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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 31 March 2008

SUBJECT: **Gamma-Cyhalothrin. Human Health Risk Assessment for the Proposed Use of the Insecticide in Food-Handling Establishments, Use on Okra and Pistachios, and Use of Ear Tags on Beef and Non-Lactating Dairy Cattle.**

PC Code: 128807
MRID Numbers: (None)
Petition Numbers: 6H7114, 7E7287
Assessment Type: Single Chemical/Aggregate
TXR Number: (None)
Regulatory Citation: 40CFR §180.438
Chemical Class: Pyrethroid Ester Insecticide
DP Barcodes: 333324, 346771, 348227
Decision Numbers: 370874, 386097, 386871
Registration Numbers: 74921-5, 74921-3
File Symbol: 72642-I
Regulatory Action: Section 3
Reregistration Case Number: (None)
CAS Number: 76703-62-3
Trade Names: Proaxis™ GPC, Proaxis™, Gammacyhalothrin Ear Tag

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1.0 BACKGROUND

Gamma-cyhalothrin is a single, resolved isomer of the pyrethroid insecticide cyhalothrin. As such, it shares physical, chemical and biological properties with both cyhalothrin and lambda-cyhalothrin, which are mixtures of 4 and 2 isomers, respectively. Gamma-cyhalothrin is the most insecticidally active isomer of cyhalothrin/lambda-cyhalothrin, and thus the gamma-cyhalothrin technical product may be considered a refined form of cyhalothrin/lambda-cyhalothrin that has been purified by removal of less-active and inactive isomers. Therefore, similar levels of insecticidal efficacy for gamma-cyhalothrin can be obtained with significantly reduced application rates as compared with either cyhalothrin or lambda-cyhalothrin. HED has previously concluded (D288067; Yan Donovan, 11 March 2004) that residue data supporting registered uses of lambda-cyhalothrin are sufficient to support registration of gamma-cyhalothrin for the same uses, as long as the use rates of gamma-cyhalothrin are no greater than half the corresponding use rates of lambda-cyhalothrin. Various petitioners have proposed Section 3 registration for new food uses of gamma-cyhalothrin, in food-handling establishments, on okra and pistachios, and in cattle ear tags. The proposed application rates of gamma-cyhalothrin for the requested new uses (considered herein) are no greater than half of the corresponding, existing application rates for similar registered uses of lambda-cyhalothrin.

Dow AgroSciences (on behalf of Pytech Chemicals), has submitted PP#6H7114, which requests the establishment of a permanent food additive tolerance (at 0.01 ppm) arising from the use of gamma-cyhalothrin in food preparation, serving and holding areas of food-handling establishments. The petition is predicated on the registered use of lambda-cyhalothrin for the same purpose, as listed in 40CFR §180.438[a][3]. The gamma-cyhalothrin end-use product (EP) proposed for this use is Proaxis GPC (EPA Registration #74921-5). The currently registered label for Proaxis GPC already allows use in food-handling establishments, but has language which prohibits use in food preparation and holding areas, and in serving areas while food is exposed. HED notes that the term "food additive tolerance" is obsolete, since pesticide residues are no longer regulated under Section 409 of the Federal Food, Drug and Cosmetic Act (FFDCA). HED further notes that the correct tolerance expression for the proposed tolerance consists of gamma-cyhalothrin and its epimer.

The Interregional Research Project #4 (IR-4), in conjunction with Dow AgroSciences (on behalf of Pytech Chemicals), has submitted PP#7E7287, which requests the establishment of permanent tolerances arising from the use of gamma-cyhalothrin on okra and pistachios. The petition is based upon the registered use of lambda-cyhalothrin on fruiting vegetables (crop group 8), and pistachios, as listed in 40CFR §180.438[a][1]. The gamma-cyhalothrin EP proposed for this use is Proaxis (EPA Registration #74921-3). Section F of the petition correctly states that the tolerance expression for the proposed tolerances consists of gamma-cyhalothrin and its epimer.

Elanco Animal Health has submitted Action #72642-I, which requests Section 3 registration for the use of gamma-cyhalothrin on beef cattle, and non-lactating dairy cattle. The request is predicated on the registered use of lambda-cyhalothrin for the same purpose in Saber Extra Insecticide Ear Tags (EPA Registration #773-75), with tolerances in cattle commodities, as listed in 40CFR §180.438[a][1]. The gamma-cyhalothrin EP proposed for this use is Gammacyhalothrin Ear Tag (EPA File Symbol 72642-I). HED notes that the correct tolerance expression consists of gamma-cyhalothrin and its epimer.

2.0 CONCLUSIONS AND REGULATORY RECOMMENDATIONS

Through the use of bridging data, the toxicology database for gamma-cyhalothrin has been completed using developmental, reproduction, chronic (rodent), and oncogenicity studies conducted with cyhalothrin and lambda-cyhalothrin. The toxicology database for gamma-cyhalothrin, when bridged with cyhalothrin and lambda-cyhalothrin, is complete for the purposes of supporting the proposed uses, and selecting endpoints for 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 gamma-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.

The toxicological endpoints selected for gamma-cyhalothrin are at least half of the lambda-cyhalothrin endpoints. In studies where direct comparison can be made between the effect levels of gamma and lambda cyhalothrin, the gamma-cyhalothrin LOAEL is approximately half the lambda-cyhalothrin LOAEL (in other words, gamma-cyhalothrin is no more than twice as toxic as lambda-cyhalothrin). Therefore, because use rates of gamma-cyhalothrin are no greater than half the corresponding use rates of lambda-cyhalothrin, risks from gamma-cyhalothrin and lambda-cyhalothrin are expected to be similar. HED's previous risk assessments for lambda-cyhalothrin (D313315, D324219, D330542; William T. Drew; 18 July 2007, and D284860; Kit Farwell; 15 August 2002) are sufficient to cover the requested new uses of gamma-cyhalothrin. A new aggregate risk assessment for gamma-cyhalothrin is unnecessary, because the aggregate risks arising from the existing uses of lambda-cyhalothrin (and, therefore, the proposed uses of gamma-cyhalothrin) are not of concern.

Tolerances are established under 40CFR §180.438 for residues of lambda-cyhalothrin arising from uses in food-handling establishments, and on pistachios and cattle, which are the same as those requested in the subject petitions (except okra) for the enriched isomer, gamma-cyhalothrin. These tolerances for lambda-cyhalothrin will be adequate to cover residues of gamma-cyhalothrin in the requested commodities (except okra), based on the relative application rates. A tolerance for residues of lambda-cyhalothrin in okra has not been established; however, there are adequate residue data for lambda-cyhalothrin on fruiting vegetables (crop group 8) to support a tolerance for residues in okra. The residue data for lambda-cyhalothrin on fruiting vegetables are, therefore, also adequate to support the proposed tolerance for residues of gamma-cyhalothrin in okra. HED recommends that RD advise IR-4 that the residue data which support the existing tolerance for lambda-cyhalothrin in fruiting vegetables are sufficient to support the establishment of a lambda-cyhalothrin tolerance in okra without the need for further residue data. IR-4 merely needs to submit a petition proposing such a tolerance.

HED has no objection to the establishment of permanent tolerances for gamma-cyhalothrin residues in okra and pistachios (arising from use of Proaxis on these crops). HED also has no objection to the establishment of a permanent tolerance for gamma-cyhalothrin residues arising from the use of Proaxis GPC in food-handling establishments. It is unnecessary to establish tolerances for gamma-cyhalothrin residues in cattle meat, meat byproducts and fat (arising from use of Gammacyhalothrin Ear Tags on beef cattle, and non-lactating dairy cattle), as these tolerances have already been established in conjunction with previously registered uses.

Additionally, HED recommends investigation of gamma-and lambda-cyhalothrin nomenclature in, and some modifications to, the entry under 40CFR §180.438:

(1) Confirm the correct IUPAC designation for lambda-cyhalothrin (and its epimers). It is listed in 40CFR §180.438 as a 1:1 mixture of (S)-[alpha]-cyano-3-phenoxybenzyl-(Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and (R)-[alpha]-cyano-3-phenoxybenzyl-(Z)-(1S,3S)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate. (The epimers have very similar designations.) However, in Alan Wood's internet website, *Compendium of Pesticide Common Names*, it is listed as (*S*)-α-cyano-3-phenoxybenzyl (1*S*,3*S*)-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate and (*R*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate. (The epimers are not listed.)

(2) Make the tolerance expression for lambda-cyhalothrin uniform throughout 40CFR §180.438, as there are currently 2 different nomenclatures given for lambda-cyhalothrin in the citation. HED recommends that the tolerance expression in [a][3] be stated as either simply lambda-cyhalothrin, or exactly as the IUPAC designation is listed in [a][1], once the correct IUPAC terminology has been determined.

(3) Confirm the correct IUPAC designation for gamma-cyhalothrin. It is listed in the internet 40CFR §180.438 as (S)-[min]-cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate. In the printed edition of 40CFR §180.438, it is listed as (S)-'-cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate. (The epimer has a very similar designation.) However, in Alan Wood's internet website, *Compendium of Pesticide Common Names*, it is listed as (*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate. (The epimer is not listed.)

(4) Remove specific instructions for food-handling establishments (4 paragraphs, [a][3][ii] thru [a][3][v]), and delete the [i] preceding the second paragraph of [a][3].

HED also recommends that RD direct the petitioners to include language in the proposed labels that precludes the use of lambda-cyhalothrin on crops/livestock (or in facilities) which have already been treated with gamma-cyhalothrin, and vice-versa.

Furthermore, HED recommends that RD direct the registrant (Pytech Chemicals) to correct the Proaxis GPC label, such that footnote #4 on page 7 reads, "For residual control, use 0.03% rate." The footnote in the previously submitted version incorrectly stated this residual control use rate as 0.06%.

The established lambda-cyhalothrin tolerances, and the corresponding recommended gamma-cyhalothrin tolerances, arising from the subject petitions reviewed herein, are summarized in Table 2.0, below (reproduced as Table 3.3.1 in Section 3.3).

TABLE 2.0 Tolerance Summary for Gamma-Cyhalothrin.

Commodity	Established Lambda-Cyhalothrin Tolerance (ppm)	Recommended Gamma-Cyhalothrin Tolerance (ppm)
All food commodities (other than those already covered by a higher tolerance as a result of use on growing crops) in food-handling establishments where food products are held, processed or prepared.	0.01	0.01

TABLE 2.0 Tolerance Summary for Gamma-Cyhalothrin.		
Commodity	**Established Lambda-Cyhalothrin Tolerance (ppm)**	**Recommended Gamma-Cyhalothrin Tolerance (ppm)**
Pistachio	0.05	0.05
Okra	None	0.20
Vegetables, fruiting, group 8	0.20	0.20*
Cattle, fat	3.0	3.0*
Cattle, meat	0.2	0.2*
Cattle, meat byproducts	0.2	0.2*

* These tolerances have already been established for gamma-cyhalothrin (arising from previously registered uses).

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 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 B) have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical.

3.0 DETAILED DISCUSSIONS

3.1 PHYSICOCHEMICAL PROPERTIES

Gamma-cyhalothrin (with CAS number 76703-62-3, CAS name (*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate, and IUPAC name (*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate) is a single, resolved isomer of the pyrethroid insecticide cyhalothrin. The nomenclature and physicochemical properties of gamma-cyhalothrin are presented below in Tables 3.1.1 and 3.1.2, respectively.

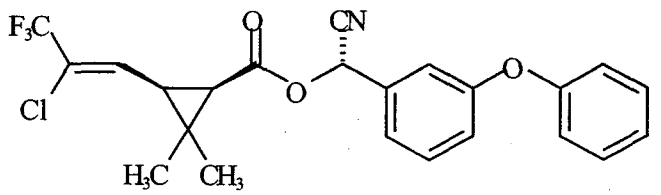
Table 3.1.1 Gamma-Cyhalothrin Nomenclature.	
Compound	(Z)-(1R,3R), S-ester 
Common Name	Gamma-Cyhalothrin
Company Experimental Names	XDE-225, XR-225
Molecular Formula	$C_{23}H_{19}ClF_3NO_3$
Molecular Weight	449.86
IUPAC Name	(*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate) **or** (*S*)-α-cyano-3-phenoxybenzyl (1*R*)-*cis*-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Name	(*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number	76703-62-3
End-use Products (EPs)	0.5 lb ai/gal (Proaxis™ GPC; EPA Registration #74921-5) 0.5 lb ai/gal (Proaxis™; EPA Registration #74921-3) 0.38 g ai/ear tag (Gamma-Cyhalothrin Ear Tag; EPA File Symbol 72642-I)

Table 3.1.2 Physicochemical Properties of Technical Grade Gamma-Cyhalothrin.			
Parameter	**Value**		**Reference**
Melting Point/Range (°C)	55.6		D288058 [1]
pH	NA [2]		
Density (g/mL at 20°C)	1.319		
Water Solubility (mg/L at 20°C)	0.0021		
Solvent Solubility (at 19°C)	Acetone	>500 g/kg	
	Ethyl Acetate	>500 g/kg	
	1,2-Dichloroethane	>500 g/kg	
	p-Xylene	>500 g/kg	
	Heptane	0.0307 g/mL	
	Methanol	0.138 g/mL	
	n-Octanol	0.0366 g/mL	
Vapor Pressure (mm Hg at 25°C)	2.59×10^{-9}		
Dissociation Constant (pK_a at 20°C)	NA		
Octanol/water Partition Coefficient (Log[K_{OW}])	4.96		
UV/Visible Absorption Spectrum (nm)	Maxima at 204, 277 (in Methanol)		

1. Shyam B. Mathur, 10 June 2003.
2. NA = Not Applicable (owing to the relative insolubility of gamma-cyhalothrin in water).

3.2 TOXICOLOGY

3.2.1 HAZARD CHARACTERIZATION

Gamma-cyhalothrin is moderately acutely toxic via the oral and dermal routes (Category II), and acutely toxic via the inhalation route (Category I). It is a moderate eye irritant without

TABLE 3.2.1 Summary of Toxicological Doses and Endpoints for Gamma-Cyhalothrin.			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern (LOC) for Risk Assessment**	**Study and Toxicological Effects**
Short-Term Dermal (1 to 30 days) Long-Term Dermal (>6 months)	Dermal Dose* = 5.0 mg/kg/day	**Residential** LOC for MOE < 100 **Occupational** LOC for MOE < 100	21-day dermal toxicity study in rats (lambda-cyhalothrin). Clinical signs of neurotoxicity (observed from day 2), decreased body weight and body weight gain.
Short-Term Inhalation (1 to 30 days) Intermediate-Term Dermal (1 to 6 months) Long-Term Dermal (>6 months)	Inhalation Dose* = 0.04 mg/kg/day	**Residential** LOC for MOE < 100 **Occupational** LOC for MOE < 100	21-day inhalation study in rats (lambda-cyhalothrin). Clinical signs of neurotoxicity and systemic toxicity.
Cancer	Classified as "Not likely to be Carcinogenic to Humans."		

UF = Uncertainty Factor, FQPA SF = FQPA Safety Factor, NOAEL = No Observed Adverse Effect Level, LOAEL = Lowest Observed Adverse Effect Level, PAD = Population Adjusted Dose (a = acute, c = chronic), RfD = Reference Dose, MOE = Margin Of Exposure, LOC = Level Of Concern.

* The values indicated above for acute dietary, dermal and inhalation exposure scenarios are the adjusted NOAELs (multiplied by a factor of 0.5), based on the purity of the lambda-cyhalothrin isomer compared to the enriched isomer gamma-cyhalothrin.

The rationales which HED utilized in selecting the various gamma-cyhalothrin endpoints are as follows:

For **acute dietary exposure**, the dose and endpoint from the chronic study in dogs using lambda-cyhalothrin were selected for risk assessment. The dog is the most sensitive species and clinical signs were apparent within several hours of dosing, making this endpoint suitable for acute dietary exposure assessment. The dose value listed in Table 3.1.1 (0.25 mg/kg) is not the study NOAEL. This dose value is the adjusted NOAEL (study NOAEL of 0.5 mg/kg/day multiplied by a factor of 0.5) selected only for this risk assessment. The lambda-cyhalothrin NOAEL was adjusted based on the purity of the lambda-cyhalothrin isomer as compared to the enriched isomer gamma-cyhalothrin.

For **chronic dietary exposure**, no adjustment for the increased toxicity of gamma-cyhalothrin was necessary since:

(1) The most sensitive species (dogs) was selected.

(2) The selected NOAEL is 25-fold lower than the next-lowest gamma-cyhalothrin NOAEL of 2.5 mg/kg/day established in the two-year study in rats.

(3) The basis for the LOAEL is very conservative (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).

For **short- and intermediate-term incidental oral exposure**, the endpoint is appropriate for the population of concern (infants and children). It is applicable to both short- and intermediate-term exposure scenarios because the first effect was observed in the male during

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), and is a skin sensitizer in guinea pigs.

On 12 February 2004, HED examined the recommendations of the toxicology reviewer for gamma-cyhalothrin with regard to the acute and chronic reference doses (RfDs), and the toxicological endpoint selections, for use in occupational and/or residential exposure risk assessments, as appropriate. The potential for increased susceptibility of infants and children from exposure to gamma-cyhalothrin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996, in accordance with the 2002 OPP 10X Guidance Document. For detailed hazard characterization and endpoint selection, refer to HED's document of 1 March 2004, TXR #0052388. The toxicological endpoints selected for gamma-cyhalothrin are at least half of the lambda-cyhalothrin endpoints (in other words, gamma-cyhalothrin is no more than twice as toxic as lambda-cyhalothrin).

The toxicological evaluation of gamma-cyhalothrin can be accomplished by studies on gamma-cyhalothrin itself, as well as by studies on lambda-cyhalothrin and/or cyhalothrin (the less-purified and unpurified isomeric compounds, respectively). Cyhalothrin and lambda-cyhalothrin have been reviewed by HED for FQPA risk assessment, as well as toxicity endpoint selection, for the various exposure scenarios (TXR #0051125). Because gamma-cyhalothrin is a component of the other two mixed-isomer compounds, gamma-cyhalothrin essentially has been evaluated in the previous toxicological studies on cyhalothrin and lambda-cyhalothrin. Table 3.2.1 (below) contains a summary of the toxicological doses and endpoints for gamma-cyhalothrin. The toxicity profiles for cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin are provided in the appendices.

TABLE 3.2.1 Summary of Toxicological Doses and Endpoints for Gamma-Cyhalothrin.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population, including infants and children)	Dose* = 0.25 mg/kg UF = 100 **Acute RfD** = 0.0025 mg/kg	FQPA SF = 1 X **aPAD** = $\frac{\text{acute RfD}}{\text{FQPA SF}}$ = 0.0025 mg/kg/day	Chronic oral study in dogs (lambda-cyhalothrin). Clinical signs of neurotoxicity (ataxia) observed from day 2, three to seven hours post-dosing.
Chronic Dietary (All populations)	NOAEL = 0.1 mg/kg/day UF = 100 **Chronic RfD** = 0.001 mg/kg/day	FQPA SF = 1 X **cPAD** = $\frac{\text{chronic RfD}}{\text{FQPA SF}}$ = 0.001 mg/kg/day	Chronic oral study in dogs (lambda-cyhalothrin). Gait abnormalities observed in 2 dogs.
Short-Term Incidental Oral (1 to 30 days) Intermediate-Term Incidental Oral (1 to 6 months)	NOAEL = 0.1 mg/kg/day	**Residential** LOC for MOE < 100 **Occupational** = NA	Chronic oral study in dogs (lambda-cyhalothrin). Gait abnormalities observed in 2 dogs.

week 2 and again 2 days later immediately after dosing, and in the female 4 times during week 9. No adjustment for the increased toxicity of gamma-cyhalothrin was necessary since a very conservative endpoint was selected from the most sensitive species (dogs), and the selected NOAEL is 34-fold lower than the NOAEL of 3.4 mg/kg/day established in the 90-day study with gamma-cyhalothrin.

For **dermal exposure (all durations)**, the dose value listed in Table 3.1.1 (5.0 mg/kg/day) is not the study NOAEL. This dose value is the adjusted NOAEL (study NOAEL of 10 mg/kg/day multiplied by a factor of 0.5) selected only for this risk assessment. The lambda-cyhalothrin NOAEL was adjusted based on the purity of the lambda-cyhalothrin isomer as compared to the enriched isomer gamma-cyhalothrin.

For **inhalation exposure (all durations)**, the dose value listed in Table 3.1.1 (0.04 mg/kg/day) is not the study NOAEL. This dose value is the adjusted NOAEL (study NOAEL of 0.08 mg/kg/day multiplied by a factor of 0.5) selected only for this risk assessment. The lambda-cyhalothrin NOAEL was adjusted based on the purity of the lambda-cyhalothrin isomer as compared to the enriched isomer gamma-cyhalothrin.

3.2.2 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 developmental neurotoxicity (DNT) study is available for lambda-cyhalothrin. 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) was 10 mg/kg bw/day, with a NOAEL of 4 mg/kg bw/day. Effects in offspring and adult animals were 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 included:

(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.

(4) Missing low- and mid-dose morphometry data.

However, it is not likely that these limitations would impact 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 was 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 was 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 owing to the high variability, and the lack of habituation, these data were considered equivocal. If a 10-fold factor is applied to the NOAEL in the study (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 (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 would not likely underestimate risks. There was no published literature found that would indicate a neurodevelopmental concern for gamma-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 (the most sensitive species) should assure protection of human health, including children.

3.3 RESIDUE CHEMISTRY

Dow AgroSciences (on behalf of Pytech Chemicals), has submitted PP#6H7114, which requests the establishment of a permanent food additive tolerance arising from the use of gamma-cyhalothrin in food-handling establishments. (HED notes that the term "food additive tolerance" is obsolete, since pesticide residues are no longer regulated under Section 409 of FFDCA.) The petition is predicated on the registered use of lambda-cyhalothrin for the same purpose, as listed in 40CFR §180.438[a][3]. The gamma-cyhalothrin EP proposed for this use is Proaxis GPC (EPA Registration #74921-5). The directions for use of lambda-cyhalothrin in food-handling establishments (as listed in 40CFR §180.438[a][3]) specify that the spray solution used for spot and/or crack and crevice treatment be prepared at a maximum concentration of 0.06% active ingredient (ai) by weight. Therefore, Proaxis GPC should be used for spot and/or crack and crevice treatment at a maximum concentration of 0.03% ai by weight. However, in the proposed Proaxis GPC label, note 4 on page 7 states that "For residual control, use 0.06% rate." Following correspondence with Kenneth D. Racke of Regulatory Sciences and Government Affairs at Dow AgroSciences, it was determined that this was a typographical error, and that the label should have stated the use rate for residual control as 0.03%. This proposed use of gamma-cyhalothrin thus meets the requirement that the use rate be no more than half the use rate of lambda-cyhalothrin when utilized in the same fashion.

IR-4, in conjunction with Dow AgroSciences (on behalf of Pytech Chemicals), has submitted PP#7E7287, which requests the establishment of permanent tolerances arising from the use of gamma-cyhalothrin on okra and pistachios. The petition is based upon the registered use of lambda-cyhalothrin on fruiting vegetables (crop group 8), and pistachios, as listed in 40CFR §180.438[a][1]. The gamma-cyhalothrin EP proposed for this use is Proaxis (EPA Registration #74921-3). A tolerance in pistachios is established under 40CFR §180.438 for residues of lambda-cyhalothrin arising from a use which is the same as that requested for the enriched isomer, gamma-cyhalothrin. The tolerance for lambda-cyhalothrin will be adequate to cover residues of gamma-cyhalothrin in pistachios, based on the relative application rates. Similarly, the existing tolerance for lambda-cyhalothrin in fruiting vegetables (crop group 8) will be adequate to cover residues of gamma-cyhalothrin in okra, based on HED's memo analyzing a proposal to add okra to crop group 8 (D272782; Bernard A. Schneider; 20 September 2002). HED recommends that RD inform IR-4 that the residue data which support the existing tolerance for lambda-cyhalothrin in fruiting vegetables are sufficient to support the establishment of a

lambda-cyhalothrin tolerance in okra without the need for further residue data. IR-4 merely needs to submit a petition proposing such a tolerance.

Elanco Animal Health has submitted Action #72642-I, which requests Section 3 registration for the use of gamma-cyhalothrin on beef cattle, and non-lactating dairy cattle. The request is predicated on the registered use of lambda-cyhalothrin for the same purpose in Saber Extra Insecticide Ear Tags (EPA Registration #773-75), with tolerances in cattle commodities, as listed in 40CFR §180.438[a][1]. The gamma-cyhalothrin EP proposed for this use is Gammacyhalothrin Ear Tag (EPA File Symbol 72642-I). The Saber Extra tag delivers 1.90 grams of lambda-cyhalothrin (over a duration of 5 months), for a theoretical daily release of 12.26 mg. The Gammacyhalothrin tag delivers 0.38 grams of gamma-cyhalothrin (over 5 months), for a theoretical daily release of 2.47 mg. This proposed use of gamma-cyhalothrin thus meets the requirement that the use rate be no more than half the use rate of lambda-cyhalothrin when utilized in the same fashion.

HED recommends that RD direct the petitioners to include language in the proposed labels that precludes the use of lambda-cyhalothrin on crops/livestock (or in facilities) which have already been treated with gamma-cyhalothrin, and vice-versa.

The established lambda-cyhalothrin tolerances, and the corresponding recommended gamma-cyhalothrin tolerances arising from the subject petitions reviewed herein are summarized in Table 3.3.1 (below). There are no Codex, Mexican or Canadian maximum residue limits (MRLs) for gamma-cyhalothrin *per se*, but there are numerous international MRLs for lambda-cyhalothrin and/or cyhalothrin.

TABLE 3.3.1 Tolerance Summary for Gamma-Cyhalothrin.

Commodity	Established Lambda-Cyhalothrin Tolerance (ppm)	Recommended Gamma-Cyhalothrin Tolerance (ppm)
All food commodities (other than those already covered by a higher tolerance as a result of use on growing crops) in food-handling establishments where food products are held, processed or prepared.	0.01	0.01
Pistachio	0.05	0.05
Okra	None	0.20
Vegetables, fruiting, group 8	0.20	0.20*
Cattle, fat	3.0	3.0*
Cattle, meat	0.2	0.2*
Cattle, meat byproducts	0.2	0.2*

* These tolerances have already been established for gamma-cyhalothrin (arising from previously registered uses).

Analytical Enforcement Methods: Adequate enforcement methods are available for determination of lambda-cyhalothrin residues in plant and animal commodities. ICI Method 81 (PRAM 81) is used to determine the residues of lambda-cyhalothrin and its epimer in plant matrices, while ICI Method 86 is used to determine residues of lambda-cyhalothrin and its epimer in animal matrices. Both methods have been validated by EPA as adequate enforcement methods for determination of parent lambda-cyhalothrin and its epimer in the respective matrices. ICI Method 96 is used to determine lambda-cyhalothrin metabolites in meat, milk, poultry and eggs. The limit of quantitation (LOQ) for all three methods is 0.01 ppm. Since gamma- and lambda-cyhalothrin differ only in the relative content of enantiomers, and the

enforcement methods do not use chiral columns, the lambda-cyhalothrin methods are applicable to gamma-cyhalothrin.

Dietary Exposure: The chronic and acute dietary exposure and risk assessments conducted for lambda-cyhalothrin (D324223; Anant Parmar; 12 March 2007) are also applicable to gamma-cyhalothrin. They adequately address the dietary exposure and risk arising from the requested new uses of gamma-cyhalothrin. HED used percent crop treated (PCT) information in both the chronic and acute lambda-cyhalothrin dietary exposure analyses. PCT estimates of agricultural uses for lambda-cyhalothrin were obtained in the form of a screening-level usage assessment (SLUA), based on data years 1999–2004. Average and maximum values for percent crop treated data were used in the chronic and acute analyses, respectively, for the following commodities with established tolerances: Almonds (5 chronic, 5 acute), Apples (5 chronic, 10 acute), Beans, Green (10 chronic, 20 acute), Broccoli (10 chronic, 20 acute), Cabbage (30 chronic, 45 acute), Canola/Rapeseed (1 chronic, 2.5 acute), Cauliflower (20 chronic, 30 acute), Cherries (5 chronic, 15 acute), Corn (1 chronic, 2.5 acute), Cotton (10 chronic, 10 acute), Dry Beans/Peas (1 chronic, 2.5 acute), Garlic (10 chronic, 30 acute), Lettuce (30 chronic, 45 acute), Onions (50 chronic, 55 acute), Peaches (5 chronic, 10 acute), Peanuts (5 chronic, 10 acute), Pears (15 chronic, 30 acute), Peas, Green (1 chronic, 2.5 acute), Pecans (1 chronic, 5 acute), Peppers (5 chronic, 15 acute), Prunes and Plums (5 chronic, 5 acute), Rice (15 chronic, 30 acute), Sorghum (1 chronic, 2.5 acute), Soybeans (5 chronic, 10 acute), Sugarcane (5 chronic, 10 acute), Sunflowers (10 chronic, 20 acute), Sweet Corn (45 chronic, 60 acute), Tomatoes (20 chronic, 20 acute), and Wheat (1 chronic, 2.5 acute). For all other commodities and for new uses, 100% PCT was assumed. 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 subgroup 1C) except potatoes. Anticipated residues were used for all other commodities.

Table 3.3.2 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%

Table 3.3.2 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**
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.

Table 3.3.3 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.

Estimated Drinking Water Concentrations (EDWCs): The drinking water residues used in the dietary risk assessment were provided by EFED in a memorandum (D324222, D330149; Jose Melendez; 26 October 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 EDWCs are adequate to cover potential drinking water exposures to gamma-cyhalothrin, based on the proposed uses.

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 of lambda-cyhalothrin and degradate XV in surface drinking water was 5.35 ppb; the chronic level of lambda-cyhalothrin and degradate XV in drinking water was 0.130 ppb. 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.

3.4 AGGREGATE RISK ASSESSMENT AND 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).

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, and do not exceed HED's LOC.

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 are greater than the Agency target MOE of 100 (ranging from 140 to 490), and there are thus no concerns for aggregate exposure. These MOEs were taken from the most recent lambda-cyhalothrin risk assessment (D313315, D324219, D330542; William T. Drew; 18 July 2007).

TABLE 3.4 Gamma-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.

Long-Term Aggregate Risk: The dietary exposure (food and drinking water) pathway is the only source of exposure to gamma-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, and do not exceed HED's LOC.

Cancer Aggregate Risk: Gamma-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.

3.5 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/.

3.6 OCCUPATIONAL EXPOSURE/RISK PATHWAY

The occupational exposure analyses conducted on lambda-cyhalothrin for similar uses are adequate to cover the proposed uses of gamma-cyhalothrin requested in the subject petitions, and the resultant MOEs do not exceed HED's LOC.

4.0 REFERENCES

Hazard Characterization Memorandum

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

Residue Chemistry Data Review Memoranda

PP#4F6812. Request for the Use of Gamma-Cyhalothrin in/on crops with Uses for Lambda-Cyhalothrin.; D288067; Yan Donovan; 11 March 2004.

Analysis of the Proposal to Amend the Crop Group Regulation (40CFR §180.41) by Adding Okra to the Fruiting Vegetable Crop Group 8 and to Amend the Pepper Commodity Definition (40CFR §180.1[h]).; D272782; Bernard A. Schneider; 20 September 2002.

Risk Assessment Memoranda

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.; D313315, D324219, D330542; William T. Drew; 18 July 2007.

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; 15 August 2002.

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; 26 October 2006.

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; 12 March 2007.

APPENDIX A: TOXICOLOGY ASSESSMENT

A.1 Toxicity Profiles

TABLE A.1.1 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 (gamma-cyhalothrin)**	45447321 1999 Acceptable/non-guideline 0, 2.5, 10, 50, 125, or 250 ppm M: 0, 0.22, 0.85, 4.2, or 8.81 mg/kg/day F: 0, 0.24, 0.95, 4.5, or 10.24 mg/kg/day	**NOAEL:** 4.2/4.5 mg/kg/day (M/F) **LOAEL:** 8.81/10.24 mg/kg/day, based on decreases in body weight gain and neurotoxic effects (incoordination, abnormal posture, flaccid musculature)
NA	**28-day oral toxicity – rat (cydalothrin)**	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 (gamma-cyhalothrin)**	45447322 2000 Acceptable/guideline 0, 2.5, 10, 50, or 100 ppm M: 0, 0.2, 0.7, 3.4, or 6.6 mg/kg/day F: 0, 0.2, 0.8, 4.2 or 8.0 mg/kg/day	**NOAEL**: 3.4/4.2 mg/kg/day (M/F) **LOAEL**: 6.6/8.0 mg/kg/day (M/F), based on mortality in males, neuromuscular effects in both sexes, dermatitis, and gross and microscopic skin lesions in females
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).

TABLE A.1.1 Subchronic, Chronic and Other Toxicity Profile.			
Guideline Number	**Study Type**	**MRID Number/Year/ Classification /Doses**	**Results**
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 (gamma-cyhalothrin)**	45447324 2000 Acceptable/guideline 0, 0.1, 0.5, or 2.0 mg/kg/day	**Maternal NOAEL:** 0.5 mg/kg/day **Maternal LOAEL**: 2.0 mg/kg/day, based on decreased body weights, body weight gains, and food consumption, as well as clinical signs **Developmental NOAEL**: 2.0 mg/kg/day **Developmental LOAEL**: not established
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

TABLE A.1.1 Subchronic, Chronic and Other Toxicity Profile.			
Guideline Number	**Study Type**	**MRID Number/Year/ Classification /Doses**	**Results**
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.
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).

TABLE A.1.1 Subchronic, Chronic and Other Toxicity Profile.			
Guideline Number	**Study Type**	**MRID Number/Year/ Classification /Doses**	**Results**
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).
870.5100	**Bacterial reverse gene mutation**	45447402 2001 Acceptable/guideline TA98, TA100, TA1535, TA1537, and WP2 *uvr*A 33.3-5000 µg/plate (+/-S9)	There was no increase in test plate revertants over controls in any strain up to the limit of solubility.
870.5100	**Bacterial reverse gene mutation**	45447327 2001 Acceptable/guideline TA98, TA100, TA1535, TA1537, and WP2 *uvr*A Concentrations up to 5000 µg/plate (+/-S9)	There was no increase in test plate revertants over controls in any strain up to the limit of solubility.
870.5100	**Bacterial reverse gene mutation**	45447325 2000 Acceptable/guideline TA98, TA100, TA1535, TA1537, and WP2 *uvr*A 10-5000 µg/plate	There was no increase in test plate revertants over controls in any strain up to the limit of solubility.
870.5300	**In vitro mammalian gene mutation**	45447404 2000 Acceptable/guideline 3.9-1000 µg/mL (+S9) 156-4500 µg/mL (-S9)	There was no evidence of mutagenicity in this mouse lymphoma forward mutation assay at the thymidine kinase locus at concentrations up to the limit of solubility.
870.5375	**In vitro cytogenic mutagenicity study**	45447405 2000 Acceptable/guideline 4.5-4500 µg/mL (+/-S9)	XR-225 is considered negative for clastogenicity in this *in vitro* chromosomal aberration study in rat lymphocytes.
870.5395	**In vivo cytogenic mutagenicity study**	45447403 2001 Acceptable/guideline 5.9% ai 300, 600 or 1000 mg/kg/day	There were no statistically significant increases in the frequencies of MNPCEs in test article-treated mice compared to those in negative control animals.
870.5395	**In vivo cytogenic mutagenicity study**	45447401 2001 Acceptable/guideline 14.7% a.i 50, 100 or 200 mg/kg/day	There were no statistically significant increases in the frequencies of MNPCEs in test article-treated mice compared to those in negative control animals.

TABLE A.1.1 Subchronic, Chronic and Other Toxicity Profile.			
Guideline Number	**Study Type**	**MRID Number/Year/ Classification /Doses**	**Results**
870.5395	**In vivo cytogenic mutagenicity study**	45447326 2000 Acceptable/guideline 100% ai 1, 2 or 4 mg/kg/day	There were no statistically significant increases in the frequencies of MNPCEs in test article-treated mice compared to those in negative control animals.
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.
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).

TABLE A.1.1 Subchronic, Chronic and Other Toxicity Profile.			
Guideline Number	**Study Type**	**MRID Number/Year/ Classification /Doses**	**Results**
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.

TABLE A.1.2 Acute Toxicity Profile (Technical)			
Pyrethroid Type →	**Cyhalothrin**	**Lambda-Cyhalothrin**	**Gamma-Cyhalothrin**
Acute Oral	LD_{50}: 243 mg/kg (m) LD_{50}: 144 mg/kg (f) **Tox.Cat. II**	LD_{50}: 79 mg/kg (m) LD_{50}: 56 mg/kg (f) **Tox.Cat. II**	LD_{50}: >50 mg/kg (m) LD_{50}: 55 mg/kg (f) **Tox.Cat. II**
Acute Dermal	LD_{50}: >1000 mg/kg (m) LD_{50}: >2000 mg/kg (f) **Tox.Cat. II**	LD_{50}: 632 mg/kg (m) LD_{50}: 696 mg/kg (f) **Tox.Cat. II**	LD_{50}: >1500 mg/kg (m) LD_{50}: 1643 mg/kg (f) **Tox.Cat. II**
Acute Inhalation	LC_{50}: 0.173 mg/L (m) LC_{50}: 0.183 mg/L (f) **Tox.Cat. II**	LC_{50}: 0.065 mg/L **Tox.Cat. II**	LC_{50}: 0.042 mg/L (m) LC_{50}: 0.028 mg/L (f) **Tox.Cat. I**
Eye Irritation	Moderate irritant **Tox.Cat. III**	Mild irritant **Tox.Cat. III**	Moderate irritant **Tox.Cat. III**
Skin Irritation	Mild irritant **Tox.Cat. IV**	Non-irritant **Tox.Cat. IV**	Slight irritant **Tox.Cat. IV**
Dermal Sensitization	Sensitizer	Non-sensitizer	Sensitizer

APPENDIX B: HUMAN RESEARCH REFERENCES

The Metabolism and Pharmacokinetics of Lambda-Cyhalothrin in Man.; Zeneca Report #CTL/P/4208, Study #XH2429; MRID #44333801; J.R. March, B.H. Woolen, and M.F. Wilks; 1/28/1994.

The Pesticide Handlers Exposure Database, Version 1.1 (Electronic Database); The PHED Task Force, 1995; (Task Force members: Health Canada, US Environmental Protection Agency, and the National Agricultural Chemicals Association); released February, 1995.

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Chemical:	**Cyclopropanecarboxylic acid, 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2, 2-dimethyl-, cyano(3-phenoxyphenyl)methyl ester, [1R-[1 alpha(S*), 3 alpha(Z)]]-**
	PC Code: 128807
HED File Code:	**14000 Risk Reviews**
Memo Date:	**3/31/2008**
File ID:	**TX0052388 TX0051125**
Accession #:	**000-00-0125**

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