in a high degree of contact with the treated lawn,

(3) HED assumed that the pesticide was applied at the maximum application rate,

(4) post-application oral exposure for children on lawns was also calculated, which resulted in MOEs that are not of concern (aggregate MOE = 500); this approach is thought to provide conservative estimates of exposure and it is not a route of consideration for adult handlers.

As noted in Section 6.2 of this document, all residential (non-occupational) MOEs calculated using this screening-level approach were well above the target MOE of 100.

6.2 Post-Application

The Agency uses the term "post-application" to describe exposure of individuals that occurs as a result of being in an environment that has been previously treated with a pesticide. Lambda-cyhalothrin can be used in many areas that could be frequented by the general population, including residential areas such as lawns. As a result, individuals can be exposed by entering these areas if the areas have been previously treated.

The post-application assessment for treatment on lawns is based on a screening-level approach, in which children's and adults' exposures to treated turf were selected as representing the highest anticipated exposure scenarios. In this case, the Agency believes that exposures associated with contact to treated turf represent the high-end exposure scenario. Adults and children of varying ages can potentially be exposed to dermal and inhalation routes of exposure when they contact previously treated turf. Children may also be exposed by incidental non-dietary ingestion of turf. Each of these elements was considered in the calculation of post-

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application exposure to lambda-cyhalothrin on turf. The residential MOEs were aggregated together because, regardless of the exposure route (dermal, inhalation, or oral), lambda-cyhalothrin has similar adverse effects (neurotoxicity).

All residential (non-occupational) MOEs calculated using this screening-level approach were well above the Agency target MOE of 100 for the inhalation, dermal, and oral routes (ranging from 700 to 15,000), and therefore do not exceed HED's level of concern. Furthermore, when total MOEs were calculated (all routes added together), MOEs still were not of concern (MOEs for children were 460 to 500, and the MOE for adults was 3000).

A quantitative post-application risk assessment for termiticide use was not performed for this use. Since the lambda-cyhalothrin used as a termiticide (in the form of Impasse® Barrier) is placed under the foundation (poured concrete) of houses, the potential for dermal exposure is negligible. The potential for post-application inhalation exposure is also expected to be extremely minimal due to the vapor pressure for lambda-cyhalothrin being very low (1.5×10^{-9} mm Hg). HED does not anticipate any significant air concentrations of lambda-cyhalothrin accumulating.

Table 6.2 Lambda-Cyhalothrin Residential Risk Calculations.

Population Subgroup	Inhalation		Dermal		Oral		Total MOE [4]
	Exposure (mg/kg/day)	MOE [1]	Exposure (mg/kg/day)	MOE [2]	Exposure (mg/kg/day)	MOE [3]	
Adults	5.46E-06	15,000	2.6E-03	3800	NA [5]	NA	3,000
Children [1-6 years]	1.35E-05	5,900	4.96E-03	2000	1.34E-04	750	500
Infants [<1 year]	1.68E-05	4,800	5.12E-03	2000	1.43E-04	700	460

1. Inhalation MOE = inhalation NOAEL (0.08 mg/kg/day) ÷ inhalation exposure (mg/kg/day).
2. Dermal MOE = dermal NOAEL (10 mg/kg/day) ÷ dermal exposure (mg/kg/day).
3. Oral MOE = oral NOAEL (0.1 mg/kg/day) ÷ oral exposure (mg/kg/day).
4. Total MOE = 1/[(1/dermal MOE) + (1/inhalation MOE) + (1/oral MOE)].
5. NA = Not Applicable.

6.3 Spray Drift

Spray drift is a potential source of exposure for residents living in close proximity to spraying operations. This situation is particularly the case with aerial application. However, to a lesser extent, spray drift resulting from the ground application of lambda-cyhalothrin could also be a potential source of exposure. The Agency has been working with the Spray Drift Task Force (a membership of US pesticide registrants), EPA Regional Offices, State Lead Agencies for pesticide regulation, and other parties to develop the best spray drift management practices. 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, 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, and risks associated with pesticide application.

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7.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate risk includes exposure from non-occupational sources, including exposure from drinking water, food, and residential pathways. Residential exposure routes include dermal, inhalation, and incidental oral exposure (hand-to-mouth-type inadvertent exposure).

7.1 Acute Aggregate Risk

For acute aggregate risk assessments, contributions to risk include food and water exposures. Residential exposure is not assessed for this time period. Therefore, the acute aggregate exposure and risk estimates are equivalent to the acute dietary exposure and risk estimates discussed in Section 5.2.1, and do not exceed HED's LOC.

7.2 Short- and Intermediate-Term Aggregate Risk

Aggregate risk for short- and intermediate-term durations of exposure includes food, drinking water, and residential exposure pathways. In estimating short- and intermediate-term aggregate risk, HED combines the chronic dietary (food and drinking water) exposure estimate, and the total non-dietary (residential) exposure estimate for adults and children. The chronic dietary exposure estimate reflects average dietary exposure, and serves as an estimate of dietary exposure that co-occurs with potential short- and intermediate-term non-dietary exposure to adults and children. The residential exposure pathway includes dermal, inhalation, and incidental oral (hand-to-mouth-type inadvertent exposure) routes of exposure. This aggregate risk assessment incorporates lawn post-application exposure (the scenario with the highest potential for exposure), and is a day-0 screening-level assessment. The resulting aggregate MOEs were greater than the Agency target MOE of 100 (ranging from 140 to 490), and there were thus no concerns for aggregate exposure.

TABLE 7.2 Lambda-Cyhalothrin Short- and Intermediate-Term Aggregate Risk Calculations.

Population Subgroup	Dietary Exposure Estimate [1] (mg/kg/day)	Dietary MOE [2]	Inhalation MOE	Dermal MOE	Oral MOE	Aggregate MOE [3] (Dietary and Residential)
Adults	0.000173	580	15,000	3800	NA [4]	490
Children [1-2 years]	0.000503	200	5,900	2000	750	140
Infants [<1 year]	0.000222	450	4,800	2000	700	230

1. Dietary exposure = [food exposure + drinking water exposure].
2. Dietary MOE = dietary NOAEL (0.1 mg/kg/day) ÷ dietary exposure (mg/kg/day).
3. Aggregate MOE = 1/[(1/dermal MOE) + (1/inhalation MOE) + (1/oral MOE) + (1/dietary MOE)].
4. NA = Not Applicable.

7.3 Long-Term Aggregate Risk

The dietary exposure (food and drinking water) pathway is the only source of exposure to lambda-cyhalothrin that is expected to be of long term (180 to 365 days). Therefore, the long-term aggregate exposure and risk estimates are equivalent to the chronic dietary exposure and risk estimates discussed in Section 5.2.2, and do not exceed HED's LOC.

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7.4 Cancer Aggregate Risk

Lambda-cyhalothrin is classified as "not likely to be carcinogenic to humans." Therefore, there is no aggregate cancer risk associated with the existing or proposed uses.

8.0 CUMULATIVE RISK CHARACTERIZATION/ASSESSMENT

Lambda-cyhalothrin is a member of the pyrethroid class of pesticides. Although all pyrethroids alter nerve function by modifying the normal biochemistry and physiology of nerve membrane sodium channels, EPA is not currently following a cumulative risk approach (based on a common mechanism of toxicity) for the pyrethroids. Although all pyrethroids interact with sodium channels, there are multiple types of sodium channels, and it is currently unknown whether the pyrethroids have similar effects on all channels. Nor is there a clear understanding of effects on key downstream neuronal function (nerve excitability), nor do we understand how these key events interact to produce their compound specific patterns of neurotoxicity. 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. When available, the Agency will consider this research, and make a determination of common mechanism as a basis for assessing cumulative risk. Information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism can be found on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 OCCUPATIONAL EXPOSURE/RISK PATHWAY

The occupational and residential exposure analyses were explicated in the *Nondietary Exposure/Risk Assessment* memorandum for lambda-cyhalothrin (D334896; Mark I. Dow; 12/26/2006).

9.1 Short- and Intermediate-Term Handler Risk

These products will be applied using groundboom, aerial, or chemigation equipment. Based on the use pattern, several major occupational exposure scenarios were identified for lambda-cyhalothrin:

(1) mixing/loading liquid formulations for aerial application,
(2) mixing/loading liquid formulations for chemigation application,
(3) mixing/loading liquid formulation for groundboom application,
(4) applying spray with aerial equipment,
(5) applying spray with groundboom equipment, and
(6) flagging for aerial spray applications.

The duration of exposure is expected to be short-duration exposure (1-30 days), and intermediate-term duration exposure (1-6 months) for all scenarios. Long-term exposures (6 months of continuous exposure) are not expected to occur.

Inhalation and dermal exposures of occupational handlers were calculated using data from the *Pesticide Handlers Exposure Database* (PHED) *Version 1.1*, as presented in the *PHED*

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Surrogate Exposure Guide (August 1998). Defaults established by the HED's Science Advisory Council for Exposure (ExpoSAC) were used for acres treated per day and body weight. For pesticide handlers, it is HED's standard practice to present estimates of dermal exposure for "baseline", which 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" plus the use of protective gloves, or other PPE as might be necessary. The product labels in this case direct applicators and other handlers to wear PPE consisting of long-sleeved shirt, long pants, shoes plus socks, chemical resistant gloves (such as barrier laminate or viton), and protective eyewear. Aerial applicators (pilots) are not required to wear protective gloves or protective eyewear.

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposures. These include administrative controls, the use of PPE, and the use of engineering controls. Occupational handler exposure assessments were completed by HED using baseline attire, PPE, and engineering controls. (Note: administrative controls available generally involve altering application rates for handler exposure scenarios. These are typically not utilized for completing handler exposure assessments.) The baseline clothing level scenario for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical resistant gloves, and no respirator. The first level of mitigation generally applied is PPE. As reflected in the calculations included herein, PPE may involve the use of an additional layer of clothing, chemical-resistant gloves, and a respirator. The next level of mitigation considered in the risk assessment process is the use of appropriate engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly-used engineering controls include enclosed tractor cabs and cockpits, closed mixing/loading/transfer systems, and water-soluble packets.

Since the inhalation and dermal endpoints are based on similar adverse effects (neurotoxicity and decreased body weight gains), dermal and inhalation exposures are combined. See Table 9.1 (below) for a summary of estimated exposures and risks to occupational pesticide handlers. An MOE of 100 or more is adequate to protect occupational pesticide handlers from exposures to lambda-cyhalothrin. Provided mixer/loaders wear personal protective equipment (PPE) as directed by the labels, all MOEs are greater than 100 (ranging from 110 to 1700), except for mixer/loaders supporting aerial applications to wild rice at a rate of 0.04 lb ai/A, and 1200 A/day. Their exposure can be mitigated by reducing the amount of ai handled per day, or by the use of a dust-mist respirator (as indicated below in Table 9.1). Baseline MOEs for applicators and flaggers range from 820 to 4900.

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Table 9.1 Short- and Intermediate-Term Exposure and Risk Assessment For Lambda-Cyhalothrin Handlers.

Exposure Scenario (Scenario #)	Crop	Dermal Unit Exposure (mg/lb ai)		Inhalation Unit Exposure (µg/lb ai)		App. Rate (lb ai/A)	Amount Treated[5] (Acres)	Dermal Daily Dose[6] (mg/kg/day)		Inhalation Daily Dose[6] (mg/kg/day)		Dermal MOEs[7] (UF= 100)		Inhalation MOEs[8] (UF = 100)		Total MOE[9] (UF = 100		
		Baseline[1] (unless indicated)	PPE-G[2]	Baseline[3] (unless indicated)	80% R[4]			Baseline[1] (unless indicated)	PPE-G[2]	Baseline[3] (unless indicated)	80% R[4]	Baseline[1] (unless indicated)	PPE-G[2]	Baseline[1] (unless indicated)	80% R[4]	Baseline Dermal + Baseline Inh. (unless indicated)	PPE-G, SL Dermal + Baseline Inh.	PPE-G, SL Dermal + 80% R[4] Inh.
Mixer/Loader Exposure																		
Mixing/ Loading Liquid Concentrate for Aerial Application (Scenario 1)	Wild rice	2.9	0.023	1.2	0.24	0.04	1,200	2	0.016	0.00082	0.00016	5	630	97	490	4.8	84	280
	Barley, buckwheat, oats, rye	2.9	0.023	1.2	0.24	0.03	1,200	1.5	0.012	0.00062	0.00012	6.7	850	130	NA	6.4	110	NA[10]
	Cucurbit vegetables, tuberous and corm vegetables	2.9	0.023	1.2	0.24	0.03	350	0.44	0.0035	0.00018	0.000036	23	2,900	440	NA	22	390	NA
Mixing/ Loading Liquid Concentrate for Chemigation Application (Scenario 2)	Barley, buckwheat, oats, rye, cucurbit vegetables, tuberous and corm vegetables	2.9	0.023	1.2	0.24	0.03	350	0.44	0.0035	0.00018	0.000036	23	2,900	440	NA	22	390	NA
Mixing/ Loading Liquid Concentrate for Groundboom Application (Scenario 3)	Wild rice	2.9	0.023	1.2	0.24	0.03	200	0.33	0.0026	0.00014	0.000027	30	3,800	580	NA	29	510	NA
	Barley, buckwheat, oats, rye	2.9	0.023	1.2	0.24	0.03	200	0.25	0.002	0.0001	0.000021	40	5,100	780	NA	38	670	NA

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Table 9.1 Short- and Intermediate-Term Exposure and Risk Assessment For Lambda-Cyhalothrin Handlers.

Exposure Scenario (Scenario #)	Crop	Dermal Unit Exposure (mg/lb ai)		Inhalation Unit Exposure (µg/lb ai)		App. Rate (lb ai/A)	Amount Treated[5] (Acres)	Dermal Daily Dose[6] (mg/kg/day)		Inhalation Daily Dose[6] (mg/kg/day)		Dermal MOEs[7] (UF= 100)		Inhalation MOEs[8] (UF = 100)		Total MOE[9] (UF = 100		
		Baseline[1] (unless indicated)	PPE-G[2]	Baseline[3] (unless indicated)	80% R[4]			Baseline[1] (unless indicated)	PPE-G[2]	Baseline[3] (unless indicated)	80% R[4]	Baseline[1] (unless indicated)	PPE-G[2]	Baseline[1] (unless indicated)	80% R[4]	Baseline Dermal + Baseline Inh. (unless indicated)	PPE-G, SL Dermal + Baseline Inh.	PPE-G, SL Dermal + 80% R[4] Inh.
Mixing/ Loading Liquid Concentrate for Groundboom Application (Scenario 3)	Cucurbit vegetables, tuberous and corm vegetables	2.9	0.023	1.2	0.24	0.03	80	0.099	0.00079	0.000041	8.2E-06	100	NA	1,900	NA	96	1,700	NA
Applicator Exposure																		
Applying Sprays via Aerial Equipment (Scenario 4)	Wild rice	0.005 (eng. control[11])	No Data	0.068 (eng. control)	No Data	0.04	1,200	0.0034 (eng. control)	No Data	0.000047 (eng. control)	No Data	2,900 (eng. control)	No Data	1,700 (eng. control)	No Data	1,100 (eng. control)	NA	NA
	Barley, buckwheat, oats, rye	0.005 (eng. control)	No Data	0.068 (eng. control)	No Data	0.03	1,200	0.0026 (eng. control)	No Data	0.000035 (eng. control)	No Data	3,900 (eng. control)	No Data	2,300 (eng. control)	No Data	1,400 (eng. control)	NA	NA
	Cucurbit vegetables, tuberous and corm vegetables	0.005 (eng. control)	No Data	0.068 (eng. control)	No Data	0.03	350	0.00075 (eng. control)	No Data	0.00001 (eng. control)	No Data	13,000 (eng. control)	No Data	7,800 (eng. control)	No Data	4,900 (eng. control)	NA	NA
Applying Sprays via Groundboom Equipment (Scenario 5)	Wild rice	0.014	0.014	0.74	0.148	0.04	200	0.0016	0.0016	0.000085	0.000017	6,300	NA	950	NA	820	NA	NA
	Barley, buckwheat, oats, rye	0.014	0.014	0.74	0.148	0.03	200	0.0012	0.0012	0.000063	0.000013	8,300	NA	1,300	NA	1,100	NA	NA
	Cucurbit vegetables, tuberous and corm vegetables	0.014	0.014	0.74	0.148	0.03	80	0.00048	0.00048	0.000025	5.1E-06	21,000	NA	3,200	NA	2,700	NA	NA

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Table 9.1 Short- and Intermediate-Term Exposure and Risk Assessment For Lambda-Cyhalothrin Handlers.

Exposure Scenario (Scenario #)	Crop	Dermal Unit Exposure (mg/lb ai)		Inhalation Unit Exposure (µg/lb ai)		App. Rate (lb ai/A)	Amount Treated[5] (Acres)	Dermal Daily Dose[6] (mg/kg/day)		Inhalation Daily Dose[6] (mg/kg/day)		Dermal MOEs[7] (UF= 100)		Inhalation MOEs[8] (UF = 100)		Total MOE[9] (UF = 100		
		Baseline[1] (unless indicated)	PPE-G[2]	Baseline[3] (unless indicated)	80% R[4]			Baseline[1] (unless indicated)	PPE-G[2]	Baseline[3] (unless indicated)	80% R[4]	Baseline[1] (unless indicated)	PPE-G[2]	Baseline[1] (unless indicated)	80% R[4]	Baseline Dermal + Baseline Inh. (unless indicated)	PPE-G, SL Dermal + Baseline Inh.	PPE-G, SL Dermal + 80% R[4] Inh.
Flagger Exposure																		
Flagging for Aerial Spray Applications (Scenario 6)	Wild rice	0.011	No data	0.35	0.07	0.04	350	0.0022	No data	0.00007	0.000014	4,500	No data	1,100	NA	910	NA	NA
	Barley, buckwheat, oats, rye, cucurbit vegetables, tuberous and corm vegetables	0.011	No data	0.35	0.07	0.03	350	0.0017	No data	0.000053	0.000011	6,100	No data	1,500	NA	1200	NA	NA

1. Baseline dermal = long-sleeve shirt, long pants, shoes, socks, and no gloves or respirator (open mixing/loading or open cab or enclosed cockpit).
2. PPE-G dermal = baseline dermal plus chemical-resistant gloves (open mixing/loading).
3. Baseline inhalation = no respirator (open mixing/loading or open cab or enclosed cockpit).
4. 80% R inhalation = quarter-face dust/mist respirator resulting in 80% reduction (open mixing/loading).
5. Acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern, based on the application method, and formulation/packaging type.
6. Daily dose (mg/kg/day) = [unit exposure (mg/lb ai)] x [absorption (100%)] x [application rate (lb ai/acre)] x [amount treated (acres/day)] / [body weight (70 kg)].
7. Dermal MOE (with UF = 100) = [dermal NOAEL (10 mg/kg/day)] / [daily dermal dose].
8. Inhalation MOE (with UF = 100) = [inhalation NOAEL (0.08 mg/kg/day)] / [daily inhalation dose].
9. Total MOE = 1/ [1/dermal MOE] + [1/inhalation MOE].
10. NA = Not Applicable (because MOEs do not exceed HED's LOC at the next lowest mitigation level).
11. Engineering control data for enclosed cockpits used for pilots.

9.2 Short- and Intermediate-Term Post-Application Risk

It is possible for agricultural workers to have post-application exposures to pesticide residues during the course of typical agricultural activities. HED, in conjunction with the Agricultural Re-entry Task Force (ARTF), has identified a number of post-application agricultural activities that may occur, and which may result in post-application exposures to pesticide residues. HED has also identified Transfer Coefficients (TCs), having units of cm²/hr, relative to the various activities, which express the amount of foliar contact over time during each of the activities identified**.** For the proposed new uses, the highest TC (1,500 cm²/hr) occurs during "scouting" by crop advisors in flax, leafy green vegetables, legume vegetables, and safflower. Therefore, as a screening-level assessment, HED herein uses a TC of 1,500 cm²/hr.

The TCs used in this assessment are from an interim *TC Standard Operating Procedure* (SOP) developed by HED's ExpoSAC, using proprietary data from the ARTF database (SOP #3.1). It is the intended by HED's ExpoSAC that this SOP 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.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20% of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP #003 of 5/7/1998 (revised 8/7/2000).

$$\text{Daily dermal dose}_t = \frac{DFR_t\ (\mu g/cm^2) \times 1E\text{-}3\ mg/\mu g \times TC\ (cm^2/hr) \times DA \times ET\ (hrs)}{BW\ (kg)}$$

Where:	t	=	number of days after application day (days),
	DFR_t	=	dislodgeable foliar residue on day "t" ($\mu g/cm^2$),
	TC	=	transfer coefficient (cm^2/hr),
	DA	=	dermal absorption factor (unitless),
	ET	=	exposure time (hr/day), and
	BW	=	body weight (kg).

$$DFR_t\ (\mu g/cm^2) = AR\ (lb\ ai/acre) \times F \times (1\text{-}D)^t \times 4.54E8\ \mu g/lb \times 24.7E\text{-}9\ acre/cm^2$$

Where:	AR	=	application rate (lb ai/acre),
	F	=	fraction of ai retained on foliage or 20% (unitless), and
	D	=	fraction of residue that dissipates daily or 10% (unitless).

See Table 9.2 (below) for a summary of post-application exposures and risks. An MOE of 100 or more is adequate to protect persons from post-application exposures to lambda-cyhalothrin, as described in the proposed use patterns. Because the estimated MOEs are all greater than 100 (ranging from 520 to 13,000), post-application exposures arising from the proposed uses do not exceed HED's LOC.

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Table 9.2 Exposure and Risk Assessment for Occupational Post-Application [1] Activities.								
Proposed Crops	**Use Rate (lb ai/A)**	**Policy Crop Group Category**	**Exposure Potential**	**Transfer Coefficient [2] (cm^2/hour)**	**Activities**	**DFR [3] (µg/cm^2)**	**Daily Dose [4] (mg/kg/day)**	**MOE [5]**
Wild Rice	0.04	Field & Row Crops: Low to Medium	Low	100	Scouting	0.090	0.0010	9,700
			Medium	1,500	Scouting	0.090	0.015	650
Barley, Oats, Rye, Buckwheat	0.03	Field & Row Crops: Low to Medium	Low	100	Scouting	0.067	0.00077	13,000
			Medium	1,500	Scouting	0.067	0.012	870
Cucurbit Vegetables	0.03	Vegetable: Cucurbit	Low	500	Irrigating, scouting, hand-weeding for immature crops	0.067	0.0038	2600
			Medium	1,500	Irrigating, scouting, hand-weeding	0.067	0.012	870
			High	2,500	Hand-harvesting, hand-pruning, thinning	0.067	0.019	520
Tuberous and Corm Vegetables [Potato]	0.03	Vegetable: Root & Tuber	Low	300	Irrigating, scouting, hand-weeding for immature crops, thinning	0.067	0.0023	4,300
			Medium	1,500	Irrigation, scouting	0.067	0.012	870
Tuberous and Corm Vegetables [All Others]	0.03	Vegetable: Root & Tuber	Low	300	Irrigating, scouting, hand-weeding for immature crops, thinning	0.067	0.0023	4,300
			Medium	1,500	Irrigation, scouting	0.067	0.012	870
			High	2,500	Hand-harvesting	0.067	0.019	520

1. Post-application day is taken to be Day 0 for all activities (day after treatment represents approximately 12 hours following application, when sprays have dried).
2. Transfer coefficient from ExpoSAC *Policy Memo #003.1 "Agricultural Transfer Coefficients"* of 8/7/2000.
3. DFR = [application rate (lb ai/acre)] x [fraction of active ingredient that remains on the foliage when sprays have dried] x [4.54E8 µg/lb] x [24.7E-9 acre/cm^2].
4. Daily dose = [DFR (µg/cm^2)] x [TC (cm^2/hr)] x [conversion factor (1 mg/1,000 µg)] x [exposure time (8 hrs/day)] / [body weight (70 kg)].
5. MOE = [NOAEL (10 mg/kg/day)] / [daily dose (mg/kg/day)].

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10.0 DATA NEEDS AND LABEL RECOMMENDATIONS

10.1 Toxicology

None

10.2 Residue Chemistry

No major deficiencies were noted in the subject petitions that would preclude the establishment of permanent tolerances for lambda-cyhalothrin on the proposed commodities. Only minor deficiencies were noted pertaining to the proposed label directions and recommended tolerance levels (listed below). HED recommends in favor of establishing permanent tolerances for lambda-cyhalothrin residues at the levels listed in Table 1.0.

(1) Use directions for grasses should be clarified to specify that the restriction of 0.03 lb ai/A per cutting includes pastures and rangeland in addition to grasses grown for seed. A minimum re-treatment interval (RTI) of 30 days should be specified for pastures and rangeland which are not cut between applications. In addition, the PHI for forage should be changed to 0 days, as PHIs for forage are not practical for rangeland applications.

(2) A tolerance was not proposed in rye bran. Based on the available wheat residue data, a separate tolerance is required at 0.2 ppm in rye, bran.

(3) Based on the calculated TDBs for livestock, and the available livestock residue studies, the current tolerance for lambda-cyhalothrin in milk fat is too low. An increased tolerance should be proposed in milk fat at 10 ppm (reflecting 0.4 ppm in whole milk). The data also indicate that the current tolerances in hog commodities could be lowered to 0.2 ppm in fat, 0.01 ppm in meat, and 0.02 ppm in meat byproducts.

10.3 Occupational and Residential Exposure

The labels for Warrior® Insecticide (EPA Registration #100-1112) and Karate® Insecticide (EPA Registration #100-1097) should state that mixer/loaders supporting aerial applications to wild rice at a rate of 0.04 lb ai/A, and treating 1200 acres (or more) per day, are required to use a dust-mist respirator.

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REFERENCES:

Carcinogenicity Determination

GAMMA CYHALOTHRIN - 1ST Report of the Hazard Identification Assessment Review Committee.; TXR #0052388; Jess Rowland; 3/1/2004.

Dietary Exposure Memorandum

Lambda-cyhalothrin: Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment for Section 3 Uses on Barley, Oat, Rye, Wild Rice, Buckwheat, Pistachio, Cucurbit Vegetables (crop group 9), Grass Forage & Hay (crop group 17), and Tuberous & Corm vegetables (crop group 1-C).; D324223; Anant Parmar; 3/12/07

Drinking Water Memorandum

Tier I Estimated Environmental Concentrations of Lambda-Cyhalothrin and It's Transformation Product of Concern XV for the Use in the Human Health Risk Assessment.; D324222, D330149; Jose Melendez; 10/26/2006.

Occupational and Residential Exposure Memorandum

LAMBDA-CYHALOTHRIN - Human, Nondietary Exposure/Risk Assessment for the Proposed New Uses of Lambda-Cyhalothrin on Barley, Buckwheat, Oat, Rye, Wild Rice, Cucurbit and Tuberous and Corm Vegetables.; D334896; Mark I. Dow; 12/26/2006.

Lambda Cyhalothrin: Occupational and Residential Risk Assessment for the use on Cereal Grains, Corn, Soybeans, Sunflowers, Sorghum, Lettuce, Cole Crops, Onions, Garlic, Legumes, Fruiting Vegetables, Stone and Pome Fruits, Tree Nuts, Sugar Cane, Cotton, Rice, Tobacco, Canola for Seed and as a Termiticide.; D280103; Margarita Collantes; 8/14/2002.

Residue Chemistry Data Review Memorandum

Lambda-Cyhalothrin. Petitions Requesting Permanent Tolerances (Associated with Section 3 Registration) for Food/Feed Use of the Insecticide on Cucurbit Vegetables (Group 9), Tuberous and Corm Vegetables (Subgroup 1C), Grass Forage, Fodder, and Hay (Group 17), Barley, Buckwheat, Oat, Rye, Wild Rice, and Pistachios. Summary of Analytical Chemistry and Residue Data. Petition Numbers 5F6994, 3E6593, and 6E7077; D313315, D324219, D330542; William T. Drew; 12/27/2006.

Risk Assessment Document

PP#0F6092. Request for the Use of Lambda-Cyhalothrin in/on Canola, Pome Fruits, Stone Fruits, Tree Nuts, Almond Hulls, and Tobacco. PP#9F4875. Request for the Use of Lambda-Cyhalothrin on Imported Avocados; Cereal Grains (except Rice); Fruiting Vegetables (except Cucurbits); Peanut Hay; Peas and Beans, Dried and Succulent Shelled, and Edible Podded; Sorghum Forage and Fodder; and Sugarcane. New Use: IMPASSE Barrier Termiticide End-use Product.; D284860; Kit Farwell; 8/15/2002.

Risk Assessment for Extension of Tolerances for Synthetic Pyrethroids; D238737; Pamela Hurley, John Whalan, Jeff Evans, George Herndon, Steve Knizner; 11/14/1997.

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APPENDIX A: TOXICOLOGY ASSESSMENT

A.1 Toxicology Data Requirements

The requirements (40 CFR §158.340) for food-use of lambda-cyhalothrin are in Table 1, below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Toxicology Data Requirements.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (non-rodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	yes	yes
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (non-rodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	no	-
870.4100b Chronic Toxicity (non-rodent)	yes	yes
870.4200a Carcinogenicity (rat)	no	-
870.4200b Carcinogenicity (mouse)	no	-
870.4300 Chronic/carcinogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	no	-
870.6300 Developmental Neurotoxicity	yes	no[1]
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	yes
Special Studies for Ocular Effects Acute Oral (rat) Subchronic Oral (rat) Six-month Oral (dog)	no	-

[1] Although classified unacceptable, a repeat DNT study is not required. See section 3.3.6 for more details.

A.2 Toxicity Profiles

Table A.2.1a Acute Toxicity Profile – Lambda-cyhalothrin.				
Guideline Number	**Study Type**	**MRI Number(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral - rat	00151582	LD_{50} = 79 mg/kg (♂) = 56 mg/kg (♀)	II
870.1200	Acute dermal - rat	00151583	LD_{50} = 632 mg/kg (♂) = 696 mg/kg (♀)	II
870.1300	Acute inhalation - rat	40994701	LC_{50} = 0.065 mg/L (♂& ♀)	II
870.2400	Acute eye irritation	00151586	Mild irritant.	II
870.2500	Acute dermal irritation - rabbit	00151584	Not an irritant.	IV
870.2600	Skin sensitization - guinea pig	00151585	Not a sensitizer in the guinea pig.	N/A

Table A.2.1b Acute Toxicity Profile –Cyhalothrin				
Guideline Number	**Study Type**	**MRID Number(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral rat	00154865	LD_{50} = 243 mg/kg (♂) = 144 mg/kg (♀)	II
870.1200	Acute dermal - rat	00154865	LD_{50} > 1000 mg/kg (♂& ♀)	II
	Acute dermal - rabbit	00154865	LD_{50} > 2 g/kg (♂& ♀)	III
870.1300	Acute inhalation - rat	00150847	LC_{50} = 0.173 mg/L (♂) LC_{50} = 0.183 mg/L (♀)	II
870.2400	Acute eye irritation	00154868	Moderate irritant without irrigation; mild irritant with irrigation.	III
870.2500	Acute dermal irritation - rat	00154867	Mild dermal irritant	IV
	Acute dermal irritation - rabbit	00154867	Not an irritant.	IV
870.2600	Skin sensitization - guinea pig	00154866	Not a sensitizer in the guinea pig.	N/A

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Table A.2.2 Subchronic, Chronic and Other Toxicity Profile.			
Guideline Number	**Study Type**	**MRID Number/Year/ Classification /Doses**	**Results**
NA*	**28-Day oral toxicity – rat (cyhalothrin)**	00153029 1984 Acceptable non-guideline 0, 2, 10, 25, 50, 75 mg/kg/day	**NOAEL**: 2 mg/kg/day **LOAEL**: 10 mg/kg/day (clinical signs of neurotoxicity). At higher doses, decreases in body weight gain and food consumption, and changes in organ weights.
NA	**28-Day oral toxicity – rat (cyhalothrin)**	00154806 1984 Acceptable non-guideline 0, 0.1, 0.5, 1.0, 2.0, or 25.0 mg/kg/day	**NOAEL**: 1.0 mg/kg/day **LOAEL**: 2.0 mg/kg/day (decreases in mean body weight gain in females).
NA	**28-Day oral toxicity – mouse (cyhalothrin)**	43241901 1981 Acceptable non-guideline 0, 0.65, 3.30, 13.5, 64.2, 309 mg/kg/day (males) 0, 0.80, 4.17, 15.2, 77.9, 294 mg/kg/day (females)	**NOAEL**: 64.2/77.9 mg/kg/day **LOAEL**: 309/294 mg/kg/day (mortality, clinical signs of toxicity, decreases in body weight gain and food consumption, changes in hematology and organ weights, minimal centrilobular hepatocyte enlargement).
870.3100	**90-Day oral toxicity – rat (cyhalothrin)**	00154805 1981 Acceptable 0, 0.5, 2.5, 12.5 mg/kg/day	**NOAEL**: 2.5 mg/kg/day **LOAEL**: 12.5 mg/kg/day (decreased body weight gain in males).
870.3100	**90-Day oral toxicity – rat (lambda-cyhalothrin)**	00153028 1985 Acceptable 0, 0.5, 2.5, 12.5 mg/kg/day	**NOAEL**: 2.5 mg/kg/day **LOAEL**: 12.5 mg/kg/day (reduced body weight gain and food consumption in both sexes, and food efficiency in females).
870.3150	**26-Week feeding study – dog (cyhalothrin)**	00154795 1981 Acceptable 0, 1.0, 2.5, 10.0 mg/kg/day	**NOAEL**: 1.0 mg/kg/day **LOAEL**: 2.5 mg/kg/day (increase in liquid feces. At 10.0 mg/kg/day, clinical signs of neurotoxicity)
870.3200	**21-Day dermal toxicity – rat (lambda-cyhalothrin)**	44333802 1989 Acceptable 0, 1, 10 mg/kg/day for 6 hours/day for 21 consecutive days; 2-3 applications at 100 mg/kg/day, reduced to 50 mg/kg/day for 21 consecutive days.	**NOAEL**: 10 mg/kg/day **LOAEL**: 50 mg/kg/day (clinical signs of toxicity, decreased body weight and body weight gain).
870.3200	**21-Day dermal toxicity – rabbit (cyhalothrin)**	00154869 1982 Acceptable 0, 10, 100, 1000 mg/kg/day for 6 hours/day, 5 days/week, for total of 15 applications.	**NOAEL**: 100 mg/kg/day **LOAEL**: 1000 mg/kg/day (significant weight loss).

870.3465	**21-Day inhalation toxicity – rat (lambda-cyhalothrin)**	41387702 1990 Acceptable non-guideline 0, 0.3, 3.3, 16.7 g/L (approximately 0, 0.08, 0.90, 4.5 mg/kg/day)	**NOAEL**: 0.08 mg/kg/day **LOAEL**: 0.90 mg/kg/day (clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in cornea, slight reductions in cholesterol in females, slight changes in selected urinalysis parameters).
870.3700a	**Pre-natal developmental – rat (cyhalothrin)**	00154800 1981 Acceptable 0, 5, 10, 15 mg/kg/day	**Maternal NOAEL**: 10 mg/kg/day **Maternal LOAEL**: 15 mg/kg/day (uncoordinated limbs, reduced body weight gain and food consumption). **Developmental NOAEL**: 15 mg/kg/day (HDT) **Developmental LOAEL**: > 15 mg/kg/day
870.3700b	**Pre-natal developmental – rabbit (cyhalothrin)**	00154801 1981 Acceptable 0, 3, 10, 30 mg/kg/day	**Maternal NOAEL**: 10 mg/kg/day **Maternal LOAEL**: 30 mg/kg/day (reduced body weight gain and food consumption). **Developmental NOAEL**: 30 mg/kg/day (HDT) **Developmental LOAEL**: > 30 mg/kg/day
870.3800	**Reproduction and fertility effects – rat (cyhalothrin)**	00154802 1984 Acceptable 0, 0.5, 1.5, 5.0 mg/kg/day	**Parental/Offspring NOAEL**: 1.5 mg/kg/day **Parental/Offspring LOAEL**: 5.0 mg/kg/day (decreased parental body weight and body weight gain during premating and gestation periods and reduced pup weight and weight gain during lactation). **Reproductive NOAEL**: 5.0 mg/kg/day (HDT).
870.4100b	**Chronic toxicity – dog (lambda-cyhalothrin)**	40027902 1986 Acceptable 0, 0.1, 0.5, 3.5 mg/kg/day	**NOAEL**: 0.1 mg/kg/day **LOAEL**: 0.5 mg/kg/day (clinical signs of neurotoxicity).
870.4200	**Carcinogenicity – mouse (cyhalothrin)**	00150842 1984 Acceptable 0, 3, 15, 75 mg/kg/day	**NOAEL**: 15 mg/kg/day **LOAEL**: 75 mg/kg/day (increased incidence of piloerection, hunched posture; decreased body weight gain in males). Not oncogenic under conditions of study. HDT was inadequate; however, a new study not required at this time.
870.4300	**Carcinogenicity – rat (cyhalothrin)**	00154803 1984 Acceptable 0, 0.5, 2.5, 12.5 mg/kg/day	**NOAEL**: 2.5 mg/kg/day **LOAEL**: 12.5 mg/kg/day (decreases in mean body weight). Not oncogenic under conditions of study.

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870.6200a	**Acute neurotoxicity screening battery – rat** **(lambda-cyhalothrin)**	44861510 1999 Acceptable 0, 2.5, 10, 35 mg/kg	**NOAEL**: 10 mg/kg **LOAEL**: 35 mg/kg (clinical observations indicative of neurotoxicity, and changes in FOB parameters).
870.6300	**Developmental neurotoxicity** **(lambda-cyhalothrin)**	46449102 2004 Unacceptable 0, 25, 60, 150 ppm 0, 2, 4, 20 mg/kg/day	**Maternal NOAEL:** 4 mg/kg/day **Maternal LOAEL:** 10 mg/kg/day (decreased body weight, body weight gain, and food consumption). Although Offspring neurotoxicity was seen with a LOAEL/NOAEL of 10/4, a definitive LOAEL/NOAEL cannot be determined due to many data insufficiencies. (officially – for effects observed in the acceptable parameters of the DNT study see Section 3.3.2).
870.7485	**Metabolism and pharmacokinetics – rat**	00151116, 00150852, 00150852, 00150852, 00153036, 00153037 1981, 1984, 1985 Acceptable when combined together.	In the rat, approximately 55% of the oral dose is absorbed. It is extensively metabolized when absorbed. After subcutaneous administration, the urinary/fecal excretion ratio is 2.5:1.0. Over 50% of the dose remained in the carcass 7 days after a subcutaneous dose. Metabolism includes cleavage of the ester to cyclopropylcarboxylic acid and a phenoxybenzyl derivative. The distribution patterns and excretion rates in the multiple oral dose studies are similar to the single oral dose studies. There is accumulation of unchanged compound in the fat upon chronic administration. Otherwise, cyhalothrin is rapidly metabolized and excreted. Cyclopropyl carboxylic acid, 3 phenoxybenzoic acid, glucuronide conjugated 3-4'- hydroxyphenoxy benzoic acid and a sulfate conjugate were identified in the urine. Cyhalothrin is taken up slowly by the fat and released slowly. It is rapidly released by blood, kidneys, liver. The rate of metabolism of both enantiomer pairs are likely identical (i.e. PP321 & PP563). The absorption, distribution, metabolism and excretion patterns of PP321 and cyhalothrin following a single dose of 1 mg/kg in the male rat appear to be identical.

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870.7485	**Metabolism and pharmacokinetics – dog**	00150843, 00150852 1984 Acceptable when combined together.	In the dog, absorption of the C_{14} benzyl label was 80% and absorption of the C_{14} cyclopropyl label was 48%. The metabolite patterns were different, indicating extensive cleavage of the ester bond. Seven metabolites in urine were identified for the benzyl label, and 12 metabolites for the isopropyl label. In the feces, a large proportion of the radioactivity was due to unchanged compound. Excretion in urine and feces was rapid (nearly all in 48 hours).
870.7600	**Dermal penetration**	44990402 1991 Acceptable 0.979, 0.099, 0.001 and 0.0008 mg/cm^2 for 0.5, 1, 2, 4, 10, and 24 hours.	Absorption ranged from 3.46 to 15.89%.
870.7600	**Dermal penetration**	44333801 1984 Acceptable non-guideline Dermal studies: 1.25 mg/50 cm^2 dermal and 20 mg/800 cm^2. Dermal dose washed quantitatively after 8 hours. Oral study: 5 mg	Mild paresthesia of varying degrees was observed following dermal dosing. The minimal oral absorption was estimated to be from 50.35 to 56.71%. The minimal dermal absorption was estimated to be from 0.115 to 0.122%. **The estimated dermal absorption value of 1% was determined by rounding these values up to the nearest whole number.** No metabolites were found near the limit of detection in plasma from the oral dose study. Blood was not analyzed from the dermal study.

* NA = Not Applicable.

A.3 Executive Summaries

A.3.1 Subchronic Toxicity

Non-Guideline 28-Day Oral Toxicity – Rat

In a 28-day feeding study (MRID #00153029) in male and female SPF AlpklAP Wistar-derived rats (16/sex/dose), cyhalothrin (PP563, 89.0%) and PP654, an isomer mixture similar to cyhalothrin which contains both cis and trans isomers (cyhalothrin contains only the cis isomer), were fed in the diet at levels of 0, 20, 100, 250, 500, or 750 ppm (estimated to be approximately 0, 2, 10, 25, 50, or 75mg/kg/day cyhalothrin, based on use of very young animals; clinical signs upon which the NOAEL is based started on day 3), and 500 or 750 ppm (approximately 50 or 75 mg/kg/day PP564). The animals were examined once daily for clinical signs of toxicity. Body weights, food consumption, hematological and clinical chemistry parameters, ophthalmological examinations, urinalysis parameters, organ weights, and macroscopic examinations were conducted and/or measured. For cyhalothrin, livers from up to 8/sex/group were fixed in formol corrosive for microscopic examination. The remaining livers plus selected tissues (including sciatic nerves, brain, and spinal cord) from 8/sex/group were fixed in formol saline for

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microscopic examination. The livers from the PP564 animals were included in this group. In addition, the left sciatic, and posterior tibial nerves from 4 male and 4 female controls and high dose cyhalothrin groups were fixed in formol glutaraldehyde for microscopic examination. With all remaining animals, only abnormal appearing tissues were examined microscopically. Livers from 6/sex/group were taken for measurement of hepatic aminopyrine N-demethylase (APDM) activity and electron microscopy. Smooth endoplasmic reticulum (SER) was quantified.

At 20 ppm and above, a dose-related increase in APDM activity was observed in males. At 20 ppm, the increase was only slight (26.00 versus 22.30 tmoles HCHO/hr/g liver). Slight hypersensitivity to touch was observed in 4 females starting on day 2; however, this had a variable dose-response. At 100 ppm and above, a dose-related increase in APDM activity was observed in females. At 100 ppm, the increase was only slight (14.21 versus 12.03 imoles HCHO/hr/g liver). Clinical signs included high stepping gait in 1 male on day 3, and slight hypersensitivity to touch (2 males on days 2-4, 3 females on day 2) and sound (2 males on day 23; again, variable dose-response). At 250 ppm, 1 male and 2 females had high-stepping gait starting on day 2, 2 males had ataxia starting on day 3, 3 males had hunched posture starting on day 4, and 5 females had increased activity starting on day 4. In addition, significant decreases in mean body weight gain and food consumption (both sexes), increases in mean relative liver weights, and decreases in mean heart weights were observed at 250 ppm and above. At 500 ppm and above, high stepping gait, ataxia, hunched posture, tail erect, increased activity, lack of grooming, and salivation were the major dose-related clinical signs with cyhalothrin. Reductions in serum plasma triglyceride levels, and protein excretion levels in urine were observed in males. At higher dose levels, the reductions in serum plasma triglyceride levels were observed in both sexes. With PP564, high stepping gait, ataxia, hunched posture, and increased activity in females were observed, but to a lesser extent. Reductions in serum plasma triglyceride levels were also observed. At 750 ppm an additional clinical sign of loss of stability was observed in 1 male and 3 females. With PP564, similar clinical signs were observed as with cyhalothrin, but to a lesser extent. Loss of stability was not observed.

The NOAEL for cyhalothrin is 20 ppm (2 mg/kg/day), and the LOAEL is 100 ppm (10 mg/kg/day), based on clinical signs of neurotoxicity. At higher dose levels, decreases in body weight gain and food consumption, and changes in organ weights were also observed. The NOAEL for PP564 is less than 500 ppm (50 mg/kg/day).

This study is classified as acceptable (non-guideline), and does not satisfy any particular guideline requirement.

Non-Guideline 28-Day Oral Toxicity – Rat

In an oral toxicity study (MRID #00154806), SPF Wistar (Alderly Park strain) rats (8/sex/dose) were dosed with cyhalothrin (89.2% ai) in the diet at 0, 1, 5, 10, 20, or 250 ppm (approximately 0, 0.1, 0.5, 1.0, 2.0, or 25.0 mg/kg/day using a factor of 10 for young animals) for 28 days (MRID #00154806). Animals were examined for clinical signs of toxicity, and the following parameters were measured: body weights, liver weights, and hepatic aminopyrene-N-demethylase (APDM) activity. In addition, the livers were subjected to electron microscopic examinations.

No effects were observed at 1, 5, and 10 ppm. At 20 ppm and above, a reduction in mean body weight gain was observed in females ($p < 0.05$; 22% less than the control value for weeks 0-4); however, body weight was not affected. At 250 ppm, a reduction in mean body weight

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gain was observed in males (13% less than the control value for weeks 0-4). In addition, increases and/or proliferation in APDM (14-40%), and smooth endoplasmic reticulum (SER) was observed in both sexes. Relative liver weights were increased in males (7%); however, absolute liver weights were not affected.

The NOAEL is 10 ppm (1.0 mg/kg/day in females) and 20 ppm (2.0 mg/kg/day in males), and the LOAEL is 20 ppm (2.0 mg/kg/day in females), and 250 ppm (25.0 mg/kg/day in males) based on decreases in mean body weight gain in females at 20 ppm and above, and in males at 250 ppm, and increases and/or proliferation in APDM and SER in both sexes at 250 ppm.

This study is classified as acceptable (non-guideline), and does not satisfy any particular guideline requirement.

Non-Guideline 28-Day Oral Toxicity – Mouse

Cyhalothrin (technical, no purity available) was tested in a 4-week oral feeding study (MRID #43241901) in CD-l mice as a range-finding study for the carcinogenicity study. Twelve mice/sex/dose level were tested at 0, 5, 25, 100, 500, or 2000 ppm in the diet (0, 0.65, 3.30, 13.5, 64.2, or 309 mg/kg/day for males, and 0, 0.80, 4.17, 15.2, 77.9, or 294 mg/kg/day for females).

At 2000 ppm, piloerection, abnormal gait (walking on toes), hunched posture, increase in respiration rate, and emaciated appearance were observed. Six males and 3 females died during the study. Both males and females had a significant decrease in body weight gain over the treatment period when compared to controls (-l g versus 5 g in controls for males, $p < 0.001$, and 0 g versus 3 g in controls for females, $p < 0.001$) . A decrease in food consumption was observed in both sexes during the first week (60.8% of controls for males, and 62.5% of controls for females), and in females for the remainder of the study (82% of controls, $p < 0.05$). Males had a slightly lower mean total white blood cell count (6.8%). The differential white cell count revealed lower lymphocyte counts (58.7%), and higher neutrophil counts (62.5% above controls), $p < 0.01$, for all hematological values in males at this dose level. Significantly higher APDM activity was observed in both sexes (61.9% above controls for males, and 77.8% above controls for females). Slight increases in kidney weights (28.8% over controls for males, $p < 0.001$), and liver weights (17% over controls for males, $p < 0.05$, and 3.1 % over controls for females) were observed. In females, the differences were not statistically significant. Slightly lower heart weights were also observed in females (87.7% of controls, $p < 0.05$). Minimal centrilobular hepatocyte enlargement was observed in 2 of 12 females.

At 500 ppm, piloerection was observed in several mice, several males had low white blood cell counts (not statistically significant) as well as marginally lower lymphocyte numbers (80%). Significantly higher APDM activity was observed in females (26.2% over controls). Slightly higher kidney weights were observed in males (13.5% over controls, $p < 0.02$), and slightly lower heart weights were observed in females (93.0%, $p < 0.05$).

At 100 ppm, piloerection was also observed in several mice. One female had an emaciated appearance. Marginally lower lymphocyte numbers were noted for males (79% of controls). Significantly higher APOM activity was observed in females (24.8% over controls). Slightly higher kidney weights were observed in males (13.0% over controls, $p < 0.01$), and marginally lower heart weights were observed in females (87.7%, $p < 0.01$).

The NOAEL is 500 ppm, and the LOAEL is 2000 ppm, based on mortality, clinical signs of toxicity, decreases in body weight gain and food consumption, changes in hematology and organ weights, and minimal centrilobular hepatocyte enlargement. The minimal effects observed

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at 500 and 100 ppm are not considered to be toxicologically significant.

This study is not a guideline requirement, and thus does not satisfy any guideline requirements.

870.3100 90-Day Oral Toxicity – Rat

In a 90-day feeding study (MRID #00154805) in male and female SPF Alderley Park Wistar-derived rats, technical cyhalothrin (92.2% w/w pyrethroids of which 96.8% was cyhalothrin) was fed in the diet at levels of 0, 10, 50, or 250 ppm (estimated to be 0, 0.5, 2.5, or 12.5 mg/kg/day). Twenty rats/sex/dose level were assigned. The animals were examined for clinical signs of toxicity. Body weights, food consumption, hematological and clinical chemistry parameters, urinalysis parameters, organ weights, and macroscopic and microscopic observations were recorded. In addition, hepatic aminopyrine-N-demethylase activity was measured.

No significant treatment-related effects were observed at 0.5 or 2.5 mg/kg/day. At 12.5 mg/kg/day, mean body weight (10-16% less than controls) and body weight gain (13% less than controls) were significantly reduced in males ($p < 0.01$). Mean body weight was also significantly reduced in females at this level, but only during the first week ($p < 0.05$). This decrease in body weight gain was accompanied by a decrease in food consumption; however, there was no effect on food utilization at any dose level. Dietary palatability, and food refusal with concurrent reduced body weight may be a factor. A dose-related reduction in mean red cell volume values was observed in both sexes at all dose levels at week 13; however, a downward trend was also observed in the controls. Hemoglobin, hematocrit, and red blood cell counts were elevated, indicating an opposite trend or an accommodation. Small isolated differences in selected clinical chemistry parameters; however they were not dose related, or recurring on the time basis, nor were they supported by microscopic findings. Hence, neither the hematological nor the clinical chemistry changes are considered compound-related. Hepatic aminopyrine-N-demethylase activity was increased in both sexes at 12.5 mg/kg/day, and in the males at 2.5 mg/kg/day. This is a reversible, compensatory change usually considered to be adaptive rather than an adverse toxicological response.

The NOAEL is 2.5 mg/kg/day, and the LOAEL is 12.5 mg/kg/day, based on decreased body weight gain in males.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a subchronic oral study (§82-1) in the rat.

870.3100 90-Day Oral Toxicity – Rat

In a 90-day feeding study (MRID #00153028) in male and female SPF Alk/AP Wistar-derived rats (20/sex/dose), lambda-cyhalothrin (96.5%) was fed in the diet at levels of 0, 10, 50, or 250 ppm (0, 0.5, 2.5, or 12.5 mg/kg/day). The animals were examined once daily for clinical signs of toxicity. Body weights, food consumption, hematological and clinical chemistry parameters, urinalysis parameters, organ weights, and macroscopic and microscopic observations were recorded.

No treatment-related effects were observed at 0.5 mg/kg/day. At 2.5 mg/kg/day, increased mean liver weight, and increased activity of hepatic aminopyrine-N-demethylase (APDM) were observed in males. This is considered to be an adaptive response. At 12.5 mg/kg/day, significantly reduced body weight gain and food consumption were observed in both sexes, as well as increased mean liver weight, and increased APDM activity in both sexes. There

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was also a slight but statistically significant reduction in food efficiency in females at this dose level.

The NOAEL is 2.5 mg/kg/day, and the LOAEL is 12.5 mg/kg/day, based on reduction in body weight gain and food consumption in both sexes, and food efficiency in females.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a subchronic feeding study (§82-1) in the rat.

870.3150 180-Day Oral Toxicity – Dog

In a 26-week oral study in male and female beagle dogs (MRID #00154795), six dogs/sex/dose level received technical cyhalothrin (pyrethroid content = 92.2% w/w, of which 96.8% is cyhalothrin) via oral administration in gelatin capsules. The test chemical had been dissolved in corn oil prior to placement in the capsules. The following dose levels were tested: 0, 1.0, 2.5, or 10.0 mg/kg/day. The following parameters were measured and/or recorded: daily clinical observations, body weights, food consumption, ophthalmological examinations, neurological examinations, clinical biochemistry, urinalysis, gross necropsy, and microscopic examinations.

At 1.0 mg/kg/day, a slight increase in the passage of liquid feces was observed in both sexes combined (7% over the control group). This was the only effect observed at this dose level and it was not considered to be of toxicological significance.

At 2.5 mg/kg/day, liquid feces were observed at an increased rate (26% over the control group, both sexes combined). No other effects were observed. At this dose level, due to the greater number of animals affected, and the greater increase in incidence, the liquid feces was considered to be a toxicological effect.

At 10.0 mg/kg/day, liquid feces were observed at an increased rate over the control group (both sexes). In addition, the following effects were observed: increase in water consumption during first 4 weeks, vomiting, usually within a few hours following dosing, and occasional unsteadiness and/or muscular trembling. During week 2, head shaking, and excessive salivation were observed in several dogs. These signs were observed only occasionally during the subsequent test weeks. One male had more severe signs. During the second week, excessive salivation, and head shaking were noted. On day 14, 3 hours post-dosing, the dog was in a state of collapse, stiff-limbed, and frothing at the mouth with the presence of vomitus. It recovered in 6 hours. In the following weeks with this dog, there were periods of head shaking, salivation, loss of appetite, episodes of collapse, muscular spasms, marked incoordination, vocalization, and one episode of convulsive behavior (week 8).

The NOAEL is 1.0 mg/kg/day, and the LOAEL is 2.5 mg/kg/day, based on an increase in incidence of liquid feces. At 10.0mg/kg/day, liquid feces, and clinical signs of neurotoxicity (occasional unsteadiness and/or muscular trembling, head shaking, excessive salivation, frothing at the mouth, stiff-limbed, episodes of collapse, muscular spasms, marked incoordination, vocalization, and one episode of convulsive behavior in week 8) were observed.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a subchronic oral study (§82-1) in the dog.

870.3200 21-Day Dermal Toxicity – Rat

In a repeated-dose dermal toxicity study (MRID #44333802), lambda-cyhalothrin (96.6% ai) was applied to the clipped skin of five albino rats/sex/dose at dose levels of 1 or 10

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mg/kg/day for 6 hours/day for 21 consecutive days. Five rats/sex were similarly treated with two or three applications at 100 mg/kg/day, reduced to 50 mg/kg/day for 21 consecutive days.

Two males which were found dead after three applications of 100 mg/kg/day had reduced, moderately atrophied seminal vesicles, and slightly atrophied spleens. Clinical signs indicative of neurotoxicity were observed in the 100/50 mg/kg/day treatment groups. Males exhibited reduced splay reflex, downward curvature of the spine, splayed gait, bizarre behavior, pinched-in sides, dehydration, reduced stability, and thin appearance. Females exhibited an increased incidence of tiptoe gait, upward curvature of the spine, an increased incidence in signs of urinary incontinence, urinary incontinence, chromodacryorrhea, and reduced splay reflex. The clinical signs commenced on day 2 of dosing. Body weight gains for males were significantly reduced throughout the study; the final gain was 58% lower than the control gain. The final mean body weight was 19% lower than the mean control value. Body weight gains for females were somewhat reduced only during the first half of the study. Food consumption was somewhat reduced for males throughout the study. No dermal irritation was observed at 100/50 mg/kg/day in either sex. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related. No treatment-related differences in hematology or clinical blood chemistry parameters, organ weights, or histopathology were observed between the treatment and control groups. No neoplastic tissue was observed.

The LOAEL is 50 mg/kg/day for both sexes, based on clinical signs of toxicity and decreased body weight and body weight gain. The NOAEL is 10 mg/kg/day for males and females.

This dermal toxicity study is classified acceptable (§82-2), and satisfies the guideline requirement for a repeated-dose dermal toxicity study.

870-3200 21-Day Dermal Toxicity – Rabbit

In a repeated-dose dermal toxicity study (MRIDs #00154869, #41062701), cyhalothrin (90.2% ai) was applied to the clipped skin of 10 New Zealand White rabbits/sex/dose at dose levels of 10, 100, or 1000 mg/kg/day for 6 hours/day, 5 days/week, for a total of 15 applications. One half the animals had abraded skin, and the other half had non-abraded skin. The control group consisted of 14/sex treated with 2 ml/kg/day of polyethylene glycol 300 (PEG 300). The rabbits were observed daily for clinical signs of toxicity, skin irritation, and individual body weights. Food consumption, hematology, and clinical chemistry measurements were also taken. Gross necropsy, and microscopic examinations were conducted.

There was no difference in clinical signs of toxicity between the abraded and non-abraded animals. No treatment-related clinical signs of toxicity were observed at any dose level. Some of the clinical signs which are similar to those normally observed with pyrethroids were due to physical injury. In non-abraded animals, with the exception of low dose males, all rabbits lost weight, including the controls. Statistical significance in weight loss was achieved at 1000 mg/kg/day in males. This dose group lost 10% of their body weight. The controls lost <1% of their body weight. In females, the controls lost 5% of their body weight, and the 1000 mg/kg/day group lost 11% of their body weight. Food consumption in the high-dose group varied. At times it was less and at times it was more. There was no consistent pattern. Slight to severe irritation was observed in all test groups, including controls. In non-abraded animals, there appeared to be an increase in the number of animals affected by irritation starting at 100

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mg/kg/day.

The NOAEL for dermal irritation is 10 mg/kg/day, and the LOAEL for dermal irritation is 100 mg/kg/day. The systemic NOAEL is 100 mg/kg/day for both sexes. The systemic LOAEL is 1000 mg/kg/day for both sexes, based on significant weight loss when compared to the control groups.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a repeated dose dermal study (§82-2) in the rabbit.

870.3465 21-Day Inhalation – Rat

In a 21-day inhalation study (MRID #41387702), 10/sex/dose SPF Alpk:APfSD Wistar-derived albino rats were exposed nose-only 6 hours/day, 5 days/week, for 21 days to lambda-cyhalothrin (81.5% pure) at 0, 0.3, 3.3, or 16.7 µg/L (estimated to be approximately 0, 0.08, 0.90, or 4.5 mg/kg/day). The MMAD ranged from 1.47 to 1.91 µm, and the GSD ranged from 1.02 to 2.24 µm.

No treatment-related effects were observed at 0.3 µg/L. At 3.3 µg/L, the following was observed: salivation, lachrymation, paw flicking (males only), tail erections, and splayed gait (males only); decreased body weight (94-95%, $p < 0.05$) and body weight gain (53-65%, $p < 0.01$) of control values; an increased incidence of punctate foci on the comea; slight reductions in cholesterol levels in females ($p < 0.05$); decreased urine volume in males, slightly raised specific gravity of the urine in both sexes, and reductions in urinary protein levels in males. At 16.7 µg/L, the following was observed: salivation, lachrymation, auditory hypoaesthesia, paw flicking, tail erection, splayed gait, decreased activity, reduced foot withdrawal (males only), head flicking, reduced righting reflex, shaking (males only), sides pinched in, reduced splay reflex, decreased visual placing response, absent puma reflex (females only), ungroomed appearance (females only), tiptoe gait (males only), respiratory noise; decreased body weight (85-88%, $p < 0.01$) and body weight gain (<3-14%, $p < 0.01$ of control values); decreased food consumption (46-91% ♂, 56-87% ♀ of controls); changes in selected clinical chemistry values, particularly in females; decreased urine volume, increased urine specific gravity, and decreased urinary protein. There was also a slight increase in the incidence of alveolitis in high dose females.

The NOAEL is 0.3 µg/L (0.08 mg/kg/day), and the LOAEL is 3.3 µg/L (0.90 mg/kg/day), based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females, and slight changes in selected urinalysis parameters.

This inhalation toxicity study is classified as acceptable (non-guideline), and does not satisfy any particular guideline requirement. The study is too short for a guideline study, and individual animal data were not provided.

A.3.2 Pre-Natal Developmental Toxicity

870.3700a Pre-Natal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID #00154800), technical cyhalothrin (89.25%) was administered by gavage to 24 SPF CD rats/dose at the following dose levels: 0, 5, 10, or 15 mg/kg/day during the gestation period (days 6 through 15). Maize oil was used as the vehicle.

No treatment-related effects were observed in the dams at dose levels of either 5 or 10

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mg/kg/day. At 15 mg/kg/day, uncoordinated movements in the limbs were observed in two dams, one from gestation days 8-10, and the other from gestation days 12-18. In addition, a statistically significant reduction in mean body weight gain was observed, both during dosing (70% of control value), and throughout the entire gestation period (88% of control value). The adjusted mean gestational body weight gain was 67% of the control value. Mean body weight gain was comparable to the control group during the post-dosing period. Food consumption was also significantly reduced during gestation days 6-12 (77-91%). No treatment-related developmental effects were observed at any dose level.

The maternal NOAEL is 10 mg/kg/day, and the maternal LOAEL is 15 mg/kg/day, based on uncoordinated movements in the limbs starting on gestation day 8, and reduced body weight gain and food consumption during the dosing period.

The developmental NOAEL is greater than 15 mg/kg/day (HDT). No developmental effects were observed.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a study (§83-3) in the rat.

870.3700b Pre-Natal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID #00154801), technical cyhalothrin (89.25%) was administered by gavage to 18-22 New Zealand White rabbits/dose at the following dose levels: 0, 3, 10, or 30 mg/kg/day, during the gestation period (days 6 through 18). Corn oil was used as the vehicle.

No treatment-related effects were observed in the does at dose levels of either 3 or 10 mg/kg/day. At 30 mg/kg/day, a statistically significant reduction in mean body weight gain was observed from gestation days 6-9, when compared to the control group. Mean body weight gain was 48% of the control value during the dosing period. It was 122% of the control value during the post-dosing period, and 88% of the control value for the entire gestation period (days 0-28). The % adjusted mean gestational body weight gain was 59% of the control value. Food consumption was also significantly reduced during gestation days 6-15 (71-77%). No treatment-related developmental effects were observed at any dose level.

The maternal NOAEL is 10 mg/kg/day, and the maternal LOAEL is 30 mg/kg/day, based on decreased body weight gain during the dosing period.

The developmental NOAEL is 30 mg/kg/day (HDT). No effects were observed.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a study (§83-3) in the rabbit.

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

In the three-generation reproduction study (MRID #00154802), groups of 5 male and 30 female SPF Wistar-derived rats/dose were fed technical cyhalothrin (89.2%) in the diet at 0, 10, 30, or 100 ppm (approximately 0, 0.5, 1.5, or 5.0 mg/kg/day). The pre-mating periods were 12 weeks for the F_0 animals, and 11 weeks for the F_1 and F_2 animals.

Parental toxicity was observed as decreased mean body weight and body weight gain during the pre-mating and gestation periods at 5.0 mg/kg/day. There were no other treatment-related effects. Offspring toxicity was observed as reduced mean pup weight and pup weight

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gains during lactation, again at 5.0 mg/kg/day. No other treatment-related effects were observed.

The parental/offspring systemic NOAELs are 1.5 mg/kg/day, and the parental/offspring systemic LOAELs are 5.0 mg/kg/day, based on decreased mean body weight and body weight gain during the pre-mating and gestation periods, and reduced mean pup weight and pup weight gain during lactation. The reproductive NOAEL is 5.0 mg/kg/day (highest dose tested).

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a multi-generation reproduction study (§83-4) in the rat.

A.3.4 Chronic Toxicity

870.4100a Chronic Toxicity – Rat

See Section A.3.5, 870.4300 (Chronic/Carcinogenicity – Rat).

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study (MRID #40027902), beagle dogs (6/sex/dose) were given oral administration of gelatin capsules containing lambda-cyhalothrin (96.5%) at 0, 0.1, 0.5, or 3.5 mg/kg/day, 7 days/week, for 12 months. The test chemical had been dissolved in corn oil prior to placement in the capsules. The following parameters were measured and/or recorded: daily clinical observations, body weights, food consumption, ophthalmological examinations, clinical biochemistry, urinalysis, gross necropsy, and microscopic examinations.

No treatment-related toxicity was observed at 0.1 mg/kg/day. At 0.5 mg/kg/day, 1 male and 1 female dog exhibited gait abnormalities, with the effects seen in the male 7-hours post dosing during week 2, and again 2 days later immediately after dosing, and in the female 4 times during week 9. Convulsions were seen in two other dogs (both males); the convulsions appeared to be precipitated by the stress of handling or noise. At 3.5 mg/kg/day, the principal neurological clinical signs following dosing were ataxia (all dogs, apparent from day 2 in 2 dogs, observed 3-7 hours post-dosing), muscle tremors and convulsions, occasional subdued behavior, worn or bleeding claws, regurgitation of food during first 2 weeks, and fluid feces in all dogs. Treatment had no effect on body weights, hematology, clinical chemistry, urinalysis, gross or histopathology.

The NOAEL is 0.1 mg/kg/day, and the LOAEL is 0.5 mg/kg/day, based on clinical signs of neurotoxicity.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a study (§83-1) in the dog.

A.3.5 Carcinogenicity

870.4200 Carcinogenicity (Feeding) - Mouse

Groups of 52/sex CD-1 mice (MRID #00150842) were fed technical cyhalothrin (89.25%) in the diet at 0, 20, 100, or 500 ppm (approximately 0, 3, 15, or 75mg/kg/day) for 104 weeks. In addition, 4 satellite groups of 12 mice/sex were fed the same dietary concentrations, and terminated at week 52.

No treatment-related effects were observed at 3 mg/kg/day. At 15 mg/kg/day, an increased incidence of piloerection was observed in males between weeks 13 and 52. This was the only observed effect at 15 mg/kg/day. After week 52, the incidences of piloerection were

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comparable to the control group. At 75 mg/kg/day, an increased incidence of piloerection was observed in both sexes, and hunched posture was observed up to 78 weeks, particularly in males. After 78 weeks, the incidences of hunched posture were similar between treated and control groups. Decreased body weight gain was also observed in males during the first 13 weeks (54% of the control group). Mean body weight was 10 percent lower than the controls at week 13. For the entire two years, body weight gain in males was 77% of the control value.

On 2/12/1993 and 6/16/1994, the HED RfD/Peer Review Committee concluded that cyhalothrin was not tested at a sufficiently high dose level for an adequate carcinogenicity study in mice. Following the decision by the Committee, Toxicology Branch 1 (TB-1) determined that there was not enough toxicological concern to warrant a requirement for a new carcinogenicity study in the mouse at that time. However, there was sufficient concern about the adequacy of dosing in this study that additional testing may be required in the future. This decision was based on data from the mouse chronic feeding/oncogenicity study, the 28-day range finding study in the mouse, and the results from mouse and rat carcinogenicity studies conducted with similar pyrethroids.

The 2/12/1993 RfD/Peer Review Committee also had concern over the increased incidences of mammary tumors in females (1/52, 0/52, 7/52, 6/52). On 6/16/1994, the HED RfD/Peer Review Committee evaluated the study in more detail, and noted that the concurrent control value was low when compared to historical control values. Because of the equivocal nature of the findings, and in view of the inadequacy of the dose levels tested, the Committee concluded that the chemical should be classified as a Group B chemical.

The LOAEL for systemic chronic toxicity is 75 mg/kg/day, based on an increased incidence of piloerection and hunched posture, and decreased mean body weight gain in males, and the NOAEL is 15 mg/kg/day.

Under the conditions of the study, cyhalothrin is not considered to be oncogenic in mice. However, there is concern over the adequacy of the dosing in the study, and additional testing may be required in the future, particularly if new uses result in significantly higher residues in human foods, and/or there is significantly higher occupational (or future residential) exposure due to changes in parameters such as the method of application.

This study is classified as acceptable (guideline), and satisfies the guideline requirements for a chronic feeding/oncogenicity study (§83-5) in the mouse.

870.4300 Carcinogenicity Study - Rat

In a chronic feeding/carcinogenicity study in rats (MRID #00154803), groups of 52 male and 52 female AlpklAP strain rats were fed 0, 10, 50, or 250 ppm (0, 0.5, 2.5, or 12.5 mg/kg/day) cyhalothrin (89.2%) in the diet for 2 years. Additional groups of 20 males and females were added to each dose level as extras, and for the purpose of interim sacrifice.

No treatment-related effects were observed at either 0.5 or 2.5 mg/kg/day. At 12.5 mg/kg/day, decreased mean body weight (11% for males, and 8.5% for females) and food consumption in both sexes were observed. There were no neurological effects noted.

The LOAEL for chronic toxicity in rats is 12.5 mg/kg/day, and the NOAEL is 2.5 mg/kg/day, based on decreases in mean body weight.

Under the conditions of the study, there was no indication of oncogenic activity for this chemical.

This study is classified as acceptable (guideline), and satisfies the guideline requirements

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for a chronic feeding/oncogenicity study (§83-5) in the rat.

A.3.6 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

In this acute oral neurotoxicity study (MRID #44861510), lambda-cyhalothrin in corn oil was administered in a single dose by gavage to 10 Alpk:APSD rats/sex/dose at doses of 2.5, 10, or 35 mg/kg. Functional observation battery (FOB) and motor activity measurements were performed during week 1 (acclimation), day 1 (at 7 hours post-dosing), day 8, and day 15. Five animals/sex/group were sacrificed by perfusion fixation, and subjected to neuropathological examination.

No animals died during the study. No treatment-related changes in body weight, body weight gain; food consumption, motor activity, or gross pathology were observed. No differences relative to concurrent controls were observed in brain widths or dimensions. No treatment- related findings were observed in the 2.5 mg/kg group.

At 10 mg/kg, the following clinical signs were observed (# incidences):

(1) increased breathing rate (males 5, females 5),
(2) slight piloerection (males 1, females 3),
(3) signs of urinary incontinence (1, females only),
(4) upward spine curvature (2, females only), and
(5) urinary incontinence (3, males only).

None of the clinical signs were observed in the concurrent controls. The following observations were noted during the day 1 FOB: slight signs of salivation (1, males only); slight signs of urinary incontinence (1, females only); and slight urinary incontinence (2, males only). None of the clinical observations were observed in the concurrent controls. These findings are not considered to be adverse, and very few animals were observed to have effects.

At 35 mg/kg, clinical signs were similar in nature to those observed in the FOB, and consisted of the following (# incidences):

(1) slightly decreased activity (males 7, females 3),
(2) ataxia (males 5, females 5),
(3) increased breathing rate (males l6, females 13),
(4) piloerection (males 27, females 20),
(5) reduced stability (males 2, females 4),
(6) sides pinched in (males 3, females 4),
(7) signs of salivation (males 6, females 11),
(8) signs of urinary incontinence (males 2, females5),
(9) stains around mouth (males 4, females 3),
(10) tiptoe gait (males 5, females 3),
(11) un-groomed appearance (males 3, females 2),
(12) upward curvature of the spine (males 25, females 20), and
(13) urinary incontinence (males 5, females 7).

The following findings were noted during the FOB on day 1:

(1) slightly decreased activity (2, males only),
(2) slight ataxia (males-3, females 2),
(3) extreme ataxia (2, females only),

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(4) lacrimation (males- 1, females-2),
(5) slight piloerection (males-6, females-7),
(6) moderately reduced stability (1, females only),
(7) extremely reduced stability. (1, females only),
(8) moderate salivation (1, males only),
(9) extreme salivation (males-i, females-i),
(10) slight signs of salivation (males-6, females-4),
(11) moderate signs of salivation (1, females, only),
(12) sides pinched in (1, females only),
(13) slight tip toe gait (males-4, females-I),
(14) upward curvature of the spine (males-8, females-8),
(15) tremors (1, females only),
(16) slight signs of urinary incontinence (males-l, females- 1), and
(17) slight urinary incontinence (thales-3,females-6).

Landing foot-splay values were decreased on day 1 (121%, $p < 0.05$), and decreased ($p < 0.05$ or 0.01) hindlimb grip strength was observed on days 1, 8, and 15 (119%, 131%, 132%) in males. Females displayed increased time to tail-flick on day 1 (171%, $p < 0.05$). In addition, one female was found to have minimal pigmentation of the olfactory bulb, but no other associated pathology. Minimal fiber degeneration of the sciatic nerve was observed in another female.

The LOAEL for this study is 35 mg/kg, based on clinical observations indicative of neurotoxicity, and changes in FOB parameters. The NOAEL for this study is 10 mg/kg.

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

870.6300 Developmental Neurotoxicity Test

In a developmental neurotoxicity study (MRID 46449102), Lambda-cyhalothrin (87.7% a.i., batch #P31 (BX E624)) was administered in the diet to 30 mated female Alpk:AP_fSD (Wistar-derived) rats/group at nominal concentrations of 0, 25, 60 or 150 ppm from gestation day (GD) 7 through day 23 post partum. Average doses to the animals, adjusted for purity, were 1.8, 4.3, and 10.0 mg/kg/day, respectively, during gestation and 4.0, 9.4, and 23.1 mg/kg/day, respectively, during lactation. Dietary concentrations were based on the results of a preliminary developmental neurotoxicity study (MRID 46449101). A Functional Observational Battery (FOB) was performed on all dams on GDs 10 and 17 and on lactation days (LDs) 2 and 9. On postnatal day (PND) 5, litters were culled to yield four males and four females (as closely as possible). Offspring, representing at least 20 litters/dose, were allocated for detailed clinical observations and assessment of motor activity, auditory startle response, and learning and memory. Neural tissues were collected from selected offspring (10/sex/dose, representing 20 litters) on PND 12 and at study termination (PND 63). Pup body weights were recorded, and the age of sexual maturation was assessed (vaginal opening in females and preputial separation in males).

In the dams, no treatment-related effects were observed on mortality, reproductive performance, or gross pathology. Treatment-related maternal toxicity included decreased ($p \leq 0.05$ or 0.01) body weights, body weight gains, and food consumption during gestation and lactation at the high dose (150 ppm). At this dose, absolute maternal body weights were

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consistently decreased by 8-9%, compared to controls, throughout the treatment period and persisting through LD 15.

The maternal LOAEL is 150 ppm (10.0 mg/kg/day during gestation), based on decreased body weight, body weight gain, and food consumption. The maternal NOAEL is 60 ppm (4.3 mg/kg/day during gestation).

In offspring, no treatment-related effects were observed on clinical signs, developmental landmarks, the functional observational battery, brain weights, macroscopic neuropathology, or microscopic neuropathology.

A significant decrease (6%; $p \leq 0.01$) in the number of pups surviving from PNDs 1-5 (pre-cull), compared to controls, was observed at 150 ppm. Survival was unaffected by treatment with 25 or 60 ppm.

Pup body weights and body weight gains were consistently lower ($p \leq 0.01$) in both sexes at 150 ppm from PNDs 5-29, with a maximum decrease in body weight of 12%, compared to controls.

The motor activity data were considered inadequate for assessment. Of the control animals, habituation was only observed in PND 22 females. Although habituation might not be expected in PND 14 animals (*e.g.,* the pups' eyes may still be closed, and their brains may not yet be developed enough so that habituation is possible), failure for all but one of the other control groups to properly habituate indicates a lack of an adequate assessment of this parameter in this study.

No treatment-related effects were seen in auditory startle response in PND 23 males or females or in PND 61 males. In PND 61 females, decreases in maximum auditory startle response were seen in all treated groups for repetitions 11-50, compared to controls. The magnitude of the decreases were similar across all doses (*i.e.*, the dose-response was flat), and the decreases reached statistical significance at the low and high doses ($p \leq 0.01$). However, while the behavior of the treated PND 61 females is different from the controls, it is not possible to determine whether this difference is due to treatment or if it is because the PND 61 control females failed to exhibit the expected habituation. Failure for these animals to properly habituate indicates an inadequate assessment of auditory startle in the PND 61 females tested in this study. Habituation was evident in PND 61 males.

High-dose females showed differences in water maze performance on PNDs 21 and 24. Learning was affected on PND 21, in that mean time to completion was longer, and the proportion of successful trials was lower than controls for cut-off times ranging from 3-10 seconds. When the cut-off was expressed in relation to the time taken to complete the straight channel, the group mean success rate at 1.5 the straight channel swim time on PND 21 was decreased, although this change was not statistically significant. When memory was tested on PND 24, high-dose females showed only a slight increase in the mean time per trial, compared to controls, but the proportion of successful trials for cut-off times from 3-9 seconds were still decreased. Treatment-related effects on learning and memory were not seen in PND 59/62 females or in males at either time point.

At the high dose, statistically significant decreases were seen in the molecular layer of the preculminate fissure of the cerebellum (13%), the overall width of the hippocampus (7%), and the level 3 dorsal cortex 1 (7%) of PND 12 males. In PND 12 females, statistically significant decreases were observed at 150 ppm in the level 5 dorsal cortex (6%), the level 4 dorsal cortex (7%), the thalamus width (4%), and the thalamus/cortex width (4%). At PND 63, a statistically

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significant decrease (7%) was observed in the level 3 piriform cortex of high-dose males. Data for these measurements at the mid and low doses should be provided to confirm whether or not the effects are limited to the high dose.

The offspring NOAEL/LOAEL cannot be determined due to the lack of brain morphometrics at the low and mid doses, as well as inadequate assessments of auditory startle response in PND 61 females and of motor activity.

This study is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6). The motor activity data were considered inadequate for assessment. It was not possible to determine whether the difference in auditory startle response between treated and control PND 61 females was due to treatment because the PND 61 control females failed to exhibit the expected habituation. Finally, morphometric data at the mid and low doses were not available for the measurements in which effects were observed at the high dose.

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APPENDIX B: METABOLISM ASSESSMENT

B.1. Metabolism Guidance and Considerations

Table B.1 Summary of Degradate Formation from Degradation of Lambda-cyhalothrin.

Study Type	Source	Degradate and Maximum Concentration		
		Compound Ia (% Applied) [1]	Compound Ib (% Applied) [2]	Degradate XV (% Applied) [3]
Aqueous Photolysis	MRID #44861501	13.7 at 282 hours (cyclopropane ring).	7.1% at 282 hours (cyclopropane ring).	Others: 3-phenoxybenzoic acid was 25.0% at 247 hours; phenoxybenzaldehyde was a minor degradate (5.5% at 247 hours).
Aerobic Aquatic Metabolism	MRID #44861506	11.4% at 30 days in a 98 day study, and 11.4% at 14 days in the sediment of the SL sediment system.	NA [4]	11.4% at 30 days, and 10.6% at 30 days in the sediment of the SL sediment system.
Aerobic Aquatic Metabolism	MRID #44367402	14.4% at 14 days, and 0.7 to 3.3% from 4 to 30 days in the sediment of the sand sediment system.	NA	0.4-1.3% at 0.125-7 days, and 8.7at 7 days in the sediment of the sand sediment system.
Terrestrial Field Dissipation	MRID #40052407	Transformation products monitored at the two sites were reported to be at low levels.		
Data for hydrolysis, soil photolysis, aerobic soil metabolism, and anaerobic aquatic metabolism were not available.				

1. Compound Ia = (1*RS*)-cis-3(*ZE*)-2-chloro-3,3,3-trifluro-1-propenyl)-2,2-dimethylcylopropane-carboxylate.
2. Compound Ib = (1RS)-trans-3-(ZE-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylic acid.
3. Degradate XV = (1*R*) *cis* α-(*S*) *cis* α-(*R*) α-cyano-3-(4-hydroxy-phenoxy) benzyl 3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclo-propanecarbo-xylate.
4. NA = Not Applicable.

APPENDIX C: HUMAN RESEARCH REFERENCES

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