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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: January 27, 2010

MEMORANDUM

SUBJECT: **Beta Cyfluthrin: Human Health Risk Assessment to Add Bed Bug Use to Label.**

PC Code: 118831	DP Barcode: D367398
MRID No.: 47795901	Registration No.: 432-1483
Petition No.: NA	Regulatory Action: Section 3
Assessment Type: Single Chemical Aggregate	Registration Case No.: None
TXR No.: None	CAS No.: 68359-37-5
Decision No.: 416677	40 CFR 180.436

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Rec'd in RRC 2/2/2010

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1.0 Executive Summary

Beta-cyfluthrin (an enriched isomer of cyfluthrin) is a non-systemic pyrethroid insecticide, which is registered for use in outdoor and indoor spot and crack and crevice product, Temprid ™ SC Insecticide. Temprid ™ SC is formulated as a liquid concentrate suspension containing 10.5% beta-cyfluthrin. Temprid also contains the insecticide imidacloprid, which is being addressed in a separate risk assessment by HED. The registrant is requesting permission to add the use for treatment of bed bugs to the current registered label. This new use site would include treatment of spots, cracks and crevices as well as direct application to mattresses. There are no new food uses associated with this action.

A complete human health risk analysis was previously completed for cyfluthrin/beta-cyfluthrin (Cyfluthrin/Beta-cyfluthrin – Human Health Risk Assessment; Thomas Moriarty; 2007; D331951) in 2007. There have been no changes to the hazard characterization or dietary (food and drinking water) exposure to date, with the exception of the immunotoxicity study as a part of new data requirements [40 CFR Part 158]. Furthermore, the residential exposure risks have been re-evaluated since the 2007 assessment using the HED Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001).

Hazard Characterization

Cyfluthrin toxicity data have been used as bridging data for beta-cyfluthrin. The toxicology databases together are considered complete and adequate for selecting toxicity endpoints for this risk assessment. The scientific quality is relatively high, and the toxicity profiles of beta-cyfluthrin can be characterized for all effects, including potential developmental, reproductive, and neurotoxic effects.

An immunotoxicity study is required as a part of new data requirements [40 CFR Part 158] for conventional pesticide registration. However, there were no signs of immunotoxicity in any of the available toxicology studies.

Toxicologically, the primary target for cyfluthrin/beta-cyfluthrin is the neuromuscular system; other non-specific effects include decreased body weight gain, and decreased food consumption.

The doses and endpoints for both dietary and non-dietary exposures are based on neurological and/or body weight effects.

Beta-cyfluthrin has been classified as "Not Likely to be Carcinogenic to Humans" and, there is no concern of mutagenicity. Therefore, there is no concern over cancer risk with the proposed or existing uses.

The database does not indicate that beta-cyfluthrin induces any endocrine disruption.

FQPA and Uncertainty Factors

Based upon the hazard data and the methods used to estimate exposure, it is recommended that the 10X FQPA SF for the protection of infants and children be reduced to 1X. The total uncertainty factor and level of concern that has been applied to the non-cancer risk assessment for beta-cyfluthrin is 100 for occupational/commercial and residential exposure. A 10X uncertainty factor for lack of an immunotoxicity study is not required since there is no evidence of effects to the immune system in the available studies.

Dietary Risk

The dietary analysis is refined and includes processing factors, percent crop treated estimates, and monitoring data. As there are no food uses associated with this action a new dietary risk assessment was not conducted for purposes of this assessment. As noted in the previous 2007 assessment, dietary risk estimates are not of concern.

Residential Exposure and Risk

No chemical-specific data were available with which to assess potential exposure to residential pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handler Exposure Database (PHED) (v. 1.1, 1998). The handler MOE is greater than 100 and, therefore, is not of concern.

There is a potential for postapplication exposure from contact with treated mattresses (including the box spring, headboard and frame), in addition to entering areas previously treated with beta-cyfluthrin. Postapplication exposure scenarios were assessed using the HED Draft Standard Operating Procedures (SOPs) for Residential Expsoure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001).

All post-application inhalation and dermal scenarios resulted in MOEs greater than 100 and are not of concern to HED. Only incidental oral exposures resulting from the crack and crevice use have been assessed here since they are considered to be protective of the mattress application. The hand-to-mouth transfer postapplication exposure assessment resulted in oral MOEs greater than 100 for all scenarios and is not of concern to HED.

Aggregate Risk

HED has conducted aggregate risk estimates for beta-cyfluthrin, examining various sources and routes of exposure. As there are no new food uses associated with this action, an acute aggregate risk assessment was not conducted. Aggregate risk estimates for short-, intermediate- and long-term durations do not pose a risk concern for HED. Although HED does not have risk concerns for the proposed use, HED does recommend that the immunotoxicity study be made a condition of registration for this use.

Occupational Exposure and Risk

Chemical-specific data were not submitted to the Agency in support of this Section 3 application. HED used data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures. For purposes of assessing a crack and crevice exposure scenario for commercial applicators, HED used the mixer/loader/applicator low pressure handwand using a

wettable powder scenario as a surrogate to assess applicator exposure for Temprid ™ SC Insecticide which is formulated as a liquid. Risks for commercial handler exposures are of concern (MOEs < 100) with the use of only dermal PPE (i.e., gloves in addition to baseline attire). When use of a NIOSH-approved quarter-face, cup-style dust mist respirator [Protection Factor (PF) 5] was added, all short-term handler risk estimates are not of concern (total MOEs > 100). With the addition of a NIOSH-approved half-face (PF 10) respirator, the intermediate-term risk for treatment of mattresses (MOE = 150) was not of concern: however, the handler exposure for treatment of cracks and crevices resulted in a total MOE of 77.

HED realizes that the intermediate-term MOEs of 77 and 150 are conservative estimates since Temprid ™ SC Insecticide is formulated as a liquid and the assumption that 40 gallons of diluted product will be used daily for treatments. Therefore, HED believes that the use of Temprid ™ SC Insecticide with the addition of a NIOSH-approved half-face (PF 10) respirator, when treating crack and crevices and mattresses over an intermediate-term duration (1 to 6 months) should not result in risks of concern. HED cannot further refine risk estimates without the use of chemical specific data or indication of a decrease in the application rate or amount of product used.

HED recommends that the Registration Division ensure that the appropriate PPE language for use of respirator (A PF 5 respirator is generally referred to as the 80% PF respirator and is a "quarter-face, cup-style dust/mist filtering respirator" and a PF 10 respirator is the 90% PF respirator or a "half- or full-face cartridge or canister style respirator or powered air-purifying respirator") **be added to the registered label.**

Since the commercial applicators are not returning to the treated area, a postapplication exposure assessment was not performed for commercial applicators.

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, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

Environmental Justice

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.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

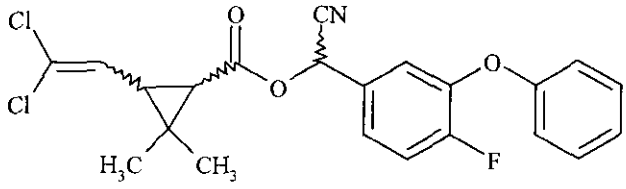
Temprid ™ SC Insecticide is a liquid concentrate suspension containing 10.5% beta-cyfluthrin (1 lb ai/gallon). **Table 2.1** provides a summary of the proposed use to control bed bugs and the registered use for indoor and outdoor spot and crack and crevice applications. The total a.i. percentages in the table include the second active ingredient (imidacloprid).

Table 2.1 Use Profile for Beta-Cyfluthrin

Product, Formulation	Use Scenario	Application Equipment	Application Rate	Timing of application and Treatment Interval
Temprid ™ SC Insecticide (Reg. No. 432-1483) 1 lb ai/gallon	Outdoor and Indoor spot and crack and crevice and perimeter treatment (outdoor only) of buildings and structures	Spot application – low-pressure system w/ fan-type nozzle Spray, mist, foam crack and crevice or void application – low pressure system with pinpoint nozzle	Indoor and outdoor spot treatment = 0.075% total ai (contains 0.025% B-cyfluthrin) 0.15% total ai(contains 0.05% B-cyfluthrin) 0.27 fl oz. product/gal. = 0.002 lb ai. B-cyfluthrin/gal 0.51 fl oz. product/gal. = 0.004 lb ai. B-cyfluthrin/gal	Re-apply every 7 to 10 days if needed Bed Bugs – allow to dry before making bed. **Product should not be applied to furniture with prolonged human contact.**
	Bed Bug (tufts, seams, folds, edges of mattress and/or upholstered furniture until moist, box springs, bed frames, headboard and joints, baseboards, moldings, floor coverings etc)		Bed bugs treatment = 0.075% total a.i. (contains 0.025% B-cyfluthrin) 0.27 fl oz. product/gal. = 0.002 lb ai./gal	

2.2 Structure and Nomenclature

Both cyfluthrin and beta-cyfluthrin are mixtures of the same four diastereomers. Isomers I and II are in the *cis* configuration, and Isomers III and IV are in the *trans* configuration. Cyfluthrin is comprised of approximately equal parts: Isomer I is approximately 25%, Isomer II is approximately 19%, Isomer III is approximately 34% and, Isomer IV is approximately 23%. Beta-cyfluthrin on the other hand, is enriched in Isomer II (approximately 35%) and Isomer IV (approximately 62%), and contains only minor amounts of Isomer I and Isomer III (less than 3% of total). The structure, nomenclature and physicochemical properties of cyfluthrin and beta-cyfluthrin are presented below in **Tables 2.2 and 2.3**.

Table 2.2 Cyfluthrin and β-Cyfluthrin Nomenclature.		
	 Diastereomer I (1R,3R,αR + 1S,3S,αS; 1:1; cis) Diastereomer II (1R,3R,αS + 1S,3S,αR; 1:1; cis) Diastereomer III (1R,3S,αR + 1S,3R,αS; 1:1; trans) Diastereomer IV (1R,3S,αS + 1S,3R,αR; 1:1; trans)	
	Cyfluthrin: Isomer I (23-27%), Isomer II (17-21%), Isomer III (32-36%), and Isomer IV (21-25%)	**beta-Cyfluthrin**: Isomer I (<2%), Isomer II (30-40%), Isomer III (<3%), and Isomer IV (57-60%)
Common names	Cyfluthrin and beta-Cyfluthrin	
Company experimental name	Baythroid®, FCR1272	
IUPAC names	**Cyfluthrin**: (RS)-α-cyano-4-fluoro-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2- dimethylcyclopropanecarboxylate **beta-Cyfluthrin**: enantiomeric pair (R)-α-cyano-4-fluoro-3-phenoxybenzyl (1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1R,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate in ratio 1:2 with the enantiomeric pair (R)-α-cyano-4-fluoro-3-phenoxybenzyl (1S,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate	
CAS name	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	
CAS registry number	68359-37-5	
End-use products (EPs)	beta-Cyfluthrin: Temprid ™ SC Insecticide (1 lb/gal; EPA Reg. No. 4321483)	

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Technical Grade Cyfluthrin	
Parameter	Value
Melting point/range (°C)	Isomer I: 57 Isomer II: 73-74 Isomer III: 65-66 Isomer IV: 101-102
pH	not measurable because of low solubility in water
Density (g/mL at 20°C)	1.28
Water solubility (μg/L at 20°C)	Isomer I: 2.2 Isomer II: 1.9 Isomer III: 2.2 Isomer IV: 2.9
Solvent solubility (g/L room temperature)	Methylene chloride >200 Toluene >200 Hexane 10-20 Isopropanol 20-50
Vapor pressure (20 or 25°C)	3.3×10^{-8} mmHg
Dissociation constant, pK_a	does not dissociate
Octanol/water partition coefficient, Log(K_{OW})	Isomer I: 6 Isomer II: 5.9 Isomer III: 6 Isomer IV: 5.9
UV/visible absorption spectrum	Absorption maxima: primary: 196 nm, secondary 275 nm

3.0 Hazard Characterization/Assessment

A complete hazard characterization was previously assessed for beta-cyfluthrin (Cyfluthrin/Beta-cyfluthrin – Human Health Risk Assessment; Thomas Moriarty; D331951) in 2007. There are no changes to the hazard characterization to date, with the exception of the new data requirements [40 CFR Part 158] for an immunotoxicity study.

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Mode of action, metabolism, toxicokinetic data

Cyfluthrin is a type II pyrethroid. Beta-cyfluthrin is an enriched isomer of cyfluthrin. Pyrethroids initially stimulate nerve cells to produce repetitive discharges which can eventually lead to paralysis. Such effects are caused by their action on the sodium channel through which sodium ions enter the axon to cause excitation. These effects are produced in an insect's nerve cord, which contains ganglia and synapses, as well as in giant nerve fiber axons.[1] Type II pyrethroids give rise to the C-S syndrome of clinical signs of toxicity. The C-S syndrome consists of initial pawing and burrowing and later abnormal movements, salivation, coarse tremors, and convulsions.

Orally, cyfluthrin is rapidly and nearly completely absorbed. Peak plasma levels occurred at about 2 hours after dosing. Greater than 95% was excreted within 48 hours. Excretion was via the urine and feces with about 90% in the urine within 24 hours. Different dose levels or multiple doses did not affect the findings. The results of intravenous and oral dosing were similar. There was evidence of enterohepatic circulation. Parent cyfluthrin is cleaved at the ester bond and then oxidized to yield 3-phenoxy-4-fluorobenzoic acid. This intermediate is then either hydroxylated and subsequently conjugated and excreted, or first bound to glycine and then hydroxylated, conjugated and excreted.

3.1.1.2 Sufficiency of studies/data

Cyfluthrin toxicity data have been used as bridging data for beta-cyfluthrin. The toxicology databases together are considered complete and adequate for selecting toxicity endpoints for risk assessment. The scientific quality is relatively high, and the toxicity profiles of both cyfluthrin and beta-cyfluthrin can be characterized for all effects, including potential developmental, reproductive, and neurotoxic effects. For a complete discussion of the toxicological effects of beta-cyfluthrin, excluding the developmental neurotoxicity study, refer to "Toxicology Chapter for Cyfluthrin/Beta-Cyfluthrin" (D283924, V. Dobozy, 7/18/2002).

Data requirements for pesticides [40 CFR Part 158] were amended in 2007 to include an immunotoxicity study. Since the Agency has not received this study, it remains a data gap and is

[1] Ware, G.W. *The Pesticide Book.* Fresno, CA, Thomson Publications, 1994, pgs 171-172.

required. However, there is no indication in any submitted studies with either cyfluthrin or beta-cyfluthrin that the immune system was compromised.

3.1.2 Toxicological Effects

The acute toxicity of beta-cyfluthrin is low to moderate via the oral route of exposure (Categories II to III, depending on the vehicle), moderate via the inhalation route (Categories II to III, depending upon the vehicle), and low via the dermal route (Category IV). Beta-cyfluthrin is a slight eye and dermal irritant, but not a dermal sensitizer.

The primary target for cyfluthrin/beta-cyfluthrin is the neuromuscular system. Observed neuromuscular effects (tremors, gait abnormalities, abnormal postural reactions, splaying of limbs and decreases in activity) occurred mainly in oral studies in the dog and rat. Other effects include decreased body weight gain and decreased food consumption. Generally, the toxicity data base did not indicate that any major differences in toxicity existed between cyfluthrin and beta-cyfluthrin via the oral route. The inhalation study showed clinical signs as well as hypothermia and decreased body weight gains. In a postnatal inhalation study in mice, there were clinical signs of neurotoxicity in the pups as well as increased spontaneous motor activity and paresthesia (tingling, burning or prickling – also seen in oral studies).

In oral developmental studies in the rat and rabbit, there was no increased qualitative or quantitative susceptibility in the offspring. However, increased susceptibility was observed in inhalation developmental studies. Increased susceptibility was also seen in oral reproduction studies and in a developmental neurotoxicity study with beta-cyfluthrin. There was increased susceptibility of rats and mice to cyfluthrin postnatally.

Cyfluthrin/beta-cyfluthrin was classified as "not likely to be carcinogenic to humans." No evidence of mutagenicity was observed.

There was no indication that either cyfluthrin or beta-cyfluthrin induced any endocrine disruption.

3.2 FQPA Considerations

3.2.1 Adequacy of the Toxicity Database

With the exception of the immunotoxicity study (a data gap), the database for beta-cyfluthrin is complete and adequate for FQPA considerations. It includes an acceptable developmental neurotoxicity study, which evaluates the effects (neurotoxicity) of particular concern for pyrethroids.

3.2.2 Evidence of Neurotoxicity

Evidence of neurotoxicity, typical of the pyrethroids, was observed throughout the database. Specific findings in the neurotoxicity studies included changes in the Functional Observational Battery (FOB) and decreased motor activity. In the DNT study, decreased brain weights were

noted in female offspring along with decreased body weights and body weight gains in pups of both sexes. In other studies, following oral and/or inhalation exposure to rats, dogs and mice, neurotoxic effects included gait abnormalities, changes in motor activity, tremors and abnormal postural reactions.

3.2.3 Developmental and Reproductive Toxicity Studies

In the developmental studies, there was no evidence of any increase in susceptibility of rats or rabbits regarding either chemical via the oral route. However, via inhalation, there was evidence of increased qualitative and quantitative susceptibility. A special post natal inhalation study in mice demonstrated increased qualitative and quantitative susceptibility of offspring following exposure to cyfluthrin. Increased susceptibility was also noted in rats in oral reproduction studies with cyfluthrin and in a developmental neurotoxicity study with beta-cyfluthrin.

3.2.4 Pre-and/or Postnatal Toxicity

3.2.4.1 Determination of Susceptibility

There is concern for pre-and/or postnatal toxicity from exposure to beta-cyfluthrin.

3.2.4.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and /or Postnatal Susceptibility

The degree of concern for all of the prenatal developmental, special postnatal, reproduction and developmental neurotoxicity studies that demonstrated quantitative and/or qualitative susceptibility is low because the effects in each of these studies are well characterized, with conservative NOAELs established for all developmental and offspring effects. There are no residual uncertainties because the points of departure (NOAELs) selected for risk assessment are lower than the NOAELs from these studies and, thus, are protective of any potential pre- and post-natal effects.

3.2.5 FQPA Safety Factor for Infants and Children

HED has reduced the 10X FQPA Safety Factor for the protection of infants and children to 1X based on the following considerations:

- the lack of residual concerns regarding pre- and post-natal toxicity and the reliance on exposure data that are unlikely to underestimate exposure to the pesticide and

- although an immunotoxicity study data requirement [40 CFR Part 158] has not been submitted, there is no evidence the beta-cyfluthrin affects the immune system, so a database uncertainty factor is not needed to account for the missing data.

3.3 Hazard Identification and Toxicity Endpoint Selection

A complete hazard characterization was previously assessed for beta-cyfluthrin

(Cyfluthrin/Beta-cyfluthrin – Human Health Risk Assessment; Thomas Moriarty; D331951) in 2007. There are no changes to the hazard characterization to date, with the exception of the new data requirements [40 CFR Part 158] for an immunotoxicity study.

3.3.1 Level of Concern for Margin of Exposure

Table 3.2.4 Summary of Levels of Concern for Risk Assessment.			
Route	**Short-Term (1 - 30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A
Residential Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A
Incidental Oral	100	100	N/A

3.3.2 Recommendation for Aggregate Exposure Risk Assessments

Consistent with FQPA, 1996, HED considers an aggregate risk assessment when there are potential residential exposures that may result in exposure from three major sources (oral, dermal, and inhalation). For beta-cyfluthrin, risks for the different routes of exposure may be aggregated due to the presence of a common toxicity endpoint (clinical signs of neurotoxicity and/or body weight effects).

3.3.3 Classification of Carcinogenic Potential

Beta-cyfluthrin is classified as "not likely to be carcinogenic to humans".

3.3.4 Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessments

A summary of toxicological endpoints and doses for use in both the dietary and non-occupational risk (residential) assessments as well as the occupational assessment of beta-cyfluthrin is contained in **Tables 3.3.4a** and **3.3.4b**, below.

Table 3.3.4a Toxicological Doses and Endpoints for Beta-Cyfluthrin for Use in Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	NOAEL = 2 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.02 mg/kg/day aPAD = 0.02 mg/kg/day	Acute neurotoxicity in rats (beta-cyfluthrin) LOAEL = 10 mg/kg/day based on clinical signs, changes in FOB parameters, and decreases in motor activity.
Chronic Dietary (All Populations)	NOAEL= 2.4 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Chronic RfD = 0.024 mg/kg/day cPAD = 0.024 mg/kg/day	Chronic toxicity in dogs (cyfluthrin) LOAEL = 10.64 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions.
Incidental Oral Short- (1-30 Days) and Intermediate-Term (1 - 6 Months)	NOAEL= 2.36 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	90-Day feeding study in dogs (beta-cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.
Dermal Short- (1-30 Days) and Intermediate-Term (1 - 6 Months)	NOAEL= 2.36 mg/kg/day Dermal absorption rate = 5%	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	90-Day dog feeding study in dogs (beta-cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.
Dermal Long-Term (>6 Months)	NOAEL= 2.4 mg/kg/day Dermal absorption rate = 5%	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Chronic toxicity in dogs (cyfluthrin) LOAEL = 10.64 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions.
Inhalation Short-Term (1-30 Days)	NOAEL= 0.00026 mg/L (0.07 mg/kg/day)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	28-Day rat inhalation study (beta-cyfluthrin) LOAEL = 0.0027 mg/L (0.73 mg/kg/day) based on decreases in body weight in both sexes and decreased urinary pH in males.
Inhalation Intermediate- (1-6 months) and Long-Term (>6 months)	NOAEL= 0.00009 mg/L (0.02 mg/kg/day)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	13-Week rat inhalation study (cyfluthrin) LOAEL = 0.00071 mg/L (0.16 mg/kg/day) based on decreases in body weight and body weight gain in males and clinical signs in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

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 (interspecies). UF_H = potential variation in

sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.3.4b Toxicological Doses and Endpoints for Beta-Cyfluthrin for Use 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- (1-30 Days) and Intermediate-Term (1 - 6 Months)	NOAEL= 2.36 mg/kg/day Dermal absorption rate = 5%	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	90-Day dog feeding study in dogs (beta-cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.
Dermal Long-Term (>6 Months)	NOAEL= 2.4 mg/kg/day Dermal absorption rate = 5%	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Chronic toxicity in dogs (cyfluthrin) LOAEL = 10.64 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions.
Inhalation Short-Term (1-30 Days)	NOAEL= 0.00026 mg/L (0.07 mg/kg/day)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	28-Day rat inhalation study (beta-cyfluthrin) LOAEL = 0.0027 mg/L (0.73 mg/kg/day) based on decreases in body weight in both sexes and decreased urinary pH in males.
Inhalation Intermediate- (1-6 months) and Long-Term (>6 months)	NOAEL= 0.00009 mg/L (0.02 mg/kg/day)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	13-Week rat inhalation study (cyfluthrin) LOAEL = 0.00071 mg/L (0.16 mg/kg/day) based on decreases in body weight and body weight gain in males and clinical signs in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

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 (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.4 Endocrine disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a

chemical substance to interact with the estrogen, androgen, and or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Beta-cyfluthrin is among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. The Agency will review the EDSP Tier 1 data and any "other scientifically relevant information" submitted in response to test orders. Based on this review the Agency will determine the need for additional testing. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Public Health and Pesticide Epidemiology Data and Incident Reports

No public health, pesticide epidemiology or incident data were examined in conjunction with this action.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Degradates of Concern

The metabolism of beta-cyfluthrin is well understood in all matrices (plants, animal and drinking water) and analytical methods for the currently registered uses have been submitted and validated (Cyfluthrin and beta-Cyfluthrin: Summary of Analytical Chemistry and Residue Data. 10/15/2007; D.Dotson; D339413; and, Tier I Drinking Water Assessment for the Registration for the New Uses of Cyfluthrin and Beta-cyfluthrin; Sep. 24, 2007; J.L. Meléndez; D331952, and D340739). HED determined that the residue of concern in plants and animals is cyfluthrin *per se* (MARC Decision Memorandum; 6/13/02; TXR 0050805). The beta-cyfluthrin risk assessment team is in agreement with this previous determination. A summary of metabolites and degradates is provided in **Table 5.1**.

Primary Crop	Cyfluthrin	Cyfluthrin

Rotational Crop	N/A	N/A
Ruminant	Cyfluthrin	Cyfluthrin
Poultry	Cyfluthrin	Cyfluthrin
Drinking Water	Cyfluthrin	Not Applicable

* Although most of the residue from use of beta-cyfluthrin consists of the enriched isomers of that active ingredient, low percentages of the other isomers are present and the analytical method does not distinguish between the isomers of cyfluthrin and beta-cyfluthrin. Therefore, the residue of concern from use of beta-cyfluthrin for practical purposes is cyfluthrin.

5.1.1 Drinking Water Residue Profile

Estimates of cyfluthrin residues in drinking water were provided by the Environmental Fate and Effects Division (J.L. Melendez 9/6/2007; D331952; D340739) and incorporated directly into the dietary assessment. Acute and chronic screening level estimates of drinking water concentrations (EDWCs) in surface water were generated using FIRST v.1.1.0, (Dec. 12, 2005), and ground water concentration estimates were generated using SCI-GROW v.2.3, (Jul 29, 2003).

Based on survey of all the currently registered and proposed uses of cyfluthrin, it was determined that cyfluthrin use on alfalfa and cotton would lead to the highest surface water and ground water drinking water exposure estimates (EDWCs), respectively. Based upon the proposed use of cyfluthrin on alfalfa (0.35 lb ai/acre/season), the acute drinking water concentration in surface water is 3.677 ppb, and the chronic EDWC is estimated to be 0.155 ppb. The SCI-GROW generated EDWC (in groundwater) is 0.457 ppb of cyfluthrin, which is recommended for use both for acute and chronic exposures. EDWCs are summarized in **Table 5.1.1**.

Table 5.1.1 Summary of Estimated Surface Water and Groundwater Concentrations for Cyfluthrin/Beta-cyfluthrin

	Chemical	
	Surface Water Conc., ppb [a]	Groundwater Conc., ppb [b]
Acute	3.677	0.457
Chronic (non-cancer)	0.155	0.457

[a] From the FIRST v.1.1.0
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.35 lb ai/A for alfalfa.

5.2 Dietary Exposure and Risk

While there are no new dietary exposures associated with the proposed use, discussion of chronic dietary exposure via food and drinking water resulting from the currently registered uses of cyfluthrin/beta-cyfluthrin is provided for purposes of completing the aggregate assessment.

The dietary analysis is refined and includes processing factors, percent crop treated estimates, and monitoring data. The dietary analysis also includes secondary residues, and reflects revised tolerance values associated with the subject petitions. The drinking water analysis considers all

currently registered uses. A full discussion of the refined dietary exposure from the registered uses of cyfluthrin/beta-cyfluthrin can be found in the HED memorandum *Cyfluthrin and Beta-Cyfluthrin Acute Probabilistic and Chronic Dietary Exposure Assessments for the Section 3 Registration Actions*, (D. Dotson; 10/15/07; D339414). The results of the chronic dietary exposure analysis are reported in **Table 5.2**.

Table 5.2. Result of Chronic Dietary Exposure and Risk Estimates for Beta-Cyfluthrin

Population Subgroup	Chronic Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.001195	5
All Infants < 1 yr old	0.002075	9
Children 1-2 yrs old	0.004084	17
Children 3-5 yrs old	0.002951	12
Children 6-12 yrs old	0.001750	7
Youth 13-19 yrs old	0.000973	4
Adults 20-40 yrs old	0.000865	4
Adults 50+ yrs old	0.000909	4
Females 13-49 yrs old	0.000855	4

5.2.1 Cancer Dietary Risk

HED has classified cyfluthrin as "not likely to be carcinogenic to humans." Based upon this classification, HED has determined there is insufficient hazard to warrant a cancer dietary risk assessment.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

The registrant has requested the proposed use of Temprid ™ SC Insecticide to control bed bugs be added to the current label. This assessment will provide a summary of the potential risk associated with commercial and residential applicators and residential postapplication activities resulting from the use of beta-cyfluthrin for treatment of bed bugs. A more detailed explanation of this assessment is provided in the following residential assessment: Beta Cyfluthrin: Residential Exposure Assessment for Use of Beta Cyfluthrin to Control Bed Bugs, M. Collantes, 1/15/10, D371724.

6.1 Residential Handler Exposure

Temprid ™ SC Insecticide is available as a 0.15% total active ingredient (0.05% B-cyfluthrin) and/or 0.075% total active ingredient (0.025% B-cyfluthrin) spray to be applied as a spot (crack and crevice) and bed bug treatment by use of low pressure systems or equipment (w/ fan-type or pinpoint nozzles) as a liquid or foam. The registered label indicates that Temprid ™ SC Insecticide is intended to be applied by pest management professionals and commercial applicators only; however; the product is not a restricted-use pesticide and could potentially be used by homeowners.

No chemical-specific data were available with which to assess potential exposure to residential pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). **Table 6.1** provides estimates of exposure and risk for residential handlers. The level of concern (LOC) for the margin of exposure (MOE) is 100 for all residential uses. The handler MOE is greater than 100 and, therefore, is not of concern.

Table 6.1 Residential Handler Exposure and Risk for Beta-cyfluthrin										
Exposure Scenario	**Target**	**Application Rate[a] (lb ai/gal)**	**Amount Treated Daily[b]**	**Unit Exposure[c]**		**Dose (mg/kg/day)**		**MOEs**		
				Dermal (mg/lb ai)	**Inhalation (µg/lb ai)**	**Dermal [d]**	**Inhalation[e]**	**Dermal[f]**	**Inhalation[g]**	**Total [h]**
Mixing/Loading/Applying										
Short-term Exposure										
Low Pressure Handwand (Liquid) (PHED) shorts, short-sleeved shirts, socks, and shoes	Indoor Crack and Crevice	0.004	0.5 gals	250	1,063	0.00036	0.00003	6,600	2,200	1,700
	Bed bug treatment	0.002				0.00018	0.000015	13,000	4,500	3,300
Intermediate-term Exposure										
Low Pressure Handwand (Liquid) (PHED) shorts, short-sleeved shirts, socks, and shoes	Indoor Crack and Crevice	0.004	0.5 gals	250	1,063	0.00036	0.00003	6,600	600	580
	Bed bug treatment	0.002				0.00018	0.000015	13,000	1,300	1,200

a. Application Rates based on proposed uses on label for beta-cyfluthrin product Temprid™ SC Insecticide (Reg. No. 432-1483)
b. Science Advisory Council Policy # 9.1
c. Unit Exposures based on PHED Version 1.1.
d. Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/gal) x amount treated x dermal absorption factor (5%) / body weight (70 kg).
e. Inhalation Dose (mg/kg/day) daily unit exposure (µg/lb ai) x application rate (lb ai/gal) x amount treated x inhalation absorption (100%) x conversion factor (1 mg/1,000 µg) / body weight (70 kg).
f. Dermal MOE = NOAEL (2.36 mg/kg/day) / dermal daily dose (mg/kg/day). Level of concern = 100.
g. Short-term Inhalation MOE = NOAEL (0.07 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
Intermediate-term Inhalation MOE = NOAEL (0.02 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
h. Total MOE = 1/ (1/Dermal MOE + 1/ Inhalation MOE)

6.2. Residential Postapplication Exposure

There is a potential for exposure from contact with treated mattresses (including the box spring, headboard and frame), in addition to exposure when entering areas previously treated with beta-cyfluthrin that could lead to exposures for adults and children. HED believes that short-, intermediate- and long-term residential post-application exposures are likely; however, only short- and intermediate-term exposures have been assessed. Intermediate-term exposures have been estimated using Day 0 residue values along with an intermediate-term point of departure (applicable for exposures up to 6 months), which is considered a conservative assumption and protective for longer-term exposures since residue values would be expected to dissipate over time.

6.2.1 Inhalation Postapplication Exposure

Post-application inhalation exposure can result from the registered crack and crevice use, as well as the proposed bed bug/mattress use. HED performed a short- and intermediate-term postapplication inhalation assessment for beta-cyfluthrin using a Tier 1 (Air Saturation Concentration), Tier II (Instantaneous Release Well-Mixed Box Model) and Tier III (First Order Decay Rate) analysis.

The Tier 1 analysis resulted in MOEs great than 100 for all short-term post application inhalation exposure scenarios; however, the intermediate-term post-application inhalation MOE for toddlers is 67 and is of concern to HED. As indicated previously, intermediate-term exposures have been estimated using Day 0 residue values along with an intermediate-term point of departure (applicable for exposures up to 6 months), which is considered a conservative assumption for longer-term exposures since residue values would be expected to dissipate over time. Therefore, a Tier II and III analysis was performed to refine intermediate-term postapplication inhalation exposure for toddlers.

All postapplication inhalation exposure scenarios resulted in MOEs greater than 100 using a Tier II analysis. However, for purposes of incorporating post application inhalation exposures into an aggregate exposure assessment, HED performed a Tier III inhalation exposure assessment to further refine intermediate-term inhalation postapplication exposure.

Based on a refined analysis, all postapplication inhalation exposure scenarios resulted in MOE greater than 100 and are not of concern to HED for indoor inhalation or combined residential exposure. **Table 6.2.1** summarizes the post-application inhalation exposure and risk from the indoor uses of beta-cyfluthrin.

Table 6.2.1: Tier III Postapplication Inhalation Exposure

Population	IR [1] (m3/hr)	M [2] (mg)	Volume of Room [3] (m3)	ACH [4] (1/hr)	K [5] (1/hr)	ET [6] (hr)	Inhalation Dose [7] (mg/kg/day)	Inhalation MOE	
								Short-term [8]	Intermediate-term [9]
Adult	0.55	19.7	33	0.18	$3.80E^{-7}$	16	1.07E-7	650,000	190,000
Toddler	0.36						3.25E-7	220,000	62,000

1. IR = Inhalation Rate = Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001).
2. M = Mass of active ingredient (mg) = mass of ai (0.0000433lbs) * conversion factor (454000 mg/lb) = 19.7 mg
3. Volume of room (m^3) = based on typical dimensions of residential rooms from Exposure Factors Handbook (U.S. EPA, 1997). For a 12 foot

room, with an 8 foot ceiling, the typical volume is 33 m^3.
4. ACH = air changes per hour ($hour^{-1}$) for 10^{th} percentile
5. K = *first order decay rate (1/hr)* – decay rate is based on 90% drying time (Evans 1994) which is calculated based on evaporation time and volatility of the chemical using equations from Chinn (1981)
6. ET = Exposure Time based on U.S. EPA Exposure Factors Handbook (1997) and Child-specific Exposure Factors Handbook (2008)
7. Inhalation Dose (mg/kg/day) = $E = \frac{IR * M}{ACH * V} * \left[1 - \left[\frac{\left(ACH * e^{-k*ET}\right) - \left(k * e^{-ACH*ET}\right)}{ACH - k}\right]\right]$ $D = \frac{E * AF}{BW}$
8. *Short-term Inhalation* MOE = NOAEL (0.07 mg/kg/day) / Dose (mg/kg/day)
9. Intermediate-term Inhalation MOE = NOAEL (0.02 mg/kg/day) / Dose (mg/kg/day)

6.2.2 Dermal Postapplication Exposure

For purposes of assessing dermal postapplication exposure resulting from the use of beta-cyfluthrin to treat bed bugs, HED has performed a crack and crevice assessment (for both carpets and hard floors) in addition to performing an assessment for treated mattresses. Post-application dermal exposure can result from pesticide residue transfer to the skin of individuals who contact previously treated indoor surfaces (e.g., carpets, floors, furniture, and other surfaces) during standard activities such as recreation, housework or other occupant activities. Such exposure is assumed to occur for adults and toddlers.

For the bed bug use, applications are allowed for both mattresses and furniture (tufts, seams, folds and edges); however, this assessment covers exposure from applications to mattresses only. The assessment for the mattress application is based on an assumption regarding the amount of product applied per area (i.e., a twin size bed). It is assumed that the surface area of a standard size couch would be similar to that of a twin size bed, and that the exposure time for dermal contact with furniture would be less than that for a bed. In addition, the product label includes a statement which indicates that the product should not be applied to furniture or upholstery where prolonged contact with humans will occur. For these reasons, an assessment for exposure to treated furniture was not included in this document and the assessment for treatment of a mattress is considered worst-case and protective of treatment of furniture.

6.2.2.1 Crack and Crevice Exposure and Risk:

Dermal crack and crevice scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). All postapplication dermal scenarios resulted in MOEs greater than 100 and are not of concern to HED. A summary of the dermal postapplication exposure and risks are included in **Table 6.2.2.1**.

Table 6.2.2.1: Postapplication Dermal Exposure for Children and Adults for Crack and Crevice Use											
Surface	**Population Subgroup**	**% Spray (Cyfluthrin)**	**ISR[1] ($\mu g/cm^2$)**	**Fraction Transferred**	**CF**	**TC[2] (cm^2/hr)**	**ED[3] (hrs)**	**Dermal Absorption (mg/kg/day)**	**BW (kg)**	**Dermal Dose[4] (mg/kg/day)**	**MOE[5]**
carpet	adult	0.05%	1.2	5%	0.001	16,700	8	0.05	70	0.0057	410
	toddler		1.2			6,000			15	0.0096	250
	adult	0.025%	0.6			16,700			70	0.0029	820
	toddler		0.6			6,000			15	0.0048	490
vinyl	adult	0.05%	1.2	10%		16,700	4		70	0.0057	410
	toddler		1.2			6,000			15	0.0096	250
	adult	0.025%	0.6			16,700			70	0.0029	820
	toddler		0.6			6,000			15	0.0048	490

1. ISR = indoor surface transferable residues = (see data and assumption section for deposition residue value). Deposition residue (0.5 ug/cm^2) x fraction of residue available for transfer from carpet vs. hard surface (0.05/0.1)
2. TC = transfer coefficient based on HED Residential SOPs
3. ED =exposure duration based on HED Residential SOPs
4. Dermal Dose = $\frac{\text{ISR } (ug/cm^2) \times \text{Fraction Transferred} \times 0.001 \text{ (mg/ug)} \times \text{TC } (cm^2/hr) \times \text{ED (hrs/day)} \times \text{dermal absorption}}{\text{BW (kg)}}$
5. MOE = $\frac{\text{NOAEL (2.36 mg/kg/day)}}{\text{Dermal Dose}}$

6.2.2.2 Bed Bug Treatment - Mattress Application Risk Assessment

In order to assess the dermal post-application exposure from the proposed bed bug use, HED used the best available data and several assumptions outlined below. The surface residue on the mattress was estimated based on an assumption that 20% of a twin mattress is treated and that 5 gallons of solution are used to treat 1000 ft^2. The assessment was performed for an adult or toddler on a twin mattress as it is assumed that this scenario would result in the greatest body surface area to treated surface ratio and, therefore, the highest exposure.

Dermal Postapplication Exposure and Risk

All postapplication dermal scenarios for the bed bug use on mattresses resulted in MOEs greater than 100 and are not of concern to HED. **Table 6.2.2.2** summarizes the dermal exposure and risk from the bed bug use on mattresses.

Table 6.2.2.2: Postapplication Dermal Exposure for Children and Adults for Bed Bug Mattress Use

Surface Type	Population	Surface Residue (ug/cm^2)[a]	Surface Area/ Body Weight Ratio (cm^2/kg)	Fraction of skin in contact with surface	Transfer Efficiency	Protection factor	Dermal Dose (mg/kg/day)[b]	Dermal MOE
Mattress	Adult	1.03	290	0.5	0.05	0.5	0.000186	13,000
	Toddler		620				0.0004	5,900

a. Residue value determined based on application rate (0.025% b-cyfluthrin spray; 0.002 lb ai/gal) and assumptions for area treated and amount applied.

b. Dermal dose (mg/kg/day) = Surface residue (ug/cm2) * Surface Area/Body Weight Ratio (cm^2/kg)) * Fraction of body that contacts residue (0.5) * Conversion factor (0.001 mg/ug) * Transfer efficiency (0.05) * Protection factor (0.5)*DAF (0.05)

c. Dermal MOE = NOAEL (mg/kg/day) / Dose (mg/kg/day), where short-term dermal NOAEL = 2.36 mg/kg/day

6.2.3 Oral Exposure

The hand-to-mouth transfer scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). This scenario assumes pesticide residues are transferred to the skin of children during postapplication contact with treated indoor areas and are subsequently ingested as a result of hand-to-mouth transfer.

Only incidental oral exposures resulting from the crack and crevice use have been assessed here since they are considered to be protective of the mattress application for the following reasons: (1) a lower application rate is allowed for the mattress application compared to the crack and crevice application, (2) a protection factor of 0.5 is assumed for the mattress exposures due to the presence of a bed sheet over the mattress, and (3) the replenishment interval for hand-to-mouth activity is assumed to be less while a child is sleeping than while they are awake.

Hand-To-Mouth Exposure and Risk

A hand-to-mouth transfer postapplication exposure assessment resulted in oral MOEs greater than 100 for all scenarios and is not of concern to HED. **Table 6.2.3** summarizes the MOEs for hand-to-mouth transfer of pesticide residues from indoor crack and crevice use.

Table 6.2.3: Postapplication Oral Exposure for Children for Crack and Crevice

Surface	% Spray (b-cyfluthrin)	% ai dislodgeable	ISR[1] (µg/cm^2)	SA	FQ (event/hr)	ED (hrs)	SE	CF	Oral Dose[2] (mg/kg/day)	Oral MOE[3]
Short-term										
carpet	0.15%	5%	1.2	20	20	8	0.5	0.001	0.0064	370
	0.075%		0.60			8			0.0032	740
vinyl	0.15%	10%	1.20			4			0.0064	370
	0.075%		0.60			4			0.0032	740
Intermediate-term										
carpet	0.15%	5%	1.2	20	9.5	8	0.5	0.001	0.0030	780
	0.075%		0.60			8			0.0015	1500
vinyl	0.15%	10%	1.20			4			0.0030	780
	0.075%		0.60			4			0.0015	1500

1. ISR = indoor surface transferable residues = (see data and assumption section for deposition residue value) deposition residue (0.5 ug/cm^2) x fraction of residue available for transfer from carpet vs. hard surface (0.05/0.1)
2. Oral Dose = $\frac{\%\text{ ai Dislodgeable}}{\text{BW (15 kg)}} \times \frac{\text{ISR x SA x FQ x ED x SE x CF1}}{}$
3.. Oral MOE = $\frac{\text{NOAEL (2.36 mg/kg/day)}}{\text{Oral Dose}}$

6.3 Combined Residential Risk Estimates

HED combines risk values resulting from separate residential exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. Furthermore, since similar endpoints were selected for dermal, inhalation and oral exposures (clinical signs of neurotoxicity and/or body weight effects), risks from the three exposure routes may be combined (Cyfluthrin/Beta-Cyfluthrin Human Health Risk Assessment, T. Moriarty, D331951, October 23, 2007). For all residential exposure scenarios, the level of concern for the margin of exposure (MOE) is 100.

These scenarios consisted of adult and toddler dermal and inhalation (Tier III) postapplication exposure and oral (hand-to-mouth) exposures for toddlers resulting from indoor crack and crevice applications as well as dermal postapplication exposure resulting from mattress treatment for bed bugs. Handler dermal and inhalation exposures were not included since the postapplication exposures resulted in higher risks (see Tables 6.1 and 6.2.2.1) and represented the worst case scenarios. All combined postapplication scenarios resulted in combined MOEs greater than 100 and were not of concern to HED. **Table 6.3** provides a summary of the combined residential indoor crack and crevice exposures and risks.

Table 6.3. Combined Residential Exposure and Risk Estimates from the Indoor Crack and Crevice Bed Bug Mattress Use			
Postapplication Scenarios	**Daily Dose (mg/kg/day) [1]**	**MOE [2]**	**Combined MOE [3]**
Short-term			
Adult Dermal – indoor crack & crevice	0.0057	410	400
Adult Inhalation (Tier III) – crack & crevice	0.000000107	650,000	
Adult Dermal - mattress treatment	0.00019	13,000	
Toddler Dermal - indoor crack & crevice	0.0096	250	150
Toddler Inhalation (Tier III) - Crack & Crevice	0.000000325	220,000	
Toddler Dermal - Mattress treatment	0.0004	5,900	
Toddler Hand-to-Mouth	0.0064	370	
Intermediate-term			
Adult Dermal - indoor crack & crevice	0.0057	410	400
Adult Inhalation (Tier III) – crack & crevice	0.000000107	190,000	
Adult Dermal Mattress Treatment	0.00019	13,000	
Toddler Dermal - indoor crack & crevice	0.0096	250	180
Toddler Inhalation (Tier III) - Crack & Crevice	0.000000325	62,000	
Toddler Dermal - Mattress treatment	0.0004	5,900	
Toddler Hand-to-Mouth	0.0030	780	

[1] Daily Dose = see Tables 6.2.2a, 6.2.2.2 and 6.2.3

[2]. Dermal MOE = $\frac{\text{NOAEL (2.36 mg/kg/day)}}{\text{Dermal Dose}}$

Short-term Inhalation MOE = $\frac{\text{NOAEL (0.07 mg/kg/day)}}{\text{Short-term Inhalation Dose}}$

Intermediate-term Inhalation MOE = $\frac{\text{NOAEL (0.02 mg/kg/day)}}{\text{Intermediate-term Inhalation Dose}}$

Hand-to-Mouth MOE = $\frac{\text{NOAEL (2.36 mg/kg/day)}}{\text{Oral Dose}}$

[3] Adult Combined MOE = $1/ [(1/MOE_{\text{Dermal- crack and crevice}}) + (1/MOE_{\text{Inhalation- crack and crevice}}) + (1/MOE_{\text{Dermal - mattress treatment}})]$

Toddler Combined MOE = $1/ [(1/MOE_{\text{Dermal- crack and crevice}}) + (1/MOE_{\text{Inhalation- crack and crevice}}) + (1/MOE_{\text{Dermal - mattress treatment}}) + (1/MOE\ \text{Oral})]$

7.0 Aggregate Risk Assessments and Risk Characterization

HED has conducted aggregate risk estimates for short- and intermediate-term exposure durations. In conducting the aggregate risk estimates for beta cyfluthrin, HED combines risk values resulting from chronic dietary (food + water) and residential exposure. Separate residential exposure scenarios (dermal, inhalation and oral) are combined when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population.

7.1 Acute Aggregate Risk

The acute aggregate risk assessment is based on exposure resulting from food and water. As there are no food uses associated with this action an acute aggregate risk assessment was not conducted for purposes of this assessment. It should also be noted that previous risk estimates ((Cyfluthrin/Beta-cyfluthrin – Human Health Risk Assessment; Thomas Moriaty; 2007; D331951) are not of conern.

7.2 Short-Term Aggregate Risk

To estimate short-term aggregate risk, HED combined the chronic dietary (food + water) exposures (as a measure of average dietary exposure) with the short-term residential postapplication exposure. All short-term aggregate exposures resulted in MOEs greater than 100 for all populations and are not of concern to HED. Short-term aggregate risks are summarized in **Table 7.2** below.

Table 7.2. Short-Term Aggregate Risk Calculations

Population	LOC for Aggregate Risk[1]	MOE food & water[2]	MOE oral[3]	MOE dermal[4] (C&C + Mattress)	MOE inhalation Tier III [5]	Aggregate MOE (food and residential)[6]
US Population	100	2000	NA	400	650,000	330
Child (1-2 yrs)	100	580	370	240	220,000	120
Infant (<1 yr)	100	1100	370	240	220,000	130

[1] see Table 3.2.4 - basis for the LOC.

2 $MOE_{food + water}$: short-term oral NOAEL = (2.36 mg/kg/day) / chronic dietary exposure from DEEM.

3 MOE oral = short-term incidental oral NOAEL (2.36 mg/kg/day)/hand-to-mouth residential exposure.

4 MOE dermal = short-term dermal NOAEL (2.36 mg/kg/day)/dermal residential exposure. Dermal exposure adjusted with 5% dermal absorption factor.

5 MOE inhalation = short-term inhalation NOAEL (0.07 mg/kg/day)/residential inhalation exposure

6 Aggregate MOE (food + water + residential) =

$$\frac{1}{1/MOE_{f+w} + 1/MOE_I + 1/MOE_D + 1/MOE_O}$$

7.3 Intermediate-Term Aggregate Risk

To estimate intermediate-term aggregate risk HED combined chronic dietary (food + water) exposures with intermediate term residential postapplication exposure. All intermediate-term aggregate exposures resulted in MOEs greater than 100 for all populations and not of concern to HED. Intermediate-term aggregate risks are summarized in **Table 7.3** below.

Table 7.3 Intermediate-Term Aggregate Risk Calculations

Population	LOC for Aggregate Risk[1]	MOE food & water[2]	MOE oral[3]	MOE dermal[4]	MOE inhalation Tier III[5]	Aggregate MOE (food and residential)[6]
US Population	100	2,000	NA	400	190,000	330
Child (1-2 yrs)	100	580	780	240	62,000	140
Infant (<1 yr)	100	1,100	780	240	62,000	160

1: [1] see Table 3.2.4 - basis for the LOC
2: MOE food + water = intermediate-term oral NOAEL (2.36 mg/kg/day)/chronic dietary exposure from DEEM.
3: MOE oral = intermediate-term incidental oral NOAEL (2.36 mg/kg/day)/hand-to-mouth residential exposure
4: MOE dermal = intermediate-term dermal NOAEL (2.36 mg/kg/day)/dermal residential exposure. Dermal exposure adjusted with 5% dermal absorption factor.
5: MOE inhalation = intermediate-term inhalation NOAEL (0.02 mg/kg/day)/residential inhalation exposure
6: Aggregate MOE (food + water + residential) =

$$\frac{1}{1/MOE_{f+w} + 1/MOE_I + 1/MOE_D + 1/MOE_O}$$

7.4 Long-Term Aggregate Risk

The dietary exposure pathway (food and drinking water) is the only source of chronic exposure to beta-cyfluthrin. Therefore, the long-term aggregate exposure and risk estimates are equivalent to the chronic dietary exposure and risk estimates discussed in Section 5.2. The chronic aggregate risks for beta-cyfluthrin are less than 100% of the cPAD for all population subgroups, and therefore, do not pose a risk concern for HED.

7.5 Cancer Risk

Based upon HED's cancer classification of beta-cyfluthrin (Not likely to be carcinogenic to humans) and consequently the lack of hazard to warrant a cancer dietary risk assessment, a cancer aggregate risk assessment was not conducted.

8.0 Cumulative Risk Characterization/Assessment

Cyfluthrin and beta-cyfluthrin are members 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. The Agency does not have a clear understanding of effects on key downstream neuronal function e.g., 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 the results of the research become available, the Agency will consider the findings 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

HED has assessed the commercial handler exposure resulting from the use of Temprid ™ SC Insecticide applied to mattresses tufts, folds and edges, box springs, bead frames, headboards, upholstered furniture and crack and crevice application to baseboards, molding and under carpets. Based on application rate and label information, exposure is expected to occur for short- and intermediate-term durations.

9.1 Handler Risk

Chemical-specific data were not submitted to the Agency in support of this Section 3 application. It is HED policy to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures when chemical specific data are not submitted. For purposes of assessing a crack and crevice exposure scenario for commercial applicators, HED used the mixer/loader/applicator low-pressure handwand using a wettable powder scenario as a surrogate. The unit exposure values provided for the low pressure handwand scenario for wettable powders are based on actual measured exposure resulting from application to cracks and crevices; whereas the unit exposure values for the liquid formulation are based on application to chicken houses and greenhouses. Therefore, although the Temprid ™ SC Insecticide is formulated as a liquid, HED believes that the use of actual unit exposure values resulting from applications to cracks and crevices provides a more accurate representation of true exposure values to provide surrogate and treatment of mattress and bed.

The total uncertainty factor that has been applied to the non-cancer risk assessment for beta-cyfluthrin is 100 for occupational/commercial exposure. Occupational/ commercial exposure and risk resulting in MOEs greater than or equal to 100 will not exceed HED's level of concern.

The MOEs for commercial handler exposures were significantly below 100 with the use of only dermal PPE (i.e., gloves in addition to baseline attire). When use of a NIOSH-approved quarter-face, cup-style dust mist respirator [Protection Factor (PF) 5] was added, all handler scenarios resulted in total MOEs greater than 100 with the exception of intermediate-term crack and crevice handler application. Even with the addition of a NIOSH-approved half-face (PF 10) respirator, the intermediate-term crack and crevice scenario resulted in a total MOE of **77**. Summaries of the risks for commercial handlers are included in **Table 9.1a and b** for indoor crack and crevice and bed bug applications.

Characterization of Risk
As indicated previously, HED used the mixer/loader/applicator low-pressure handwand using a

wettable powder scenario as a surrogate for a liquid formulation. The unit exposure values provided for the low pressure handwand scenario for wettable powders are based on actual measured exposure resulting from application to cracks and crevices. Although use of the crack and crevice treatment scenario is appropriate, HED realizes that the intermediate-term MOEs of 77 and 150 are conservative estimates since Temprid ™ SC Insecticide is formulated as a liquid and it is assumed that 40 gallons of diluted product will be used daily for treatments. Therefore, HED believes that the use of Temprid ™ SC Insecticide with the addition of a NIOSH-approved half-face (PF 10) respirator, when treating crack and crevices and mattresses over an intermediate-term duration (1 to 6 months) should not result in risks of concern. HED cannot further refine risk estimates without the use of chemical specific data or indication of a decrease in the application rate or amount of product used.

HED recommends that the Registration Division ensure that the appropriate PPE language for use of respirator (A PF 5 respirator is generally referred to as the 80% PF respirator and is a "quarter-face, cup-style dust/mist filtering respirator" and a PF 10 respirator is the 90% PF respirator or a "half- or full-face cartridge or canister style respirator or powered air-purifying respirator") **be added to the registered label.**

9.2 Postapplication Risk

Since the commercial applicators are simply applying the pesticide and not returning to the treated areas, a postapplication exposure assessment was not performed for commercial applicators.

Table 9.1a Commercial Handler Exposure and Risk for Beta Cyfluthrin – Single Layer, Gloves and No Respirator										
Exposure Scenario	**Target**	**Application Rate[a] (lb ai/gal)**	**Amount Treated Daily[b]**	**Unit Exposure[c]**		**Dose (mg/kg/day)**		**MOEs**		
				Dermal (mg/lb ai)	**Inhalation (mg/lb ai)**	**Dermal[d]**	**Inhalation[e]**	**Dermal[f]**	**Inhalation[g]**	**Total[h]**
Mixing/Loading/Applying										
Short-term Exposure										
Low Pressure Handwand (Wettable Powder) (PHED) **Single Layer w/gloves**	Indoor Crack and Crevice	0.004	40 gals	8.6	1.1	0.00098	0.0025	2400	28	**27**
	Bed bug treatment	0.002				0.00049	0.0013	4800	55	**55**
Intermediate-term Exposure										
Low Pressure Handwand (Wettable Powder) (PHED) **Single Layer w/gloves**	Indoor Crack and Crevice	0.004	40 gals	8.6	1.1	0.00098	0.0025	2400	8 *	**8**
	Bed bug treatment	0.002				0.00049	0.0013	4800	16 *	**16**

a. Application Rates based on proposed uses on label for beta-cyfluthrin product Temprid™ SC Insecticide (Reg. No. 432-1483)
b. Science Advisory Council Policy # 9.1
c. Unit Exposures based on PHED Version 1.1. Unit exposures are for baseline attire, gloves and no respirator.
d. Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/gal) x amount treated x dermal absorption factor (5%) / body weight (70 kg).
e. Inhalation Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/gal) x amount treated x inhalation absorption (100%) / body weight (70 kg).
f. Dermal MOE = NOAEL (2.36 mg/kg/day) / dermal daily dose (mg/kg/day). Level of concern = 100.
g. Short-term Inhalation MOE = NOAEL (0.07 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
g.* Intermediate-term Inhalation MOE = NOAEL (0.02 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
h. Total MOE = 1/ (1/Dermal MOE + 1/ Inhalation MOE)

Table 9.1b Commercial Handler Exposure and Risk for Beta Cyfluthrin – Single Layer, Gloves and Respirator										
Exposure Scenario	**Target**	**Application Rate[a] (lb ai/gal)**	**Amout Treated Daily[b]**	**Unit Exposure[c]**		**Dose (mg/kg/day)**		**MOEs**		
				Dermal (mg/lb ai)	**Inhalation (mg/lb ai)**	**Dermal[d]**	**Inhalation[e]**	**Dermal[f]**	**Inhalation[g]**	**Total[h]**
Mixing/Loading/Applying										
Short-term Exposure										
Low Pressure Handwand (Wettable Powder) (PHED) **Single Layer w/gloves and dust mist respirator (PF 5)**	Indoor Crack and Crevice	0.004	40 gals	8.6	0.22	0.00098	0.00050	2400	140	130
	Bed bug treatment	0.002				0.00049	0.00025	4800	280	260
Intermediate-term Exposure										
Low Pressure Handwand (Wettable Powder) (PHED) **Single Layer w/gloves and respirator (PF 10)**	Indoor Crack and Crevice	0.004	40 gals	8.6	0.11	0.00098	0.00025	2400	80 *	77
	Bed bug treatment	0.002				0.00049	0.00013	4800	160 *	150

a. Application Rates based on proposed uses on label for beta-cyfluthrin product Temprid™ SC Insecticide (Reg. No. 432-1483)
b. Science Advisory Council Policy # 9.1
c. Unit Exposures based on PHED Version 1.1. Unit exposures used to calculate short-term exposures are for baseline attire, gloves and NIOSH-approved quarter-face, cup-style dust mist respirator [Protection Factor (PF) 5]. Unit exposures used to calculate intermediate-term exposures are for baseline attire, gloves and NIOSH-approved half-face (PF 10) respirator.
d. Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated x dermal absorption factor (5%) / body weight (70 kg).
e. Inhalation Dose (mg/kg/day) daily unit exposure (µg/lb ai) x application rate (lb ai/acre) x acres treated x inhalation absorption (100%) x conversion factor (1 mg/1,000 µg) / body weight (70 kg).
f. Dermal MOE = NOAEL (2.36 mg/kg/day) / dermal daily dose (mg/kg/day). Level of concern = 100.
g. Short-term Inhalation MOE = NOAEL (0.07 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
g.* Intermediate-term Inhalation MOE = NOAEL (0.02 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
h. Total MOE = 1/ (1/Dermal MOE + 1/ Inhalation MOE)

10.0 Data Needs and Label Recommendations

10.1 Toxicology

The immunotoxicity study is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). See Appendix A., Table A.4 for rationale. HED recommends this study be made a condition of registration for the proposed use.

10.2 Residue Chemistry

None

10.3 Occupational and Residential Exposure

HED recommends that the Registration Division ensure that the appropriate PPE language for use of respirator be added to the registered label. The actual label language for types of respirators includes:

"a NIOSH-approved respirator with a dust-mist filter with MSHA/NIOSH approval number prefix TC-21 or any N, R, P or HE filter," or

"a respirator with an organic-vapor removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14G), or a NIOSH-approved respirator with an organic vapor (OV) cartridge or canister with any N, R or P or HE prefilter."

References:

1. Beta Cyfluthrin: Occupational and Residential Exposure Assessment for Use of Beta Cyfluthrin to Control Bed Bugs; Margarita Collantes, January 2010; DD371724

2. Cyfluthrin/Beta-cyfluthrin – Human Health Risk Assessment For New Uses on Grasses, Alfalfa, and Sugar Beet Seed and Revised Tolerances on Cereal Grain Commodities; Thomas Moriarty; October 23, 2007; D331951.

3. Tier I Drinking Water Assessment for the Registration for the New Uses of Cyfluthrin and Beta-cyfluthrin; Sep. 24, 2007; J.L. Meléndez; D331952, and D340739

Appendix A: Toxicology Assessment

Appendix A, Table 1
Toxicology Data Requirements – cyfluthrin/beta-cyfluthrin

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes[1]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	yes	yes
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotox. Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	-
870.7800	Immunotoxicity	yes	no

[1] Satisfied with combined chronic toxicity/carcinogenicity study

A.2 Toxicity Profiles

Appendix A, Table 2
Acute Toxicity Profile – Beta-Cyfluthrin

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	41244101	**In xylene** Fasted: LD_{50} = 211 mg/kg (♂) LD_{50} = 336 mg/kg (♀) Fed: LD_{50} = 307 mg/kg (♂) LD_{50} = 343 mg/kg (♀)	II
870.1100	Acute oral – rat	41244102	**In PEG 400** Fasted: LD_{50} = 380 mg/kg (♂) LD_{50} = 651 mg/kg (♀) Fed: LD_{50} = 655 mg/kg (♂) LD_{50} = 1369 mg/kg (♀)	II (♂) III (♀)
870.1100	Acute oral – rat	41244104	**In acetone/peanut oil** Fasted: LD_{50} = 84 mg/kg (♂) LD_{50} = 77 mg/kg (♀) Fed: LD_{50} = 141 mg/kg (♂) LD_{50} = 108 mg/kg (♀)	II
870.1100	Acute oral – mouse	41244103	**In PEG 400** Fasted: LD_{50} = 91 mg/kg (♂) LD_{50} = 165 mg/kg (♀)	II
870.1200	Acute dermal – rat	41244105	**In xylene** LD_{50} > 5000 mg/kg (♂) LD_{50} > 5000 mg/kg (♀)	IV
870.1200	Acute dermal – rat	41244106	**In PEG 400** LD_{50} > 5000 mg/kg (♂) LD_{50} > 5000 mg/kg (♀)	IV
870.1300	Acute inhalation – rat	41205701	**Aerosol** LC_{50} = 0.081-0.082 mg/L (♂+♀) **Dust** LC_{50} = 0.532 mg/L (♂+♀)	II III
870.2400	Acute eye irritation – rabbit	41205702	Slight ocular irritant	III
870.2500	Acute dermal irritation – rabbit	41205702	Very slight dermal irritant	IV
870.2600	Skin sensitization – guinea pig	43611601	Not a sensitizer; however, positive control data not available	N/A

Toxicology Profile of Cyfluthrin and Beta-cyfluthrin

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day oral toxicity (rat) **Beta-cyfluthrin** (99.7% a.i.)	41244108 (1986) Acceptable/guideline M: 0, 2.3, 9.5, 18.9 mg/kg/day F: 0, 2.5, 10.9, 42.4 mg/kg/day M: 0, 37.0 mg/kg/day F: 0, 43.0 mg/kg/day	**NOAEL** = 9.5/10.9 mg/kg/day (M/F) **LOAEL** = 37.0/43.0 mg/kg/day (M/F) based on gait abnormalities, necrosis in head and neck region, mortality (2), decreased body weight gain.
870.3100	90-Day oral toxicity (rat) **Cyfluthrin** (84.2% a.i.)	00131524 (1980) **Unacceptable**/guideline M: 0, 2.2, 7.4, 22.3 mg/kg/day F: 0, 2.7, 8.8, 28.0 mg/kg/day	**NOAEL** = 22.3/28.0 mg/kg/day (M/F) **LOAEL** = not observed
870.3150	90-Day oral toxicity (dog) **Beta-cyfluthrin** (99% a.i.)	41267801 (1987) Acceptable/guideline M: 0, 0.39, 2.36, 13.9 mg/kg/day F: 0, 0.39, 2.5, 15.4 mg/kg/day	**NOAEL** = 2.36/2.5 mg/kg/day (M/F) **LOAEL** = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities (both sexes), vomiting (both sexes) and suggestive decrease in body weight gain.
870.3200	21/28-Day dermal toxicity (rat) **Cyfluthrin** (≥95.5%)	44066001 (1996) Acceptable/guideline 0, 113, 376, 1077 mg/kg/day In acetone, 6 hrs/day, for 18 applications within 23 days (♂) or 17 applications within 22 days (♀)	**Dermal NOAEL** = 113 mg/kg/day **Dermal LOAEL** = 376 mg/kg/day based on gross and histological skin lesions. **Systemic NOAEL** = 376 mg/kg/day **Systemic LOAEL** = 1077 mg/kg/day based on decreased food consumption, red nasal discharge and urine staining.
Non-guideline	28-Day oral toxicity (rat) **Cyfluthrin**	00131525 (1983) Supplementary 0, 5, 15, 50 mg/kg/day	**NOAEL** = 15 mg/kg/day **LOAEL** = 50 mg/kg/day based on gait abnormalities, salivation, nervousness, decrease in body weight, food consumption, changes in hematological, clinical chem. & urinalysis parameters, increases in selected organ wts., cytoplasmic swelling of glandular epithelium of submaxillary gland, minimal degrees of fiber degeneration in sciatic nerve (# not reported) which disappeared after recovery period. *Note: The NOAEL was changed to 15 mg/kg/day and the LOAEL to 50 mg/kg/day by the HIARC (May 21, 2002 report).*
870.3465	90-Day inhalation toxicity (rat) **Cyfluthrin** (94.9% a.i.)	00157793 (1984), 40082901, 40239301 Acceptable/guideline 0, 0.00009, 0.00071, 0.00451 mg/L	**NOAEL** = 0.00009 mg/L (0.02 mg/kg/day) **LOAEL** = 0.00071 mg/L (0.16 mg/kg/day) based on decreased body weights and body weight gains in males and clinical signs in females.

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
		(0, 0.02, 0.16, 0.91 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day, 5 consecutive days/week	
Non-guideline	4-Week inhalation toxicity (rat) **Cyfluthrin** (93.8% a.i.)	41842601 (1989) Acceptable/non-guideline 0, 0.00044, 0.006, 0.047 mg/L (0, 0.12, 1.6, 12.8 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day, 5 consecutive days/week	**NOAEL** = 0.00044 mg/L (0.12 mg/kg/day) **LOAEL** = 0.006 mg/L (1.6 mg/kg/day) based on decreases in body weight and body weight gain in males, hypothermia, reduction in leukocyte counts (F) and low serum protein.
Non-guideline	4-Week inhalation toxicity (rat) **Beta-cyfluthrin** (97.9% a.i.)	41783001 (1989) Acceptable/non-guideline 0, 0.00026, 0.0027, 0.023 mg/L (0, 0.07, 0.73, 6.3 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day, 5 consecutive days/week	**NOAEL** = 0.00026 mg/L (0.07 mg/kg/day) **LOAEL** = 0.0027 mg/L (0.73 mg/kg/day) based on decreased body weights, ↓ urine pH in males.
Non-guideline	5-Day inhalation study (rat) **Beta-cyfluthrin** (98% a.i.)	41205708 (1988) Acceptable/non-guideline 0, 0.00025, 0.0038, 0.028 mg/L (0, 0.07, 1.03, 7.6 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day	**NOAEL** = 0.00025 mg/L (0.07 mg/kg/day) **LOAEL** = 0.0038 mg/L (1.03 mg/kg/day) based on unpreened hair coat, piloerection, hepatoid foci in lungs.
Non-guideline	28-Day oral toxicity (dog) **Beta-cyfluthrin**	41244109 (1986) Acceptable/non-guideline 0, 0.25, 2.0, 16.0/8.0 mg/kg/day (2 dogs/sex/dose)	**NOAEL** = 2.0 mg/kg/day (both sexes) **LOAEL** = 8.0 mg/kg/day based on impaired movement and conjunctival irritation.

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a	Prenatal oral developmental toxicity in rodents (rat) **Beta-cyfluthrin** (96.5-97.3% a.i.)	44116501 (1996) Acceptable/guideline 0, 3, 10, 40 mg/kg/day 1% Cremophor in municipal tap water	**Maternal NOAEL** = 3 mg/kg/day **Maternal LOAEL** = 10 mg/kg/day based on reduced body weight gain and reduced food consumption with post-treatment recovery. **Developmental NOAEL** = 10 mg/kg/day **Developmental LOAEL** = 40 mg/kg/day based on reduced fetal body weights and increased skeletal variations.
870.3700a	Prenatal oral developmental toxicity in rodents (rat) **Cyfluthrin** (93.4%)	00157794 (1983) **Unacceptable**/guideline 0, 1, 3, 10 mg/kg/day 1% Cremophor EL in distilled water	**Maternal NOAEL** = 10 mg/kg/day **Maternal LOAEL** = not observed **Developmental NOAEL** = 10 mg/kg/day **Developmental LOAEL** = not observed
870.3700b	Prenatal oral developmental toxicity in non-rodents (rabbit) **Cyfluthrin** (96% a.i.)	42675401 (1992) Acceptable/guideline 0, 20, 60, 180 mg/kg/day In corn oil, by gavage	**Maternal NOAEL** = 20 mg/kg/day **Maternal LOAEL** = 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period. **Developmental NOAEL** = 180 mg/kg/day **Developmental LOAEL** = not observed
870.3700a	Prenatal inhalation developmental toxicity in rodents (rat) **Cyfluthrin** (96.2% a.i.)	43393401 (1991-1994) Acceptable/guideline 0, 0.00046, 0.00255, 0.0119, 0.0128 mg/L/day (0.125, 0.692, 3.234, 3.478 mg/kg/day) In PEG-400:ethanol for 6 hrs/day	**Maternal NOAEL** = not determined **Maternal LOAEL** = 0.00046 mg/L (0.125 mg/kg/day) based on decreased body weight gain and relative food efficiency. **Developmental NOAEL** = 0.00046 mg/L (0.125 mg/kg/day) **Developmental LOAEL** = 0.00255 mg/L (0.692 mg/kg/day) based on reduced fetal and placental weights and reduced ossification in phalanx, metacarpals, vertebrae.
870.3700a	Prenatal inhalation developmental toxicity in rodents (rat) **Cyfluthrin** (92.9% and 93%)	40780401 (1988) Acceptable/guideline **1.** 0, 0.0011, 0.0047, 0.0237 mg/L/day (0, 0.299, 1.277, 6.44 mg/kg/day) **2.** 0, 0.00009, 0.00025, 0.00059, 0.0042 mg/L/day (0, 0.0245, 0.0679, 0.160, 1.141 mg/kg/day) Dissolved in a 1:1 mixture of Lutrol and ethanol for 6 hrs/day.	**Maternal NOAEL** = 0.0011 mg/L (0.299 mg/kg/day) **Maternal LOAEL** = 0.0047 mg/L (1.277 mg/kg/day) based on reduced motility, dyspnea, piloerection, ungroomed coats, eye irritation. **Developmental NOAEL** = 0.00059 mg/L (0.160 mg/kg/day) **Developmental LOAEL** = 0.0011 mg/L (0.299 mg/kg/day) based on increased incidence of runts and skeletal anomalies in sternum.

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
Non-guideline	7-Day postnatal inhalation study (pups & dams) in mice with spontaneous motor activity measurements **Cyfluthrin** (96.8% a.i.)	44373401 (1997) Acceptable/non-guideline 0, 0.006, 0.015, 0.058 mg/L (0, 2.48, 6.21, 24.0 mg/kg/day) In PEG 400, 6 hrs/day, for 7 consecutive days	**Maternal NOAEL** = 0.058 mg/L (24.0 mg/kg/day) **Maternal LOAEL** = not determined **Offspring NOAEL** = 0.006 mg/L (2.48 mg/kg/day) **Offspring LOAEL** = 0.015 mg/L (6.21 mg/kg/day) based on clinical signs of toxicity and spontaneous motor activity observed in females 4 months after exposure.
870.3800	Reproduction and fertility effects (rat) **Cyfluthrin** (95.4% a.i.), corn oil/acetone premix	44371401 (1996) Acceptable/guideline **Premating and gestation:** M: 0, 3, 9, 29 mg/kg/day F: 0, 4, 10, 33 mg/kg/day **First 2 weeks of lactation:** 0, 7, 19, 59 mg/kg/day	**Parental/Systemic NOAEL** = 3/4 mg/kg/day (M/F) **Parental/Systemic LOAEL** = 9/10 mg/kg/day (M/F) based on reductions in body weights and food consumption. **Offspring NOAEL** = 7 mg/kg/day (M/F) **Offspring LOAEL** = 19 mg/kg/day based on coarse tremors in pups during lactation and decreases in mean litter weight.
Non-guideline	"Supplemental" 2-generation reproduction study (rat) **Cyfluthrin** (95.5% a.i.)	44371402 (1997) Acceptable/non-guideline M: 0, 1.9, 3.8 mg/kg/day F: 0, 2.1, 4.2 mg/kg/day Corn oil/acetone premix	**Parental/Systemic NOAEL** = 3.8/4.2 mg/kg/day (M/F) **Parental/Systemic LOAEL** = not determined **Offspring NOAEL** = 3.8/4.2 mg/kg/day (M/F) **Offspring LOAEL** = not determined
Non-guideline	Pilot one-generation reproduction study (rat) **Cyfluthrin (95.7-96.2% a.i.), corn oil/acetone premix**	43792901 (1995) Acceptable/non-guideline M: 0, 3.4, 9.3, 24.2, 38.9 mg/kg/day F: 0, 4.1, 10.5, 27.2, 43.9 mg/kg/day **Gestation:** 0, 3.9, 10.1, 27.2, 45.0 mg/kg/day **Lactation:** 0, 7.8, 22.9, 59.6, 95.9 mg/kg/day	**Parental/Systemic NOAEL** = 22.9 mg/kg/day **Parental/Systemic LOAEL** = 59.6 mg/kg/day based on hind leg splay, ataxia, reduction in body weight gain. **Offspring NOAEL** = 7.8 mg/kg/day **Offspring LOAEL** = 22.9 mg/kg/day based on tremors during lactation and pup weight decreases. Dosages for the NOAEL and LOAEL calculated from weekly mean test material consumption during lactation because both the large variation in consumption values and the increased test material consumption during the time that the effects were noted.

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800	Reproduction and fertility effects (rat) (1983) **Cyfluthrin**	00131532 (1983) Acceptable M: 0, 3.8, 12.3, 37.2 mg/kg/day F: 0, 5.4, 15.1, 48.5 mg/kg/day This study was classified core minimum, although it had a number of deficiencies: test article 50% premix with Wessalon S, no individual litter observations, limited necropsy & histopathology, other reporting deficiencies.	**Parental/Systemic NOAEL** = 12.3/15.1 mg/kg/day (M/F) **Parental/Systemic LOAEL** = 37.2/48.5 mg/kg/day (M/F) based on decreased body weight gain. ***Offspring* NOAEL** = 5.4 mg/kg/day **Offspring LOAEL** = 15.1 mg/kg/day based on decreased viability during lactation period and decreased body weight gains.
870.4100b	Chronic toxicity (dog) **Cyfluthrin** (94.9-95.1% a.i.)	44435401 (1997) Acceptable/guideline M: 0, 1.36, 2.43, 10.64, 15.47 mg/kg/day F: 0, 1.46, 3.61, 10.74, 17.99 mg/kg/day Corn oil premix	**NOAEL** = 2.43/3.61 mg/kg/day (M/F) **LOAEL** = 10.64/10.74 mg/kg/day (M/F) based on clinical signs, gait abnormalities, and abnormal postural reactions in males and females.
870.4100b	Chronic toxicity (dog) **Cyfluthrin**	00151358 (1983) Core minimum 0, 1, 4, 16 mg/kg/day 50% premix with Wessalon S	**NOAEL** = 4.0 mg/kg/day **LOAEL** = 16.0 mg/kg/day based on gait abnormalities, vomiting, liquid feces, decreased body weights (males).
870.4100b	6-Month oral toxicity (dog) **Cyfluthrin**	*00131530* (1981) Core minimum 0, 1.62, 5, 15 mg/kg/day	**NOAEL** = 5.0 mg/kg/day **LOAEL** = 15.0 mg/kg/day based on gait abnormalities, arching backs, vomiting, diarrhea.
870.4200	Carcinogenicity (mouse) **Cyfluthrin** (≥93.9% a.i.)	44589701 (1998) Acceptable/guideline M: 0, 31.9, 114.8, 232.7 *mg/kg/day* F: 0, 38.4, 140.6, 309.7 mg/kg/day Corn oil premix	**NOAEL** = 31.9/140.6 mg/kg/day (M/F) **LOAEL** = 114.8 mg/kg/day (M) based on ear skin lesions and reduced body weight gains. 309.7 mg/kg/day (F) based on clinical signs, macroscopic and microscopic pathology findings, and reduced body weights, body weight gains, and food consumption. ***No evidence of carcinogenicity***

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4200	Carcinogenicity (mouse) **Cyfluthrin** (49.7-51.0% a.i.)	00137304 (1983) Acceptable/guideline M: 0, 11.6, 45.8, 194.5 mg/kg/day F: 0, 15.3, 63.0, 259.9 mg/kg/day Premix in Wessalon S	Study not acceptable for chronic toxicity. ***No evidence of carcinogenicity***
870.4300	Combined chronic feeding/ carcinogenicity (rat) **Cyfluthrin** (94.7% a.i.),	44459301 (1997) Acceptable/guideline M: 0, 2.6, 11.6, 22.8 mg/kg/day F: 0, 3.3, 14.4, 28.3 mg/kg/day Acetone/corn oil pre-mix	**NOAEL** = 2.6/3.3 mg/kg/day (M/F) **LOAEL** = 11.6/14.4 mg/kg/day (M/F) based on overall declines in body weight gain by 12 and 10% in males and females, respectively. ***No evidence of carcinogenicity***
870.4300	Combined chronic feeding/ carcinogenicity (rat) **Cyfluthrin** (49.7-51.0% purity as a premix concentrate in Wessalon S)	00137303 (1983) Acceptable/guideline M: 0, 2.02, 6.19, 19.20 mg/kg/day F: 0, 2.71, 8.15, 25.47 mg/kg/day	**NOAEL** = 6.19/8.15 mg/kg/day (M/F) **LOAEL** = 19.20/25.47 mg/kg/day (M/F) based on decreased body weights and body weight gains. ***No evidence of carcinogenicity***
870.5100	Gene mutation – bacterial reverse mutation assay **Cyfluthrin**	00131539 (1982) Acceptable/guideline 5-5000 ug/plate	Negative. No increases in reverse mutations with and without activation.
870.5100	Gene mutation – yeast reverse mutation assay **Cyfluthrin**	00131541, 00144017 (1982) Acceptable/guideline 312.5-1000 ug/mL	Negative. No increase in number of revertants with S138 cultures. Increase in number of revertants with S211 culture but not dose-related; no increase in number of revertants when assay repeated.
870.5100	Gene mutation – bacterial reverse mutation assay **Cyfluthrin**	00131540 (1982) Acceptable/guideline	Negative. No increases in reverse mutations with and without activation.
870.5100	Gene mutation – bacterial reverse mutation assay **Beta-cyfluthrin**	41244110 (1986) Acceptable/guideline Initial assay: 20-12500 ug/plate Confirmatory assay: 500-8000 ug/plate	Negative. No increases in reverse mutations in *S. typhimurium* strains TA 1535, TA 1537, TA 98 or TA 100 with and without activation.

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5300	Gene mutation – *in vitro* mammalian cell gene forward mutation assay **Cyfluthrin**	00157796 (1985) Acceptable/guideline 3, 5, 7, 9, 10 ul/ml	Negative. Cyfluthrin did not induce forward mutations under conditions of assay
870.5300	Gene mutation – *in vitro* mammalian cell gene forward mutation assay **Beta-cyfluthrin**	41244112 (1989) Acceptable/guideline 50-100 ug/mL (insoluble), 20-40 ug/mL (soluble)	Negative. No mutagenic response in CHO cells HGPRT assay with and without activation.
870.5375	Cytogenetics - *in vitro* mammalian cell chromosome aberration test **Beta-cyfluthrin**	41205703 (1988) Acceptable/guideline 500, 1000, 5000 ug/mL	Negative. Not clastogenic in human lymphocytes.
870.5395	Cytogenetics – mammalian erythrocyte micronucleus test **Beta-cyfluthrin**	4124411 (1988) Acceptable/guideline 80 mg/kg	Negative. No increased frequency of micronucleated polychromatic erythrocytes in mice bone marrow cells.
870.5500	Other effects – bacterial DNA damage **Cyfluthrin**	00131540 (1982) Acceptable/guideline	Negative. In rec assay, no inhibition at doses of 100-10000 ug/disk.
870.5550	Other effects – bacterial DNA damage and repair in *E. coli* **Cyfluthrin**	00131538 (1981) Acceptable/guideline 62.5-1000 ug/plate	Negative. No induction of inhibition, both with and without activation.
870.5550	Other effects – unscheduled DNA synthesis in cultured rat hepatocytes **Cyfluthrin**	00157798 (1985) Acceptable/guideline 17, 50, 167, 500, 1667, 5000 ug/ml	Negative.
870.5550	Other effects – unscheduled DNA synthesis in mammalian cells in culture **Beta-cyfluthrin**	41205704 (1987) Acceptable/guideline 1.01-1010 ug/mL	Negative.

Appendix A, Table 3 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5575	Other effects – mitotic gene conversion in *Saccharomyces cerevisiae* **Cyfluthrin**	00131542 (1982) Acceptable/guideline 625-10000 ug/ml	Negative.
870.5915	Other effects – *in vivo* sister chromatid exchange assay in Chinese hamster ovary cells **Cyfluthrin**	00157795 (1985) Acceptable/guideline Non-activated assays: 3, 5, 10, 20 ug/ml Activated assays: 125, 250, 500, 1000 ug/ml	Negative. no increase in SCE frequency in treated cells
870.6100	Delayed neurotoxicity (hen) **Cyfluthrin**	00156585 (1985) Supplementary 0 and 5000 mg/kg/day for 3 days	All hens died within 3 days; NTE activity was not inhibited
870.6100	Oral delayed neurotoxicity (hen) **Cyfluthrin**	00131543 (1981) Supplementary 10 hens: 1000 (1x), 2500 (1x), 5000 (1x) mg/kg; 30 hens: 5000 mg/kg (2x, 21 days apart); 10 hens: 5000 mg/kg (5x daily for 1 week)	**In the single dose study**, at 5000 mg/kg, five of the ten hens died. Moderate fiber alterations (axon fragmentation, occasional swelling and eosinophilia of the axon fragments and vacuolation of the myelin sheaths) in the sciatic nerve were observed in 2 hens. Six hens at 2500 mg/kg showed signs of excitation during the first 3 days following treatment. **In the two dose study**, hens showed initial signs of intoxication during the first 3 days but were normal until the second dose was administered when 4 hens died. Symptoms following the second treatment subsided; however, a second set of symptoms developed in 4/30 hens. These symptoms resembled delayed type neurotoxicity. Nerve fiber degeneration was present in the majority of the hens. The myelin sheath was distended and the myelin sheath was described as being optically void or granularly disintegrated. The axons were described as swollen or fragmented and in some areas activated or proliferated Schwann's cells were noted. The nerves also contained macrophages in which cytoplasm contained granular material. **In the 5-day study**, 4/10 hens died. All hens showed initial toxic responses which eventually disappeared. Behavioral disorders accompanied by drowsiness and a cramped gait were observed in 3 of the 6 survivors. Mottled kidneys and brittle livers were noted at

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			necropsy. Treatment-related fiber degeneration (distension or granular disintegration of the medullary sheath, swollen or fragmented axis cylinders and proliferated Schwann's cell in the sciatic nerve were reported. One hen had similar lesions in the spinal marrow.
870.6100	Oral delayed neurotoxicity (hen) **Cyfluthrin**	00131544 (1982) 10 hens: (5000 mg/kg, 1 x) or 20 hens: (5000 mg/kg, 2 x, 7 days apart). The first study was classified as Core supplementary - no histopathology conducted) and the second study was classified as Core minimum.	In the single dose study, the hens showed an initial weight loss but recovered. No other treatment-related effects were observed. In the two-dose study, 1 hen showed some signs of neurotoxicity on day 30. There were no microscopic lesions in the nervous system.
870.6100	Dermal delayed neurotoxicity (hen) **Cyfluthrin**	00131545 (1982) Minimum 5000 mg/kg (paste with cellulose powder); in the first study, 10 hens were exposed for 5 days for 23 hours/day. In the second study, 10 hens were exposed for 3 weeks, 5 days/week, 6 hours/day.	In the first study there were 2 deaths on the 3rd and 10th day. All other hens had symptoms (apathy and disturbed behavior) but recovered. Local irritation and weight loss were also noted. Two hens had minimal segment-like nerve fiber degeneration (sciatic nerve), but this type is often found in hens. In the second study, the hens were apathetic. These symptoms disappeared after the first week in all hens except 2, in which they persisted until the 38th and 51st day after the start of the treatment, respectively. Local irritation and body weight loss were also observed. No other neurologic effects were observed, including microscopic.
870.6100	Acute delayed neurotoxicity (hen) **Cyfluthrin**	00131510 (1983) Core minimum single 4-hour exposure or to 15 six-hour exposures over a 3-week period at concentrations of 0.285, 0.445 or 0.596 mg/L in the single dose study and 0.614 mg/L in the 3 week study	Nine of 10 hens died at 0.596 mg/L and none died in any of the lower concentrations. These had some nonspecific symptoms (behavior disturbances, sedation, eye irritancy), which disappeared after 2 days. Some initial weight loss was also noted. In the 3-week study, one hen died. Nonspecific symptoms were again observed. Nothing remarkable was noted at necropsy.
870.6100	Acute delayed neurotoxicity (hen) **Cyfluthrin**	00163040 (1986) Core Minimum 4300 (1x), 4300 (2x: days 1 & 21), 1500 (5 consecutive days).	4300, 1500: mortality, aggression, somnolence, cyanosis of crest. Sl. axonal degeneration of sciatic nerve in 1 hen given a single dose; sl. axonal degeneration of spinal cord in 1 hen given 2 doses. No treatment-related changes in NTE activity.

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200a	Acute neurotoxicity (rat) **Beta-cyfluthrin** (≥96.9% a.i.)	44401101 (1997) Acceptable/guideline 0, 0.5, 2, 10 mg/kg In 1% Cremophor EL in deionized water	**NOAEL** = 2 mg/kg **LOAEL** = 10 mg/kg based on clinical signs, changes in FOB parameters, and decreases in motor activity.
870.6200b	Subchronic neurotoxicity (rat) **Beta-cyfluthrin** (≥96.5% a.i.)	44296001 (1997) Acceptable/guideline M: 0, 2.02, 7.99, 26.81 mg/kg/day F: 0, 2.34, 9.40, 30.83 mg/kg/day In corn oil, 1% by weight in diet	**NOAEL** = 7.99/9.40 mg/kg/day (M/F) **LOAEL** = 26.81/30.83 mg/kg/day (M/F) based on clinical signs, changes in FOB measurements and possibly decreased body weights, body weight gains, and food consumption
870.6300	Developmental neurotoxicity (rat) **Beta-cyfluthrin** (95.1-97.6% a.i.)	46054101 (2003) Acceptable/non-guideline 0, 30, 125, 200 ppm (Gestation: 0, 2.4, 11.0, 17.8 mg/kg/day)	**Maternal NOAEL** = 17.8 mg/kg/day **Maternal LOAEL** = not observed **Offspring NOAEL** = 11.0 mg/kg/day **Offspring LOAEL** = 17.8 mg/kg/day based on decreased body weight and body weight gain and decreased brain weights in females at termination.
870.7485	Metabolism and Pharmacokinetics **Cyfluthrin** (98% purity in 5% Cremophor EL)	00072007 (1983) Core Minimum when considered together with metabolism part of study **Single oral dose:** 0.5 and 10 mg/kg **Single i.v.** dose: 0.5 and 10 mg/kg **Repeated oral dose:** 0.5 mg/kg/day unlabeled for 14 days, then single dose labeled	Following oral administration, the test material was rapidly and nearly completely absorbed. Peak plasma levels of radioactivity were observed at about 2 hours after dosing. Greater than 95% of the administered radioactivity was excreted within 48 hours. Radioactivity was excreted in the urine and feces with virtually none being excreted in expired air. By 48 hours after dosing, >98% of the total retrieved radioactivity was recovered in the urine and feces. The ratio of radioactivity in urine/feces was higher in males than in females. About 50% of the total urinary radioactivity was recovered during the first 6-8 hours after dosing and about 90% within the first 24 hours. At 48 hours, only the fat tissue (renal fat) contained levels of radioactivity that clearly exceeded the overall mean body level, being 6-11X higher. Levels of radioactivity in brain were quite low, being 15-20X lower than the overall mean body level. Different dose levels (0.5 or 10 mg/kg) or pretreatment (14X) did not appreciably affect the above findings. Some sex differences, however, were observed as indicated by higher urine/feces ratios in males and slightly higher organ/tissue levels of radioactivity in females (except for fat tissue).

Appendix A, Table 3
Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			Following intravenous administration, a 2 phase plasma elimination pattern was observed with plasma half-lives of about 2.1 and 20 hours. The apparent volume of distribution (Vd) was about 17% of the total body volume, corresponding to the "readily diffusable part of the extracellular fluid". Greater than 90% of the administered radioactivity was excreted within 48 hours. By 48 hours after dosing, about 93-94% of the total retrieved radioactivity was recovered in the urine and feces. Residual levels of radioactivity in the body and in individual organs/tissues were higher than after oral administration. In other respects, the results following intravenous dosing were quite similar to those described for oral dosing. Studies in male rats with bile fistulas indicated an enterohepatic circulation of test material.
870.7485	Metabolism and Pharmacokinetics **Cyfluthrin** (98% purity in 5% Cremophor EL)	00072007 (1983) Core Minimum when considered together with biokinetic part of study **Single oral dose:** 0.5 and 10 mg/kg **Single *i.v.* dose:** 0.5 and 10 mg/kg **Repeated oral dose:** 0.5 mg/kg/day unlabeled for 14 days, then single dose labeled	Excretion of radioactivity was rapid. Following oral administration, >95% of the administered radioactivity was excreted within 48 hours, and following intravenous injection, >90% within 48 hours. Most of the radioactivity was excreted in urine, the urine/fecal ratio being about 2-3X in males and about 1.6-1.8X in females following oral administration and about 2.5X in males and about 2.6X in females following intravenous injection. Parent cyfluthrin is cleaved at the ester bond and then oxidized to yield 3-phenoxy-4-fluorobenzoic acid. This intermediate is then either hydroxylated and subsequently conjugated and excreted or first bound to glycine and then hydroxylated, conjugated and excreted. Identified metabolites and parent cyfluthrin (in urine, feces and body) accounted for 65-73% of the recovered radioactivity after a single oral or intravenous dose of 0.5 mg/kg and about 82-83% of the recovered radioactivity after a single oral dose of 10 mg/kg or after 14 daily oral doses.

Table A.4 Guideline Number: 870.7800
Study Title: Immunotoxicity

Rationale for Requiring the Data

The immunotoxicity study is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.

Practical Utility of the Data

How will the data be used?
Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).

How could the data impact the Agency's future decision-making?
If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

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R180680

Chemical Name: *beta-cyfluthrin*

PC Code: 118831
HED File Code: 14000 Risk Reviews
Memo Date: 1/27/2010
File ID: 00000000
Accession #: 000-00-0134

HED Records Reference Center
2/2/2010