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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

**MEMORANDUM**

**Date:** **9/1/2017**

**SUBJECT:** **Cyfluthrin and Beta-Cyfluthrin.** Draft Human Health Risk Assessment for Registration Review

**PC Code:** 128831 (Cyfluthrin)
118831 (Beta-Cyfluthrin)
**Decision No.:** 517007
**Petition No.:** NA
**Risk Assessment Type:** Single Chemical Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** D433405

**Registration Nos.:** Numerous
**Regulatory Action:** Reg Review DRA
**Case No.:** 7405-1

**CAS No.:** 68359-37-5
**40 CFR:** §180.436

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The Pesticide Reevaluation Division (PRD) requested that the Health Effects Division (HED) conduct a draft risk assessment (DRA) for the pyrethroid insecticide, cyfluthrin and its enriched isomer, beta-cyfluthrin. This document contains HED's DRA to support registration review. It

incorporates updated endpoints for risk assessment as well as the most recent data and assumptions for conducting dietary, residential, occupational, and aggregate exposure assessments.

Since the most recent human health risk assessment (2007, Human Health Risk Assessment for New Uses on Grasses, Alfalfa, and Sugar Beet Seed, and Revised Tolerances on Cereal Grain Commodities) and registration review scoping document (2010), HED has made the following changes to the cyfluthrins risk assessment:

1) Updated endpoints and doses for risk assessment;
2) Re-evaluated the FQPA Safety Factor (in accordance with the 2011 Pyrethroids Cumulative Risk Assessment) and reduced it to 3X for children <6 years old;
3) Updated the dietary exposure and risk assessment based on the most recent food consumption survey data and updated usage information;
4) Updated the residential exposure assessment using the 2012 Residential Standard Operating Procedures (SOPs), as well as considered potential exposure from spray drift; and
5) Updated the occupational exposure assessment using the most recent unit exposure data.

## 1.0 Executive Summary

Cyfluthrin and beta-cyfluthrin (an enriched isomer of cyfluthrin) are non-systemic pyrethroid insecticides. Cyfluthrin was first registered in 1989, and currently there are 145 active products, whereas beta-cyfluthrin was first registered in 1995, and currently there are 27 active registrations. Permanent tolerances are established for residues of cyfluthrin (40 CFR §180.436). Tolerances for cyfluthrin also cover beta-cyfluthrin, provided that the use rates for beta-cyfluthrin are one-half those of cyfluthrin. Cyfluthrin and beta-cyfluthrin are both mixtures of four isomers of the same compound. The difference between the two is that cyfluthrin is composed of comparable percentages of the four isomers, whereas beta-cyfluthrin is an enrichment of the two most efficacious isomers.

Use Profile

Cyfluthrin and beta-cyfluthrin are currently formulated as liquids, aerosol sprays, wettable powders, water-soluble packages, granules, dusts, baits, gels/pastes, total release foggers, and solid end-use products containing between 0.0015% and 40% active ingredient (ai). Cyfluthrin and beta-cyfluthrin are currently registered for use on a wide variety of food/feed crops, including use as a seed treatment. It is also registered for use in a variety of commercial settings (e.g., food handling establishments, etc.) or residential settings (e.g., apartments, etc). Cyfluthrin and beta-cyfluthrin may be applied to agricultural crops via aerial, ground, chemigation, and hand-held equipment (e.g. manually-pressurized handwands, etc.). Hand-held equipment is also used to apply cyfluthrin and beta-cyfluthrin end-use products inside and around commercial and residential areas.

The personal protective equipment (PPE) statement on the registered agricultural labels requires handlers to wear coveralls over short-sleeved shirt and short pants in addition to chemical resistant gloves, footwear, eyewear, and a chemical-resistant apron when mixing, loading, or cleaning equipment. On several labels, specific respirators are required. Most non-agricultural labels do not require handlers to wear any PPE, as they do not fall within the scope of the Worker Protection Standard (WPS).

Agricultural labels list a restricted-entry interval (REI) of at least 12 hours, in accordance with the WPS. Re-entry restrictions are also found on the registered labels for indoor total release foggers, which direct applicators to exit treated areas immediately and remain outside the treated area until aerosols and vapors have dispersed. Adults, children, and pets should not enter treated areas until sprays have dried or vapors, mist, and aerosols have dispersed and rooms are ventilated. All indoor total release fogger products considered in this assessment require a re-entry restriction of two hours, followed by opening of doors and windows to ventilate the room before re-occupancy.

Exposure Profile

Occupational and residential handler dermal and inhalation exposures and post-application dermal, inhalation, and incidental oral exposures are anticipated based on the registered uses of cyfluthrin and beta-cyfluthrin. Non-occupational spray drift exposure is also expected. For all registered uses, there is a potential for short-term (1 to 30 days) and intermediate term (1 to 6

months) exposure to cyfluthrin and beta-cyfluthrin during mixing, loading, applying, and other handling tasks. However, only short-term non-cancer risks have been quantitatively assessed, as repeat exposure results in either decreased or very similar toxicity. Occupational and residential handler assessments were completed assuming the labeled maximum single application rate for each scenario.

Hazard Characterization

Cyfluthrin and beta-cyfluthrin are Type II pyrethroids, that is, they contain an alpha-cyano moiety. The adverse outcome pathway (AOP) shared by pyrethroids involves the ability to interact with voltage-gated sodium channels (VGSCs) in the central and peripheral nervous system, leading to changes in neuron firing and, ultimately, neurotoxicity.

The toxicology database for cyfluthrin and beta-cyfluthrin is complete with respect to guideline toxicity studies and published studies, thus providing a comprehensive database. However, the EPA lacks additional data to fully characterize the potential for juvenile sensitivity to many pyrethroids, including cyfluthrin and beta-cyfluthrin. Literature studies indicate a possibility of increased sensitivity in juvenile rats to the neurotoxic effects of pyrethroid insecticides. In light of the literature studies, and pending receipt of additional information to better characterize potential sensitivity of the young, an additional 3X Food Quality Protection Act (FQPA) Safety Factor (as estimated by pharmacokinetic (PK) modeling) has been retained for risk assessments for infants and children <6 years old. Cyfluthrin and beta cyfluthrin are classified as "not likely to be carcinogenic to humans," and there is no concern for mutagenicity.

Cyfluthrin and beta-cyfluthrin have been evaluated for a variety of toxicological effects in a variety of experimental toxicity studies. Beta-cyfluthrin is about twice as potent as cyfluthrin via the oral and inhalation routes. Neurotoxic effects are generally the most sensitive effects for both cyfluthrin and beta-cyfluthrin, as seen in all species, routes, and exposure durations tested, and are protective of all other effects observed, such as decreased body weight and decreased survival. Clinical signs and/or behaviors indicative of neurotoxicity were observed in mice, rats, dogs, and hens. Nerve fiber degeneration was observed in rats and hens. Moreover, the acute exposure or bolus dosing studies generally result in lower NOAELs compared to longer term dietary administration studies, consistent with other pyrethroids in this class.

Cyfluthrin exhibits high to moderate acute toxicity via the oral route (Category I to III) depending on the vehicle used. Beta-cyfluthrin exhibits high acute toxicity via the oral route (Category II) regardless of the vehicle used. Both cyfluthrin and beta-cyfluthrin exhibit low dermal acute toxicity (Category IV), high inhalation acute toxicity (Category II), are not dermal irritants (Category IV) or dermal sensitizers, but cause mild eye irritation (Category III).

For assessing risk for all oral exposure scenarios, a published study by Wolansky, et al. (2006) provides the most robust data set and the most sensitive endpoint based on decreased motor activity after one bolus (gavage) dose. As there is no apparent increase in hazard from repeated/chronic exposures to cyfluthrin or beta-cyfluthrin, the acute dietary exposure and risk assessment is protective of chronic dietary risk. Based on the weight of the evidence, HED concluded that using the oral endpoint and point of departure (POD) from the Wolansky study, together with the estimated dermal absorption factor, would be protective of effects observed in

adults and offspring exposed via the dermal route. The POD for short- and intermediate-term inhalation exposure is based on a route-specific prenatal developmental study in rats with cyfluthrin, in which the fetal effects included increased incidence of runts and skeletal anomalies.

The 3X FQPA Safety Factor was retained for all applicable exposure scenarios, to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PK and the increased quantitative juvenile susceptibility observed in high dose studies. For acute dietary, incidental oral and dermal risks, an uncertainty factor of 100X was applied for adults and children ≥6 years old, based on the combined 10X interspecies and 10X intraspecies factors. For acute dietary, incidental oral and dermal exposure in children <6 years old, an uncertainty factor of 300X was applied (10X interspecies, 10X intraspecies, and 3X FQPA Safety Factor). The levels of concern (LOC) for inhalation risks is 30 for adults and children >6 years old, based on a 10X factor for intraspecies variability and 3X for interspecies extrapolation (since the human equivalent concentration (HEC) calculation already incorporates pharmacokinetic differences between species). The LOC for inhalation risks is 100 for children <6 years old, based on a 10X factor for intraspecies variability, a 3X for interspecies extrapolation, and 3X based on the increased quantitative susceptibility in pyrethroid PK and increased quantitative juvenile susceptibility in high dose studies.

Dietary Exposure and Risk Assessment

Adequate residue chemistry data are available for supporting the established tolerances and for evaluating dietary exposure and risk from residues of cyfluthrins in or on food commodities. The submitted studies include those related to analytical methods, metabolism in plants and livestock, storage stability, residue levels in plants and livestock, and residue levels in rotational crops.

HED conducted acute and chronic aggregate dietary (food and drinking water) exposure assessments using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). HED conducted the chronic assessment solely for the purpose of obtaining estimates of background levels of dietary exposure for estimating aggregate risk.

The acute dietary exposure assessment was highly refined. The analysis was based on Pesticide Data Program (PDP) monitoring data for most commodities, tolerance level residues for some commodities, and crop field trial data for a limited number of commodities. For livestock commodities, either tolerance level residues or monitoring data were used. Residue levels for some commodities were modified with either default or empirical processing factors (including drying and concentration in oil, etc.). HED used the maximum percent crop treated estimates provided by the Biological and Economic Analysis Division (BEAD) and, for drinking water, HED used the water solubility of 2 ppb for the acute estimated drinking water concentration (EDWC). The acute dietary risk estimates for the cyfluthrins are not of concern for the general U.S. population or any population subgroup, including those comprised of infants and children. The most highly exposed population subgroup is Children 1-2 years of age, which uses 96% of

the acute Population Ajusted Dose (aPAD). The most highly exposed adult population subgroup is Adults 20-49 years of age, which uses 82% of the aPAD.

The chronic dietary exposure analysis was also highly refined and was based on tolerance level residues, crop field trial data, PDP monitoring data, anticipated residues in livestock commodities, and default and empirical processing factors. In addition, for agricultural uses, HED included average percent crop treated estimates from BEAD. Cyfluthrin has food handling establishment (FHE) uses. For these uses, HED used a residue value of 0.025 ppm and a 4.65% probability that a food item is treated in an FHE. HED also used the FHE values for commodities for which the total FHE anticipated residue was higher than the total agricultural use anticipated residue. For drinking water, HED used a modeled EDWC provided by the Environmental Fate and Effects Division (EFED).

Cancer risk is not of concern for cyfluthrin because the compound is classified as "not likely to be carcinogenic to humans."

Residential Exposure and Risk Assessment

Residential handler dermal and inhalation exposures, and post-application dermal, inhalation, and incidental oral exposures are anticipated based on the registered uses of cyfluthrin and beta-cyfluthrin. Non-occupational spray drift exposure is also expected. Incidental oral and dermal exposures were combined in this assessment, since the toxicological effects for these exposure routes are similar; however, inhalation exposure was not combined, as toxicological effects for this route are different.

There are no residential handler risk estimates of concern. All residential handler scenarios resulted in dermal and inhalation risk estimates greater than their respective LOCs (dermal LOC = 100 and inhalation LOC = 30) and are not of concern.

There are several post-application scenarios of concern, with risk estimates less than their LOCs (adult and children ≥ 6 years old: dermal LOC = 100, inhalation LOC = 30; children < 6 years old: dermal/incidental oral/acute dietary LOC =300, inhalation LOC = 100). Most risks of concern occur from exposure to end-use products used indoors as broadcast and perimeter/spot/bedbug treatments, with combined MOEs (dermal/incidental oral exposures) of 140 and 220, respectively. The majority of post-application risks come from incidental oral exposure, especially from application on carpets. There is also a risk of concern from outdoor aerosol space sprays, with an inhalation MOE of 40.

While HED does expect bystander exposure to drift from sprays applied to agricultural areas, spray drift was not assessed. There are registered turf uses of cyfluthrin and beta-cyfluthrin that result in worst case exposure to children (1 < 2 years) and adults from treated lawns that are considered protective of exposure from spray drift.

Aggregate Exposure and Risk Assessment

The acute aggregate risk estimates are equivalent to the corresponding dietary (food plus water) risk estimates, which are not of concern. The short-term aggregate risk assessment is based on

background dietary exposure from food and drinking water and potential residential exposure for adults (dermal) and children (dermal and incidental oral). For children, the scenarios with risk estimates of concern were not aggregated with exposure from food and water. The short-term aggregate risk estimates for adults are not of concern. However, most of the short-term aggregate risk estimates for Children 1-2 are of concern. Aggregate MOEs for the following scenarios range from 210-270, and are of concern: high contact lawn activities after treatment with both solid and liquid formulations, indoor perimeter/spot/bedbug treatment with liquid formulations, and exposure after fogger treatment. The aggregate risk estimate for exposure after outdoor aerosol space spray is not of concern for children 1-2.

Occupational Exposure and Risk Assessment

HED has provided updated occupational/commercial handler (i.e., those who mix, load, and apply products) exposure and risk estimates, as well as post-application exposure and risk estimates for re-entry workers in agricultural fields. Dermal and inhalation exposures were not combined in this assessment, since the toxicological effects for these exposure pathways are different. There are several occupational handler scenarios that result in risk estimates of concern. These include handheld equipment/hand dispersal of several formulation types, with dermal MOEs ranging from 9-12 and inhalation MOEs ranging from 1.1 to 28 (dermal LOC = 100, inhalation LOC = 30). The remaining occupational handler scenarios are not of concern. All occupational post-application scenarios are not of concern.

Environmental Justice

Potential areas of environmental justice concerns were considered in this human health risk assessment to the extent possible. Section 3.5: Considerations of Environmental Justice, discusses this topic in more detail.

Human Studies Review

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 data, which include studies from PHED 1.1; the AHETF database; and the Residential SOPs (Treated Lawns/Turf, Indoor Environments, Outdoor Fogging and Misting Systems, and Pets); are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website.

## 2.0 HED Conclusions

### 2.1 Data Deficiencies

None

## 2.2 Tolerance Considerations

Tolerances for cyfluthrin are listed in 40CFR §180.436. This CFR entry is divided into four sections. Section 180.436(a)(1) is for residues resulting from agricultural applications of cyfluthrin, §180.436(a)(2) is for residues resulting from cyfluthrin application in food handling establishments, §180.436(a)(3) is for residues resulting from cyfluthrin application in feed handling establishments, and §180.436(a)(4) is for residues resulting from agricultural applications of beta-cyfluthrin.

For cyfluthrin, the residue of concern for tolerance enforcement is parent cyfluthrin. For beta-cyfluthrin, the residue of concern for tolerance enforcement is a mixture of 4 diastereomers (two enantiomeric pairs). The tolerance expressions for both cyfluthrin and beta-cyfluthrin need to be updated to address both coverage and compliance as delineated in HED's *Interim Guidance on Tolerance Expressions* (S. Knizner; 27 May 2009).

The tolerance expression for cyfluthrin in 40CFR §180.436(a)(1) should be revised to state: "Tolerances are established for residues of cyfluthrin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only cyfluthrin, (cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2dimethyl-cyclopropane-carboxylate, in or on the commodity."

The tolerance expression for residues of cyfluthrin resulting from application in food and feed handling establishments should be consolidated into one section, as they are for the pyrethroid, deltamethrin in the previous 40CFR entry (40CFR §180.436(a)(2)). The CFR entries for cyfluthrin residues resulting from application in food and feed handling establishments contain label directions that do not need to be included in the 40 CFR entry. As a result, the label directions in 40CFR §180.436(a)(2)(i), (ii), and (iii) as well as those in 40CFR §180.436(a)(3)(i), (ii), and (iii), should be deleted. As a result, the tolerance expression for cyfluthrin in 40CFR §180.436(a)(2) should be revised to state: "A tolerance of 0.05 ppm is established for residues of cyfluthrin, including its metabolites and degradates, in or on all food and feed items when cyfluthrin is used in food or feed handling establishments. Compliance with the tolerance level specified is to be determined by measuring only cyfluthrin, (cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2dimethyl-cyclopropane-carboxylate, in or on the commodity." Section 180.436(a)(3) should be deleted.

The tolerance expression for beta-cyfluthrin in 40CFR §180.436(a)(4) should be revised to state: "Tolerances are established for residues of beta-cyfluthrin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of beta-cyfluthrin, cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate [mixture comprising the enantiomeric pair (*R*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate with the enantiomeric pair (*R*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*S*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (*S*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate], in or on the commodity."

A tolerance of 0.5 ppm is established for the fruiting vegetable crop group (Group 8). A tolerance is also established for pepper at 0.5 ppm and tomato at 0.2 ppm. These tolerances are covered by the crop group tolerance and can be deleted. Similarly, a tolerance of 6.0 ppm is established for the leafy vegetable, except Brassica crop group (Group 4). Tolerances are also established for head lettuce at 2.0 ppm and leaf lettuce at 3.0 ppm. These tolerances are covered by the crop group tolerance and can be deleted.

Several of the crop groups and subgroups with tolerances have been updated. The groups and subgroups that currently have cyfluthrin tolerances are as follows: citrus fruit (Group 10), pome fruit (Group 11), stone fruit (Group 12), tree nuts (Group 14), fruiting vegetables (Group 8), and leafy vegetables (Group 4), Brassica leafy greens (Subgroup 5B), and head and stem Brassica (Subgroup 5A). Groups 8, 10, 11, 12, and 14 can be updated to their respective groups 8-10, 10-10, 11-10, 12-12, and 14-12 because the current and updated groups have the same representative commodities. The tolerances for the updated groups should be the same as those for the current groups. Because of changes in the representative commodities for the leafy vegetable groups and subgroups and the establishment of the new group, Stalk, Stem, and Leaf Petiole Vegetable Group (22), the leafy vegetable group (Vegetable Leafy, Except Brassica, Group 4), the Brassica, Head and Stem, Subgroup 5A, and the Brassica, Leafy Greens Subgroup 5B, cannot be directly updated to the new and updated groups and subgroups. Instead, they should be replaced with the following groups and subgroups. A tolerance of 6.0 ppm should be established for the Leafy green subgroup 4-16A. A tolerance of 7.0 ppm should be established for the Brassica leafy greens subgroup 4-16B. A tolerance of 2.5 ppm should be established for the Brassica head and stem vegetable group, 5-16. A tolerance of 6.0 ppm should be established for the Leaf petiole vegetable subgroup, 22B. An individual tolerance of 6.0 ppm should be established for celtuce, an individual tolerance of 6.0 ppm should be established for Fennel, Florence, and an individual tolerance of 2.5 ppm should be established for Kohlrabi. When the tolerances for the updated crop groups are established, the tolerances for the previous crop groups should be conceled. There is currently a tolerance of 7.0 ppm for mustard greens. As mustard greens is a member of crop subgroup 4B, and a tolerance of 7.0 ppm is being established for this subgroup, the individual mustard greens tolerance should be canceled. The following tables provide summaries of the recommended tolerance changes. Table 2.2.a lists the tolerances that should be established for the updated groups and subgroups. Table .2.2.b lists the current tolerances that should be canceled when the tolerances for the updated groups and subgroups are established.

**TABLE 2.2.a. Tolerance Summary for Cyfluthrin and beta-Cyfluthrin (40CFR §180.436). Tolerances to be Established**

| Commodity | Current Tolerance (ppm) | Recommended Tolerance (ppm) | Comments; *Correct Commodity Definition* |
|---|---|---|---|
| Brassica, head and stem, group 5-16 | None | 2.5 | Updated crop group tolerance |
| Brassica, leafy greens, subgroup 4-16B | None | 7.0 | Updated crop group tolerance |
| Fruit, citrus, group 10-10 | None | 0.2 | Updated crop group tolerance |
| Fruit, pome, group 11-10 | None | 0.5 | Updated crop group tolerance |
| Fruit, stone, group 12-12 | None | 0.3 | Updated crop group tolerance |
| Leafy greens, subgroup 4-16A | None | 6.0 | Updated crop subgroup tolerance |

| TABLE 2.2.a. Tolerance Summary for Cyfluthrin and beta-Cyfluthrin (40CFR §180.436). Tolerances to be Established | | | |
|---|---|---|---|
| **Commodity** | **Current Tolerance (ppm)** | **Recommended Tolerance (ppm)** | **Comments; *Correct Commodity Definition*** |
| Nut, tree, group 14-12 | None | 0.01 | Updated crop group tolerance |
| Stalk, stem, and leaf petiole vegetable, subgroup 22B | None | 6.0 | New crop subgroup tolerance |
| Vegetable, fruiting, group 8-10 | None | 0.5 | Updated crop group tolerance |
| Celtuce | None | 6.0 | Now in subgroup 22A (no subgroup tolerance) |
| Fennel, Florence | None | 6.0 | Now in subgroup 22A (no subgroup tolerance) |
| Kohlrabi | None | 2.5 | Now in subgroup 22A (no subgroup tolerance) |

| TABLE 2.2.b. Tolerance Summary for Cyfluthrin and beta-Cyfluthrin (40CFR §180.436). Tolerances to be Canceled when Updated Tolerances are Established | | | |
|---|---|---|---|
| **Commodity** | **Current Tolerance (ppm)** | **Recommended Tolerance (ppm)** | **Comments; *Correct Commodity Definition*** |
| Brassica, head and stem, subgroup 5A | 2.5 | None | Cancel |
| Brassica, leafy greens, subgroup 5B | 7.0 | None | Cancel |
| Fruit, citrus, group 10 | 0.2 | None | Cancel |
| Fruit, pome, group 11 | 0.5 | None | Cancel |
| Fruit, stone, group 12 | 0.3 | None | Cancel |
| Nut, tree, group 14 | 0.01 | None | Cancel |
| Vegetable, fruiting, group 8 | 0.5 | None | Cancel |
| Vegetable, leafy, except Brassica, group 4 | 6.0 | None | Cancel |
| Mustard greens | 7.0 | None | Cancel |

These tolerance revisions should be made to both 40CFR §180.436(a)(1) (cyfluthrin) and §180.436(a)(4) (beta-cyfluthrin).

### 2.2.1 Enforcement Analytical Method

Adequate GC/ECD methods are available in PAM Vol. II for enforcing tolerances for cyfluthrin/beta-cyfluthrin residues in/on plant commodities (Method 85823) and animal commodities (Method 85883). The limit of detection for cyfluthrin and beta-cyfluthrin by both methods is 0.01 ppm in the tested plant and animal commodities.

Data pertaining to the recovery of cyfluthrin using FDA's multiresidue methods were submitted in 1998 (MRID 40355901), and forwarded to FDA. The FDA Pestrak Data Base (PAM Vol. I, Appendix, dated 11/6/90) indicates that complete recovery has been obtained for cyfluthrin using FDA multiresidue methods.

### 2.2.2 International Harmonization

There are numerous Codex MRLs for cyfluthrin. The commodities with Codex MRLs are listed in the international residue limits status sheet in Appendix E. U.S. tolerances are in effect for some of these commodities. When there are both U.S. tolerances and Codex MRLs for the same commodity, the MRLs are generally not harmonized. The U.S. tolerances are usually higher than the Codex MRLs. In these cases, harmonization might not be feasible because the tolerances are based on residue trials that resulted in residues that necessitated the higher residue limit. In two cases, however, the U.S. tolerances are lower than the Codex MRLs. These MRLs are the citrus fruit tolerance of 0.2 ppm and the hog, meat byproduct tolerance of 0.01 ppm. These tolerances could potentially be harmonized with the Codex MRLs of 0.3 ppm for citrus fruit and 0.02 ppm for hog meat byproducts.

Canada's Pest Management Regulatory Agency (PMRA) has also established cyfluthrin MRLs for several commodities. None of the MRLs are harmonized with the U.S. tolerances, with one exception (egg at 0.01 ppm).

## 2.3 Label Recommendations

The Occupational and Residential risk assessment (G. Thornton; D435058; 9/1/2017) relies on a 2015 study by the Agricultural Handler Exposure Task Force (AHETF) that measured dermal and inhalation exposure for workers who mixed and loaded water-soluble packet pesticide products. Commensurate with the behaviors and practices represented by these data, labels for products formulated in water-soluble packaging should incorporate the Agency's revised instructions for proper mixing and loading of water-soluble packets. This revised language is aimed at ensuring that water-soluble packets are allowed to dissolve in water via mechanical agitation as intended and prevent them from being ruptured by streams of water or other means.

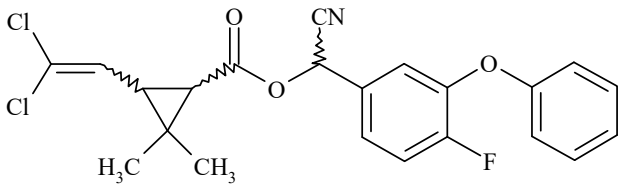
Additionally, HED has identified several scenarios of concern where risks could be mitigated through the addition of PPE, such as dermal or respiratory protection. Additionally, label information (e.g., concentration of liquid formulation) and application rates (listed as product applied per area, as well as dilutions of the product to be applied) should be included where appropriate.

## 3.0 Introduction

## 3.1 Chemical Identity

The chemical structure and nomenclature are given in the table below.

**Table 3.1 Cyfluthrin and β-Cyfluthrin Nomenclature.**

| | | |
|---|---|---|
| |  <br>Diastereomer I (1R,3R,αR + 1S,3S,αS; 1:1; cis)<br>Diastereomer II (1R,3R,αS + 1S,3S,αR; 1:1; cis)<br>Diastereomer III (1R,3S,αR + 1S,3R,αS; 1:1; trans)<br>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<br><br>**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) | 145 Active End-Use Products | |

## 3.2 Physical/Chemical Characteristics

Cyfluthrin has very low water solubility (2 ppb at 20ºC) and a relatively high octanol/water partition coefficient (log $K_{OW}$ = 6). These values account for the low surface and groundwater concentrations and indicate that the compound has potential to partition into fatty tissues. The chemical has a vapor pressure of 1.5 x $10^{-10}$ mm Hg at 20ºC. See Appendix B for a listing of additional physical and chemical properties.

## 3.3 Pesticide Use Pattern

Cyfluthrin is currently formulated as liquids, aerosol sprays, wettable powders, water-soluble packages, granules, dusts, gels/pastes, and solid end-use products containing between 0.0015% and 40% ai. Cyfluthrin is currently registered for use on a wide variety of food/feed crops,

including use as a seed treatment. It is also registered for use in a variety of commercial and residential settings (e.g., food handling establishments, warehouses, schools, apartments, auditoriums, institutions, supermarkets, parks, lawns, landscaping, nurseries, greenhouses, etc.). Cyfluthrin may be applied to agricultural crops via aerial, ground, chemigation, and hand held equipment (e.g., manually-pressurized handwands, mechanically-pressurized handguns). Hand held equipment, such as push type rotary spreaders, aerosol spray cans, total release foggers, trigger-spray bottles, injectors, hose-end sprayers, hand dusting equipment, belly grinder, etc., are used to apply cyfluthrin end-use products inside and around commercial and residential areas. A summary of the registered residential and occupational uses is provided in Appendix F:

- Table F.1. Summary of Directions for Residential Uses of Cyfluthrin.
- Table F.2a. Summary of Directions for Occupational (Agricultural, Non-seed Treatment) Uses of Cyfluthrin.
- Table F.2b. Summary of Directions for Crop Uses of Cyfluthrin.
- Table F.3. Summary of Directions for Occupational (Agricultural, Seed Treatment) Uses of Cyfluthrin.
- Table F.4. Summary of Directions for Occupational (Non-Agricultural) Uses of Cyfluthrin.

The PPE statement on the registered agricultural labels requires handlers to wear coveralls over short-sleeved shirt and short pants in addition to chemical resistant gloves, footwear, eyewear, and a chemical-resistant apron when mixing, loading, or cleaning equipment. On several labels, specific respirators are required. Most non-agricultural labels do not require handlers to wear any PPE, as they do not fall within the scope of the Worker Protection Standards (WPS).

The agricultural labels list a restricted-entry interval (REI) of at least 12 hours, in accordance with the WPS. Re-entry restrictions are also found on the registered labels for indoor foggers, which direct applicators to exit treated areas immediately and remain outside the treated area until aerosols and vapors have dispersed. Adults, children, and pets should not enter treated areas until sprays have dried or vapors, mist, and aerosols have dispersed and rooms are ventilated. All indoor fogger products considered in this assessment require a re-entry restriction of two hours, followed by opening of doors and windows to ventilate the room before re-occupancy.

### 3.4 Anticipated Exposure Pathways

Humans could be exposed to cyfluthrin residues from consuming plant and livestock commodities containing residues resulting from agricultural applications, consuming food treated in FHEs, and from contacting treated residential turf and indoor environments. In addition, occupational workers can be exposed while handling the pesticide prior to application as well as during mixing, loading, and applying the chemical, or while planting treated seed. The agricultural applications can result in cyfluthrin reaching surface and groundwater, both of which can serve as sources of drinking water. However, because of the low water solubility of the chemical and its affinity to bind to soil organic matter, drinking water concentrations will be very low. Homeowners can be exposed dermally and via inhalation during mixing, loading, and applying non-restricted end-use products in residential settings. There is also potential for residential post-application exposure via inhalation, dermal, and incidental oral (children only)

routes of exposure, as well as non-occupational bystander exposure to spray drift from occupational applications.

### 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.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 the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) 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 and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure, and it was considered in this analysis. Further considerations are also currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

## 4.0 Hazard Characterization and Dose-Response Assessment

Cyfluthrin and beta-cyfluthrin are members of the pyrethroid class of insecticides. Cyfluthrin and beta-cyfluthrin are both mixtures of four isomers of the same compound. The difference between the two is that cyfluthrin is composed of comparable percentages of the four isomers, whereas beta-cyfluthrin is an enrichment of the two most efficacious isomers. Beta-cyfluthrin is about twice as potent as cyfluthrin *via* the oral and inhalation routes (see Appendix A.2). Pyrethroids have historically been classified into two groups, Type I and Type II, based on chemical structure and toxicological effects. Type I pyrethroids, which lack an alpha-cyano moiety, induce in rats a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, hyperthermia, and fine tremor progressing to whole-body tremor and prostration (T-syndrome). Type II pyrethroids, which contain an alpha-cyano moiety, in rats produce a syndrome that includes pawing, burrowing, salivation, hypothermia, and coarse tremors leading to choreoathetosis (CS-syndrome) (Verschoyle and Aldridge 1980; Lawrence and Casida 1982). Cyfluthrin and beta-cyfluthrin are Type II pyrethroids. The adverse outcome pathway (AOP, based on the Bradford-Hill criteria) shared by pyrethroids involves the ability to interact with VGSCs in the central and peripheral nervous systems, leading to changes in neuron firing and, ultimately, neurotoxicity (Figure 4.0).

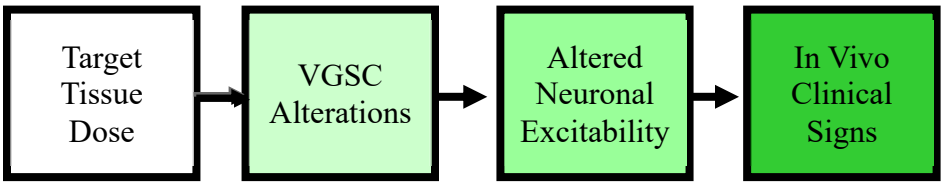



Figure 4.0. Adverse outcome pathway for pyrethroids

## 4.1 Toxicology Studies Available for Analysis

The database of experimental toxicology studies available for cyfluthrin and beta-cyfluthrin provides a robust characterization of the hazard potential for children 6 years old and older as well as for adults. New immunotoxicity study and dermal penetration studies (*in vivo* and *in vitro*) have been submitted since the most recent risk assessment. In addition, there are ongoing efforts to develop data to inform the potential sensitivity of infants and young children to pyrethroids as a class (see Section 4.4). Despite the ongoing scientific efforts, HED has chosen points of departure and uncertainty factors in this risk assessment that are protective of the effects associated with exposure to cyfluthrin and/or beta-cyfluthrin.

Data from the following published scientific literature and guideline studies (submitted by registrants) in support of registered uses were used to evaluate the hazard potential of cyfluthrin and beta-cyfluthrin:

-Wolansky Acute Oral Study in the Rat (Wolansky et al. 2006)
-WIL Laboratory Acute Oral Study in the Rat (Weiner at al. 2009)
-21-Day Dermal Study in the Rat
-90-Day Oral Studies in the Rat and Dog
-5-Day, 28-Day and 90-Day Inhalation Toxicity Studies in the Rat
-Developmental Toxicity Study in Rat *via* the Inhalation Route
-Carcinogenicity Studies in the Rat and Mouse
-Chronic Studies in the Rat and Dog
-Developmental Studies in the Rat and Rabbit
-Reproduction Study in the Rat
-Acute, Subchronic, and Developmental Neurotoxicity (DNT) Studies in the Rat
-Acute Delayed Neurotoxicity Studies in the Hen
-Immunotoxicity Study in the Rat
-Mutagenicity Battery of Studies
-Metabolism Studies in the Rat
-Dermal Penetration Study in the Rat

The studies available for consideration of cyfluthrin and beta-cyfluthrin toxicity provide a comprehensive database. The Wolansky and WIL studies are acceptable acute oral non-guideline studies that measure locomotor and functional observational battery (FOB) activity, respectively, and provide robust data to evaluate the hazard potential of pyrethroids. Only beta-cyfluthrin was examined in the WIL and Wolansky studies. In addition, numerous studies from the scientific literature conducted over several decades describe the pharmacodynamic (PD) and

pharmacokinetic (PK) profile of the pyrethroids in general (see Section 4.3 for more detail). This scientific literature has been reviewed by several groups (Soderlund *et al*. 2002; Shafer *et. al.* 2005; Wolansky and Harrill 2008).

## 4.2 Toxicological Profile

Cyfluthrin and beta-cyfluthrin have been evaluated for a variety of toxicological effects in experimental toxicity studies. Neurotoxic effects were generally the most sensitive effects for both cyfluthrin and beta-cyfluthrin, as seen in all species, routes, and exposure durations tested. Neurotoxic effects were seen in both general toxicology studies and studies specially designed to measure neurotoxicity. Such effects were observed at lower doses in the latter, which include guideline studies (acute, subchronic, and developmental), literature studies, and special studies submitted by the registrant.

Oral studies in rat, dog, mouse, and hen showed clinical signs suggestive of neurotoxicity. Rats showed gait abnormalities, salivation, and hypoactivity in most oral guideline studies. The following effects were also observed in rats: clonic convulsions were observed in the WIL study (2006); decreased motor activity was observed by Wolansky *et al*. (2006); clinical signs (ear injuries, ataxia) and Functional Observational Battery (FOB) changes (gait incoordination, repetitive chewing, decreased fore- and hindlimb grip strength) were observed in the subchronic neurotoxicity study; and splayed hind limbs and ataxia were observed in lactating dams in the guideline reproductive study. Dogs showed gait abnormalities and vomiting in subchronic and chronic studies, the latter showing additional signs of neurotoxicity (i.e. seizures, convulsions, tremors, ataxia) and diarrhea. A chronic mouse study showed ear skin lesions, hunched back and reduced body weights. In hens, gait abnormalities, reduced motor activity, and behavioral disturbances were observed. Microscopic analysis found nerve fiber degeneration in rats and hens. Decreased survival was also observed in oral rat and hen studies.

Five inhalation studies of various durations (5 to 90 days) are available for cyfluthrin and β-cyfluthrin, with a concentration range of 0.00009 – 0.05 mg/L. While studies of different exposure duration are available, the Agency does not expect that duration of exposure in the inhalation studies will be a determining factor in the toxicity of cyfluthrin and β-cyfluthrin, given what is known about the toxicokinetics of the pyrethroids. As explained in Section 4.3 below, rapid absorption, metabolism, and elimination preclude increases in the body burden that would lead to increased toxicity following repeated exposure to cyfluthrin. Consequently, the Agency does not expect that toxicity would increase (*e.g.,* lower NOAELs/LOAELs, increased severity of effects) over time. Neurotoxic effects (piloerection, decreased mobility, dyspnea, and agitation) related to cyfluthrin and/or β-cyfluthrin exposure were consistently observed at concentrations ≥ 0.0038 mg/L in four of the inhalation studies. Piloerection was first reported in the 5-day toxicity study with beta-cyfluthrin. At a slightly higher concentration (0.0045 mg/L) in the inhalation developmental toxicity study with cyfluthrin, piloerection, eye irritation, decreased motility, and dyspnea were reported within the first 2 days of exposure. Similar effects were reported in both of the 28-day studies (one each for cyfluthrin and beta-cyfluthrin). The only study that did not elicit the expected pyrethroid toxicity profile was the 90-day study with cyfluthrin. Several inconsistencies are observed in the 90-day study compared to other inhalation studies with the cyfluthrins: (i) no findings were reported until the second week of exposure and (ii) the observations (unkempt fur and lethargy) were not replicated in subsequent

studies at similar concentrations. Based on a weight-of-evidence (WOE) analysis that compared findings in all available inhalation studies (see Appendix A, Table A.3.2.1), the Agency concluded that observations occurring only after two weeks or more of exposure (6 hours/day, 5 days per week) in the 90-day inhalation study were spurious findings unrelated to treatment. Non-neurotoxic effects (↓ fetal weights, ↑ incidence of runts and skeletal variations) were reported in the inhalation developmental study with cyfluthrin at concentrations ≥0.00059 mg/L. Higher concentrations resulted in an increased incidence of late resorptions and post-implantation losses. In adults, body weight decrements – though marginal – were also reported at concentrations ≥ 0.003 mg/L in both of the 28-day inhalation studies

A dermal study in rats showed gross skin lesions, nasal discharge, and urine stains, but no signs of neurotoxicity. In the dermal penetration studies, the total potentially absorbed dose (absorbed systemically plus associated with the skin) of beta-cyfluthrin in rats was 8.9% *in vivo*, and rat skin showed 15.9-fold more absorption than human skin *in vitro*. Combining the *in vivo* rat and *in vitro* rat and human data results in a human *in vivo* absorption estimate of 0.56%. This is typical of the pyrethroids, as they are lipophilic, and much of the radioactivity measured in the skin of dermal penetration studies with pyrethroids is captured in the upper dermal layers and not available for absorption or systemic circulation.

Cyfluthrin has been evaluated for potential developmental effects in the rat and rabbit. There were no developmental effects in the rabbit. Skeletal variations and decreased fetal weight were observed in rats after exposure by the oral or inhalation routes. In the oral study, fetal effects occurred at the same doses at which maternal clinical signs (hypoactivity, salivation, locomotive incoordination) were observed. In two inhalation studies, fetal effects (increased incidence of runts, decreased fetal weight and skeletal anomalies) occurred at a lower dose than that at which maternal clinical signs (reduced motility/hypoactivity, dyspnea, piloerection, ungroomed coat, eye irritation, high-stepping gait) were observed.

The potential reproductive toxicity of cyfluthrin was examined in several multi-generation oral reproduction studies in the rat. In addition, an oral developmental neurotoxicity study in rats and an inhalation 7-day postnatal neurotoxicity study in mice examined the potential for toxicity in offspring. There were no effects on reproductive parameters. Coarse tremors or tonic seizures were observed in offspring during lactation in two oral studies and in the mouse inhalation study. Decreased viability and body weights were observed in lactating pups in another oral study with a formulation of 50% cyfluthrin and 50% Wessalon S (silica desiccant). In all studies in which lactating pups were exposed/dosed, effects in the pups were observed at lower doses than those that resulted in parental effects (leg splay, ataxia, decreased body weight).

Cyfluthrin and beta-cyfluthrin are "not likely to be carcinogenic to humans" based on the results from carcinogenicity studies in rats and mice. A battery of *in vivo* and *in vitro* genotoxicity studies does not indicate mutagenic or clastogenic potential.

With respect to acute lethality studies, cyfluthrin exhibits high to moderate acute toxicity via the oral route depending on the vehicle used (Category I in Cremophor; III in PEG 400; for comparison, longer-term oral studies did not use these vehicles). Beta-cyfluthrin exhibits high acute toxicity via the oral route (Category II using xylene, PEG or acetone/peanut butter as vehicle). Both cyfluthrin and beta-cyfluthrin exhibit low dermal acute toxicity (Category IV),

high inhalation acute toxicity (Category II), are not dermal irritants (Category IV) or dermal sensitizers, but cause moderate eye irritation (Category III).

As noted in Tables A.2.1 and A.2.2 (see Appendix A.2), a comparison of the $LD_{50}$ indicates that in rats, beta-cyfluthrin is about 1.6-1.7 times as potent as cyfluthrin. When comparing inhalation studies, beta-cyfluthrin appears to be 2.2 times as potent as cyfluthrin; however, this may be an artifact of dose spacing in the studies. When comparing oral studies, clinical signs at 39-42 mg/kg/day beta cyfluthrin and 50 mg/kg/day cyfluthrin are the most sensitive signs of toxicity. The acute neurotoxicity screening battery studies with beta-cyfluthrin, which are specifically designed to detect neurotoxic effects, detected effects at a lower dose of 10 mg/kg/day, compared to other oral studies. In all oral studies, the most common effect was gait abnormalities.

The PK profile for cyfluthrin and beta-cyfluthrin is similar to the general PK profile of other pyrethroids, i.e., rapid absorption and clearance, and extensive metabolism. Following a single oral dose of 0.5 or 10 mg/kg radiolabeled cyfluthrin in saline containing 5% Cremophor EL, plasma levels reached a maximum concentration about 2 hours after oral dosing (regardless of dose level or pretreatment). The apparent volume of distribution (Vd) was calculated to be about 17% of the total body volume. Within 48 hours, 95-98% of the dose was excreted via the urinary and fecal pathways, with the majority being excreted within 24 hours (~90%). A greater proportion was eliminated in the urine than in the feces (2-3x in males; about 2x in females) with virtually none in exhaled air. At 48 hours, only fat contained levels that clearly exceeded (6-11x) the overall mean body level. Levels in brain were lower (15-20x) than overall mean body level. Different dose levels or multiple doses did not affect the above findings significantly. Some sex differences were observed: higher urine/feces ratios in males, and slightly higher organ/tissue levels in females (except for fat tissue). Cyfluthrin is cleaved at the ester bond and then oxidized to 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.

### 4.3 Pyrethroid Pharmacokinetic and Pharmacodynamic Profile

OPP is making best use of the extensive scientific knowledge about the AOP on pyrethroids in the risk assessments for this class of pesticides. In this way, information on a subset of pyrethroids can be used to help interpret and understand the toxicological profile for other members of the class. In that regard, a group of pesticide registrants and product formulators known as the Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) has been conducting multiple experiments with permethrin and deltamethrin as model Type I and Type II compounds, respectively, in order to develop an initial extensive database of *in vitro* and *in vivo* toxicology studies and highly refined physiologically-based pharmacokinetic (PBPK) models. These data will be used to inform the development of PBPK models for the pyrethroids. The CAPHRA presented its most recent experimental data and proposed path forward to the SAP on May19th 2015 (USEPA 2015). Based on the comments from the Scientific Advisory Panel (SAP), the CAPHRA continued to pursue its research efforts and submitted additional data to the Agency. However, EPA was not able to use the data available from the CAPHRA for deriving PODs or for species extrapolation. The CAPHRA data continue to be reviewed by the Agency, but have not been included in the current draft risk assessment. The Agency anticipates further data submissions as part of the upcoming October 2017 SAP on the CAHPRA work.

In addition to the efforts of the CAPHRA, the extensive body of scientific literature on the pyrethroids provides insight into the contributions of PK and PD to the general toxicity profile of this class of chemicals. This information also furthers understanding surrounding the potential age-related differences in toxicity for the pyrethroids. This scientific literature has been reviewed by several groups (Soderlund *et al*. 2002; Shafer *et al*., 2005; Wolansky and Harrill 2008) and the following sections of the risk assessment discuss the specific issues related to pyrethroid PK, pyrethroid PD, and age-related differences in pyrethroid toxicity. Furthermore, the Agency will be updating its literature review for pyrethroids in 2017 as described below prior to completion of the revised risk assessments.

In recent years, the National Academies' National Research Council (NRC) has encouraged the Agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making (NRC 2011, 2014). The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies" (NRC 2014). According to the NRC, systematic reviews "have several common elements: transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language." EPA's Office of Chemical Safety and Pollution Prevention is currently developing systematic review policies and procedures. The Agency is currently working to develop a systematic review for the pyrethroids.

### 4.3.1 Pharmacokinetics (PK)

PK can be defined as what the body does to the chemical; in this case, how pyrethroids are distributed and eliminated following exposure. Specific to pyrethroids, PK refers to the process(es) that determine(s) the concentration of the pyrethroids reaching sodium channels. The underlying PK of pyrethroids is an important determination of their toxicity because the concentration of pyrethroid at the sodium channel relates to the extent of toxicity; greater pyrethroid concentration translates as increased neurotoxicity. Physiological processes that significantly contribute to the PK include metabolism, protein binding, and partitioning. Carboxylesterases and cytochrome P450 enzymes are the two major enzyme families responsible for the metabolism of pyrethroids. It is the ontogeny of these enzymes that accounts for the age-related sensitivity observed after pyrethroid exposures, as described below in more detail. In terms of partitioning, pyrethroids tend to distribute into fat. However, pyrethroid residues in fatty tissue are not available to interact with the VGSCs in vital tissues and, therefore, do not contribute to overall toxicity.

Age-dependent PK differences have been identified for several pyrethroids; that is, there are differences in the ability of adults and juveniles to metabolize pyrethroids. The enzymes that metabolize and detoxify pyrethroids are present in rats and humans at birth (Koukouritaki *et al*. 2004; Yang *et al*. 2009). As a result, both juveniles and adults are able to tolerate low doses of pyrethroids when the internal dose, or the amount of pyrethroid at the sodium channel, is low. However, the expression, and therefore activity, of these enzymes increases with age, conveying in adults a greater capacity than juveniles to detoxify pyrethroids (Anand *et al*. 2006; de Zwart *et al*. 2008; Yang *et al*. 2009). For example, the rate of *in vitro* metabolism of deltamethrin by

plasma carboxylesterases, plus hepatic carboxylesterases and cytochrome P450s (microsomes) is at least 6 times as high for post-natal day (PND) 90 rats as for PND 10 rats (Anand *et al*. 2006). In humans, expression of hepatic carboxylesterases is significantly lower in infants <3 weeks old but then increase to near adult levels (Hines *et al*., 2016). Similar information is also available for the major human P450s involved in pyrethroid metabolism (CYP2C8, CYP2C19, and CYP3A4). CYP2C19 levels are approximately 80% of adult values from >5 months to 10 years, CYP3A4 reaches near adult levels by 1-2 years, and CYP2C8 levels are comparable to adult levels after 6 months of age (Koukouritaki *et al*., 2004; Stevens *et al*., 2003; Song *et al*., 2015). As a consequence, higher internal doses (i.e., those associated with high doses in experimental toxicology studies) overwhelm the clearance mechanisms in juveniles; however, as adults have greater enzyme activity, they are able to tolerate higher doses prior to the onset of toxicity. As a matter of perspective, the anticipated exposures from typical dietary or residential activities are not expected to overwhelm the premature metabolic systems in juveniles.

To better understand the role of PK and reduce uncertainty associated with extrapolating across species (i.e., rat to human) and life stages, the Agency developed PBPK models designed to predict pyrethroid concentration in tissues following *in vivo* exposure. The Agency has determined that the important PK properties relevant to the metabolism and distribution of pyrethroids in the body are sufficiently similar for members of this class such that using a 'generic' or family model structure for this class is scientifically appropriate. In other words, because of the similarities in the PK profiles of pyrethroids, a single model structure is able to predict the tissue dose based on the PK of every member of the class. The family modeling approach was primarily developed based on PBPK modeling performed with deltamethrin and was presented to, and supported by, the Federal Insecticide, Fungicide, and Rodenticide Scientific Advisory Panel (FIFRA SAP), (USEPA 2007).

The initial deltamethrin PBPK model presented to the SAP was developed in the adult male Sprague Dawley (SD) rat (Mirfazaelian *et al*. 2006). The deltamethrin PBPK model was further refined based on oral bioavailability and disposition studies in rats and included estimates for target tissue concentrations in humans (Godin *et al*. 2010). The initial PBPK model was also extended by accounting for age-dependent changes in physiological and biochemical parameters (Tornero-Velez *et al*. 2010) to address juvenile sensitivity in rats. This model predicts that, compared to adult rats (i.e., 90-days old), equivalent brain concentrations of deltamethrin would be achieved with a 3.8x fold lower oral dose in 10-day old rats and 2.5x lower dose in 21-day old rats. For example, the internal dose from an administered dose of 1 mg/kg in the adult is equivalent to the internal dose from an administered dose of 0.26 mg/kg (≈1 mg/kg÷3.8mg/kg) in the 10-day old rat and to an administered dose of 0.4 mg/kg (≈1 mg/kg÷2.5mg/kg) in the 21-day old rat. As a result, the Agency concludes that juvenile rats are three times as sensitive as adult rats with respect to pyrethroid PK. At this time, the Agency considers that the differences in the PK profile observed in the rat are relevant to humans. Therefore, the PK contribution to the FQPA Safety Factor is 3X for children less than 6 years old, and it is 1x for children 6 years of age or older and for adults. Further information regarding the decision to retain the FQPA Safety Factor and the choice of age groups it applies to can be found in HED's memorandum, Re-Evaluation of the FQPA Safety Factor of Pyrethroid Pesticides (D381210, E. Scollon, 6/27/2011).

Currently, the CAPHRA is collecting metabolism and tissue dosimetry data from rats and human tissues across different life stages. These data will be used to inform the development of PBPK models for the pyrethroids. The CAPHRA presented its most recent experimental data and proposed path forward to the SAP on May19th 2015 (USEPA 2015). Based on the comments from the SAP, the CAPHRA continued to pursue its research efforts and submitted additional data to the Agency. However, EPA was not able to use the data available from the CAPHRA for deriving PODs or for species extrapolation. The CAPHRA data continue to be reviewed by the Agency, but have not been included in the current draft risk assessment. The Agency anticipates further data submissions as part of the upcoming October 2017 SAP on the CAHPRA work.

### 4.3.2 Pharmacodynamics (PD)

PD can be defined as the changes that chemicals cause to the body, in this case, how pyrethroids interact with the sodium channels. Substantial evidence from *in vitro* and *in vivo* studies support the AOP illustrated in Figure 4.0 and the disruption of sodium channels by pyrethroids as an early key event (Lund and Narahashi 1982; Salgado *et al*. 1989; Song and Narahashi 1996; Tabarean and Narahashi 1998; Soderlund *et al*. 2002). There are several studies that provide specific information for beta-cyfluthrin. Choi and Soderlund (2006) examined interactions of several pyrethroids, including beta-cyfluthrin, with mammalian VGSCs expressed in *Xenopus* oocytes (i.e., frog oocytes). With respect to altered neuronal excitability, Type I pyrethroids cause slight prolongations of the sodium current tails (e.g. ~20 ms), often resulting in long trains of action potentials. In contrast, Type II pyrethroids significantly prolong sodium current tails (e.g. 200 ms to minutes) typically resulting in increased resting membrane potential and ultimately causing depolarization dependent action potential block. Beta-cyfluthrin produced modifications of sodium channel kinetics characteristic of Type II compounds (Figure 4.3.2). Specifically, beta-cyfluthrin caused slow activation and inactivation, like Type II compounds. Cao *et al*. (2011a) measured sodium influx in primary cultures of mammalian (mouse) neurons and demonstrated that beta-cyfluthrin caused increases in sodium influx in this model; this confirms the ability of beta-cyfluthrin to interact with VGSC in intact mammalian neurons. An additional study by Cao *et al*. (2011b) demonstrated that the interaction of beta-cyfluthrin with VGSC caused changes in neuronal excitability that resulted in calcium influx into intact mouse neurons. As this effect of beta-cyfluthrin was entirely blocked by the VGSC blocker tetrodotoxin, it provides evidence that the changes in sodium channel function lead to changes in neuronal excitability, as illustrated in Figure 4.3.2.

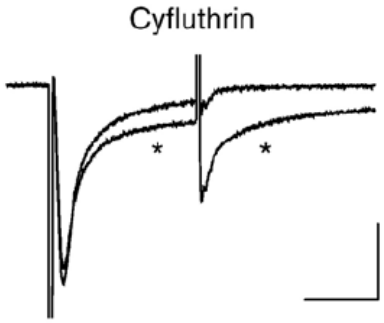



Figure 4.3.2 Resting modification of rat Nav1.8 sodium channels by beta-cyfluthrin expressed in *Xenopus* oocytes. Channel current vs time traces from individual representative oocytes in the absence or presence (*) of 100 µM beta-cyfluthrin were obtained during and after 40-ms depolarizations from 100 mV to 10 mV. Calibration bars: 20 ms for the x-axis and 500 nAmp on the y-axis. Figure 4.3.2 was extracted from Figure 3 in Choi and Soderlund (2006).

HED would prefer to use an early key event in the AOP for pyrethroids in selection of points of departure, such as sodium channel modification. However, *in vivo* techniques used to detect VGSC alteration and altered neuronal excitability are not practical for use in risk assessment at this time, and approaches for extrapolating *in vitro* findings to *in vivo* measures are not yet developed. As such, the Agency is focusing its efforts for all pyrethroids in hazard characterization and identification on the apical endpoint (i.e., changes in neurobehavior in laboratory animals). Neurotoxicity resulting from pyrethroids is generally characterized by tremors, hyper- or hypothermia, heightened response to stimuli, salivation, reduced locomotor activity, or convulsions (Soderlund *et al*. 2002; Wolansky and Harrill 2008; Weiner *et al*. 2009). In addition, results from a study by Wolansky *et al*. (2006) indicated that motor activity is a sensitive and robust measure of neurotoxicity for this class of compounds. The changes in motor activity observed were not specific to either of the syndromes described for pyrethroids and were observed with both Type I and Type II pyrethroids.

In contrast to the age-related PK differences identified in the 2011 analysis, PD contributions to pyrethroid toxicity are not age-dependent, even though there are several variations of sodium channels, called isoforms that are differentially expressed by tissue and age. Because of the nature of the interaction of pyrethroids with sodium channels, it is difficult to obtain dynamic information *in vivo.* To date, a readily useable biomarker of *in vivo* pyrethroid interaction with sodium channels has not been identified, making it impractical to determine the isoform combinations that are present and being acted upon by pyrethroids. Therefore, much of the information available to the Agency to characterize the PD relationship between pyrethroids and sodium channels has been derived from *in vitro* studies using frog oocytes or neuronal cells cultured in defined media. These *in vitro* techniques do not provide a direct quantitative measure of *in vivo* pyrethroid activity. However, these techniques consistently and qualitatively demonstrate that sodium channel isoforms expressed in juveniles are not more sensitive to pyrethroid perturbation compared to isoforms expressed in adults and that, pharmacodynamically, the rat is a conservative model for humans. For example, Meacham *et al*. (2008), expressed adult and juvenile isoforms of rat sodium channels in frog oocytes and compared their

sensitivity following exposure to deltamethrin. The isoforms had comparable responses at environmentally relevant concentrations (<500 nM) of deltamethrin, suggesting a lack of PD difference between juveniles and adults at low exposure levels. In addition, in a direct comparison of a homologous rat and human VGSC isoform, $NaV_{1.3}$, the rat isoform was 4-fold more sensitive than the equivalent human sodium channel to the pyrethroid tefluthrin (Tan and Soderlund 2009). This observation suggests that the rat is a highly sensitive model, and extrapolations from the rat would be protective of human health. The occurrence and ontogeny of VGSCs in humans are not as well characterized as those of the rat. However, based on the comparable function and distribution of sodium channels between the species, the rat is an appropriate surrogate for the evaluation of human PD (Goldin *et al*. 2000; Goldin 2002). As a result, the Agency concludes that juvenile rats are not more sensitive than adults with respect to pyrethroid PD based on sodium channel data. Therefore, the PD contribution to the FQPA Safety Factor is 1X.

### 4.3.3 Critical Duration of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, cyfluthrin and beta-cyfluthrin are absorbed quickly in rats. Effects such as tremors and ataxia were observed within 10 and 60 minutes following dosing in the $LD_{50}$ acute rat oral studies, and within 1 and 3 hours in a range finding study for the guideline rat acute neurotoxicity study and also in a non-guideline rat acute neurotoxicity study. Differences in time of onset for these gavage studies are probably due to differences in vehicle, since vehicle also seems to affect the dose of acute lethality ($LD_{50}$). Rats typically recover within 12 days in the acute oral studies; however, similar information is not available for other studies. These observations are consistent with the toxicity profiles for other pyrethroids that are marked by rapid absorption, metabolism, and elimination, with a time to peak effect for neurobehavioral effects ranging from 4 to 8 hours. The time to peak effect is approximately 2 hours for beta-cyfluthrin (Wolansky *et al* 2006; Weiner *et al*. 2009).

The combination of rapid absorption, metabolism, and elimination precludes accumulation and increased potency following repeated dosing. Therefore, for most pyrethroids including cyfluthrin and beta-cyfluthrin, the acute toxicity studies typically result in neurotoxicity at lower doses than in the repeat-dose studies. In the case of cyfluthrin and beta-cyfluthrin, the NOAELs and LOAELs for the most common clinical signs – gait abnormalities – observed in oral toxicity studies are remarkably consistent across durations of exposure, ranging from a single dose up to 6 months of dosing (Table 4.3.3). Motor activity changes in rats (as measured in the Wolansky study) serve as the most sensitive effect (Table 4.3.3). Most guideline rat studies did not measure motor activity, with the exception of the acute neurotoxicity guideline study, which has a NOAEL consistent with the BMDL calculated from the Wolansky study and, therefore, confirms those results.

For pyrethroids in general, rat dietary studies tend to have higher NOAELs/LOAELs than gavage studies because rats feed continuously. The pyrethroids are metabolized and excreted from the system relatively quickly, resulting in the overall systemic concentration in the rat remaining low. In contrast, bolus/gavage dosing results in greater maximal plasma concentrations immediately after dosing. The results from cyfluthrin and beta-cyfluthrin studies are similar in

this respect, with dietary studies generally resulting in higher LOAELs than gavage studies. Comparing the POD established from the Wolansky acute study and the repeat-dosing studies, it is apparent that repeat exposures result in either higher or very similar PODs (Table 4.3.3). This observation is consistent with the general kinetic profile for pyrethroids. Therefore, the endpoint from the Wolansky acute study with beta-cyfluthrin is protective of the endpoints from the repeat oral dosing studies and, for the purposes of endpoint selection and exposure assessment, only single-day oral risk assessments need to be conducted.

**Table 4.3.3. Cyfluthrin and Beta-Cyfluthrin NOAEL and LOAEL Values versus Treatment Time in Adult Rats and Dogs** (studies with cyfluthrin are marked §; studies with beta-cyfluthrin are not marked)

| Study | Exposure Duration | Study findings | | |
|---|---|---|---|---|
| | | Main Endpoint | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) |
| Oral Studies – Rat | | | | |
| Wolansky (gavage) | Acute | Motor activity | 1.17 (BMDL[A]) | 1.42 (BMD[A]) |
| WIL (gavage) | Acute | Abnormal gait | NA | 12.5 |
| Acute neurotoxicity (gavage) | Acute | Abnormal gait | 2 | 10 |
| Developmental (gavage) | 10 days | Incoordination, mortality | 3 | 40 |
| 28-Day (dietary) § | 28 days | Abnormal gait | 15 | 50 |
| DNT (dietary) | 42 days | NA | 18 | NA |
| Subchronic (dietary) | 90 days | Abnormal gait | 9.5 | 39 |
| Subchronic (dietary) § | 90 days | NA | 28 | NA |
| Subchronic neurotoxicity (dietary) | 90 days | Abnormal gait | 8.0 | 27 |
| Reproductive (dietary) § | 120 days | Abnormal gait lactating dams only | 7 | 19 |
| Chronic/cancer (dietary) § | 2 years | Decreased body weight (↓BW) | 12 | 23 |
| Oral Studies – Dog | | | | |
| 28-Day (dietary) | 28 days | Abnormal gait | 2.0 | 8.0 |
| Subchronic (dietary) | 90 days | Abnormal gait | 2.4 | 14 |
| 6-Month (dietary) § | 182 days | Abnormal gait | 5.0 | 15 |
| Chronic (dietary) § | 1 year | Abnormal gait | 2.4 | 11 |
| Inhalation Studies – Rat (NOAEL/LOAELs are animal equivalent doses) | | | | |
| 5-Day | 5 days | Unkempt fur, piloerection | 0.07 | 1.0 |
| Developmental § | 10 days | ↓Fetal BW; ↑ incidence of runts and skeletal alterations | 0.16 | 0.29 |
| 28-Day § | 28 days | Male ↓BW and ↓RR; | 0.12 | 1.6 |
| 28-Day | 28 days | Male ↓BW and ↓RR | 0.07 | 0.71 |
| Subchronic § | 86 days | clinical signs; male ↓BW | 0.19 | 1.2 |

[A] BMD is the central estimate of the dose that results in decreased motor activity compared to control animals based upon a 1 standard deviation using Benchmark Dose Analysis. BMDL is the 95% lower confidence limit of the central estimate. Data extrapolated from Wolansky (2006), MRID 47885701.

## 4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[1]

There is evidence of offspring susceptibility for cyfluthrin and beta-cyfluthrin as explained in subsection 4.4.3 below. The toxicological database for cyfluthrin and beta-cyfluthrin is extensive and sufficient to access susceptibility for infants and children. In addition, this assessment relies on peer-reviewed literature on pyrethroids in general, which is also extensive.

After reviewing the extensive body of peer-reviewed literature on pyrethroids, the Agency has no residual uncertainties regarding age-related sensitivity for women of child bearing age as well as for all adult populations and children ≥6 years of age, based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids and the scientific literature. Additionally, no evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to PD. The Agency is retaining a 3X FQPA Safety Factor to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PKs and the increased quantitative juvenile susceptibility observed in high dose studies in the literature. The dietary and residential assessments are based on reliable data and will not underestimate exposure.

### 4.4.1 Completeness of the Toxicology Database

The toxicology database for cyfluthrin and beta-cyfluthrin is extensive and includes the following guideline studies: developmental toxicity studies in rats and rabbits; a reproduction study in rats; ACN, SCN, DNT studies; a dermal study; and several inhalation studies (including a developmental study in rats via the inhalation route); as well as studies from peer-reviewed literature. As noted previously, additional research efforts are underway to address juvenile sensitivity for the pyrethroids including the cyfluthrins.

### 4.4.2 Evidence of Neurotoxicity

There are no residual uncertainties with regard to evidence of neurotoxicity for cyfluthrin and beta-cyfluthrin. As with other pyrethroids, cyfluthrin and beta-cyfluthrin cause neurotoxicity from interaction with sodium channels leading to clinical signs of neurotoxicity. These effects are well characterized and adequately assessed by the available guideline and non-guideline studies.

### 4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence of pre-natal susceptibility in the oral developmental studies in the rabbit or rat. There is evidence of quantitative susceptibility for the rat, in a developmental study via the inhalation route, in reproductive studies via the oral route, and a developmental neurotoxicity study via the oral route. Skeletal variations were observed in rat fetuses after exposure by the inhalation route at doses below those that showed maternal effects (reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation) in the same studies. Tremors and/or decreased weight in pups were observed in rat reproductive studies and the developmental neurotoxicity

[1] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

study at doses below those that caused maternal effects (hind leg splay, ataxia). Mouse pups showed clinical signs (decreased motility, poor general condition, tonic seizures, scratching) and adult female offspring showed increased spontaneous activity in a postnatal inhalation study, in the absence of maternal effects.

High-dose oral studies in the scientific literature indicate that younger animals are more susceptible to the toxicity of pyrethroids. For example, Sheets *et al*. (1994) found increased brain deltamethrin levels in young rats (PND 11 and 21) relative to adult rats (PND 72). These age-related differences in toxicity are principally due to age-dependent PK. The activity of enzymes associated with the metabolism of pyrethroids increases with age (Anand *et al*., 2006). However, in context, normal dietary or residential exposures of juveniles are not expected to overwhelm their ability to metabolize pyrethroids. In support, at a dose of 4.0 mg/kg deltamethrin (near the Wolansky study LOAEL value of 3.0 mg/kg for deltamethrin), the change in the acoustic startle response was similar between adult and young rats (Sheets *et al*, 1994). In addition, EPA's Office of Research and Development (ORD) recently developed an age-dependent PBPK model for deltamethrin (Tornero-Velez *et al*, 2010) that predicts a 3–fold increase of pyrethroid in neuronal tissue in younger animals compared to adults. There are several studies (*in vitro* and *in vivo*) that indicate that PD contributions to pyrethroid toxicity are not age-dependent. Examination of specific VGSCs has demonstrated that there is a lack of increased sensitivity in either juvenile specific isoforms (Meacham *et al*., 2008) or in human isoforms compared to rat variants (Tan and Soderlund, 2009).

After reviewing the extensive body of peer-reviewed literature on pyrethroids, the Agency has no residual uncertainties regarding age-related sensitivity for women of child bearing age as well as for all adult populations and children ≥6 years of age, based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids and the scientific literature. Additionally, no evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to PD. The Agency is retaining a 3X FQPA Safety Factor to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PK and the increased quantitative juvenile susceptibility observed in high dose studies in the literature. Further information regarding the decision to retain the FQPA Safety Factor and the choice of age groups it applies to can be found in Section 4.3.1.

### 4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to dietary exposure. The dietary exposure assessments are based on a combination of robust monitoring data and field trial residue levels that account for parent and metabolites of concern, processing factors, and percent crop treated assumptions. Furthermore, conservative, upper-bound assumptions were used to determine exposure through drinking water and residential sources, such that these exposures have not been underestimated.

## 4.5 Toxicity Endpoint and Point of Departure Selections

### 4.5.1 Dose-Response Assessment

Based on the existing use patterns for cyfluthrin and beta-cyfluthrin, the expected exposure profile will be for acute dietary, short-term incidental oral, dermal, and inhalation exposures. Based on the toxicity profile, HED did not conduct intermediate- and long-term inhalation exposure assessments for adults or children. A chronic dietary exposure assessment was conducted but not a chronic dietary risk assessment (i.e., the % cPAD is not calculated) because there is no apparent increase in hazard from repeated/chronic exposures to the cyfluthrins. Therefore, the acute endpoint is protective of the endpoints from repeat dosing studies.

As previously indicated, the oral toxicity endpoints in the cyfluthrin and beta-cyfluthrin database are consistently based on clinical signs of neurotoxicity and, more specifically, abnormal gait and decreased motor activity. These studies include multiple species, study designs, and durations (Table 4.3.3). Moreover, the acute exposure or bolus dosing studies generally result in lower NOAELs compared to longer term dietary administration studies, consistent with other pyrethroids in this class. Because uncertainty associated with the POD is propagated throughout the risk assessment, one of the key factors in POD selection is the robustness of the dose-response data. The guideline experimental toxicology studies available for cyfluthrin and beta-cyfluthrin are generally high quality and were considered in the POD selection process and in the weight of the evidence evaluation. In addition to the typical guideline studies, data from two special studies evaluating neurobehavioral outcomes are available for cyfluthrin and beta-cyfluthrin (Wolansky study on motor activity, Wolansky *et al*. 2006; and the WIL functional observational battery study, Weiner *et al*. 2009). Wolansky *et al*. measured motor activity at the time of peak effect after oral exposure to 11 pyrethroids, including beta-cyfluthrin, although other neurobehavioral parameters, such as abnormal gait, were not assessed. Dose-response relationships were determined using 6-11 doses per pyrethroid (8 doses used for beta-cyfluthrin) and 3-18 rats per dose group (4-12 animals/group used for beta-cyfluthrin), minimizing variability and increasing the confidence in the benchmark dose (BMD) estimates determined from this study. Moreover, each pyrethroid was evaluated by the same scientist, thus decreasing some of the variability associated with neurobehavioral measures. In the WIL study, 17 pyrethroids, including beta-cyfluthrin, were evaluated using a specially designed FOB study focused on the outcomes associated with pyrethroid toxicity syndromes at the time to peak effect. The beta-cyfluthrin data from the WIL study were not considered as part of endpoint and dose selection because all dose groups showed adverse effects, resulting in low confidence in the calculated BMDL (MRID 48714301).

Abnormal gait (in general, as well as high-stepping gait and hind limb splay) was the most common indication of neurotoxicity in oral studies; however, salivation, nervousness, ear lesions, lethargy, piloerection were also observed in adult rats, and tremors were observed in dogs and young rats. Neurotoxic effects were the primary and most sensitive effects seen in the toxicity database. Given the multiple strengths associated with the study design of the Wolansky, *et al*. (2006) study and the resulting well-defined dose-response curve, the Wolansky, *et al*. (2006) study provides the most robust data set for extrapolating risk from cyfluthrin and beta-cyfluthrin. Although the guideline studies typically have only three treatment groups, often do not evaluate clinical signs at the time of peak effect, and have variable scoring metrics for

abnormal gait, the NOAELs/LOAELs are consistent with, and support, the findings of the Wolansky *et al*. (2006) study.

The Agency conducted a BMD analysis for all the pyrethroids included in the Wolansky study (MRID 48714301). Overall, because of the large number of doses and high quality measurements, the BMD analysis yielded high confidence results. In performing BMD analysis, a benchmark response (BMR) must be selected. As a general approach, it is preferable to use a combination of biological and statistical factors in the BMR selection. In the case of motor activity data, the scientific community has not established a specific level of change that would be considered to be adverse. Therefore, OPP has elected to use one standard deviation (1SD) from the control group, as suggested for continuous endpoints in the Agency's BMD guidance (USEPA 2012) as the BMR. OPP has estimated both the $BMD_{1SD}$ and the $BMDL_{1SD}$ (where the $BMDL_{1SD}$ is the lower 95% confidence limit of the $BMD_{1SD}$). The $BMD_{1SD}$ and the $BMDL_{1SD}$ for cyfluthrin and beta-cyfluthrin are 1.42 mg/kg and 1.17 mg/kg, respectively. As a matter of science policy, EPA uses the BMDL, not the BMD, for deriving PODs. Therefore, the $BMDL_{1SD}$ of 1.17 mg/kg is being used as the dose for acute dietary risk assessment.

Acute Dietary (All Age Groups): Quantitation of acute dietary risk was performed using the acute oral Wolansky study, with a $BMDL_{1SD}$ value of 1.17 mg/kg and a BMD value of 1.42 mg/kg based on decreased locomotor activity. As there is no apparent increase in hazard from repeated/chronic exposures to cyfluthrin and beta-cyfluthrin, the acute dietary exposure and risk assessment is protective of chronic risk.

Short-term Incidental Oral: The oral $BMDL_{1SD}$ of 1.17 mg/kg and decreased locomotor activity from the Wolansky acute rat study is being used for the short-term incidental oral dose and endpoint because of the overall robust nature of the study, and because it is protective of all oral effects observed in the toxicology database. This endpoint is protective of offspring susceptibility observed in the reproductive and developmental neurotoxicity studies via the oral route.

Short-term Dermal: Acute dermal toxicity studies in the rat are available for cyfluthrin and beta-cyfluthrin, and a rat subchronic (21-day) dermal toxicity study is available for cyfluthrin. In these studies, no treatment-related effects were observed at doses up to the limit dose. Systemic effects were observed in the rat subchronic dermal study only above the limit dose, and they might not be indicative of neurotoxicity (urine stain, nasal discharge). In lethality ($LD_{50}$) studies, effects including apathy, ataxia, self-inflicted wounds, lethargy, gait abnormalities, salivation, and vocalization were observed at doses ≥ 100 mg/kg. However, in dermal $LD_{50}$ studies, rats were exposed to a single dose continuously for 24 hours without washing. Based on the use pattern, repeat dermal exposure is anticipated for 8-10 hours; therefore, the acute $LD_{50}$ study overestimates potential dermal exposure, and the subchronic dermal study is more indicative of anticipated exposure. Nonetheless, the database indicates offspring susceptibility; therefore, the subchronic dermal study does not provide an appropriate endpoint to assess dermal risk to the young. In the absence of an appropriate dermal study, the oral $BMDL_{1SD}$ of 1.17 mg/kg from the Wolansky acute rat study is being used together with a dermal absorption factor (DAF) to assess risks from dermal exposure to the cyfluthrins. Limited dermal absorption of cyfluthrin or beta-cyfluthrin is expected. The DAF for cyfluthrin and beta-cyfluthrin was calculated to be 0.56% based on the results of *in vitro* and *in vivo* dermal penetration studies. The limited dermal

absorption, along with the rapid metabolism/excretion, is anticipated to result in low plasma concentrations and low toxicity via the dermal route. This is consistent with the low toxicity observed in the 21-day dermal toxicity study and with the acute study findings at doses ≥ 100 mg/kg.

Based on the weight of the evidence, HED concluded that using the oral POD from the Wolansky study together with the estimated DAF would be protective of effects observed in both adults and in offspring.

Short-term Inhalation: Several route-specific inhalation studies are available for cyfluthrin and beta-cyfluthrin. The POD for inhalation is derived from the inhalation developmental toxicity study in rats conducted with cyfluthrin (there is no developmental inhalation study for beta-cyfluthrin). The NOAEL is 0.00059 mg/L based on decreased fetal weight and increased incidence of runts and skeletal alterations observed at 0.0011 mg/L. This NOAEL is also protective of clinical signs (piloerection, eye irritation, dyspnea, decreased activity) observed in rodents at higher concentrations in the other inhalation studies for cyfluthrin and beta-cyfluthin. Based on current EPA guidance[2], Human Equivalent Doses (HEDs) were calculated for the systemic/developmental effects, and the resulting HEDs for different exposure scenarios are listed in Appendix A.3. The HEDs calculated for the cyfluthrins range from 0.032 to 0.134 mg/kg/day (Human Equivalent Concentration, HEC, of 0.0003-0.002 mg/L). These HEDs/HECs represent the most sensitive, route-specific endpoints in the cyfluthrins database for the corresponding population and exposure duration of concern in each scenario. The standard interspecies extrapolation uncertainty factor ($UF_A$) can be reduced from 10X to 3X because the calculation of human equivalent concentrations accounts for pharmacokinetic differences between humans and the experimental species used in the selected study (rat). As a result, the LOC for all inhalation exposure scenarios is 30.

Uncertainty Factors/Levels of Concern (LOCs) for Risk Assessment

For acute dietary risk assessment, a combined uncertainty factor of 100X was applied for adults and children ≥6 years old, based on the 10X factors to account for interspecies extrapolation and intraspecies variability. For acute dietary exposure in children <6 years old, a combined uncertainty factor of 300X was applied (10X interspecies, 10X intraspecies, and 3X FQPA Safety Factor). The 3X FQPA factor was retained for all applicable exposure scenarios to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PK and the increased quantitative juvenile susceptibility observed in high dose studies.

For assessing incidental oral exposure resulting from contact with treated surfaces in residential settings or from spray drift, an additional 3X FQPA Safety Factor is retained for children less than 6 years old, along with the traditional 10X factors for intraspecies variability and interspecies extrapolation, resulting in an LOC of 300.

The LOC for dermal risks is 100 for adults and children >6 years old, based on the 10X factors for intraspecies variability and interspecies extrapolation. For children <6 years of age, an

[2] Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, 1994.

additional 3X FQPA factor has been retained to account for potential juvenile susceptibility, resulting in an LOC of 300.

The LOC for inhalation risk for adults and children >6 years old is 30 based on the 10X factor for intraspecies variability and a 3X factor for interspecies extrapolation (since the HEC calculation already incorporates PK differences between species). For children <6 years old, the LOC is 100 (an interspecies factor of 3X, intraspecies variability factor of 10X, and FQPA SF of 3X).

### 4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major routes: oral, dermal, and inhalation, and determine whether the individual exposures can be combined if they have the same toxicological effects. For the cyfluthrins, adult dietary and dermal exposures can be combined. For children, dietary, incidental oral (hand-to-mouth), and dermal exposures can be combined. However, inhalation exposures cannot be combined with other routes because the observed effects are different (i.e., developmental and decreased bodyweights).

### 4.5.3 Cancer Classification and Risk Assessment Recommendation

There was no evidence of carcinogenicity in either the rat or mouse long-term dietary studies, nor was there any mutagenic activity in bacteria or cultured mammalian cells. Cyfluthrin and beta-cyfluthrin are classified as "not likely to be carcinogenic to humans" in accordance with the EPA Final Guidance for Carcinogen Risk Assessment (3/29/2005).

### 4.5.4 Summary of Points of Departure and Toxicity Endpoints

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Cyfluthrin and β-Cyfluthrin for Use in Dietary and Non-Occupational Human Health Risk Assessments

| Exposure/ Scenario | Point of Departure | Uncertainty /FQPA Safety Factors | RfD, PAD, Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Acute Dietary (Adults and Children > 6 yrs old, including Females 13-49 yrs old) | $BMDL_{1SD}$ = 1.17 mg/kg | $UF_A$= 10x $UF_H$=10x FQPA SF= 1x | Acute RfD = aPAD = 0.0117 mg/kg/day | Wolansky *et. al.* (MRID 47885701) $BMD_{1SD}$ = 1.42 mg/kg based on decreased motor activity |
| Acute Dietary (Children < 6 yrs old) | | $UF_A$= 10x $UF_H$=10x FQPA SF= 3x | Acute RfD = 0.0117 mg/kg aPAD = 0.0039 mg/kg/day | |
| Chronic Dietary (All Populations) | There is no apparent increase in hazard from repeated/chronic exposures to the cyfluthrins. | | | |

| Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Cyfluthrin and β-Cyfluthrin for Use in Dietary and Non-Occupational Human Health Risk Assessments | | | | |
|---|---|---|---|---|
| Exposure/ Scenario | Point of Departure | Uncertainty /FQPA Safety Factors | RfD, PAD, Level of Concern for Risk Assessment | Study and Toxicological Effects |
| Incidental Oral Short-Term (1-30 days) (Adults and Children > 6 yrs old) | $BMDL_{1SD}$ = 1.17 mg/kg | $UF_A$= 10x $UF_H$=10x FQPA SF= 1x | Residential LOC for MOE = 100 | Wolansky *et. al.* (MRID 47885701) $BMD_{1SD}$ = 1.42 mg/kg based on decreased motor activity |
| Incidental Oral Short-Term (1-30 days) (Children < 6 yrs old) | | $UF_A$= 10x $UF_H$=10x FQPA SF= 3x | Residential LOC for MOE = 300 | |
| Dermal Short-Term (1-30 days) (Adults and Children > 6 yrs old, including Females 13-49 yrs old) | $BMDL_{1SD}$ = 1.17 mg/kg DAF = 0.56% | $UF_A$= 10x $UF_H$=10x FQPA SF= 1x | Residential LOC for MOE = 100 | Wolansky *et. al.* (MRID 47885701) $BMD_{1SD}$ = 1.42 mg/kg based on decreased motor activity |
| Dermal Short-Term (1-30 days) (Children < 6 yrs old) | | $UF_A$= 10x $UF_H$=10x FQPA SF= 3x | Residential LOC for MOE = 300 | |
| Inhalation Short-Term (1-30 days) (Adults and Children > 6 yrs old, including Females 13-49 yrs old) | NOAEL = 0.00059 mg/L $HED_{handler}$ = 0.045 mg/kg $HED_{outdoor\ post\text{-}app.}$ = 0.051 mg/kg $HED_{indoor\ post\text{-}app.}$ = 0.032 mg/kg | $UF_A$= 3x $UF_H$=10x FQPA SF= 1x | Residential LOC for MOE = 30 | Developmental inhalation study in rats MRID (40780401) LOAEL = 0.0011 mg/L based on decreased fetal weight and increased incidence of runts and skeletal alterations. Note - the NOAEL is protective of clinical signs observed at higher dose in other inhalation studies, and has therefore been used to assess inhalation exposure for infants and children < 6 years old. |
| Inhalation Short-Term (1-30 days) (Infants and Children < 6 yrs old) | | $UF_A$= 3x $UF_H$=10x FQPA SF= 3x | Residential LOC for MOE = 100 | |
| Cancer (oral, dermal, inhalation) | Classification: "not likely to be carcinogenic to humans" in accordance with the EPA Final Guidance for Carcinogen Risk Assessment (3/29/05) | | | |

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. $BMD_{1SD}$ is the central estimate of the dose that results in decreased motor activity compared to control animals based upon a 1 standard deviation using Benchmark Dose Analysis; $BMD_L$ is the 95% lower confidence limit of the central estimate. Data extrapolated from Wolansky (2006), MRID 47885701. 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 (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. HED = Human Equivalent Dose

| Table 4.5.4.2 Summary of Toxicological Doses and Endpoints for Cyfluthrin and β-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) | $BMDL_{1SD}$ = 1.17 mg/kg DAF = 0.56% | $UF_A$=10x $UF_H$=10x | Occupational LOC for MOE = 100 | Wolansky *et. al*. (MRID 47885701) $BMD_{1SD}$ = 1.42 mg/kg based on decreased motor activity |
| Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months) | NOAEL = 0.00059 mg/L $HED_{handler}$ = 0.134 mg/kg | $UF_A$=3x $UF_H$=10x | Occupational LOC for MOE = 30 | Developmental inhalation study in rats (MRID 40780401) LOAEL = 0.0011 mg/L based on decreased fetal weight and increased incidence of runts and skeletal alterations. |
| Cancer (oral, dermal, inhalation) | Classification: "not likely to be carcinogenic to humans" in accordance with the EPA Final Guidance for Carcinogen Risk Assessment (3/29/05) | | | |

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. $BMD_{1SD}$ is the central estimate of the dose that results in decreased motor activity compared to control animals based upon a 1 standard deviation using Benchmark Dose Analysis; $BMD_L$ is the 95% lower confidence limit of the central estimate. Data extrapolated from Wolansky (2006), MRID 47885701. 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). HED = Human Equivalent Dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

## 4.6 Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental, and reproductive effects in different taxonomic groups. As part of its registration review decision for cyfluthrin and beta-cyfluthrin, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), cyfluthrin and beta-cyfluthrin are subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the 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, 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.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[3] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Cyfluthrin is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2010-0684 for cyfluthrin). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines, and the Tier 1 screening battery, please visit our website[4].

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Animal Metabolism Studies

HED has concluded that the nature of cyfluthrin/beta-cyfluthrin in plants is adequately understood based on plant metabolism studies conducted in cotton, soybeans, potatoes, apples, wheat, and tomatoes. Data from those studies indicate that the nature of the residue is similar in all plant matrices. The major detected residue is the parent cyfluthrin, which comprised between 38% – 98% of the total radioactive residues (TRR) in these studies. In plants, cyfluthrin was seen to metabolize slowly with little translocation. Other metabolites detected generally comprised <10% of the TRR. HED, therefore, has determined that the residue of concern in plants for both tolerance enforcement and risk assessment is parent cyfluthrin. The nature of cyfluthrin residues in plants is summarized in the HED memorandum *Registration for Use on Grasses, Alfalfa, and Seed Treatment Use on Sugar Beets,* (D. Dotson; D339413; 10/15/2007).

[3] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals

[4] http://www.epa.gov/endo/ https://www.epa.gov/endocrine-disruption

The nature of cyfluthrin/beta-cyfluthrin is adequately understood in livestock based upon metabolism data in cattle and poultry. In lactating cows, the parent comprised 56-100% of the TRR in tissues and milk. In poultry, the parent comprised 28-56% of the TRR in muscle, fat, skin, and eggs, (in poultry liver and kidney, the parent comprised 9-12% of the TRR). The various metabolites comprised 0-43% of the TRR in cow tissues and milk and 0-19% of the TRR in poultry tissues and eggs. None of the individual metabolites were present to a significant enough level to be included as residues of concern for either tolerance enforcement or risk assessment. The residue of concern in livestock commodities is cyfluthrin/beta-cyfluthrin.

### 5.1.2 Summary of Environmental Degradation

Cyfluthrin is moderately persistent in the environment and immobile. Data suggest that the primary routes of dissipation include hydrolysis in alkaline media (at pHs of 5, 7 and 9, cyfluthrin is stable, moderately stable, and has a half life of 2.1 days, respectively); aqueous photolysis (half life = 0.7 - 4.5 days); and, soil photolysis (half life = 5.6 days). Data indicate that aerobic soil metabolism plays a secondary role in the dissipation of cyfluthrin (half life ranged from 74 to 95 days). Data show that cyfluthrin degrades slowly under normal conditions of aerobicity and organic matter, but degrades faster under anaerobic environments or in soils with higher organic matter. While moisture level does not appear to have a significant effect on cyfluthrin's rate of degradation, pH does. It degrades faster under higher pH conditions.

As with other pyrethroids, cyfluthrin is hydrophobic, binding strongly to soil surfaces. The moderate persistence of the chemical, its high soil affinity, and low solubility indicate (i) a low potential to leach to subsurfaces and to contaminate groundwater; and, (ii) that the chemical has a high potential to reach surface waters in runoff events accompanied by erosion occurring during periods of weeks to months after application. Once the chemical reaches surface waters, the potential impact to water quality appears to be mostly due to parent compound. Cyfluthrin residues could also reach surface waters via spray drift.

Once cyfluthrin reaches surface waters, the potential impact to water quality appears to be mostly due to parent cyfluthrin. Laboratory studies predict that once the chemical reaches surface waters, it may persist for moderate periods of time. Cyfluthrin's lipophilicity and affinity to particulate matter make it unavailable for photolysis. In addition, photolysis would be limited only to clear shallow waters or the upper layers of the water column.

### 5.1.3 Comparison of Metabolic Pathways

In plant metabolism studies, the major residue is parent cyfluthrin, which metabolizes slowly with little translocation. The nature of the residue in the various plants tested (cotton, soybeans, potatoes, and apples) is similar. Minor amounts of metabolites (i.e., <10% of the total radioactive residue) formed from hydrolysis of the ester linkage and hydroxylation of the aromatic ring system. In lactating cows and hens, parent compound was again the primary residue. In the rat metabolism study, excretion of radioactivity was rapid. Following oral administration, >95% of the administered radioactivity was excreted within 48 hours. Parent cyfluthrin was cleaved at the ester linkage and then oxidized to yield FPBacid (also identified in plants and livestock metabolism studies), which was then either hydroxylated and conjugated and excreted or first bound to glycine and then hydroxylated, conjugated, and excreted.

Cyfluthrin underwent the same metabolic processes in plants, livestock, and rats. As a result, the metabolites found in plants and livestock are accounted for in the rat metabolism study, and there are no plant or livestock metabolites that have not been accounted for in the toxicity testing for the cyfluthrins.

### 5.1.4 Residues of Concern Summary and Rationale

HED previously determined that the residue of concern in all matrices (plants, livestock, and drinking water) is parent cyfluthrin (MARC Decision Memorandum; 6/13/02; TXR 0050805). 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. The cyfluthrin risk assessment team continues to support the previous determination.

**Table 5.1.4. Summary of Metabolites and Degradates included in the Cyfluthrin/Beta-cyfluthrin Risk Assessment and Tolerance Expression**

| Matrix | Residues included in Risk Assessment | Residues included in Tolerance Expression |
|---|---|---|
| Primary Crop | Cyfluthrin | Cyfluthrin |
| Rotational Crop[1] | N/A | N/A |
| Ruminant | Cyfluthrin | Cyfluthrin |
| Poultry | Cyfluthrin | Cyfluthrin |
| Drinking Water | Cyfluthrin | Not Applicable |

[1] Residues of cyfluthrin show negligible uptake into rotational crops (D290921, Y. Donovan, 12/16/2004).

## 5.2 Food Residue Profile

Adequate residue data are available for the purpose of evaluating the registered uses of cyfluthrin that could potentially result in dietary exposure. These uses include agricultural uses on crops, the pour-on application to cattle, and the uses in food and feed handling establishments. The residue chemistry database consists of adequate plant metabolism, animal metabolism, field trial, storage stability, rotational crop, and analytical method studies. There are no outstanding residue chemistry studies.

## 5.3 Water Residue Profile

Modeled estimates of cyfluthrin residues in drinking water were provided by the Environmental Fate and Effects Division (D331952, J. Melendez, 9/6/2007) for a previous tolerance petition. Acute and chronic screening level EDWCs in surface water were generated using the FIRST Model, and groundwater EDWCs were generated using the SCI-GROW Model. Based on a 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 groundwater

drinking water exposure estimates (EDWCs), respectively. The EDWCs provided for the 2007 tolerance petition are summarized in Table 5.3.

**Table 5.3. Estimated Drinking Water Concentrations for Cyfluthrin/Beta-cyfluthrin**

| Duration | Application Rate | Surface Water Concentration (ppb) | Groundwater Concentration (ppb) |
|---|---|---|---|
| Acute | 0.35 lb ai/A/season(alfalfa) | 3.677 | 0.457 |
| Chronic (non-cancer) | 0.50 lb. ai/A/season (cotton) | 0.155 | 0.457 |

EFED determined that the maximum modeled value for the acute assessment exceeded the limit of solubility of cyfluthrin and informed HED that the solubility limit of 2ppb should be used for acute dietary exposure assessment. For the chronic assessment, HED used the groundwater value of 0.457 ppb because it exceeds the surface water value of 0.155 ppb and is protective of potential exposure to drinking water from both ground and surface water sources. EFED did not update the EDWCs for the cyfluthrins for this draft risk assessment.

The drinking water models EFED uses and their descriptions are available at the EPA internet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide.

## 5.4 Dietary Risk Assessment

Acute and chronic aggregate dietary (food and drinking water) exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). The chronic assessment was conducted solely for the purpose of obtaining estimates of background levels of dietary exposure for estimating aggregate risk. HED did not calculate chronic dietary risk estimates because the acute dietary risk estimates are protective for chronic dietary risk.

### 5.4.1 Description of Residue Data Used in Dietary Assessment

Acute Dietary Exposure Assessment

A refined acute probabilistic dietary exposure analysis was performed for cyfluthrin and beta-cyfluthrin. The analysis was based on PDP monitoring data for most commodities, tolerance level residues for some commodities, and crop field trial data for a limited number of commodities. For livestock commodities, either tolerance level residues or monitoring data were used. Residue levels for some commodities were modified with either DEEM default or empirical processing factors (including drying and concentration in oil, etc.). HED used the maximum percent crop treated estimates provided by the BEAD and, for drinking water, HED used the water solubility of 2 ppb for the EDWC.

Chronic Dietary Exposure Assessment

The chronic dietary exposure assessment was based on tolerance level residues for some commodities, crop field trial data, PDP monitoring data, anticipated residues in livestock commodities, and DEEM default and empirical processing factors. In addition, HED included average percent crop treated estimates from BEAD. Cyfluthrin has food handling establishment (FHE) uses. For these uses, HED used a residue value of 0.025 ppm (1/2 the tolerance) and a 4.65% probability that a food item is treated in an FHE. In cases where the total anticipated residue from the FHE use exceeded the total anticipated residue from the agricultural or stored grain use, the FHE anticipated residue was used. For drinking water, HED used the modeled EDWC of 0.457 ppb provided by EFED.

Cancer Assessment

Cancer risk is not of concern for cyfluthrin because the compound is classified as "not likely to be carcinogenic to humans." As a result, HED did not perform a cancer dietary exposure assessment.

### 5.4.2 Percent Crop Treated Used in Dietary Assessment

Maximum percent crop treated estimates (BEAD, 12/14/2015) were used in the acute dietary risk assessment for the following crops that are currently registered for cyfluthrin: alfalfa: 5%, almonds: 5%, apples: 15%, apricots: 10%, broccoli: 20%, Brussels sprouts: 10%, cabbage: 25%, cantaloupe: 2.5%, carrots: 25%, cauliflower: 15%, celery: 10%, cherries: 10%, corn: 10%, cotton: 10%, cucumber 10%, grapes: 10%, lemons: 10%, lettuce: 15%, nectarines: 10%, oranges: 15%, peas: 2.5%, peaches: 25%, peanuts: 10%, pears: 15%, pecans: 5%, peppers: 25%, pistachios: 25%, plums: 5%, potatoes: 30%, pumpkins: 15%, sorghum: 5%, soybeans: 5%, spinach: 10%, squash: 10%, sugar beets: 2.5%, sugarcane: 2.5%, sunflowers: 10%, tangerines: 20%, tomatoes: 10%, walnuts: 10%, watermelon: 10%, and wheat: 2.5%.

Average percent crop treated estimates (BEAD, 12/14/2015) were used in the chronic dietary exposure assessment for the following crops that are currently registered for cyfluthrin: alfalfa: 2.5%, cucumber 5%, grapes: 5%, lemons: 5%, lettuce: 10%, milk: 30%, oranges: 5%, peaches: 10%, peanuts: 5%, pears: 5%, pecans: 2.5%, peppers: 15%, pistachios: 10%, sorghum: 2.5%, spinach: 5%, summer squash: 5%, sugar beets: 1%, sugarcane: 2.5%, sunflowers: 5%, and wheat: 1%.

For the commodities for which the food handling establishment residue value was incorporated, a percent crop treated estimate of 4.65% was used.

### 5.4.3 Acute Dietary Risk Assessment

The U.S. population and all population subgroups have exposure and risk estimates that are not of concern. At the 99.9$^{th}$ percentile of exposure, the risk estimate for the general U.S. population is 71% of the acute population adjusted dose (aPAD). The population subgroup with the highest risk estimate is children 1-2 years old, which uses 96% of the aPAD (See Table 5.4.5).

### 5.4.4 Chronic Dietary Exposure Assessment

The chronic dietary exposure estimate for the general U.S. population is 0.000778 mg/kg/day. The most highly exposed population subgroup is children 1-2, which has a dietary exposure estimate of 0.002198 mg/kg/day. The chronic dietary exposure estimates are given in Table 5.4.5. As stated previously, the chronic assessment was conducted solely for the purpose of obtaining estimates of background levels of dietary exposure for estimating aggregate risk. HED did not calculate chronic dietary risk estimates because the acute dietary risk estimates are protective for chronic dietary risk.

### 5.4.5 Summary Table

**Table 5.4.5. Summary of the Exposure and Risk Estimates for Cyfluthrin**

| Population Subgroup | Acute Assessment (99.9th Percentile) | | | Chronic Assessment | | |
|---|---|---|---|---|---|---|
| | aPAD, mg/kg/day | Exposure Estimate, mg/kg/day | % aPAD | cPAD, mg/kg/day | Exposure Estimate, mg/kg/day | % cPAD |
| U.S. Population | 0.0117 | 0.008287 | 71 | NA | 0.000778 | NA |
| All infants | 0.0039 | 0.002937 | 75 | NA | 0.001020 | |
| **Children 1-2 yrs*** | **0.0039** | **0.003737** | **96** | NA | **0.002198** | |
| Children 3-5 yrs | 0.0039 | 0.003227 | 83 | NA | 0.001570 | |
| Children 6-12 yrs | 0.0117 | 0.002386 | 20 | NA | 0.000921 | |
| Youth 13-19 yrs | 0.0117 | 0.008535 | 73 | NA | 0.000560 | |
| Adults 20-49 yrs | 0.0117 | 0.009583 | 82 | NA | 0.000769 | |
| Adults 50-99 yrs | 0.0117 | 0.006402 | 55 | NA | 0.000566 | |
| Females 13-49 yrs | 0.0117 | 0.007034 | 60 | NA | 0.000545 | |

*Most highly exposed population subgroup

The acute and chronic dietary exposure assessments are refined. However, there are uncertainties in the analyses that overestimate residue levels. These overestimates result from the use of tolerance level residues and field trial data. In the chronic assessment, a residue value was used for every commodity. This assumption is a very conservative one. In both assessments, monitoring data were used for the commodities that make the greatest contribution to the dietary exposure estimates. As a result, it would be possible to refine the exposure estimates further, but not to a considerable extent.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There is potential residential exposure from the existing registered uses of cyfluthrin and beta-cyfluthrin. A representation of existing residential uses with the highest application rates or percent ai have been reassessed to reflect HED's 2012 Residential SOPs[5] and updated toxicity endpoints and PODs. Chemical-specific turf transferrable residue (TTR) and dislodgeable foliar residue (DFR) data are available for cyfluthrin and have been incorporated into the post-application assessment.

[5] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

## 6.1 Residential Handler Exposure and Risk Estimates

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications, and that exposures can vary depending on the specifics of each task. HED addresses residential handlers differently than occupational handlers, as homeowners are assumed to complete all elements of an application without use of any protective equipment.

There are registered cyfluthrin product labels with residential use sites (e.g., lawns, indoor environments, gardens, and trees) that do not require specific clothing (e.g., long sleeve shirt/long pants) and/or PPE, and HED has considered these labels in the residential handler assessment for cyfluthrin.

The quantitative exposure/risk assessment developed for residential handlers is based on mixing, loading, and/or applying cyfluthrin end-use products for the following scenarios:

- Dusts to indoor environments using plunger duster, bulb duster, electric/power and hand crank dusters;
- Liquids to indoor environments using manually-pressurized handwands;
- Ready-to-use formulations to indoor environments, such as aerosol spray cans and trigger-spray bottles;
- Wettable powders to indoor environments using manually-pressurized handwands;
- Water-soluble packets to indoor environments using manually-pressurized handwands;
- Granules to lawns/turf using rotary spreaders, belly grinders, spoons, cups, hand dispersal, and shaker cans;
- Liquids to lawns/turf using hose-end sprayers, manually-pressurized handwands, sprinkler cans, and backpacks;
- Ready-to-use formulations to lawns/turf using trigger-spray bottles and hose-end sprayers;
- Wettable powders to lawns/turf using manually-pressurized handwands, backpacks, and sprinkler cans;
- Water-soluble packets to lawns/turf using manually pressurized handwands and backpacks;
- Granules to gardens/trees using rotary spreaders, spoons, cups, hand dispersal, and shaker cans;
- Liquids to gardens/trees using manually-pressurized handwands, hose-end sprayers, backpacks, and sprinkler cans;
- Ready-to-use formulations to gardens/trees using hose-end sprayers;
- Wettable powders to gardens/trees using manually-pressurized handwands, hose-end sprayers, backpacks, sprinkler cans;
- Water-soluble packets to gardens/trees using manually-pressurized handwands, backpacks, and sprinkler cans; and
- Ready-to-use formulations to outdoor areas using an aerosol space spray.

HED did not quantitatively assess several use scenarios because they are considered to result in negligible exposure:

- Use of non-refillable bait stations in indoor environments;

- Ready-to-use formulations to indoor environments using total release foggers, as the label states that the area must be vacated immediately by the user once fogging is initiated.

Residential Handler Exposure Data and Assumptions
A series of standard assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

*Application Rate:* The registered application rates for the quantitative exposure/risk assessment for residential handlers can be found in Table F.1 of Appendix F. HED typically assumes the maximum single application rate allowed on the label.

*Unit Exposures and Area Treated or Amount Handled:* Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[6].

*Exposure Duration:* Residential handler exposure is expected to be short-term in duration. The single dose and repeat dosing cyfluthrin studies show that repeat exposures do not result in lower PODs (i.e. there is no evidence of increasing toxicity with an increased duration of exposure). Therefore, for the purpose of exposure assessments, only single day risk assessments need to be conducted for cyfluthrin, and these are protective of scenarios in which exposure occurs for multiple days.

*Body Weight:* The standard body weight for the general population (80 kg) was used for all adult dermal exposure scenarios covered in this risk assessment since the endpoints selected were not developmental and/or fetal effects. The endpoints selected for inhalation exposure scenarios include fetal effects. HED used the female body weight of 69 kg for those exposures.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE memo prepared in support of this draft risk assessment (D435058, G. Thornton, 9/1/2017).

Combining Exposures/Risk Estimates
HED did not combine the dermal and inhalation risk estimates in this assessment, since the toxicological effects for these exposure routes are different.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates
There are no residential handler dermal or inhalation risk estimates of concern. All dermal risk estimates were greater than the LOC of 100, with the risk estimates, referred to as the margins of exposure (MOEs), ranging from 1,300 to 51,000,000. All inhalation risk estimates were greater than the LOC of 30, with MOEs ranging from 260 to 1,800,000.

[6] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

| Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | | **Formulation** | **Dermal Unit Exposure (mg/lb ai)** | **Inhalation Unit Exposure (mg/lb ai)** | **Maximum Application Rate[1]** | **Area Treated or Amount Handled Daily[2]** | **Dermal (LOC = 100)** | | **Inhalation (LOC= 30)** | |
| | | | | | | | **Dose (mg/kg/day)[3]** | **MOE[4]** | **Dose (mg/kg/day)[5]** | **MOE[6]** |
| Indoor Environment | Plunger Duster | Dust | 250 | 1.7 | 0.001 lb ai/lb dust | 0.5 lb dust | 0.0000088 | 130,000 | 0.000012 | 3,700 |
| | Bulb Duster | | | | | 0.25 lb dust | 0.0000044 | 270,000 | 0.0000062 | 7,300 |
| | Electric/power, Hand crank Duster | | 4300 | 18 | | 0.5 lb dust | 0.00015 | 7,800 | 0.00013 | 350 |
| | Manually-pressurized handwand | Liquid | 69 | 1.1 | 0.0098 lb ai/gallon | 0.5 gallons | 0.000024 | 49,000 | 0.000078 | 580 |
| | Aerosol can | Ready-to-use | 370 | 3 | 0.004 lb ai/16-oz can | 0.5 16-oz can | 0.000013 | 90,000 | 0.000022 | 2,100 |
| | Trigger-spray bottle | Ready-to-use | 85.1 | 0.061 | 0.00834 lb ai/bottle | 0.5 bottle | 0.000025 | 47,000 | 0.0000037 | 12,000 |
| | Manually-pressurized handwand | Wettable powders | 69 | 1.1 | 0.0088 lb ai/gallon | 0.5 gallons | 0.000021 | 55,000 | 0.00007 | 640 |
| | Manually-pressurized handwand | Water-soluble packaging | 69 | 1.1 | 0.009 lb ai/gallon | 0.5 gallons | 0.000022 | 54,000 | 0.000072 | 630 |
| Lawns/Turf | Push-type rotary spreader | Granule | 0.81 | 0.0026 | 0.13 lb ai/acre | 0.5 acres | 0.0000037 | 320,000 | 0.0000024 | 18,000 |
| | Belly grinder | | 360 | 0.039 | 0.00003 lb ai/ft$^2$ | 1,200 ft$^2$ | 0.00091 | 1,300 | 0.00002 | 2,200 |
| | Spoon | | 6.2 | 0.087 | | 100 ft$^2$ | 0.0000013 | 900,000 | 0.0000038 | 12,000 |
| | Cup | | 0.11 | 0.013 | | | 0.000000023 | 51,000,000 | 0.00000057 | 80,000 |
| | Hand Dispersal | | 160 | 0.38 | | | 0.000034 | 35,000 | 0.000017 | 2,700 |
| | Shaker can | | 0.11 | 0.013 | | | 0.000000023 | 51,000,000 | 0.00000057 | 80,000 |
| | Hose-end Sprayer | Liquid | 13.4 | 0.022 | 0.13 lb ai/acre | 0.5 acres | 0.000061 | 19,000 | 0.000021 | 2,200 |
| | Manually-pressurized handwand | | 63 | 0.018 | 0.008 lb ai/gallon | 5 gallons | 0.00018 | 6,600 | 0.00001 | 4,300 |
| | Sprinkler can | | 13.4 | 0.022 | 0.000004 lb ai/ft$^2$ | 1,000 ft$^2$ | 0.0000038 | 310,000 | 0.0000013 | 35,000 |

| Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | | **Formulation** | **Dermal Unit Exposure (mg/lb ai)** | **Inhalation Unit Exposure (mg/lb ai)** | **Maximum Application Rate[1]** | **Area Treated or Amount Handled Daily[2]** | **Dermal (LOC = 100)** | | **Inhalation (LOC= 30)** | |
| | | | | | | | **Dose (mg/kg/day)[3]** | **MOE[4]** | **Dose (mg/kg/day)[5]** | **MOE[6]** |
| | Backpack | | 130 | 0.14 | 0.008 lb ai/gallon | 5 gallons | 0.00036 | 3,200 | 0.000081 | 550 |
| | Trigger-spray bottle | Ready-to-use | 85.1 | 0.061 | 0.00025 lb ai/bottle | 1 bottle | 0.0000015 | 790,000 | 0.00000022 | 200,000 |
| | Hose-end Sprayer | | 6.26 | 0.034 | 0.13 lb ai/acre | 0.5 acres | 0.000028 | 41,000 | 0.000032 | 1,400 |
| | Manually-pressurized handwand, Backpack | Wettable powder | 69 | 1.1 | 0.0022 lb ai/gallon | 5 gallons | 0.000053 | 22,000 | 0.00018 | 260 |
| | Sprinkler can | | 13.4 | 0.022 | 0.0000022 lb ai/$ft^2$ | 1,000 $ft^2$ | 0.0000021 | 570,000 | 0.0000007 | 64,000 |
| | Manually-pressurized handwand, Backpack | Water-soluble packaging | 63 | 0.018 | 0.009 lb ai/gallon | 5 gallons | 0.0002 | 5,900 | 0.000012 | 3,800 |
| Gardens/Trees | Push-type rotary spreader | Granule | 0.81 | 0.0026 | 0.000003 lb ai/$ft^2$ | 1,200 $ft^2$ | 0.0000002 | 5,700,000 | 0.00000014 | 330,000 |
| | Spoon | | 6.2 | 0.087 | | | 0.0000016 | 750,000 | 0.0000045 | 9,900 |
| | Cup | | 0.11 | 0.013 | | | 0.000000028 | 42,000,000 | 0.00000068 | 66,000 |
| | Hand dispersal | | 160 | 0.38 | | | 0.00004 | 29,000 | 0.00002 | 2,300 |
| | Shaker can | | 0.11 | 0.013 | | | 0.000000028 | 42,000,000 | 0.00000068 | 66,000 |
| | Manually-pressurized handwand | Liquid | 63 | 0.018 | 0.00024 lb ai/gallon | 5 gallons | 0.0000053 | 220,000 | 0.00000031 | 140,000 |
| | Hose-end Sprayer | | 58 | 0.0014 | | 11 gallons | 0.000011 | 110,000 | 0.000000054 | 840,000 |
| | Backpack | | 130 | 0.14 | | 5 gallons | 0.000011 | 110,000 | 0.0000024 | 18,000 |
| | Sprinkler can | | 58 | 0.0014 | | 5 gallons | 0.0000049 | 240,000 | 0.000000024 | 1,800,000 |
| | Hose-end Sprayer | Ready-to-use | 6.26 | 0.034 | 0.00024 lb ai/gallon | 11 gallons | 0.0000012 | 1,000,000 | 0.0000013 | 35,000 |
| | Manually-pressurized | Wettable | 69 | 1.1 | 0.00042 lb | 5 gallons | 0.00001 | 120,000 | 0.000033 | 1,300 |

| Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | | **Formulation** | **Dermal Unit Exposure (mg/lb ai)** | **Inhalation Unit Exposure (mg/lb ai)** | **Maximum Application Rate[1]** | **Area Treated or Amount Handled Daily[2]** | **Dermal (LOC = 100)** | | **Inhalation (LOC= 30)** | |
| | | | | | | | **Dose (mg/kg/day)[3]** | **MOE[4]** | **Dose (mg/kg/day)[5]** | **MOE[6]** |
| | handwand | powder | | | ai/gallons | | | | | |
| | Hose-end Sprayer | | 58 | 0.0014 | | 11 gallons | 0.000019 | 62,000 | 0.000000094 | 480,000 |
| | Backpack | | 69 | 1.1 | | 5 gallons | 0.00001 | 120,000 | 0.000033 | 1,300 |
| | Sprinkler can | | 58 | 0.014 | | 5 gallons | 0.0000085 | 140,000 | 0.000000043 | 1,100,000 |
| | Manually-pressurized handwand, Backpack | Water-soluble packaging | 63 | 0.018 | 0.009 lb ai/gallons | 5 gallons | 0.0002 | 5,900 | 0.000012 | 3,800 |
| | Sprinkler can | | 6.26 | 0.034 | | 5 gallons | 0.00002 | 59,000 | 0.000022 | 2,000 |
| Outdoor Fogging | Aerosol Space Spray | Ready-to-use | 370 | 3 | 0.0005 lb ai/can | 1 can | 0.000013 | 89,000 | 0.000022 | 2,000 |

1 Based on registered labels, see Appendix F, Table F.1.
2 Based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) × Dermal Absorption Factor (0.56%) ÷ Body Weight (80 kg).
4 Dermal MOE = Dermal BMDL (1.42 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ BW (69 kg).
6 Inhalation MOE = Inhalation HED (human equivalent dose) (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## 6.2 Residential Post-application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been treated with cyfluthrin or beta-cyfluthrin. The quantitative exposure and risk assessment for residential post-application exposures is based on the following scenarios:

- Adults and Children 6 < 11 years
  - Dermal exposure from contact with residues deposited in gardens, on trees, or on indoor plants from liquid/solid formulations.
- Adults and/or Children 1 < 2 years
  - Dermal exposure (adults and children) and incidental oral exposure (hand-to-mouth, children 1<2 years) from contact with residues deposited on indoor surfaces (carpets or hard surfaces) using a water-soluble packet formulation as a broadcast, perimeter/spot/bedbug (coarse or pinstream), and crack and crevice treatment.
  - Dermal exposure (adults and children) and incidental oral exposure (hand-to-mouth, children 1<2 years) from contact with residues deposited on indoor surfaces (carpets or hard surfaces) using a ready-to-use total release fogger.
  - Dermal exposure from contact with residues deposited on mattresses from application of a liquid formulation.
  - Dermal exposure (adults and children) and incidental oral exposure (hand-to-mouth, children 1<2 years) resulting from high contact lawn activities on turf treated with a liquid formulation.
  - Dermal exposure (adults and children) and incidental oral exposure (hand-to-mouth, children 1<2 years) resulting from high contact lawn activities on turf treated with a solid formulation.
  - Inhalation exposure to an outdoor aerosol space spray.
  - Dermal exposure to residues deposited on outdoor surfaces from an aerosol space spray.
  - Incidental oral exposure (hand-to-mouth, children 1 < 2 years) to residues deposited on outdoor surfaces from an aerosol space spray.
- Adults and/or Children 11 < 16 years
  - Dermal exposure from contact with residues on treated turf while mowing from application of a liquid formulation.
  - Dermal exposure from contact with residues on treated turf while mowing from application of a solid formulation.
- Adults and/or Children 6 < 11 years, and/or 11 < 16 years
  - Dermal exposure from contact with residues on treated turf while golfing from application of a liquid formulation.
- Children 1 < 2 years
  - Episodic ingestion of granules

*Post-application Inhalation Exposure resulting from Outdoor Aerosol Space Spray:* In accordance with guidance for outdoor aerosol space sprays (OASS) in the Outdoor Fogging/Misting System Residential SOP, post-application exposure can result from activities

performed following outdoor aerosol space spray pesticide applications. The SOP indicates that aerosolized pesticide exposure time is not a significant factor for calculation of inhalation exposure from these sprays because of the rapid dissipation of pesticide air concentrations. Based on the minimum airflow rate, the pesticide air concentration within the enclosed space is virtually zero after approximately 7 minutes. However, since the label for the registered outdoor aerosol space spray product (EPA Reg. No. 4822-573) does not provide a re-entry restriction, a quantitative post-application inhalation exposure assessment is required.

*Post-application Inhalation Exposure Resulting From Fogger Applications:*
Post-application inhalation exposure from the use of indoor foggers is expected to be negligible since most fogger product labels typically state a period of no-entry following application (usually up to 4 hours), as well as a ventilation period before occupants can return. In addition, because of the low vapor pressure of pyrethroids in general, and the available air concentration data collected from the EPA Office of Research and Development (ORD) test house following indoor applications of pyrethroids (D390098), HED does not have concerns for post-application inhalation exposure from indoor fogger applications of cyfluthrin.

*Pyrethroid Indoor Surface Directed Post-application Inhalation Exposure***:**
Chemical-specific post-application inhalation exposure data are not available for the surface-directed indoor use of cyfluthrin; however, HED has received and reviewed an Office of Research and Development (ORD) exposure study that was performed in the U.S. EPA's Indoor Air Quality (IAQ) Research House (D390098). This study simulated crack and crevice applications of four pesticides: two emulsifiable concentrate products applied via a handheld sprayer (permethrin and cypermethrin), one aerosol can product (propoxur), and one gel bait product (fipronil). The application pattern used in this study is considered to be a reasonable representation of an indoor crack and crevice application, but also can represent other indoor applications such as perimeter (coarse and pinstream) as well as surface directed broadcast uses because of the nature of the applications (applications were made to floor-to-ceiling paneling on three walls of an interior room). Air concentrations of all four chemicals were collected using stationary air samplers suspended 75 cm above the floor in the room of application (the living room) and two other rooms in the test house (the den and master bedroom). Air samples were collected during the application and 1, 1.5, 2, 2.5, 3, 7, 14, 21, 28, and 35 days after application. Permethrin and cypermethrin air concentrations were not found in any measurable quantities in any room in the research house.

Although the data are not chemical specific for cyfluthrin/beta-cyfluthrin, the Non Dietary Exposure Task Force (NDETF) performed an analysis of all the pyrethroid surface deposition and hand press exposure data that they produced. This analysis shows that the exposure data for one pyrethroid can generally be used to represent the entire chemical class. Based on this NDETF analysis and the generally low vapor pressure of pyrethroids, HED believes it is appropriate to use the air concentration data from the ORD study as a surrogate for pyrethroids when applied as surface-directed applications indoors. HED does not have concerns for pyrethroids in general for the post-application inhalation exposure scenario, given that all air concentration values were below the limit of quantitation in the ORD study.

*Post-application Dermal and Incidental Oral Exposure Resulting from applications in Indoor Environments:* Based on pyrethroid-specific data available in the 2012 SOPs, the following approaches/default values were used as per guidance set forth for pyrethroid registration review:

- *Broadcast applications*: A calculated deposition rate (4.41 $\mu g/cm^2$), based on application rates from registered end-use products, was used to determine the deposited residue value (100% of applied product is assumed to be deposited). See Appendix F or Table 6.1.1 for application rates.

- *Perimeter/Spot/Bedbug applications (Coarse*): The default deposited residue value of 2.6 $\mu g/cm^2$ was used with no adjustment for percent ai. This value is a combination of the pyrethroid data from Keenan (2007) and esfenvalerate data from Selim (2008) for all pyrethroids.

- *Perimeter/Spot/Bedbug applications (Pinstream)*: The default deposited residue value of 1.5 $\mu g/cm^2$ was used with no adjustment for percent ai. This value is a combination of the pyrethroid data from Keenan (2007), and the ORD test house data (D390098) for all pyrethroids

- *Crack and crevice applications*: The default deposited residue value of 0.4 $\mu g/cm^2$ was used with no adjustment for percent ai. This value is a combination of the pyrethroid data from Keenan (2007), the esfenvalerate data from Selim (2008), and the ORD test house data (D390098) for all pyrethroids

- *Fogger applications*: For the pyrethroids without chemical-specific residue data, the average residue value (of 5.4 $ug/cm^2$ for a 0.5% fogger) from the three studies was used, making an adjustment for maximum percent active ingredient registered (See Appendix F or Table 6.1.1).

- *Fraction of Residue Available for Transfer (Fai*): Chemical-specific data provided by the NDETF were used for the fraction of residue available for transfer, which is consistent with the 2011 Pyrethroid Cumulative Risk Assessment (Pyrethroid CRA; 10/4/2011; D394576). The NDETF studies examined the transferability of residues from bare hand-presses on carpets and hard surfaces for deltamethrin, permethrin, and pyrethrins. For carpets, the fraction transferred was 0.03, 0.02 and 0.01 for pyrethrins, permethrin and deltamethrin, respectively. For hard surfaces, the fraction transferred was 0.04, 0.03, and 0.05 for pyrethrins, permethrin, and deltamethrin, respectively. Since the values were so similar across the three chemicals, the average fraction transferred will be used to assess exposure to cyfluthrin: 0.02 for carpets and 0.04 for hard surfaces.

- *Contact with Residue Deposited on Indoor Surfaces from Dust Formulation:* The Indoor Residential SOPs do not make a distinction between formulations when calculating post-application incidental oral exposure. Since HED does not currently have chemical-specific residue deposition data for dust formulations, HED uses default post-application residue transferablility data from boric acid/sodium salts studies to refine incidental oral exposure and risk estimates (MRID 47579901). A transferability of 0.1% were used for

dust treatments to carpets (MRID 47579901) and 0.4% for dust treatments to hard floors and surfaces (MRID 47579902). However, since the registered dust end-use product application rates are similar to the other registered liquid end-use product application rates (0.2 lb ai/A for dust versus 0.22 lb ai/A for spray), a dust specific post-application assessment is not needed. The liquid end-use product application rate used in the assessment is protective of any exposure from dust formulations.

*Post-application Dermal and Incidental Oral Exposure Resulting from Applications on Lawn/Turf:* For the lawn/turf use scenario, chemical-specific TTR data have been submitted for four pyrethroids: cyfluthrin (liquid formulations), cypermethrin (liquid and wettable powder formulations), deltamethrin (liquid formulations), and permethrin (liquid formulations). As data have been submitted specifically for cyfluthrin, the TTR data for a liquid formulation of cyfluthrin have been used. These data were discussed in the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576). The cyfluthrin TTR data (average day 0 TTR 0.011 $\mu g/cm^2$, normalized using an application rate of 0.1 lb ai/A) were adjusted to reflect the maximum application rates listed on the cyfluthrin end-use-product labels used in this assessment (see Appendix F).

*Post-application Dermal and Incidental Oral Exposure Resulting from Applications on Gardens/Trees:* For the gardens/trees use scenario, HED used chemical-specific data submitted for the determination of dislodgeable foliar cyfluthrin residues on treated corn (M. Crowley; 03/1/2013; D403726). The study was conducted at two test sites; one at Mendota, California and the other at Stanfield, Arizona. While the data from both the CA and the AZ sites produced very similar half-lives and predicted initial residue values, for the purpose of this assessment, the CA DFR values were used. The control samples from the site in AZ showed contamination with cyfluthrin from applications of a cyfluthrin containing product that was applied several days before application of the test substance. Traditional field fortification and laboratory fortification were not prepared for the CA site. However, the registrant stated that, for both the CA site and the AZ site, the analytical results indicate that the internal standard did not degrade. Conditions that result in degradation of the cyfluthrin in the sample would also cause degradation of the internal standard. Thus, correction for field fortification recoveries was not needed. The maximum average DFR value at the CA site was 0.161 $\mu g/cm^2$ at day 0 after application. HED calculated a half-life of 19.7 days ($r^2$=0.9416) for cyfluthrin, with a maximum modeled DFR value of 0.142 $\mu g/cm^2$ at day 0 after application. The cyfluthrin DFR data were adjusted to reflect the maximum crop application rates (see Appendix F).

*Post-application Dermal and Incidental Oral Exposure Resulting from use of Bait Stations Indoors:* Since the bait comes packaged in a non-refillable station, HED is not concerned with post-application risk from exposure to the bait, which is likely to be negligible.

*Episodic Ingestion of Granules:* Ingestion of granules is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, concern for human health is related to acute poisoning rather than short-term residue exposure. Therefore, an acute dietary dose is used to estimate exposure and risk resulting from episodic ingestion of granules.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[7]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[7].

*Application Rate:* The registered application rates of cyfluthrin and beta-cyfluthrin end-use products that may result in residential exposure are listed in Appendix F, Tables F.1 and F.4.

*Exposure Duration:* Residential exposure is expected to be short-term in duration. The single dose and repeat dosing cyfluthrin and beta-cyfluthrin studies show that repeat exposures do not result in lower PODs (i.e. there is no evidence of increasing toxicity with an increased duration of exposure). Therefore, for cyfluthrin and beta-cyfluthrin, only single day risk assessments need to be conducted, and these are protective of scenarios in which exposure occurs for multiple days.

*Body Weight:* The standard body weight for the general population (80 kg) was used for all adult dermal exposure scenarios covered in this risk assessment since the endpoints selected were not developmental and/or fetal effects. The endpoints selected for inhalation exposure scenarios include fetal effects. HED used the female body weight of 69 kg for those exposures.
A body weight of 11 kg was used for children 1 to < 2 years old. A body weight of 32 kg was used for children 6 to <11 years old. A body weight of 57 kg was used for children 11 < 16 years old.

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE memo prepared in support of this draft risk assessment (D435058, G. Thornton, 9/1/2017).

Combining Exposure and Risk Estimates

Since dermal and incidental oral exposure routes share a common toxicological endpoint, risk estimates have been combined for those routes. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related, and it is likely that they occur interspersed amongst each other across time. Combining these scenarios with the dermal exposure scenario would be overly-conservative because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 to <2 years old are the dermal and hand-to-mouth scenarios. This combination should be considered a protective estimate of children's exposure.

[7] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Additionally, exposures from bedbug applications of cyfluthrin and beta-cyfluthrin to indoor surfaces and mattresses are combined. HED assumes that it is possible a homeowner would make bedbug treatments to multiple sites in a residential home and, therefore, potential exposure from bedbug treatments should be combined.

Since inhalation exposure routes do not share a common toxicological endpoint with dermal and incidental oral, these routes of exposure have not been combined.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

*Adult Post-application Risk Estimates (Table 6.2.1):* There are no risk estimates of concern for adults. Dermal exposures result in MOEs that range from 1,700 to 2,200,000 (LOC = 100). Inhalation exposure results in an MOE of 130 (LOC = 30).

*Children (11 to <16 years) Post-application Risk Estimates (Table 6.2.2):* There are no dermal risk estimates of concern for children (11 to <16 years). Dermal exposures result in MOEs that range from 47,000 to 140,000 (LOC = 100).

*Children (6 to <11 years) Post-application Risk Estimates (Table 6.2.3):* There are no dermal risk estimates of concern for children (6 to <11 years). Dermal exposures result in MOEs that range from 2,500 to 3,200,000 (LOC = 100).

*Children (1 to <2 years) Post-application Risk Estimates (Table 6.2.4):* There are several risk estimates of concern for children (1 to <2 years). Where incidental oral (hand-to-mouth) and dermal exposures are combined (dermal/incidental oral LOC = 300), the following scenarios are of concern:

- Indoor-broadcast use results in a risk estimate of concern with a combined MOE of 140; and
- Indoor-perimeter/spot/bedbug (coarse spray) uses result in a risk estimate of concern with a combined MOE of 220.

The incidental oral exposure is the primary route of exposure resulting in risks of concern. Broadcast use of cyfluthrin products indoors results in risks of concern both on hard surfaces and carpets (MOE = 270 and 140, respecitvely). The spot/perimeter/bedbug (coarse spray) uses of cyfluthrin products indoors are of concern on carpets (MOE = 230), but not of concern on hard surfaces (MOE = 460). The use of a pin stream applicator increases MOE risk estimates above the LOC (MOE =400 and 790) for uses on both hard surfaces and carpets.

For scenarios where routes of exposure are not combined (acute dietary LOC = 300; inhalation LOC = 100):

- Episodic ingestion of granules results in an acute dietary risk estimate of concern, with an MOE of 43; and
- Outdoor aerosol space spray use results in an inhalation risk estimate of concern, with an MOE of 40.

Risk estimates for all other exposure scenarios are not of concern.

**Table 6.2.1. Adult Residential Post-application Non-cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin.**

| Formulation [EPA Reg. No.] | Post-application Exposure Scenario | | Residue | Dose (mg/kg/day)[1] | MOEs[2] (Dermal LOC = 100) (Inhalation LOC = 30) |
|---|---|---|---|---|---|
| | Use Site | Route of Exposure | (µg/cm$^2$) | | |
| Solid [3125-568] | Gardens | Dermal | 0.536[a] | 0.000694 | 1,700 |
| | Trees | | | 0.000064 | 18,000 |
| | Indoor Plants | | | 0.000008 | 140,000 |
| Liquid [71995-45] | Gardens | Dermal | 0.035[b] | 0.000045 | 26,000 |
| | Trees | | | 0.000004 | 280,000 |
| | Indoor Plants | | | 0.000001 | 2,200,000 |
| Liquid [4822-375] | Indoor-Broadcast | Dermal: Carpet | 4.41[c] | 0.00034 | 3,500 |
| | | Dermal: Hard surface | | 0.00017 | 7,000 |
| | Indoor- Perimeter/Spot/Bedbug (Coarse) | Dermal: Carpet | 2.6[d] | 0.0002 | 5,900 |
| | | Dermal: Hard surface | | 0.000099 | 12,000 |
| | Indoor Perimeter/Spot/Bedbug (Pin Stream) | Dermal: Carpet | 1.5[d] | 0.00011 | 10,000 |
| | | Dermal: Hard surface | | 0.000057 | 20,000 |
| | Indoor Crack and crevice | Dermal: Carpet | 0.4[d] | 0.00003 | 38,000 |
| | | Dermal: Hard surface | | 0.000015 | 77,000 |
| Total-release Fogger [4822-481] | Fogger | Dermal: Carpet | 1.08[e] | 0.000082 | 14,000 |
| | | Dermal: Hard surface | | 0.000041 | 28,000 |
| Liquid [432-1483] | Mattress | Dermal | 5.1[f] | 0.00012 | 9,700 |
| Liquid [432-1302] | High Contact Lawn Activities | Dermal | 0.021[g] | 0.0004 | 3,000 |
| | Mowing Turf | Dermal | | 0.000008 | 150,000 |
| Liquid [432-1338] | Golfing | Dermal | 0.014[h] | 0.00002 | 55,000 |
| Solid [3125-568] | High Contact Lawn Activities | Dermal | 0.019[i] | 0.0004 | 3,000 |
| | Mowing Turf | Dermal | | 0.000007 | 160,000 |
| Ready-to-use Aerosol [4822-573] | Outdoor Aerosol Space Spray | Inhalation | 0.0006[j] | 0.0004 | 130 |
| | | Dermal | | 0.0001 | 10,000 |

1. Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide) as well as Appendix A.
2. MOE = HED/BMDL (mg/kg/day) ÷ Dose (mg/kg/day).

a. Based on an application rate of 0.17 lb ai/A (EPA Reg. No. 3125-568), using a DFRt of 0.142 µg/cm2 (M. Crowley; 03/1/2013; D403726) adjusted for the application rate.
b. Based on an application rate of 0.011 lb ai/A (EPA Reg. No. 71995-45), using a DFRt of 0.142 µg/cm2 (M. Crowley; 03/1/2013; D403726) adjusted for the application rate..
c. Based on an application rate 0.000009 lb ai/ft2 (EPA Reg. No. 4822-375), assuming 100% of what is applied is available for transfer.
d. Based on pyrethroid-specific data available in the 2012 SOPs.
e. Based on pyrethroid-specific data available in the 2012 SOPs, adjusted for percent ai in the end-use product (EPA Reg. No. 4822-481)
f. Based on an application rate of 0.0021 lb ai/A (EPA Reg. No. 432-1483).
g. Based on an application rate 0.19 lb ai/A (EPA Reg. No. 432-1302), using a TTRt of 0.011 µg/cm2 using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.
h. Based on an application rate of 0.13 lb ai/A (EPA Reg. No. 432-1338), using a TTRt of 0.011 µg/cm2 using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.
i. Based on an application rate of 0.17 lb ai/A (EPA Reg. No. 3125-568), using a TTRt of 0.011 µg/cm2 using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.
j. Based on the application rate 0.00000127 lb ai/ft2 (EPA Reg. No. 4822-573), assuming 1 can is used per day and treats up to an area of 400 ft2.

**Table 6.2.2. Children (11 to <16 years) Residential Post-application Non-cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin.**

| Formulation [EPA Reg. No.] | Post-application Exposure Scenario | | Residue | Dose (mg/kg/day)[1] | MOEs[2] (Dermal LOC = 100) |
|---|---|---|---|---|---|
| | Use Site | Route of Exposure | (µg/cm$^2$) | | |
| Liquid [432-1302] | Mowing Turf | Dermal | 0.021[a] | 0.000009 | 130,000 |
| Liquid [432-1338] | Golfing | Dermal | 0.014[b] | 0.00002 | 47,000 |
| Solid [3125-568] | Mowing Turf | Dermal | 0.019[c] | 0.000008 | 140,000 |

1. Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide)
2. MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day).

a. Based on an application rate 0.19 lb ai/A (EPA Reg. No. 432-1302), using a $TTR_0$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.
b. Based on an application rate of 0.13 lb ai/A (EPA Reg. No. 432-1338), using a $TTR_0$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.
c. Based on an application rate of 0.17 lb ai/A (EPA Reg. No. 3125-568), using a $TTR_0$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.

**Table 6.2.3. Children (6 to <11 years) Residential Post-application Non-cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin.**

| Formulation [EPA Reg. No.] | Post-application Exposure Scenario | | Residue | Dose (mg/kg/day)[1] | MOEs[2] (Dermal LOC= 100) |
|---|---|---|---|---|---|
| | Use Site | Route of Exposure | (µg/cm$^2$) | | |
| Solid [3125-568] | Gardens | Dermal | 0.536[a] | 0.00048 | 2,500 |
| | Trees | | | 0.000044 | 27,000 |
| | Indoor Plants | | | 0.000006 | 210,000 |
| Liquid [71995-45] | Gardens | Dermal | 0.035[b] | 0.000031 | 38,000 |
| | Trees | | | 0.000003 | 410,000 |
| | Indoor Plants | | | 0.0000004 | 3,200,000 |
| Liquid [432-1338] | Golfing | Dermal | 0.014[c] | 0.00003 | 40,000 |

1. Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide)
2. MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day).

a. Based on an application rate of 0.17 lb ai/A (EPA Reg. No. 3125-568), using a $DFR_0$ of 0.142 µg/cm$^2$ (M. Crowley; 03/1/2013; D403726).
b. Based on an application rate of 0.011 lb ai/A (EPA Reg. No. 71995-45), using a $DFR_0$ of 0.142 µg/cm$^2$ (M. Crowley; 03/1/2013; D403726).
c. Based on an application rate of 0.13 lb ai/A (EPA Reg. No. 432-1338), using a $TTR_0$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576).

**Table 6.2.4. Children (1 to <2 years) Residential Post-application Non-cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin.**

| Formulation [EPA Reg. No.] | Post-application Exposure Scenario | | Residue | Dose (mg/kg/day)[1] | MOEs[2] (Dermal LOC = 300) (Inhalation LOC = 100) (Incidental Oral LOC = 300) (Acute Dietary LOC = 300) | Combined Routes (X indicates included in Combined MOE) | Combined MOEs[3] (LOC = 300) |
|---|---|---|---|---|---|---|---|
| | Use Site | Route of Exposure | (µg/cm²) | | | | |
| Liquid [4822-375] | Indoor-Broadcast | Dermal: Carpet | 4.41[a] | 0.00032 | 3,600 | X | **140** |
| | | Dermal: Hard surface | | 0.00032 | 3,600 | | |
| | | Hand-to-mouth: Carpet | | 0.009 | **140** | X | |
| | | Hand-to-mouth: Hard surface | | 0.004 | **270** | | |
| | Indoor-Perimeter/ Spot/Bedbug (Coarse) | Dermal: Carpet | 2.6[b] | 0.00019 | 6,100 | X | **220** |
| | | Dermal: Hard surface | | 0.00019 | 6,100 | | |
| | | Hand-to-mouth: Carpet | | 0.005 | **230** | X | |
| | | Hand-to-mouth: Hard surface | | 0.003 | 460 | | |
| Liquid [432-1483] | Mattress | Dermal* | 5.1[c] | 0.00027 | 9,700 | X | 390 |
| Liquid [4822-375] | Indoor Perimeter/ Spot/Bedbug (Pin Stream) | Dermal: Carpet | 1.5[b] | 0.00011 | 11,000 | X | |
| | | Dermal: Hard surface | | 0.00011 | 11,000 | | |
| | | Hand-to-mouth: Carpet | | 0.003 | 400 | X | |
| | | Hand-to-mouth: Hard surface | | 0.001 | 790 | | |
| | Indoor Crack and crevice | Dermal: Carpet | 0.4[b] | 0.000029 | 40,000 | X | 1,400 |
| | | Dermal: Hard surface | | 0.000029 | 40,000 | | |
| | | Hand-to-mouth: Carpet | | 0.0008 | 1,500 | X | |
| | | Hand-to-mouth: Hard surface | | 0.0004 | 3,000 | | |
| Total-release Fogger [4822-481] | Fogger | Dermal: Carpet | 1.08[d] | 0.000079 | 15,000 | X | 530 |
| | | Dermal: Hard surface | | 0.000079 | 15,000 | | |
| | | Hand-to-mouth: Carpet | | 0.002 | 550 | X | |
| | | Hand-to-mouth: Hard surface | | 0.001 | 1,100 | | |
| Liquid [432-1302] | High Contact Lawn Activities | Dermal | 0.021[e] | 0.0008 | 1,500 | X | 320 |
| | | Hand-to-mouth | | 0.003 | 410 | X | |
| Solid [3125-568] | High Contact Lawn Activities | Dermal | 0.019[f] | 0.0008 | 1,500 | X | 570 |
| | | Hand-to-mouth | | 0.0013 | 920 | X | |
| Solid [3125-568] | Episodic Ingestion of Granules | Acute Dietary | NA[g] | 0.03 | **43** | | NA |
| Ready-to-use Aerosol [4822-573] | Outdoor Aerosol Space Spray | Inhalation | 0.0006[h] | 0.0013 | **40** | | 1,100 |
| | | Dermal | | 0.0002 | 5,100 | X | |
| | | Hand-to-mouth | | 0.0008 | 1,400 | X | |

*As per the 2012 Residential SOPs, exposures from applications from both mattress and indoor treatments should be combined, as it is possible to be exposed to pesticide residues from both treatments concurrently.

1. Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide) as well as Appendix A.
2. MOE = POD/HED (mg/kg/day) ÷ Dose (mg/kg/day). Bolded risk estimates are of concern.
3. Combined MOE = 1 ÷ [(1/dermal MOE) + (1/incidental oral MOE)], where applicable.

a. Based on an application rate 0.000009 lb ai/ft² (EPA Reg. No. 4822-375), assuming 100% of what is applied is available for transfer.
b. Based on pyrethroid-specific data available in the 2012 SOPs.

c. Based on an application rate of 0.17 lb ai/A (EPA Reg. No. 3125-568), using a $TTR_t$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576).
d. Based on an application rate 0.19 lb ai/A (EPA Reg. No. 432-1302), using a $TTR_t$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA(Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576).
e. Based on the percent active ingredient in the end-use product (EPA Reg. No. 3125-568).
f. Based on an application rate of 0.17 lb ai/A (EPA Reg. No. 3125-568), using a $TTR_t$ of 0.011 µg/cm$^2$ using cyfluthrin specific TTR data from the 2011 Pyrethroid CRA (Pyrethroid Cumulative Risk Assessment; 10/4/2011; D394576) adjusted for the application rate.
g. Based on the percent active ingredient in the end-use product (EPA Reg. No. 3125-568).
h. Based on the application rate 0.00000127 lb ai/ft$^2$ (EPA Reg. No. 4822-573), assuming 1 can is used per day and treats up to an area of 400 ft$^2$.

## 6.3 Non-Occupational Spray Drift Exposure and Risk Estimates

Several cyfluthrin and beta-cyfluthrin products have existing labels for use on turf, thus it was considered whether the risk assessment for use on turf may be considered protective of exposure that would be associated with spray drift. HED concluded that for the cyfluthrins, the registered residential uses on turf result in greater exposure than potential exposure from spray drift. Generally, if the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to the existing turf application, the existing turf assessment is considered protective of spray drift. A quantitative spray drift assessment for cyfluthrin and beta-cyfluthrin is not required because the maximum application rate to a crop/target site (0.12 lb ai/A) multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate (0.19 lb ai/A) for any cyfluthrin or beta-cyfluthrin product (i.e., 0.12 lb ai/A * 0.26 < 0.19 lb ai/A).

## 6.4 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[8]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[9]. During registration review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for cyfluthrin and beta-cyfluthrin.

# 7.0 Aggregate Exposure/Risk Characterization

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

[8] Available: https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037
[9] Available: https://www.regulations.gov/document?D=EPA-HQ-OPP-2014-0219-0002

## 7.1 Acute Aggregate Risk

Acute aggregate risk from exposure to cyfluthrin results from exposure to residues in food and drinking water alone. The acute dietary exposure analysis included both food and drinking water; therefore, acute aggregate risk estimates are equivalent to the acute dietary risk estimates, as discussed in Section 5.4.3, above. Acute aggregate risk is not of concern for the general U.S. population or any population subgroup.

## 7.2 Short-Term Aggregate Risk Estimates

Short-term aggregate risk assessments are needed for adults and children, and include exposure through the oral and dermal routes. The oral endpoint is based on neurotoxic effects seen in the Wolansky study in which the $BMDL_{1SD}$ was 1.17 mg/kg based on decreased motor activity in rats. The dermal endpoint is based on the same study and effects. As the dermal and incidental endpoints are the same (neurotoxicity), exposures from these pathways are aggregated. In accordance with the FQPA, the combined exposure from these pathways is added to the background dietary exposure from the chronic dietary exposure assessment.

As identified in the residential post-application section of this document (Section 6.2), certain exposure scenarios resulted in risk estimates below their respective LOCs and are of concern. These exposure scenarios have not been included quantitatively in the aggregate assessment because additional background exposure from food and water would only increase the risk estimates. Of the remaining residential exposure scenarios, HED selected only the most conservative, or worst case, residential adult and child scenarios to be included in the aggregate estimates, based on the lowest overall MOEs that are still greater than their respective LOCs (i.e., highest exposure and risk estimates; LOC = 100 for adults and children ≥6 years old and 300 for children <6 years old). The worst-case adult scenario resulted from adult handlers applying granular formulations to lawns using a belly grinder. For children 11 to <16 years old, the worst-case scenario resulted from dermal post-application contact with residues on treated golf courses. For children 6 to <11 years old, the worst-case scenario resulted from dermal post-application contact with residues from treated gardens. For children 1 to <2 years old, the worst-case scenario resulted from combined dermal and incidental oral post-application exposure from high contact lawn activites.

As the levels of concern are identical for the dermal and incidental oral exposure routes, and since the POD for both routes of exposure is derived from an oral study, the short-term aggregate MOEs were calculated by adding the exposures and dividing the POD (1.17 mg/kg) by the sum of the exposures.

For children 1 to <2 years old, there are aggregate risk estimates of concern for the worst-case scenario (i.e., combined dermal and incidental oral post-application exposure from high contact lawn activities) as well as several other scenarios. Aggregate MOEs for the following scenarios range from 200-270, and are of concern: high contact lawn activities after treatment with both solid and liquid formulations, contact with surfaces following indoor perimeter/spot/bedbug treatment with liquid formulations, and exposure to residues on surfaces after fogger treatment. The aggregate risk estimates for these scenarios are provided in Table 7.2.a, below.

The short-term aggregate risk assessments resulted in MOEs of 840 for children 6 to <11 years old, 2,000 for children 11 to <16, and 700 for adults 20-49 years of age. For adults and children 6 years of age and older, the aggregate MOEs are greater than the LOC, and are not of concern. For children 1 to <2 years old, the outdoor aerosol space spray scenario has an aggregate MOE of 370, which is not of concern. The short-term aggregate risk estimates are given in the tables below, and the equations used to determine the aggregate MOEs are given in Appendix D.

**Table 7.2.a. Short-Term Aggregate Risk Calculations for Scenarios with Risk Estimates of Concern for Children 1 to <2 Oral and Dermal Endpoints and Points of Departure are the Same**

| Scenario | Short- or Intermediate-Term Scenario | | | | | | |
|---|---|---|---|---|---|---|---|
| | POD mg/kg/day | LOC[1] | Max Allowable Exposure[2] mg/kg/day | Average Food and Water Exposure mg/kg/day | Residential Exposure mg/kg/day[3] | Total Exposure mg/kg/day[4] | Aggregate MOE (food, water, and residential)[5] |
| Liquid High-Contact Lawn | 1.17 | 300 | 0.00390 | 0.002198 | 0.0038 | 0.005998 | **200** |
| Solid High-Contact Lawn | 1.17 | 300 | 0.00390 | 0.002198 | 0.00210 | 0.004298 | **270** |
| Liquid Indoor Perimeter/Spot/Bedbug | 1.17 | 300 | 0.00390 | 0.002198 | 0.00349 | 0.005688 | **210** |
| Fogger | 1.17 | 300 | 0.00390 | 0.002198 | 0.002079 | 0.004277 | **270** |

[1] LOC is based on a 10x interspecies UF, a 10x intraspecies UF, and a 3x FQPA Safety Factor
[2] Maximum Allowable Exposure (mg/kg/day) = POD/LOC
[3] Residential Exposure = [Oral exposure + Dermal exposure]. See Table 6.2.4 for residential exposure values.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure
[5] Aggregate MOE = [NOAEL ÷ (Avg Food & Water Exposure + Residential Exposure)]

**Table 7.2.b. Short-Term and/or Intermediate Term Aggregate Risk Calculations Oral and Dermal Endpoints and Points of Departure are the Same**

| Population | Short- or Intermediate-Term Scenario | | | | | | |
|---|---|---|---|---|---|---|---|
| | POD mg/kg/day | LOC[1] | Max Allowable Exposure[2] mg/kg/day | Average Food and Water Exposure mg/kg/day | Residential Exposure mg/kg/day[3] | Total Exposure mg/kg/day[4] | Aggregate MOE (food, water, and residential)[5] |
| Children 1 to <2 | 1.17 | 300 | 0.0039 | 0.002198 | 0.0010 | 0.003198 | **370** |
| Children 6 to <11 | 1.17 | 100 | 0.0117 | 0.000921 | 0.00048 | 0.001401 | **840** |
| Children 11 to <16 | 1.17 | 100 | 0.0117 | 0.000560 | 0.00002 | 0.000580 | **2,000** |
| Adults 20-49 | 1.17 | 100 | 0.0117 | 0.000769 | 0.00091 | 0.001679 | **700** |

[1] LOC is based on a 10x interspecies UF, a 10x intraspecies UF. The FQPA SF is 1x for adults and children >6, and 3x for children <6.
[2] Maximum Allowable Exposure (mg/kg/day) = POD/LOC
[3] Residential Exposure = [Oral exposure + Dermal exposure]. See Tables 6.1.1, 6.2.2, 6.2.3, and 6.2.4 for residential exposure values.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure
[5] Aggregate MOE = [POD ÷ (Avg Food & Water Exposure + Residential Exposure)]

## 8.0 Cumulative Exposure and Risk Characterization

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins share a common mechanism of toxicity (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). As explained in that document, the members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. In 2011, after establishing a common mechanism grouping for the pyrethroids and pyrethrins, the Agency conducted a cumulative risk assessment (CRA) which is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. In that document, the Agency concluded that cumulative exposures to pyrethroids (based on pesticidal uses registered at the time the assessment was conducted) did not present risks of concern. For information regarding EPA's efforts to evaluate the risk of exposure to this class of chemicals, refer to https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids.

Since the 2011 CRA, for each new pyrethroid and pyrethrin use, the Agency has conducted a screen to evaluate any potential impacts on the CRA prior to those uses being granted. Prior to a final registration review decision for the cyfluthrins, the Agency will determine whether the 2011 CRA needs to be updated based on the availability of any new hazard, use, or exposure information that could potentially change the conclusions of, or otherwise impact, the 2011 CRA.

## 9.0 Occupational Exposure and Risk Characterization

(G. Thornton, D D435058, 9/1/2017)

### 9.1 Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications, and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns, current labeling, types of equipment, and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following agricultural scenarios for a variety of representative use sites:

- Mixing/loading granules for aerial and tractor-drawn spreader applications;
- Mixing/loading liquids for aerial, airblast, chemigation, groundboom, and injector applications;
- Mixing/loading wettable powders for aerial, airblast, and groundboom applications;
- Mixing/loading water-soluble packets for aerial, airblast, and groundboom applications;
- Applying granules via aerial and tractor-drawn spreader application equipment;
- Applying sprays via aerial, airblast, and groundboom application equipment;

- Flagging for aerial applications;
- Mixing/loading/applying liquids for backpack, manually-pressurized handwand, mechanically-pressurized handgun applications;
- Mixing/loading/applying wettable powders for backpack, manually-pressurized handwand, and mechanically-pressurized handgun applications;
- Mixing/loading/applying water-soluble packets for backpack, manually-pressurized handwand, and mechanically-pressurized handgun applications;
- Loading/applying liquids for a seed treatment application;
- Sewing/Bagging treated seeds;
- Doing multiple activities involving treating seeds; and
- Planting treated seeds.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following non-agricultural scenarios for a variety of representative use sites:

- Mixing/loading liquids and wettable powders for groundboom applications;
- Applying dusts via shaker cans;
- Applying granules by hand;
- Applying ready-to-use products via aerosol cans and trigger-spray bottles;
- Applying sprays via groundboom equipment;
- Loading/applying dusts via bulb dusters, dust bags, and plunger dusters;
- Loading/applying granules via belly grinders, cups, rotary spreaders, and spoons;
- Mixing/loading/applying liquids via backpack, injector, manually-pressurized handwand, mechanically-pressurized handgun, and pour-on equipment;
- Mixing/loading/applying wettable powders via backpack, manually-pressurized handwands, and mechanically-pressurized handguns; and
- Mixing/loading/applying water-soluble packets via backpack, manually-pressurized handwand, and mechanically-pressurized handgun equipment.

*Seed Treatment (Mixer/Loader, Loader/Applicator, Bagger, Sewer, Multiple Activities):* Potential occupational exposure scenarios from the use of cyfluthrin and beta-cyfluthrin as a commercial seed treatment include: mixing, loading, and applying liquid formulations to seed; bagging treated seed; and sewing bags with treated seeds. Typically, for large-scale commercial seed treatments, workers perform only those specific individual tasks listed above; however, HED assumes that workers also might perform multiple activities throughout the day. As a result, HED also assessed a "multiple activities" scenario (i.e., where one worker performs all seed treatment tasks such as mixing/loading/applying, sewing, bagging, cleaning, calibration, forklift driver, etc.).

*Planting Treated Seed (Planters):* Potential occupational exposure scenarios from the use of cyfluthrin and beta-cyfluthrin as a seed treatment include planting treated seed (secondary handler). Planting treated seed consists of the farmer purchasing bags of treated seed, placing the seed in the hopper and applying seed to fields. Planting treated seed is considered a secondary handler exposure scenario.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

*Application Rate*: The registered occupational application rates for cyfluthrin and beta-cyfluthrin are listed in Appendix F, Tables F.2a, F.2b, F.3, and F.4.

*Body Weight:* The standard body weight for the general population (80 kg) was used for all adult dermal exposure scenario covered in this risk assessment since the endpoints selected were not developmental and/or fetal effects. The endpoints selected for inhalation exposure scenarios include fetal effects. HED used the female body weight of 69 kg for those exposures.

*Unit Exposures:* It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures," are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[10]," which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[11]. However, all seed treatment unit exposures may be found in ExpoSAC Policy 14.

*Flaggers:* The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

*Aerial:* HED has no data to assess exposures to pilots using open cockpits. The only data available are for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks or coveralls over short-sleeve shirt and short pants). Per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

[10] Available: https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf
[11] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

*Water-soluble packaging:* Water-soluble packaging is an engineering control designed to prevent direct contact between users and the pesticide formulation in the packages, thereby reducing exposures. Users place the packets into water which dissolves the packaging, releasing the formulation into the water without handler exposure to significant dusts or liquid aerosols. The formulation within the packaging then mixes with the water so it can be applied as a liquid spray.

This risk assessment relies on a 2015 study by the Agricultural Handler Exposure Task Force (AHETF) that measured dermal and inhalation exposure for workers who mixed and loaded water-soluble packet pesticide products. These data are considered the most reliable data for conducting exposure and risk assessments for such products. During the initial stages of the AHETF field study, the AHETF identified work practices that the Agency agreed were inconsistent with the use of water-soluble packaging as an engineering control intended to reduce exposures. For example, AHETF observed that some workers placed the packets in removable baskets hanging from the open tank hatch and used streams of water from hoses or overhead recirculation systems as agitation methods to break open and dissolve the packaging, resulting in visible and substantial amounts of airborne powder and/or liquid aerosol where the mixer/loader was working. Current labels, including those under consideration in this risk assessment, are silent or unclear on the use of baskets in the hatch and methods of agitation.

The AHETF, in consultation with the Agency, California's Department of Pesticide Regulation (CDPR) and the Canadian Pest Management Regulatory Agency (PMRA), drafted a set of best practices for handling and adding water-soluble packets to spray tanks. The resulting AHETF "mixing/loading water-soluble packet" dataset excludes monitoring results for activities inconsistent with these practices. Commensurate with use of the new dataset, the Agency has since formatted those best practices into label language to be included on all water-soluble packet pesticide products. This revised language ensures that users know water-soluble packets are intended to dissolve in water via mechanical agitation and not to rupture them via streams of water or other means. In order to achieve the intended benefits from proper use of water-soluble packaging, these best practices should be incorporated directly on product labels, conflicting language should be removed from the same labels, and users should receive effective and timely training on the new procedures.

*Area Treated or Amount Handled:* Most of the assumptions for the area treated or the amount handled are based on ExpoSAC Policy 9.1. However, there are several exposure scenarios that do not have standard area/amount handled assumptions that have been previously set. In these situations, reasonable assumptions were made for the amount of product an occupational worker would handle daily. These assumptions are listed below:

- 1,000 $ft^2$ of poultry/livestock houses/horse barns/feed lots, residential living spaces, foundations/perimeters treated with dust end-use products using shaker cans, bulb dusters, and plunger dusters;
- 1 acre of foundations/perimeters, landscapes treated with granule end-use products using belly grinders, rotary spreaders;
- 1,000 $ft^2$ of foundations/perimeters, landscapes treated with granule end-use products via hand dispersal;

- 1,000 livestock animals treated with a dust end-use product using a shaker can[12];
- 10-100 mounds/nests treated with a granule end-use product using cups, spoons and hand dispersal;
- 10 bottles/cans used to treat foundations/perimeters, and interior landscaping;
- 2 bottles/cans used to treat residential living spaces;
- 20 bags filled to treat livestock with dust end-use products[13];
- 1,000 $ft^2$ treated with injector equipment using liquid end-use products to treat structures for termites;
- 40 gallons of liquid end-use product used to treat livestock animals as a pour-on application; and
- 100 trees treated with a liquid end-use product using injector equipment.

For seed treatment uses, the amount of active ingredient handled depends on the application rate as well as the amount of seed handled. For primary handlers (treaters), the number of seeds treated in a day (8-hour work shift) was based on ExpoSAC Policy 15.1, with 3,000 lbs of sugar beet seeds treated in a day.

For secondary seed treatment handlers (planters), it is assumed the amount of seeds planted per day equals the maximum number of acres planted, multiplied by the greatest amount of seeds planted in an acre. Using the 2011 memorandum "Acres Planted per Day and Seeding Rates of Crops Grown in the United States" (Becker, J. and Ratnayake, S., 2011), a maximum of 435,600 sugar beet seeds may be planted in an acre. It is assumed (ExpoSAC Policy 15) that 200 acres are planted a day for high-acreage field crops (such as sugar beets). This results in 87,000,000 sugar beet seeds potentially planted in one day.

*Exposure Duration:* Occupational exposure is expected to be short- and intermediate-term in duration. However, the single dose and repeat dosing cyfluthrin and beta-cyfluthrin studies show that repeat exposures do not result in lower points of departure (PODs), that is, there is no evidence of increasing toxicity with an increased duration of exposure. Therefore, for the purpose of exposure assessments, only single day risk assessments need to be conducted for cyfluthrin and beta-cyfluthrin, and these are protective of scenarios in which exposure occurs for multiple days.

*Mitigation/Personal Protective Equipment:* Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for "baseline," defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). The cyfluthrin and beta-cyfluthrin agricultural product labels direct mixers, loaders, applicators, and other handlers to wear coveralls over short-sleeved shirt and short pants, with chemical resistant gloves, footwear, eyewear, and a chemical-resistant apron when mixing, loading, or cleaning equipment. On some labels, specific

[12] The input is consistent with EPA regulatory definitions for large concentrated animal feeding operations (CAFOs). http://www.epa.gov/npdes/pubs/sector_table.pdf

[13] The input is consistent with EPA regulatory definitions for large concentrated animal feeding operations (CAFOs)http://www.epa.gov/npdes/pubs/sector_table.pdf

respirators are required. Most non-agricultural labels do not require handlers to wear any PPE, as they do not fall within the scope of the Worker Protection Standards (WPS).

*Occupational Handler Inhalation Exposure to Total Release Foggers in Greenhouses:* HED did not do an assessment of handler exposure from the use of total release foggers because dermal and inhalation exposure is expected to be negligible based on the use pattern for this method of application. A total release fogger is an aerosol pesticide device designed to automatically release its total content in one operation for the purpose of creating a permeating fog within a space to deliver the pesticide throughout the space. Therefore, total release aerosols do not need any other application equipment (PR NOTICE 98-6, 1998).

Furthermore, most product labels for total release foggers include directions for use that limit exposure to the handler, such as: 1) "tilt can away from face and depress tab," 2) "aim spray away from face and set fogger in treatment area," and 3) "immediately leave the treatment area and close the door." As a common integrated pest management (IPM) and preventive safety practice, if multiple foggers are to be activated, the labels typically recommend that the handler "start at the far end of the area, opposite from the exit door, activating and placing cans as you move across the area until you have reached the exit door." Once the handler has left the area, the labels also direct users to stay out of the treated area for a certain amount of time and to ventilate the area before re-entry.

HED recommends that PRD ensure the appropriate safety directions and re-entry restrictions are included in the labels.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE memo prepared in support of this draft risk assessment (D435058, G. Thornton, 9/1/2017).

Combining Exposures/Risk Estimates

Dermal and inhalation risk estimates were not combined in this assessment, since the toxicological effects for these exposure routes are different.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

While there are risks of concern from both dermal and inhalation exposures, inhalation exposure results in a majority of the risks of concern. The risks are detailed below.

*Occupational Handler Risk Estimates for Agricultural Uses (Table 8.1.1 and Table 8.1.2):*
There are no dermal risk estimates of concern for agricultural uses of cyfluthrin and beta-cyfluthrin (both seed treatment and non-seed treatment uses), assuming single layer clothing (i.e., coveralls over short-sleeved shirt and short pants) and no PPE. The risk estimates range from an MOE of 1,300 to 3,800,000.

With the exception of mixing/loading/applying wettable powders via mechanically-pressurized handguns, there are no inhalation risk estimates of concern for agricultural uses of cyfluthrin and beta-cyfluthrin (both seed treatment and non-seed treatment uses), using baseline clothing and no

PPE. The risk estimates for the scenarios that are not of concern assuming baseline clothing, range from an MOE of 55 to 370,000 (LOC = 30). With the addition of a protection factor 5 (PF 5) respirator, mixing/loading/applying wettable powders for use in mechanically-pressurized handguns in greenhouses and nurseries no longer results in a risk estimate of concern, with an MOE of 49.

*Occupational Handler Risk Estimates for Non-agricultural Uses (Table 9.1.3):* Many of the occupational handler dermal risk estimates are not of concern for non-agricultural uses of cyfluthrin and beta-cyfluthrin, using baseline clothing and no PPE. The dermal risk estimates for scenarios that are not of concern, assuming baseline clothing and no PPE, range from an MOE 100 to 37,000,000 (LOC = 100). However, there are several risk estimates that remain of concern even with consideration of additional PPE. Risk estimates are presented in Tables 9.1.3 where bolded risk estimates are of concern.
With the addition of gloves (i.e., single layer clothing with gloves) the following scenarios are no longer of concern:

- Applying dust via shaker can to livestock is no longer of concern with an MOE of 330;
- Hand dispersal of granules on mounds/nests (100 mounds) is still of concern with an MOE of 31.

There are a number of occupational handler inhalation risk estimates of concern for non-agricultural uses of cyfluthrin and beta-cyfluthrin, assuming baseline clothing and no PPE. The inhalation risk estimates for scenarios that are not of concern, assuming baseline clothing and no PPE, range from an MOE of 50 to 300,000. There are several risk estimates that remain of concern even with consideration of additional PPE. Risk estimates are presented below in Table 9.1.3 where bolded risk estimates are of concern.

With the addition of a PF 5 respirator, the following scenarios are no longer risk estimates of concern:

- Applying granules by hand on mounds/nests (10 mounds), is no longer of concern with an MOE of 73;
- Mixing/loading/applying liquids via manually-pressurized handwands in food handling establishments and residential living spaces is no longer of concern with MOEs of 130 and 53, respectively;
- Mixing/loading/applying liquids via mechanically-pressurized handguns on livestock and in poultry/livestock house/horse barn/feed lot is no longer of concern with MOEs of 65 and 140, respectively;
- Mixing/loading/applying wettable powders via manually-pressurized handwands in residential living spaces is no longer of concern with an MOE of 120;
- Mixing/loading/applying wettable powders via mechanically-pressurized handguns in poultry/livestock houses/horse barns/feed lots and for use in structures is no longer of concern with MOEs of 65;
- Mixing/loading/applying water-soluble packets via manually-pressurized handwands in residential living spaces is no longer of concern with an MOE of 120; and
- Mixing/loading/applying water-soluble packets via mechanically-pressurized handguns for use in structures is no longer of concern with an MOE of 65.

With the addition of a PF 10 (protection factor 10) respirator, the following scenarios no longer have risk estimates of concern:

- Loading/applying granules with a spoon on mounds/nests (100 mounds), is no longer of concern with an MOE of 57; and
- Mixing/loading/applying liquids via mechanically-pressurized handguns for use in structures is no longer of concern with an MOE of 29.

With the addition of a PF 10 respirator, the following scenarios are still of concern:

- Applying dusts via shaker can to livestock is still of concern with an MOE of 11; and
- Applying granules by hand to mounds/nests (100 mounds) is still of concern with an MOE of 15.

| Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin (Agricultural, Non-seed Treatment Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1]** | **Dermal (LOC = 100)** | **Inhalation Unit Exposure (µg/lb ai)[1]** | **Inhalation (LOC = 30)** |
| | | | **(lb ai/A)** | | **[Level of Mitigation]** | **MOE[4]** | **[Level of Mitigation]** | **MOE[5]** |
| Mixer/Loader | | | | | | | | |
| Granule | Aerial | Field crop, high-acreage | 0.0073 | 1200 acres | 8.4 [SL/No G] | 230,000 | 1.7 [No R] | 620 |
| | | Field crop, typical | 0.0073 | 350 acres | | 770,000 | | 2,100 |
| | Tractor-drawn Spreader | Field crop, high-acreage | 0.0073 | 200 acres | | 1,400,000 | | 3,700 |
| | | Field crop, typical | 0.0073 | 80 acres | | 3,400,000 | | 9,300 |
| Liquid | Aerial | Field crop, high-acreage | 0.05 | 1200 acres | 220 [SL/No G] | 1,300 | 0.219 [No R] | 710 |
| | | Field crop, typical | 0.05 | 350 acres | | 4,300 | | 2,400 |
| | | Nursery | 0.12 | 60 acres | | 11,000 | | 5,900 |
| | | Orchard/Vineyard | 0.1 | 350 acres | | 2,200 | | 1,200 |
| | Airblast | Nursery | 0.12 | 20 acres | | 32,000 | | 18,000 |
| | | Orchard/Vineyard | 0.1 | 40 acres | | 19,000 | | 11,000 |
| | Chemigation | Field crop, high-acreage | 0.05 | 350 acres | | 4,300 | | 2,400 |
| | | Field crop, typical | 0.05 | 350 acres | | 4,300 | | 2,400 |
| | | Greenhouse | 0.12 | 60 acres | | 11,000 | | 5,900 |
| | | Nursery | 0.12 | 60 acres | | 11,000 | | 5,900 |
| | | Orchard/Vineyard | 0.1 | 350 acres | | 2,200 | | 1,200 |
| | Groundboom | Field crop, high-acreage | 0.05 | 200 acres | | 7,600 | | 4,200 |
| | | Field crop, typical | 0.05 | 80 acres | | 19,000 | | 11,000 |
| | | Greenhouse | 0.12 | 60 acres | | 11,000 | | 5,900 |
| | | Nursery | 0.12 | 60 acres | | 11,000 | | 5,900 |
| | | Orchard/Vineyard | 0.1 | 40 acres | | 19,000 | | 11,000 |
| | Injector | Nursery | 0.007 lb ai/tree | 100 trees | | 110,000 | | 60,000 |
| Wettable Powder | Aerial | Nursery | 0.12 | 60 acres | 77.7 [SL/No G] | 30,000 | 2.75 [No R] | 470 |
| | Airblast | Nursery | | 20 acres | | 90,000 | | 1,400 |
| | Groundboom | Greenhouse | | 60 acres | | 30,000 | | 470 |
| | | Nursery | | 60 acres | | 30,000 | | 470 |
| Water-soluble Packaging | Aerial | Nursery | 0.12 | 60 acres | 12.5 [EC] | 190,000 | 2.6 [EC] | 490 |
| | Airblast | Nursery | | 20 acres | | 560,000 | | 1,500 |
| | Groundboom | Greenhouse | | 60 acres | | 190,000 | | 490 |
| | | Nursery | | 60 acres | | 190,000 | | 490 |
| Applicator | | | | | | | | |
| Granule | Aerial | Field crop, high-acreage | 0.0073 | 1200 acres | 1.7 [EC] | 1,100,000 | 1.3 [EC] | 810 |
| | | Field crop, typical | 0.0073 | 350 acres | 1.7 [EC] | 3,800,000 | 1.3 [EC] | 2,800 |
| | | Field crop, high-acreage | 0.0073 | 200 acres | 9.9 [SL/No G] | 1,100,000 | 1.2 [No R] | 5,300 |

| Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin (Agricultural, Non-seed Treatment Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1]** | **Dermal (LOC = 100)** | **Inhalation Unit Exposure (µg/lb ai)[1]** | **Inhalation (LOC = 30)** |
| | | | **(lb ai/A)** | | **[Level of Mitigation]** | **MOE[4]** | **[Level of Mitigation]** | **MOE[5]** |
| | Tractor-drawn Spreader | Field crop, typical | 0.0073 | 80 acres | 9.9 [SL/No G] | 2,900,000 | 1.2 [No R] | 13,000 |
| Spray (Liquid/WP/WSP staring formulations) | Aerial | Field crop, high-acreage | 0.05 | 1,200 acres | 2.08 [EC] | 130,000 | 0.0079 [EC] | 31,000 |
| | | Field crop, typical | 0.05 | 350 acres | | 460,000 | | 110,000 |
| | | Nursery | 0.12 | 60 acres | | 1,100,000 | | 260,000 |
| | | Orchard/Vineyard | 0.1 | 350 acres | | 230,000 | | 54,000 |
| | Airblast | Nursery | 0.12 | 20 acres | 1770 [SL/No G] | 3,900 | 4.71 [No R] | 820 |
| | | Orchard/Vineyard | 0.1 | 40 acres | | 2,400 | | 490 |
| | Groundboom | Field crop, high-acreage | 0.05 | 200 acres | 78.6 [SL/No G] | 21,000 | 0.34 [No R] | 2,700 |
| | | Field crop, typical | 0.05 | 80 acres | | 53,000 | | 6,800 |
| | | Greenhouse | 0.12 | 60 acres | | 30,000 | | 3,800 |
| | | Nursery | 0.12 | 60 acres | | 30,000 | | 3,800 |
| | | Orchard/Vineyard | 0.1 | 40 acres | | 53,000 | | 6,800 |
| Flagger | | | | | | | | |
| Granule | Aerial | Field crop, high-acreage/typical | 0.0073 | 350 acres | 2.75 [SL/No G] | 2,400,000 | 0.15 [No R] | 24,000 |
| Spray (Liquid/WP/WSP staring formulations) | Aerial | Field crop, high-acreage/typical | 0.05 | 350 acres | 11 [SL/No G] | 87,000 | 0.35 [No R] | 1,500 |
| | | Nursery | | 60 acres | | 210,000 | | 3,700 |
| | | Orchard/Vineyard | | 350 acres | | 43,000 | | 750 |
| Mixer/Loader/Applicator | | | | | | | | |
| Liquid | Backpack | Greenhouse | 0.0014 lb ai/gallon | 40 gallons | 13200 [SL/No G] | 23,000 | 140 [No R] | 1,200 |
| | | Nursery (Foliar) | | | 58400 [SL/No G] | 5,100 | 69.1 [No R] | 2,400 |
| | | Nursery (Ground/soil-directed) | | | 8260 [SL/No G] | 36,000 | 2.58 [No R] | 64,000 |
| | Manually-pressurized handwand | Greenhouse | | | 100000 [SL/No G] | 3,000 | 30 [No R] | 5,500 |
| | | Nursery | | | 100000 [SL/No G] | 3,000 | 30 [No R] | 5,500 |
| | Mechanically-pressurized handgun | Greenhouse | | 1,000 gallons | 3500 [SL/No G] | 3,400 | 120 [No R] | 55 |
| | | Nursery | | | 6050 [SL/No G] | 2,000 | 1.74 [No R] | 760 |
| | | Orchard/Vineyard | 0.004 lb ai/gallon | | 6050 [SL/No G] | 690 | 1.74 [No R] | 270 |
| | | Field crop, typical | 0.005 lb ai/gallon | | 6050 [SL/No G] | 550 | 1.74 [No R] | 210 |
| Wettable Powder | Backpack | Greenhouse | 0.00024 lb ai/gallon | 40 gallons | 13200 [SL/No G] | 130,000 | 140 [No R] | 6,900 |
| | | Nursery (Foliar) | | | 58400 [SL/No G] | 30,000 | 69.1 [No R] | 14,000 |

| Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin (Agricultural, Non-seed Treatment Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** (lb ai/A) | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1]** [Level of Mitigation] | **Dermal (LOC = 100)** MOE[4] | **Inhalation Unit Exposure (µg/lb ai)[1]** [Level of Mitigation] | **Inhalation (LOC = 30)** MOE[5] |
| | | Nursery (Ground/soil-directed) | | | 8260 [SL/No G] | 210,000 | 2.58 [No R] | 370,000 |
| | Manually-pressurized handwand | Greenhouse | | | 100000 [SL/No G] | 17,000 | 30 [No R] | 32,000 |
| | | Nursery | | | 100000 [SL/No G] | 17,000 | 30 [No R] | 32,000 |
| | Mechanically-pressurized handgun | Greenhouse (Broadcast) | | 1,000 gallons | 3500 [SL/No G] | 20,000 | 120 [No R] | 320 |
| | | Greenhouse (Drench/Soil-/Ground-directed) | | | 4310 [SL/No G] | 16,000 | 3931 [No R] | **10** |
| | | | | | | | 786.2 [PF 5] | 49 |
| | | Nursery (Foliar) | | | 6050 [SL/No G] | 11,000 | 8.68 [No R] | 4,500 |
| | | Nursery (Drench/Soil-/Ground-directed) | | | 4310 [SL/No G] | 130,000 | 3931 [No R] | **10** |
| | | | | | | | 786.2 [PF 5] | 49 |
| Water-soluble Packaging | Backpack | Greenhouse | 0.00024 lb ai/gallon | 40 gallons | 13200 [SL/No G] | 130,000 | 140 [No R] | 6,900 |
| | | Nursery (Foliar) | | | 58400 [SL/No G] | 30,000 | 69.1 [No R] | 14,000 |
| | | Nursery (Ground/soil-directed) | | | 8260 [SL/No G] | 210,000 | 2.58 [No R] | 370,000 |
| | Manually-pressurized handwand | Greenhouse | | | 100000 [SL/No G] | 17,000 | 30 [No R] | 32,000 |
| | | Nursery | | | 100000 [SL/No G] | 17,000 | 30 [No R] | 32,000 |
| | Mechanically-pressurized handgun | Greenhouse (Broadcast) | | 1,000 gallons | 3500 [SL/No G] | 20,000 | 120 [No R] | 320 |
| | | Greenhouse (Drench/Soil-/Ground-directed) | | | 3500 [SL/No G] | 20,000 | 120 [No R] | 320 |
| | | Nursery (Foliar) | | | 6050 [SL/No G] | 11,000 | 8.68 [No R] | 4,500 |
| | | Nursery (Drench/Soil-/Ground-directed) | | | 6050 [SL/No G] | 11,000 | 8.68 [No R] | 4,500 |

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline (SL/No G, No R), PPE (SL/G: single layer plus gloves, DL/G: double layer plus gloves, PF 5: protection factor 5 respirator, PF 10: protection factor 10 respirator), and Eng. Controls (EC).

2 Based on registered labels. See Appendix F.

3 Exposure Science Advisory Council Policy #9.1, with the exception of the "tree injection" scenario.

4 Dermal MOE = Dermal BMDL (mg/kg/day) ÷ Dermal Dose (mg/kg/day). Bolded risk estimates are of concern. Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) × DAF (0.56%) ÷ BW (80 kg).

5 Inhalation MOE = Inhalation HED (mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Bolded risk estimates are of concern. Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (69 kg).

| Table 9.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin (Agricultural, Seed Treatment). | | | | | | |
|---|---|---|---|---|---|---|
| **Crop or Target** | **Dermal Unit Exposure[1] (mg/lb ai)** | **Inhalation Unit Exposure[1] (mg/lb ai)** | **Maximum Application Rate[2]** | **Amount Of Seed Treated (T) or Planted (P) Per Day[3]** | **Dermal (LOC = 100)** | **Inhalation (LOC = 30)** |
| | **[Level of PPE]** | **[Level of PPE]** | | | **MOE[4]** | **MOE[5]** |
| Loader/Applicator | | | | | | |
| Sugarbeets | 0.079 [SL/No G] | 0.00034 [No R] | 0.007 lb ai/lb seed | 3,000 (T) lb seed/day | 10,000 | 1,300 |
| Sewer | | | | | | |
| Sugarbeets | 0.0062 [SL/No G] | 0.00023 [No R] | 0.007 lb ai/lb seed | 3,000 (T) lb seed/day | 130,000 | 1,900 |
| Bagger | | | | | | |
| Sugarbeets | 0.0091 [SL/No G] | 0.00016 [No R] | 0.007 lb ai/lb seed | 3,000 (T) lb seed/day | 87,000 | 2,800 |
| Multiple Activities | | | | | | |
| Sugarbeets | 0.134 [SL/No G]* | 0.0016 [No R] | 0.007 lb ai/lb seed | 3,000 (T) lb seed/day | 5,900 | 280 |
| Planters | | | | | | |
| Sugarbeets | 1.51 [SL/No G]** | 0.0034 [No R] | 0.00000017 lb ai/seed | 87,120,000 (P) seed/day | 750 | 180 |

* "No glove" hand exposure back-calculated from available "gloved hand" exposure data by multiplying by 10.

** "Gloved" hand exposure calculated from available "no glove" hand exposure data by dividing by 10; "PF5" respirator exposure calculated from available "no respirator" exposure data by dividing by 5.

1 Based on the Science Advisory Council for Exposure Policy 14 (May 2003); Level of mitigation: Baseline (Single layer, SL, no gloves, No G, no respirator, No R).

2 Based on registered labels, see Appendix F.

3 Based on pounds of seed treated per day (Sugar Beets) from HED Exposure Science Advisory Council Interim Policy 15.1.

4 Dermal MOE = Dermal BMDL (mg/kg/day) ÷ Dermal Dose (mg/kg/day). Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/lb of seed) × Amount Handled Daily (lb seed treated or planted/day) × DAF (0.56%) ÷ BW (80 kg). Bolded risk estimates are of concern.

5 Inhalation MOE = Inhalation HED (mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/lb of seed) × Amount Handled Daily (lb seed treated or planted/day) ÷ BW (69 kg). Bolded risk estimates are of concern.

| Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin (Non-agricultural Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1]** | **Dermal** | **Inhalation Unit Exposure (µg/lb ai)[1]** | **Inhalation** |
| | | | | | **[Level of Mitigation]** | **MOE[4]** | **[Level of Mitigation]** | **MOE[5]** |
| Mixer/Loader | | | | | | | | |
| Liquid | Groundboom | Golf course | 0.094 lb ai/A | 40 acres | 220 [SL/No G] | 20,000 | 0.219 [No R] | 11,000 |
| Wettable powder | Groundboom | Golf course | 0.134 lb ai/A | 40 acres | 77.7 [SL/No G] | 320,000 | 2.75 [No R] | 5,000 |
| Applicator | | | | | | | | |
| Dust | Shaker can | Poultry/livestock house/horse barn/feed lot | 0.00001 lb ai/ft$^2$ | 1,000 ft$^2$ | 4042000 [SL/No G] | 410 | 17500 [No R] | 50 |
| | | Livestock | 0.00046 lb ai/animal | 1000 animals | 4042000 [SL/No G] | **9** | 17500 [No R] | **1.1** |
| | | | | | 110000 [SL/G] | 330 | 1750 [PF 10] | **11** |
| Granule | Hand dispersal | Foundations/perimeter | 0.000004 lb ai/ft$^2$ | 1,000 ft$^2$ | 104000 [SL/No G] | 40,000 | 470 [No R] | 4,900 |
| | | Landscaping, plants/flowers | | | | | | |
| | | Landscaping, trees/shrubs/bushes | | | | | | |
| | | Mounds/nests | 0.135 lb ai/mound | 10 mounds | 104000 [SL/No G] | 120 | 470 [No R] | **15** |
| | | | | | | | 94 [PF 5] | 73 |
| | | | | 100 mounds | 104000 [SL/No G] | **12** | 470 [No R] | **2** |
| | | | | | 40280 [DL/G] | **31** | 47 [PF 10] | **15** |
| Ready-to-use (Liquid) | Trigger-spray bottle | Foundations/perimeter | 0.008 lb ai/bottle | 10 bottles | 3660 [SL/No G] | 57,000 | 61.2 [No R] | 1,900 |
| | | Interior landscaping | | | | | | |
| | | Residential living spaces | | 2 bottles | | 290,000 | | 9,400 |
| Ready-to-use (Pressurized liquid) | Aerosol can | Foundations/perimeter | 0.001 lb ai/can | 10 cans | 190000 [SL/No G] | 8,800 | 1300 [No R] | 710 |
| | | Interior landscaping | | | | | | |
| | | Residential living space | | 2 cans | | 44,000 | | 3,600 |
| Spray (Liquid/WP/WSP staring formulations) | Groundboom | Golf course | 0.134 lb ai/A | 40 acres | 78.6 [SL/No G] | 40,000 | 0.34 [No R] | 5,100 |
| Loader/Applicator | | | | | | | | |
| Dust | Bulb duster | Residential Living Spaces | 0.000005 lb ai/ft$^2$ | 1,000 ft$^2$ | 166000 [SL/No G] | 20,000 | 1690 [No R] | 1,100 |
| | Dust bag | Livestock | 0.023 lb ai/bag | 20 bags | 227 [SL/No G] | 160,000 | 8.96 [No R] | 2,200 |
| | Plunger Duster | Foundations/perimeter | 0.000005 lb ai/ft$^2$ | 1,000 ft$^2$ | 166000 [SL/No G] | 20,000 | 1690 [No R] | 1,100 |
| Granule | Belly grinder | Foundations/perimeter | 0.17 lb ai/A | 1 acre | 10000 [SL/No G] | 9,800 | 62 [No R] | 880 |

| Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin (Non-agricultural Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1]** | **Dermal** | **Inhalation Unit Exposure (µg/lb ai)[1]** | **Inhalation** |
| | | | | | **[Level of Mitigation]** | **MOE[4]** | **[Level of Mitigation]** | **MOE[5]** |
| | | Landscaping, turf | | | 10000 [SL/No G] | 9,800 | 62 [No R] | 880 |
| | | Landscaping, trees/shrubs/bushes | | | 10000 [SL/No G] | 9,800 | 62 [No R] | 880 |
| | | Landscaping, plants/flowers | | | 10000 [SL/No G] | 9,800 | 62 [No R] | 880 |
| | Cup | Foundations/perimeter | 0.000004 lb ai/ft$^2$ | 1,000 ft$^2$ | 112 [SL/No G] | 37,000,000 | 12.5 [No R] | 180,000 |
| | | Mounds/nests | 0.135 lb ai/mound | 10 mounds | 112 [SL/No G] | 110,000 | 12.5 [No R] | 550 |
| | | | | 100 mounds | 112 [SL/No G] | 11,000 | 12.5 [No R] | 55 |
| | | Landscaping, trees/shrubs/bushes | 0.000004 lb ai/ft$^2$ | 1,000 ft$^2$ | 112 [SL/No G] | 37,000,000 | 12.5 [No R] | 180,000 |
| | | Landscaping, plants/flowers | | | 112 [SL/No G] | 37,000,000 | 12.5 [No R] | 180,000 |
| | Rotary spreader | Landscaping, turf | 0.17 lb ai/A | 5 acre | 440 [SL/No G] | 45,000 | 10 [No R] | 1,100 |
| | Spoon | Foundations/perimeter | 0.000004 lb ai/ft$^2$ | 1,000 ft$^2$ | 4170 [SL/No G] | 1,000,000 | 121 [No R] | 19,000 |
| | | Mounds/nests | 0.135 lb ai/mound | 10 mounds | 4170 [SL/No G] | 3,000 | 121 [No R] | 57 |
| | | | | 100 mounds | 4170 [SL/No G] | 300 | 121 [No R] | **6** |
| | | | | | | | 12.1 [PF 10] | 57 |
| | | Landscaping, trees/shrubs/bushes | 0.000004 lb ai/ft$^2$ | 1,000 ft$^2$ | 4170 [SL/No G] | 1,000,000 | 121 [No R] | 19,000 |
| | | Landscaping, plants/flowers | | 1,000 ft$^2$ | 4170 [SL/No G] | 1,000,000 | 121 [No R] | 19,000 |
| Mixer/Loader/Applicator | | | | | | | | |
| Liquid | Backpack | Foundations/perimeter | 0.04 lb ai/gallon | 40 gallons | 8260 [SL/No G] | 1,300 | 2.58 [No R] | 2,200 |
| | | Landscaping, turf (Broadcast) | 0.0008 lb ai/gallon | | 58400 [SL/No G] | 8,900 | 69.1 [No R] | 4,200 |
| | | Landscaping, turf (Spot) | 0.0008 lb ai/gallon | | 8260 [SL/No G] | 63,000 | 2.58 [No R] | 110,000 |
| | | Landscaping, trees/shrubs/bushes | 0.0004 lb ai/gallon | | 58400 [SL/No G] | 18,000 | 69.1 [No R] | 8,300 |
| | | Landscaping, plants/flowers | 0.0004 lb ai/gallon | | 58400 [SL/No G] | 18,000 | 69.1 [No R] | 8,300 |
| | | Poultry/livestock house/horse barn/feed lot | 0.0042 lb ai/gallon | | 2510 [SL/No G] | 40,000 | 30 [No R] | 1,800 |
| | | Structural | 0.04 lb ai/gallon | | 2510 [SL/No G] | 4,200 | 30 [No R] | 190 |
| | Injector | Structural | 0.016 lb ai/ft$^2$ | 1000 ft$^2$ | 1300 [SL/No G] | 800 | 2.2 [No R] | 260 |

| Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin (Non-agricultural Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1]** | **Dermal** | **Inhalation Unit Exposure (µg/lb ai)[1]** | **Inhalation** |
| | | | | | **[Level of Mitigation]** | **MOE[4]** | **[Level of Mitigation]** | **MOE[5]** |
| | Manually-pressurized handwand | Livestock | 0.009 lb ai/gallon | 40 gallons | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Food handling establishment | 0.008 lb ai/gallon | | 29000 [SL/No G] | 1,800 | 1100 [No R] | **26** |
| | | | | | | | 220 [PF 5] | 130 |
| | | Foundations/perimeter | 0.04 lb ai/gallon | | 100000 [SL/No G] | 100 | 30 [No R] | 190 |
| | | Landscaping, trees/shrubs/bushes | 0.0004 lb ai/gallon | | 100000 [SL/No G] | 10,000 | 30 [No R] | 19,000 |
| | | Landscaping, plants/flowers | 0.0004 lb ai/gallon | | 100000 [SL/No G] | 10,000 | 30 [No R] | 19,000 |
| | | Landscaping, turf | 0.0008 lb ai/gallon | | 100000 [SL/No G] | 5,200 | 30 [No R] | 9,600 |
| | | Mounds/nests | 0.009 lb ai/gallon | | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Poultry/livestock house/horse barn/feed lot | 0.0042 lb ai/gallon | | 100000 [SL/No G] | 990 | 30 [No R] | 1,800 |
| | | Residential living spaces | 0.02 lb ai/gallon | | 29000 [SL/No G] | 720 | 1100 [No R] | **10** |
| | | | | | | | 220 [PF 5] | 53 |
| | | Structural | 0.04 lb ai/gallon | | 100000 [SL/No G] | 100 | 30 [No R] | 190 |
| | Mechanically-pressurized handgun | Livestock | 0.009 lb ai/gallon | 1000 gallons | 1800 [SL/No G] | 1,000 | 79 [No R] | **13** |
| | | | | | | | 15.8 [PF 5] | 65 |
| | | Golf course | 0.094 lb ai/acre | 5 acres | 1140 [SL/No G] | 31,000 | 1.9 [No R] | 10,000 |
| | | Landscaping, trees/shrubs/bushes | 0.0004 lb ai/gallon | 1000 gallons | 6050 [SL/No G] | 6,900 | 8.68 [No R] | 2,700 |
| | | Landscaping, turf | 0.17 lb ai/A | 5 acres | 1140 [SL/No G] | 17,000 | 1.9 [No R] | 5,700 |
| | | Poultry/livestock house/horse barn/feed lot | 0.0042 lb ai/gallon | 1000 gallons | 1800 [SL/No G] | 2,200 | 79 [No R] | **28** |
| | | | | | | | 15.8 [PF 5] | 140 |
| | | Structural | 0.04 lb ai/gallon | 1000 gallons | 1800 [SL/No G] | 230 | 79 [No R] | **3** |
| | | | | | | | 7.9 [PF 10] | 29 |
| | Pour-on | Livestock | 0.009 lb ai/gallon | 40 gallons | 2510 [SL/No G] | 18,000 | 30 [No R] | 850 |
| Wettable powder | Backpack | Foundations/perimeter | 0.009 lb ai/gallon | 40 gallons | 8260 [SL/No G | 5,600 | 2.58 [No R] | 9,900 |
| | | Landscaping, turf (Broadcast) | | | 58400 [SL/No G] | 800 | 69.1 [No R] | 370 |
| | | Landscaping, turf (Spot) | | | 8260 [SL/No G] | 5,600 | 2.58 [No R] | 9,900 |
| | | Landscaping, trees/shrubs/bushes | | | 58400 [SL/No G] | 800 | 69.1 [No R] | 370 |

| Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin (Non-agricultural Uses). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Formulation** | **Application Equipment** | **Representative Use Site** | **Maximum Application Rate[2]** | **Area Treated or Amount Handled Daily[3]** | **Dermal Unit Exposure (µg/lb ai)[1] [Level of Mitigation]** | **Dermal MOE[4]** | **Inhalation Unit Exposure (µg/lb ai)[1] [Level of Mitigation]** | **Inhalation MOE[5]** |
| | | Landscaping, plants/flowers | | | 58400 [SL/No G] | 800 | 69.1 [No R] | 370 |
| | | Poultry/livestock house/horse barn/feed lot | | | 2510 [SL/No G] | 18,000 | 30 [No R] | 850 |
| | | Structural | | | 2510 [SL/No G] | 18,000 | 30 [No R] | 850 |
| | Manually-pressurized handwand | Foundations/perimeter | 0.009 lb ai/gallon | 40 gallons | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Landscaping, turf | | | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Mounds/nests | | | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Poultry/livestock house/horse barn/feed lot | | | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Residential living spaces | | | 29000 [SL/No G] | 1,600 | 1100 [No R] | **23** |
| | | | | | | | 220 [PF 5] | 120 |
| | | Structural | | | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | Mechanically-pressurized handgun | Golf course | 0.134 lb ai/A | 5 acres | 1650 [SL/No G] | 15,000 | 250 [No R] | 55 |
| | | Landscaping, turf | 0.19 lb ai/A | | 1650 [SL/No G] | 11,000 | 250 [No R] | 39 |
| | | Poultry/livestock house/horse barn/feed lot | 0.009 lb ai/gallon | 1000 gallons | 1800 [SL/No G] | 1,000 | 79 [No R] | **13** |
| | | | | | | | 15.8 [PF 5] | 65 |
| | | Structural | | | 1800 [SL/No G] | 1,000 | 79 [No R] | **13** |
| | | | | | | | 15.8 [PF 5] | 65 |
| Water-soluble packaging | Backpack | Foundations/perimeter | 0.009 lb ai/gallon | 40 gallons | 8260 [SL/No G] | 5,600 | 2.58 [No R] | 9,900 |
| | | Landscaping, turf (Broadcast) | 0.0003 lb ai/gallon | | 58400 [SL/No G] | 24,000 | 69.1 [No R] | 11,000 |
| | | Landscaping, turf (Spot) | | | 8260 [SL/No G] | 170,000 | 2.58 [No R] | 300,000 |
| | | Structural | 0.009 lb ai/gallon | | 2510 [SL/No G] | 18,000 | 30 [No R] | 850 |
| | Manually-pressurized handwand | Foundations/perimeter | 0.009 lb ai/gallon | 40 gallons | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Landscaping, turf | 0.0003 lb ai/gallon | | 100000 [SL/No G] | 14,000 | 30 [No R] | 26,000 |
| | | Residential living spaces | 0.009 lb ai/gallon | | 29000 [SL/No G] | 1,600 | 1100 [No R] | **23** |
| | | | | | | | 220 [PF 5] | 120 |
| | | Structural | 0.009 lb ai/gallon | | 100000 [SL/No G] | 460 | 30 [No R] | 850 |
| | | Landscaping, turf | 0.128 lb ai/A | 5 acres | 1350 [SL/No G] | 19,000 | 18 [No R] | 800 |

**Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyfluthrin and Beta-cyfluthrin (Non-agricultural Uses).**

| Formulation | Application Equipment | Representative Use Site | Maximum Application Rate[2] | Area Treated or Amount Handled Daily[3] | Dermal Unit Exposure (µg/lb ai)[1] [Level of Mitigation] | Dermal MOE[4] | Inhalation Unit Exposure (µg/lb ai)[1] [Level of Mitigation] | Inhalation MOE[5] |
|---|---|---|---|---|---|---|---|---|
| | Mechanically-pressurized handgun | Structural | 0.009 lb ai/gallon | 1000 gallons | 1800 [SL/No G] | 1,000 | 79 [No R] | **13** |
| | | | | | | | 15.8 [PF 5] | 65 |

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline (SL/No G, No R), PPE (SL/G: single layer plus gloves, DL/G: double layer plus gloves, PF 5: protection factor 5 respirator, PF 10: protection factor 10 respirator), and Eng. Controls (EC).

2 Based on registered labels. See Appendix F.

3 Exposure Science Advisory Council Policy #9.1, with the exception of the dust applications, granule applications on foundations/perimeters/landscapes/mounds/nests, ready-to-use applications, injector applications, and liquid applications on livestock.

4 Dermal MOE = Dermal BMDL (mg/kg/day) ÷ Dermal Dose (mg/kg/day). Bolded risk estimates are of concern. Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) × DAF (0.56%) ÷ BW (80 kg).

5 Inhalation MOE = Inhalation HED (mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Bolded risk estimates are of concern. Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (69 kg).

## 9.2 Occupational Post-application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures might occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

### 9.2.1 Inhalation Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During registration review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for cyfluthrin and beta-cyfluthrin.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Furthermore, inhalation exposure during dusty mechanical activities such as shaking and mechanical harvesting is another potential source of post-application inhalation exposure. However, the airblast applicator scenario is believed to represent a reasonable worst case surrogate estimate of post-application inhalation exposure during these dusty mechanical harvesting activities. The non-cancer inhalation risk estimate for commercial airblast application is not of concern (i.e., MOE > 100)

*Greenhouse Uses:* The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements. [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)]

*Indoor Commercial Uses:* Commercial applicators do not typically return to the treated areas after an indoor commercial pesticide application (sites such as warehouses, food handling

establishments, and hotels, etc.) and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators.

*Seed Treatment Uses:* A post-application inhalation exposure assessment is not required, as exposure is expected to be negligible. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and secondary handlers (i.e., planters). It is expected that these exposure estimates would be protective of any potential low-level post-application inhalation exposure that could result from these types of applications.

### 9.2.2 Dermal Post-Application Risk

Occupational Post-application Dermal Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed below on an individual basis.

*Exposure Duration:* Occupational exposure is expected to be short-term in duration. The single dose and repeat dosing cyfluthrin and beta-cyfluthrin studies show that repeat exposures do not result in lower points of departure (PODs), that is, there is no evidence of increasing toxicity with an increased duration of exposure. Therefore, for the purpose of the exposure assessment, only single day risk assessments need to be conducted for cyfluthrin and beta-cyfluthrin, and these are protective of scenarios in which exposure occurs for multiple days.

*Transfer Coefficients:* It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients," are presented in the ExpoSAC Policy 3[14] which, along with additional information about the ARTF data, can be found at the Agency website[15]. Table 9.2.2.1 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites. The post-application activity with the highest transfer coefficient for each crop is shown below.

**Table 9.2.2.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients.**

| Crops | Policy Crop Group Category | Crop Height | Foliage Density | Transfer Coefficients ($cm^2/hr$) | Activities |
|---|---|---|---|---|---|
| Alfalfa | Field/row crop, low/medium | Low | Full | 1,900 | Irrigation (hand set) |
| Nut Tree | Tree, "nut" | High | Full | 1,400 | Harvesting, Hand |

[14] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[15] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

| Table 9.2.2.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients. | | | | | |
|---|---|---|---|---|---|
| **Crops** | **Policy Crop Group Category** | **Crop Height** | **Foliage Density** | **Transfer Coefficients ($cm^2$/hr)** | **Activities** |
| Pome, Stone Tree | Tree, "fruit", deciduous | High | Full | 3,600 | Thinning Fruit |
| Dried Shelled Legume Vegetables (and Pea, Southern) | Field/row crop, low/medium | High | Full | 1,900 | Irrigation (hand set) |
| Brassica, leafy | Vegetable, head and stem Brassica | Low | Full | 4,200 | Scouting, Hand Harvesting, Hand Weeding |
| Cucurbits | Vegetable, cucurbit | Low | Full | 1,900 | Irrigation (hand set) |
| Carrot | Vegetable, "root" | Low | Full | 1,900 | Irrigation (hand set) |
| Leafy Vegetables | Vegetable, leafy | Low | Full | 1,900 | Irrigation (hand set) |
| Corn | Field/row crop, tall | High | Full | 8,800 | Detasseling/Harvesting, Hand |
| Cotton | Field/row crop, low/medium | Low | Min | 5,050 | Harvesting, Mechanical, Tramper |
| Fruiting Vegetables | Vegetables, fruiting | High | Full | 1,900 | Irrigation (hand set) |
| Grass | Field/row crop, low/medium | Low | Full | 1,900 | Irrigation (hand set) |
| Golf course | Turf/sod | Low | Full | 3,700 | Maintenance |
| Grape | Vine/trellis | High | Full | 19,300 | Turning, girdling |
| Citrus Tree | Tree, "fruit", evergreen | High | Full | 1,400 | Harvesting, Hand |
| Greenhouse Crop | Unassigned | High | Full | 230 | Harvesting/Pruning/Weeding (hand), Scouting, Container Moving, Transplanting, Grafting, Propagating, Pinching |
| Hop | Bunch/bundle | High | Full | 1,900 | Irrigation (hand set) |
| Nursery Crop | Unassigned | High | Full | 1,900 | Irrigation (hand set) |
| Peanut | Field/row crop, low/medium | Low | Full | 1,900 | Irrigation (hand set) |
| Tuberous and Corm Vegetables | Vegetable, "root" | Low | Full | 1,900 | Irrigation (hand set) |
| Sorghum | Field/row crop, tall | High | Full | 210 | Scouting |
| Soybean | Field/row crop, low/medium | Low | Full | 1,100 | Scouting |
| Sugarcane | Sugarcane | High | Full | 8,800 | Harvesting, hand |

| Table 9.2.2.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients. | | | | | |
|---|---|---|---|---|---|
| **Crops** | **Policy Crop Group Category** | **Crop Height** | **Foliage Density** | **Transfer Coefficients ($cm^2$/hr)** | **Activities** |
| Sunflower | Field/row crop, tall | High | Full | 90 | Scouting, Bird control |
| Tobacco | Bunch/bundle | High | Full | 1,900 | Irrigation (hand set) |
| Wheat | Field/row crop, low/medium | Low | Full | 1,100 | Scouting |

*Application Rate:* Application rates for specific crops may be found in Appendix F.

*Exposure Time:* The average occupational workday is assumed to be 8 hours.

*Dislodgeable Foliar Residues:* Chemical-specific data have been submitted for the determination of dislodgeable foliar cyfluthrin residues on treated corn (M. Crowley; 03/1/2013; D403726). The study was conducted at two test sites; one at Mendota, California and the other at Stanfield, Arizona. DFR values found at the California site were much higher than those found at the Florida site. For the purpose of this assessment, HED used the California DFR values. The data from both the CA and the AZ sites produced very similar half-lives and predicted initial residue values; however, HED used the CA DFR values. The control samples from the site in AZ showed contamination with cyfluthrin from applications of a cyfluthrin containing product that was applied several days before application of the test substance. Traditional field fortification and laboratory fortification were not prepared for the CA site. However, the registrant stated that, for both the California site and the Arizona site, the analytical results indicate that the internal standard did not degrade. Conditions that result in degradation of the cyfluthrin in the sample would also cause degradation of the internal standard. Thus, correction for field fortification recoveries was not needed. The maximum average DFR value at the California site was 0.161 $\mu g/cm^2$ at day 0 after application. HED calculated a half-life of 19.7 days ($r^2$=0.9416) for cyfluthrin, with a maximum modeled DFR value of 0.142 $\mu g/cm^2$ at day 0 after application. The cyfluthrin DFR data were adjusted to reflect the maximum crop application rates (see Appendix F).

*Turf Transferable Residues:* For post-application activities on golf courses, chemical-specific turf transferable residue (TTR) data were submitted for four pyrethroids: cyfluthrin (liquid formulations), cypermethrin (liquid and wettable powder formulations), deltamethrin (liquid formulations), and permethrin (liquid formulations). HED used the cyfluthrin TTR data for a liquid formulation. The cyfluthrin TTR data (average day 0 TTR 0.011 $\mu g/cm^2$, was normalized to 0.1 lb ai/A) were adjusted to reflect the maximum golf course application rates (Appendix F).

*Dislodgeable Boll Residues:* Chemical-specific dislodgeable boll residue data have not been submitted for cyfluthrin and beta-cyfluthrin. Therefore, this assessment uses HED's default assumption that 2x the application is available for transfer on day 0 following the application, and that the residues dissipate at a rate of 10% each following day.

Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE memo prepared in support of this draft risk assessment (D435058, G. Thornton, 9/1/2017).

Summary of Occupational Post-application Non-Cancer Dermal Risk Estimates

There are no occupational post-application dermal risk estimates of concern at day 0 after last application of a cyfluthrin and beta-cyfluthrin end-use product. The dermal risk estimates range from an MOE of 500 to 170,000.

**Table 9.2.2.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin.**

| Crop/Site | Activities | Transfer Coefficient ($cm^2$/hr) | DFR/TTR/ DBR | Dermal Dose (mg/kg/day)[1] | MOE[2] |
|---|---|---|---|---|---|
| Alfalfa | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Nut Tree | Harvesting, Hand | 1,400 | 0.14 | 0.00011 | 11,000 |
| Pome, Stone Tree | Thinning Fruit | 3,600 | 0.14 | 0.00028 | 4,200 |
| Dried Shelled Legume Vegetables (and Pea, Southern) | Irrigation (hand set) | 1,900 | 0.16 | 0.00017 | 7,000 |
| Brassica, leafy | Scouting, Hand Harvesting, Hand Weeding | 4,200 | 0.16 | 0.00037 | 3,200 |
| Cucurbits | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Carrot | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Leafy Vegetables | Irrigation (hand set) | 1,900 | 0.16 | 0.00017 | 7,000 |
| Corn | Detasseling/Harvesting Hand | 8,800 | 0.14 | 0.00068 | 1,700 |
| Cotton | Harvesting, Mechanical, Tramper | 5,050 | 0.1 | 0.00028 | 4,100 |
| Fruiting Vegetables | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Grass | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Golf course | Maintenance | 3,700 | 0.015 | 0.00003 | 38,000 |
| Grape | Turning, girdling | 19,300 | 0.22 | 0.0023 | 500 |
| Citrus Tree | Harvesting, Hand | 1,400 | 0.31 | 0.00025 | 4,700 |
| Greenhouse Crop | Harvesting/Pruning/Weeding (hand), Scouting, Container Moving, Transplanting, Grafting, Propagating, Pinching | 230 | 0.38 | 0.00005 | 24,000 |
| Hop | Irrigation (hand set) | 1,900 | 0.16 | 0.00017 | 7,000 |

| Table 9.2.2.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Cyfluthrin and beta-cyfluthrin. | | | | | |
|---|---|---|---|---|---|
| **Crop/Site** | **Activities** | **Transfer Coefficient ($cm^2$/hr)** | **DFR/TTR/ DBR** | **Dermal Dose (mg/kg/day)[1]** | **MOE[2]** |
| Nursery Crop | Irrigation (hand set) | 1,900 | 0.38 | 0.0004 | 2,900 |
| Peanut | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Tuberous and Corm Vegetables | Irrigation (hand set) | 1,900 | 0.14 | 0.00015 | 7,900 |
| Sorghum | Scouting | 210 | 0.14 | 0.00002 | 72,000 |
| Soybean | Scouting | 1,100 | 0.14 | 0.00009 | 14,000 |
| Sugarcane | Harvesting, hand | 8,800 | 0.14 | 0.00068 | 1,700 |
| Sunflower | Scouting, Bird control | 90 | 0.14 | 0.000007 | 170,000 |
| Tobacco | Irrigation (hand set) | 1,900 | 0.01 | 0.00002 | 79,000 |
| Wheat | Scouting | 1,100 | 0.12 | 0.00007 | 16,000 |

1. Daily Dermal Dose = [DFR (µg/$cm^2$) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (2.6%)] ÷ BW (80 kg).
2. MOE = BMDL (mg/kg/day) / Daily Dermal Dose.

Restricted Entry Interval

Cyfluthrin and beta-cyfluthrin are classified as Toxicity Category IV via the dermal route and for skin irritation potential. They are classified as Toxicity Category III for eye irritation. It is not a skin sensitizer. Currently, labels list a range of REIs, from 12-48 hours. Short-term post-application risk estimates were not of concern on day 0 (12 hours following application) for all activities. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to cyfluthrin and beta-cyfluthrin. HED recommends an REI of 12 hours. An REI of at least 12 hours is listed on the currently registered labels that fall underneath the Worker Protection Standards, and is considered protective of post-application exposure.

## 10.0 Public Health and Pesticide Epidemiology Data

In support of this draft human health risk assessment for registration review, HED prepared a report of the incidents and epidemiology associated with cyfluthrin (D435950, E. Evans and S. Recore, 9/30/2016). The following information is a summary of the report. In the current Incident Data System (IDS) database analysis from January 1, 2011 to August 19, 2016, HED found that, in the main IDS, 141 incidents were reported for the single chemical (only). However, in the Aggregate IDS, 2644 incidents were reported involving cyfluthrins. A query of SENSOR-Pesticides 1998-2013 identified a total of 680 cases involving cyfluthrins, 387 of which involved a single active ingredient. Eighty-five percent of these cases were low in severity. Four cyfluthrin cases, however, were high in severity. A query of the National Pesticide Information Center (NPIC) from 1/1/11 to 12/31/15 identified a total of 84 human incidents involving cyfluthrins. A query of PISP from 2010-2013 identified a total of 38 cases involving cyfluthrins.

The high number of reported incidents in IDS and SENSOR-Pesticides might be related to the fact that pyrethroids are now among the most commonly used pesticides in residential settings. Pyrethroids are much less acutely toxic to humans than many older chemicals including organophosphates. EPA canceled almost all indoor organophosphate uses and now the pyrethroids have, in many cases, replaced them for residential insect control, with a variety of pyrethroid products now being widely available to consumers. The residential use of pyrethroids increased from less than 1 million pounds used in 2001, when the phase-out began, to 2–4 million pounds used in 2007, after the phase-out was completed.

Although numerous incidents were reported to IDS and SENSOR-Pesticides, the majority of these incidents were classified as minor severity. Minor severity means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly, and usually involved skin, eye, or respiratory irritation. Further, roughly half of the cyfluthrin incidents reported to Main IDS and to SENSOR-Pesticides involved exposure to multiple active ingredients. Products containing multiple active ingredients are common among pyrethroid products. Incidents involving multiple pesticides are considered to provide less certain information about the potential effects of exposure from a particular pesticide. Several cyfluthrin products were identified as being involved with a large portion of the incident reports. These products might warrant label reviews to improve label language and potentially help to mitigate exposure risks. The Agency will continue to monitor the incident information and, if a concern is triggered, conduct additional analysis.

The single AHS study that evaluated epidemiological associations of cyfluthrin exposure with adverse health outcomes concluded that cyfluthrin exposure was not significantly associated with either allergic wheeze or non-allergic wheeze. Publications resulting from the AHS will continue to be monitored for further findings, and the Agency will ensure these findings are considered and, if appropriate, fully reviewed in the risk assessment phase of the registration review process.

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# Appendix A: Toxicology Profile

## A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food uses for cyfluthrin and beta-cyfluthrin are listed in the table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

| Study | | 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 (rodent) | yes | yes |
| 870.3250 | 90-Day Dermal | no | - |
| 870.3465 | 90-Day Inhalation (rodent) | yes | yes |
| 870.3700a | Developmental Toxicity (rodent) | yes | yes |
| 870.3700b | Developmental Toxicity (nonrodent) | yes | yes |
| 870.3800 | Reproduction (rodent) | 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 (rodent) | 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 Neurotoxicity (hen) | yes | yes |
| 870.6100b | 90-Day Neurotoxicity (hen) | no | - |
| 870.6200a | Acute Neurotoxicity Screening Battery (rat) | yes | yes |
| 870.6200b | 90-Day Neurotoxicity Screening Battery (rat) | yes | yes |
| 870.6300 | Develop. Neurotoxicity (rodent) | yes | yes |
| 870.7485 | General Metabolism (rodent) | yes | yes |
| 870.7600 | Dermal Penetration (rodent) | yes | yes |
| 870.7800 | Immunotoxicity (rodent) | yes | yes |
| Special Studies for Ocular Effects | | no | - |

[1] Satisfied with combined chronic toxicity/carcinogenicity study.

## A.2 Toxicity Profile Tables

| Table A.2.1 Acute Toxicity Profile – Cyfluthrin Technical | | | | |
|---|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID(s)** | **$LD_{50}$ and Other Results** | **Toxicity Category** |
| 870.1100 | Acute oral rat | 00131499 | 590-869 mg/kg in PEG male<br>1189-1271mg/kg in PEG female | III |
| | | 00131518 | 16.2 mg/kg in Cremophor male<br>< 100 mg/kg in Cremophor female<br>590 mg/kg in PEG male<br>609 mg/kg in PEG female | I |
| | Acute oral mouse | 00131499 | 291 mg/kg male<br>609 mg/kg female | II |
| | Acute oral rabbit | 00131499 | > 1000 mg/kg male | III |
| | Acute oral dog | 00131499 | > 100 mg/kg male. Could not be properly assessed because of vomiting. | NA |
| 870.1200 | Acute dermal rat | 00131499 | > 5000 mg/kg | IV |
| 870.1300 | Acute inhalation rat | 00131499 | 0.200-0.735 mg/L | II |
| 870.2400 | Acute eye irritation rabbit | 00131499 | Transient irritation only. No corneal opacity. | III |
| 870.2500 | Acute dermal irritation rabbit | 00131499 | No irritation | IV |
| 870.2600 | Skin sensitization guinea pigs | 00131512 | Not a sensitizer | - |

PEG = polyethylene glycol

| Table A.2.2 Acute Toxicity Profile – Beta-Cyfluthrin Technical | | | | |
|---|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID(s)** | **$LD_{50}$ and Other Results** | **Toxicity Category** |
| 870.1100 | Acute oral rat | 41244101 | 211-343 mg/kg in xylene | II |
| | | 41244102 | 380-655 mg/kg in PEG males<br>655-1369 mg/kg in PEG females | II males<br>III females |
| | | 41244104 | 84-141mg/kg in acetone/peanut oil males<br>77-108 mg/kg in acetone/peanut oil females | II |
| | Acute oral mouse | 41244103 | 91-165 mg/kg | II |
| 870.1200 | Acute dermal rat | 41244105 | > 5000 mg/kg | IV |
| 870.1300 | Acute inhalation rat | 41205701 | 0.082-0.532 mg/L | II |
| 870.2400 | Acute eye irritation rabbit | 41205702 | Slight irritation | III |
| 870.2500 | Acute dermal irritation rabbit | 41205702 | Very slight irritation | IV |
| 870.2600 | Skin sensitization guinea pigs | 41244107 | Not a sensitizer | - |

PLEASE NOTE: DERs for many of studies below have not been updated to follow current toxicological practices; therefore, some of the endpoints are conservative. However, DERs for studies used to select points of departure are up to date.

| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.1100 | Acute oral rat Cyfluthrin in PEG 400 | 00131499 (1980) Core minimum 10, 50, 100, 250, 300, 350, 500, 750, 1000, 2500 mg/kg | $LD_{50}$ = 590/1189 mg/kg M/F Signs: Doses not indicated. Onset 10-60 min. Duration up to 10 days. Restlessness, salivation, hypermotility, scratching, scraping, shaking head, "slow worm-like movement." Reduced breathing rate followed by apathy, ataxia, straddled gait, reduced sensitivity. |
| | Acute oral rat Cyfluthrin in Cremophor or PEG 400 | 00131518 (1982) Core minimum Doses not listed | $LD_{50}$ = 16.2/<100 mg/kg M/F in Cremophor $LD_{50}$ = 590/609 mg/kg M/F in PEG 400 Signs: Doses or vehicle not indicated. Onset 1 hour. Duration 1-5 days. Tremors, rolling movements, disturbed motility and respiration. |
| | Acute oral rat Beta-Cyfluthrin in Xylene | 41244101 (1987) Acceptable M: l, 10, 50, 100, 250, 400, 500 mg/kg F: 1, 10, 100, 250, 315, 400, 500 mg/kg | $LD_{50}$ = 211/336 mg/kg M/F Signs: At 10 mg/kg, salivation and uncoordinated gait. At >10 mg/kg, additional signs of cramped posture, splayed gait, piloerection, digging and preening movements, and rolling. At ≥10 mg/kg, onset as early as 28 minutes and maximum duration was 9 days. |
| | Acute oral rat Beta-Cyfluthrin in PEG 400 | 41244102 (1987) Acceptable M: 10, 50, 100, 250, 500, 630, 710, 800, 1000, 1400, 2500 mg/kg F: 10, 50, 100, 800, 1000, 1400, 1500, 1600, 1800, 2000 mg/kg | $LD_{50}$ = 380/1369 mg/kg M/F Signs: Clinical signs (lethargy, digging and preening movements, uncoordinated gait, splayed gait, salivation, piloerection, soft feces, rolling, increased activity, difficult breathing) of minimal-to-moderate severity in all rats at each dose level except 10 mg/kg. Signs onset as early as 28 minutes and continued for up to 12 days. |
| | Acute oral rat Beta-Cyfluthrin in Acetone/ Peanut Butter | 41244104 Acceptable M: 1, 10, 71, 100, 160, 180, 200, 250 mg/kg F: 1, 10, 63, 71, 80, 100, 160, 200, 250 mg/kg | $LD_{50}$ = 84/77 mg/kg M/F Signs: At 10 mg/kg lethargy and cramped posture in fasted rats as early as 1 hour after exposure with a maximum duration of 3 days; fed rats also had digging and preening movements 2 hours after exposure. At > 10 mg/kg lethargy, cramped posture, digging and preening movements, uncoordinated gait, splayed gait, soft feces, salivation, piloerection, rolling, increased activity, and difficult breathing; onset as early as 33 minutes after exposure and continued for a maximum of 10 days; signs were not delayed. |
| 870.1200 | Acute dermal rat Cyfluthrin concentrate (no vehicle) | 00131499 Acceptable 2500, 5000 mg/kg | $LD_{50}$ > 5000 mg/kg M/F Signs: One female died. Symptoms of "apathy" and ataxia cleared 5-7 days after exposure (doses not indicated). |

PLEASE NOTE: DERs for many of studies below have not been updated to follow current toxicological practices; therefore, some of the endpoints are conservative. However, DERs for studies used to select points of departure are up to date.

| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Acute dermal rat<br>Beta-Cyfluthrin in xylene | 41244105<br>Acceptable<br>0, 100, 1000, 2500, 5000 mg/kg | $LD_{50}$ > 5000 mg/kg M/F<br>Signs: One high dose female terminated 24 hours after exposure due to self-inflicted bite wounds. At 100 mg/kg and above: lethargy, uncoordinated gait, splayed gait, salivation, vocalization, jumping, digging and preening movements, difficult breathing and soft feces. Time of onset 37 minutes to 3 days. Maximum duration 11 days. |
| 870.3100 | 90-Day oral toxicity (rat)<br>Beta-Cyfluthrin | 41244108 (1986)<br>Acceptable/guideline<br>0, 30, 125, 500 ppm<br>M: 0, 2.3, 9.5, 39 mg/kg/d<br>F: 0, 2.5, 11, 42 mg/kg/d | NOAEL = 9.5 mg/kg/day<br>LOAEL = 39 mg/kg/day based on gait abnormalities, necrosis in head and neck region, mortality, decreased body weight gain. |
| | 28-Day oral toxicity (rat)<br>Cyfluthrin | 00131525 (1983)<br>Supplementary<br>0, 100, 300, 1000 ppm<br>0, 5, 15, 50 mg/kg/day | NOAEL = 15 mg/kg/day<br>LOAEL = 50 mg/kg/day based on gait abnormalities, salivation, nervousness, decrease body weight, food consumption, changes in hematological, clinical chem. & urinalysis parameters, increases in selected organ weights, cytoplasmic swelling of glandular epithelium of submaxillary gland, minimal degrees of fiber degeneration in sciatic nerve (# not reported) which disappeared after recovery period. |
| | 90-Day oral toxicity (rat)<br>84% Cyfluthrin mixed with Wessalon S (silica desiccant) | 00131524 (1980)<br>Unacceptable/not upgradable<br>0, 30, 100, 300 ppm<br>M: 0, 2.2, 7.4, 22 mg/kg/d<br>F: 0, 2.7, 8.8, 28 mg/kg/d | A LOAEL was not observed. Based on weight of the evidence, the dose levels in this study would have to be at least doubled to reach a LOAEL. See chronic study MRID 44459301. |
| 870.3150 | 90-Day oral toxicity (dog)<br>Beta-Cyfluthrin | 41267801 (1987)<br>Acceptable/guideline<br>0, 10, 60, 360 ppm<br>M: 0, 0.4, 2.4, 14 mg/kg/d<br>F: 0, 0.4, 2.5, 15 mg/kg/d | NOAEL = 2.4 mg/kg/day<br>LOAEL = 14 mg/kg/day based on gait abnormalities, vomiting and decrease in body weight gain. |
| | 28-Day oral toxicity (dog)<br>Beta-cyfluthrin | 41244109 (1986)<br>Acceptable/non-guideline<br>0, 10, 80, 640/320 ppm<br>0, 0.3, 2.0, 16/8 mg/kg/d | NOAEL = 2.0 mg/kg/day<br>LOAEL = 8.0 mg/kg/day based on impaired movement and conjunctival irritation. |
| 870.3200 | 21-Day dermal toxicity (rat)<br>Cyfluthrin | 44066001 (1996)<br>Acceptable/guideline<br>0, 113, 376, 1077 mg/kg/d | Dermal NOAEL = 113 mg/kg/day<br>LOAEL = 376 mg/kg/day based on gross (crusty zones, discoloration) and microscopic lesions (ulceration with inflammatory cell infiltration, acanthosis, hyperkeratosis, dermal fibrosis).<br>Systemic NOAEL = 376 mg/kg/day<br>LOAEL = 1077 mg/kg/day based on decreased food consumption, red nasal discharge (4/8 males) and urine staining (2/8 females). |

PLEASE NOTE: DERs for many of studies below have not been updated to follow current toxicological practices; therefore, some of the endpoints are conservative. However, DERs for studies used to select points of departure are up to date.

| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3465 | 90-Day inhalation toxicity (rat) Cyfluthrin | 00157793 (1984), 40082901, 40239301 Acceptable/guideline 0, 0.00009, 0.00071, 0.00451 mg/L 0, 0.02, 0.19, 1.2 mg/kg/d | NOAEL = 0.00071 mg/L (0.19 mg/kg/day) LOAEL = 0.0045 mg/L (1.2 mg/kg/day) based on clinical signs in both sexes (agitation with erected tail on weeks 6-13 on exposure days only) and decreased body weight at week 12 in males only. |
| | 28-Day inhalation toxicity (rat) Cyfluthrin | 41842601 (1989) Acceptable/non-guideline 0, 0.00044, 0.006, 0.047 mg/L 0, 0.12, 1.6, 12 mg/kg/d | NOAEL = 0.00044 mg/L (0.12 mg/kg/day) LOAEL = 0.006 mg/L (1.6 mg/kg/day) based on decreases in male body weight, decreased respiratory rate in males; reduction in leukocyte counts in females. Neurological clinical signs observed at a higher dose. |
| | 28-Day inhalation toxicity (rat) Beta-Cyfluthrin | 41783001 (1989) Acceptable/non-guideline 0, 0.00026, 0.0027, 0.023 mg/L 0, 0.07, 0.71, 6.1 mg/kg/d | NOAEL = 0.00026 mg/L (0.07 mg/kg/day) LOAEL = 0.0027 mg/L (0.71 mg/kg/day) based on decreased respiratory rate, decreased urine pH in males. Neurological clinical signs observed at a higher dose. |
| Special Study | 5-Day inhalation study (rat) Beta-Cyfluthrin | 41205708 (1988) Acceptable/non-guideline 0, 0.00025, 0.0038, 0.028 mg/L 0, 0.07, 1.0, 7.4 mg/kg/d | NOAEL = 0.00025 mg/L (0.07 mg/kg/day) LOAEL = 0.0038 mg/L (1.0 mg/kg/day) based on unkempt fur, piloerection, hepatoi foci in lungs. |
| 870.3700a | Prenatal developmental in rat – oral Beta-Cyfluthrin | 44116501 (1996) Acceptable/guideline 0, 3, 10, 40 mg/kg/d | Maternal NOAEL = 10 mg/kg/day LOAEL = 40 mg/kg/day based on increased mortality (3/26 vs. 0/27) and increased incidence of hypoactivity, salivation and locomotive incoordination. Developmental NOAEL = 10 mg/kg/day LOAEL = 40 mg/kg/day based on reduced fetal body weights and increased skeletal variations. |
| | Prenatal developmental in rat – oral Cyfluthrin | 00157794 (1983) Unacceptable 0, 1, 3, 10 mg/kg/day | Maternal NOAEL = 10 mg/kg/day LOAEL was not observed Developmental NOAEL = 10 mg/kg/day LOAEL was not observed Data from range-finding study clearly supported higher dose levels in this study. |
| | Prenatal developmental in rat – inhalation Cyfluthrin | 40780401 (1988) Acceptable/guideline Assay 1: 0, 0.0011, 0.0047, 0.0237 mg/L/day 0, 0.299, 1.277, 6.44 mg/kg/day Assay 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 | Maternal NOAEL = 0.0011 mg/L (0.299 mg/kg/day) 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) LOAEL = 0.0011 mg/L (0.299 mg/kg/day) based on increased incidence of runts and skeletal anomalies in sternum. |

PLEASE NOTE: DERs for many of studies below have not been updated to follow current toxicological practices; therefore, some of the endpoints are conservative. However, DERs for studies used to select points of departure are up to date.

| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Prenatal developmental in rat – inhalation<br>Cyfluthrin | 43393401 (1994)<br>Acceptable/guideline<br>0, 0.00046, 0.00255, 0.0119[a], 0.0128[ab] mg/L<br>0.125, 0.692, 3.234[a], 3.478[ab] mg/kg/day<br>[a] Groups received same nominal dose 0.0125 mg/L.<br>[b] Group also dosed with 40% oxygen. | Maternal NOAEL = not determined<br>LOAEL = 0.00046 mg/L (0.125 mg/kg/day) based on decreased body weight gain and relative food efficiency.<br>Developmental NOAEL = 0.00046 mg/L (0.125 mg/kg/day)<br>LOAEL = 0.00255 mg/L (0.692 mg/kg/day) based on reduced fetal and placental weights and reduced ossification in phalanx, metacarpals, vertebrae. |
| 870.3700b | Prenatal oral developmental in (rabbit)<br>Cyfluthrin | 42675401 (1992)<br>Acceptable/guideline<br>0, 20, 60, 180 mg/kg/d | Maternal NOAEL = 20 mg/kg/day<br>LOAEL = 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period.<br>Developmental NOAEL = 180 mg/kg/day<br>LOAEL = not observed |
| 870.3800 | Reproduction and fertility effects (rat)<br>Cyfluthrin | 44371402 (1997)<br>Acceptable/non-guideline<br>0, 25, or 50 ppm<br>M: 0, 1.9, 3.8 mg/kg/d<br>F: 0, 2.1, 4.2 mg/kg/d | Parental/Systemic NOAEL = 3.8 mg/kg/day<br>LOAEL was not determined<br>Offspring NOAEL = 3.8 mg/kg/day<br>LOAEL was not determined |
| 870.3800 | Reproduction and fertility effects (rat)<br>Cyfluthrin | 44371401 (1996)<br>Acceptable/guideline<br>0, 50, 125, 400 ppm<br>Premating and gestation: M: 0, 3, 9, 29 mg/kg/d<br>F: 0, 4, 10, 33 mg/kg/d<br>Lactation:<br>0, 7, 19, or 59 mg/kg/d | Parental/Systemic NOAEL = 3 mg/kg/day<br>LOAEL = 9 mg/kg/day based on reductions in body weights and food consumption.<br>Offspring NOAEL = 7 mg/kg/day<br>LOAEL = 19 mg/kg/day based on coarse tremors in pups during lactation and decreases in mean litter weight. |
| Special Study | Pilot 1-generation reproduction study (rat)<br>Cyfluthrin | 43792901 (1995)<br>Acceptable/non-guideline<br>0, 50, 150, 400, 600 ppm<br>Premating:<br>M: 0, 3.4, 9.3, 24, 39 mg/kg/d<br>F: 0, 4.1, 11, 27, 44 mg/kg/d<br>Gestation:<br>0, 3.9, 10, 27, 45 mg/kg/d<br>Lactation:<br>0, 7.8, 23, 60, 96 mg/kg/d | Parental/Systemic NOAEL = 23 mg/kg/day<br>LOAEL = 60 mg/kg/day based on hind leg splay, ataxia, reduction in body weight gain.<br>Offspring NOAEL = 7.8 mg/kg/day<br>LOAEL = 23 mg/kg/day based on tremors during lactation and pup weight decreases. |
| | 3-generation reproduction study (rat)<br>50% Cyfluthrin mixed with 50% Wessalon S (silica desiccant) | 00131532 (1983)<br>Acceptable/non-guideline<br>0, 50, 150, 450 ppm<br>M: 0, 3.8, 12, 37 mg/kg/d<br>F: 0, 5.4, 15, 49 mg/kg/d | Parental/Systemic NOAEL = 12 mg/kg/day<br>LOAEL = 37 mg/kg/day based on decreased body weight gain.<br>Offspring NOAEL = 5.4 mg/kg/day<br>LOAEL = 15 mg/kg/day based on decreased viability during lactation period and decreased body weight gains. |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4100b | Chronic toxicity (dog)<br>Cyfluthrin | 44435401 (1997)<br>Acceptable/guideline<br>0, 50, 100, 360, 500 ppm<br>M: 0, 1.4, 2.4, 11, 15 mg/kg/d<br>F: 0, 1.5, 3.6, 11, 178 mg/kg/d | NOAEL = 2.4 mg/kg/day<br>LOAEL = 11 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions in males and females. |
| | Chronic toxicity (dog)<br>50% Cyfluthrin mixed with 50% Wessalon S (silica desiccant) | 00151358 (1983)<br>Core minimum<br>0, 40, 160, 640 ppm<br>0, 1.0, 4.0, 16 mg/kg/d | NOAEL = 4.0 mg/kg/day<br>LOAEL = 16 mg/kg/day based on gait abnormalities, vomiting, liquid feces, decreased body weights (males). |
| Special Study | 6-Month oral toxicity (dog)<br>Cyfluthrin | 00131530 (1981)<br>Core minimum<br>0, 65, 200, 600 ppm<br>0, 1.6, 5.0, 15 mg/kg/d | NOAEL = 5.0 mg/kg/day<br>LOAEL = 15 mg/kg/day based on gait abnormalities, arching backs, vomiting, diarrhea. |
| 870.4200 | Carcinogenicity (mouse)<br>Cyfluthrin | 44589701 (1998)<br>Acceptable/guideline<br>0, 200, 750, 1400/1600 (M/F) ppm<br>M: 0, 32, 115, 233 mg/kg/d<br>F: 0, 38, 141, 310 mg/kg/d | NOAEL = 32/141mg/kg/day (M/F)<br>LOAEL = 115/310 mg/kg/day (M/F) based on ear skin lesions and reduced body weight gains in males; and in females: clinical signs, macroscopic and microscopic pathology findings, and reduced body weights, body weight gains, and food consumption.<br>No evidence of carcinogenicity |
| | Carcinogenicity (mouse)<br>50% Cyfluthrin mixed with 50% Wessalon S (silica desiccant) | 00137304 (1983)<br>Acceptable/guideline for carcinogenicity<br>Unacceptable for chronic toxicity<br>0, 50, 200, 800 ppm<br>M: 0, 11.6, 45.8, 194.5 mg/kg/d<br>F: 0, 15.3, 63.0, 259.9 mg/kg/d | Female mortality by study end increased at the mid dose (52%, 60%, 74%, 68% in control, low, mid and high dose groups). Male ALK was elevated at all dose levels compared to controls 43-230% at 6 months; 37-73% at 12 months), but not at 18 months (data not available at study termination due to improper handling of samples). Histopathology did not confirm liver as a target organ<br>No evidence of carcinogenicity |
| 870.4300 | Combined chronic / carcinogenicity (rat)<br>Cyfluthrin | 44459301 (1997)<br>Acceptable/guideline<br>0, 50, 225, 450 ppm<br>M: 0, 2.6, 12, 23 mg/kg/d<br>F: 0, 3.3, 14, 28 mg/kg/d | NOAEL = 2.6 mg/kg/day<br>LOAEL = 12 mg/kg/day based on overall declines in body weight gain by 12 and 10% in males and females, respectively.<br>No evidence of carcinogenicity |
| | Combined chronic / carcinogenicity (rat)<br>50% Cyfluthrin mixed with Wessalon S (silica desiccant) | 00137303 (1983)<br>Acceptable/guideline<br>0, 50, 150 or 450 ppm<br>M: 0, 2.0, 6.2, 19 mg/kg/d<br>F: 0, 2.7, 8.2, 25 mg/kg/d | NOAEL = 6.2 mg/kg/day<br>LOAEL = 19 mg/kg/day based on decreased body weights and body weight gains.<br>No evidence of carcinogenicity |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.5100 | Bacterial Reverse Mutation Test (*S. typhimurium* and *E. coli*) Cyfluthrin | 00131539 (1982) Acceptable/guideline 5-5000 µg/plate | No increases in reverse mutations with and without activation. Positive and negative controls results as expected. |
| | Bacterial Reverse Mutation Test (*S. typhimurium* and *E.*) Cyfluthrin | 00131540 (1982) Acceptable/guideline 100-10,000 µg/plate | No increases in reverse mutations with and without activation. Positive and negative controls results as expected. |
| | Bacterial Reverse Mutation Test (*S. typhimurium*) Beta-Cyfluthrin | 41244111 (1986) Acceptable/guideline Initial assay: 20-12500 ug/plate Confirmatory assay: 500-8000 ug/plate | No increases in reverse mutations with and without activation. Positive and negative controls results as expected. |
| | Yeast Cytotoxicity and Reverse Mutation Test (*S. cerevisiae* strains S138 and S211) Cyfluthrin | 00131541, 00144017 (1982) Acceptable/guideline 312.5-1000 µg/mL | No cytotoxicity observed. S138 number of reverse mutations was similar to negative control. In one of two assay runs, S211 showed moderate increase in reverse mutations with and without activation, compared to negative control but the increase was not dose-dependent. Positive control results as expected. |
| 870.5300 | *In vitro* Mammalian Cell Gene Mutation Test (Chinese hamster ovary cells) Cyfluthrin | 00157796 (1985) Acceptable/guideline 3-10 µl/ml | Incidence of total mutant colonies was similar in treated and solvent control. Mutation frequency (per $10^6$ cells) increased 4-fold at 10 µL/mL, 76-fold in positive control, relative to solvent control. This results were not repeated in a second assay run, except for the positive control, therefore test is considered negative. |
| | *In vitro* Mammalian Cell Gene Mutation Test (Chinese hamster ovary cells) Beta-Cyfluthrin | 41244112 (1989) Acceptable/guideline 20-100 µg/mL | No mutagenic response up to insoluble doses with and without metabolic activation. |
| 870.5375 | *In vitro* Mammalian Chromosome Aberration Test (human lymphocytes) Beta-Cyfluthrin | 41205703 (1988) Acceptable/guideline 500, 1000, 5000 ug/mL | Not clastogenic up to insoluble and cytotoxic doses and without metabolic activation. |
| 870.5395 | Mammalian Erythrocyte Micronucleus Test (mouse) Beta-Cyfluthrin | 41244110 (1988) Acceptable/guideline 0, 80 mg/kg | No increased frequency of micronucleated polychromatic erythrocytes in mice bone marrow cells. Clinical signs observed (apathy, uncoordinated movement, staggering gait, rolling over, and salivation). |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.5500 | Bacterial DNA Damage or Repair Tests (*E. coli*) Cyfluthrin | 00131538 (1981) Acceptable/guideline 62.5-1000 µg/plate | No evidence of inhibition with and without metabolic activation. Positive and negative controls results as expected. |
| 870.5550 | Unscheduled DNA Synthesis in Mammalian Cells in Culture (rat hepatocytes) Cyfluthrin | 00157798 (1985) Acceptable/guideline 17, 50, 167, 500, 1667, 5000 µg/ml | The positive control was a potent inducer of unscheduled DNA synthesis, whereas the test article was not (up to the level of cytotoxicity). |
| | Unscheduled DNA Synthesis in Mammalian Cells in Culture (rat hepatocytes) Beta-Cyfluthrin | 41205704 (1987) Acceptable/guideline 1.01-1010 ug/mL | Tested over an appropriate range of concentrations (up to cytotoxic levels) with appropriate controls and showed no evidence of unscheduled DNA synthesis induction. |
| 870.5575 | Mitotic Gene Conversion in *Saccharomyces cerevisiae* Cyfluthrin | 00131542 (1982) Acceptable/guideline 625-10000 µg/ml | The number of crossovers and the frequency of tryptophan convertants were similar in dosed cultures and negative controls, both with and without activation. |
| 870.5900 | *In vitro* Sister Chromatid Exchange Assay (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 for induction of sister chromatid exchange, even at doses which were cytotoxic (non-activated systems) or at the limit of solubility (activated systems). |
| 870.6100 | Delayed Neurotoxicity – Oral (hen) Cyfluthrin | 00163040 (1986) Core Minimum Single dose: 0, 4300 mg/kg Two doses 21 days apart: 4300 mg/kg/d Five consecutive doses: 1500 mg/kg/d | Single Dose: 1/7 vehicle died. Cyfluthrin dosed hens were somnolent and emaciated. No changes in esterase activity. Two dose: All were aggressive, somnolent and emaciated. 2/16 loss so much weight and had to be terminated moribund, one of them was also ataxic. Five consecutive doses: All were aggressive, somnolent, emaciated, and had cyanosis of the crest. 3/10 loss so much weight and had to be terminated moribund. Positive (TOCP) control hens were aggressive, had slight ataxia, and signs that progressed through stages of reduced motor activity, stilted gait, stumbling, clumsy landing, sitting on hocks, and shuffling gait. Esterase activity reduced 90% in bran, 82% spinal cord. |
| | Delayed Neurotoxicity – Oral (hen) Cyfluthrin | 00156585 (1985) Supplementary 0 and 5000 mg/kg/d | The study was to last 14 days, but all dosed hens died by day 3. No changes in esterase activity. |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Delayed Neurotoxicity – Inhalation (hen) Cyfluthrin | 00131510 (1983) Core minimum Single Dose: 0.285, 0.445 or 0.596 mg/L for 4 hours 15 Doses over 3 wks: 0.614 mg/L for 6 hours | Single Dose: 9/10 showed clinical signs (behavior disturbances, sedation, eye irritancy), some weight loss, and died at 0.596 mg/L<br>Three weeks: 1 hen died. Nonspecific sings were also observed. Nothing remarkable was noted at necropsy. |
| | Delayed Neurotoxicity – Oral (hen) Cyfluthrin | 00131544 (1982) Supplementary Single dose: 5000 mg/kg Two doses 21 days apart: 5000 mg/kg | Single dose: Initial weight loss but recovered. No other treatment-related effects were observed. No histopathology conducted in the single-dose study.<br>Two dose: 1/20 clinical signs on day 30. No microscopic lesions in the nervous system. |
| | Delayed Neurotoxicity – Dermal (hen) Cyfluthrin | 00131545 (1982) Minimum Five consecutive doses: 5000 mg/kg (N=10) Three wks 5 days/wk: 5000 mg/kg (N=10) 6 hours/day | Five consecutive doses: 2/10 died. All showed apathy and disturbed behavior during treatment but later recovered, also local irritation and weight loss. 2/10 had sciatic nerve fiber degeneration.<br>Three weeks: Apathy, local irritation, weight loss. No microscopic indication of neurotoxicity. |
| | Delayed Neurotoxicity – Oral (hen) Cyfluthrin | 00131543 (1981) Supplementary Single dose: 1000, 2500, 5000 mg/kg Two doses 21 days apart: 5000 mg/kg/d Five consecutive doses: 5000 mg/kg/d | Single dose: At 5000 mg/kg, 5/10 died and 2/10 had moderate fiber alterations in the sciatic nerve (axon fragmentation; swelling and eosinophilia of axon fragments; vacuolation of myelin sheaths). At 2500 mg/kg, 6/10 showed signs of excitation during the first 3 days after treatment.<br>Two dose: Hens showed intoxication signs during first 3 days but were normal until the second dose, when 4/30 hens died. Symptoms following second dose subsided; however, a second set of symptoms developed in 4/30 hens (resembled delayed type neurotoxicity). Nerve fiber degeneration was present in majority of hens.<br>Five consecutive doses: 4/10 died. All showed initial intoxication signs which eventually disappeared. Behavioral disorders, by drowsiness and a cramped gait were observed in 3/6 survivors. Mottled kidneys and brittle livers were noted at necropsy. Treatment-related sciatic nerve fiber degeneration (distension or granular disintegration of medullary sheath, swollen or fragmented axis cylinders and proliferated Schwann's cell) were reported. One hen had similar lesions in the spinal marrow. |
| 870.6200a | Acute neurotoxicity screening battery Beta-Cyfluthrin | 44401101 (1997) Acceptable/guideline 0, 0.5, 2, 10 mg/kg | NOAEL = 2 mg/kg/day<br>LOAEL = 10 mg/kg/day based on clinical signs, changes in FOB parameters, and decreases in motor activity. |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Acute neurotoxicity screening battery<br>Beta-Cyfluthrin | 47050505 (2006), 47050504 (2005)<br>Acceptable/non-guideline<br>0, 12.5, 25, 45 mg/kg in corn oil<br><br>A NOAEL/LOAEL could not be determined because effects were observed at all dose levels | Time to peak effect 2 hours. One high dose animal found dead. Home cage observations: abnormal posture, drooping eyelids at mid and high dose; low incidence clonic convulsions all doses. In-hand observations: salivation, wet/ stained fur at mid and high dose; lacrimation at high dose. Open field observations: abnormal gait and decreased number of rears all doses; clonic convulsions, low arousal and stereotypic behavior mid and high dose. All doses increase number animals with more energetic response to tail pinch and the mid and high dose groups had a decrease in the air righting reflex (slightly uncoordinated). Hind limb weakness mid and high dose corresponded with reduced hind limb grip strength for these groups. |
| Special Acute Neurotox-icity Studies | Acute FOB effects in male rats (WIL study; Weiner at al 2009)<br>Beta-Cyfluthrin | 47050504, 47050505 (2006)<br>Acceptable/non-guideline<br>0, 12.5, 25, 45 mg/kg<br>2 hrs to peak effect | Open field observations: increased number animals with abnormal gait all dose levels; clonic convulsions, low arousal and stereotypic behavior at mid and high dose; number of rears slightly decreased all treated groups. Home cage observations: four low dose animals with clonic convulsions, only one each at mid and high dose. |
| | Acute motor function in male rats (Wolansky study; Wolansky et. al. 2006)<br>Beta-Cyfluthrin | 47885701 (2006)<br>Acceptable/non-guideline<br>0, 0.05, 0.1, 0.5, 2.5, 5.0, 7.5, 10.0, 15.0 mg/kg<br>2 hrs to peak effect | BMDL = 1.17 mg/kg<br>BMD = 1.42 mg/kg using the EPA's Benchmark Dose Software (BMDS) version 2.1.2 (exponential model, p = 0.09); based on decreased motor activity.<br>No signs of excessive toxicity were observed with cage-side observations. |
| | Acute neuromuscular disfunction in male rats (tilting plane test)<br>Cyfluthrin | 00157802 (1984)<br>Acceptable/non-guideline<br>0, 0.01, 0.03, 0.1, 0.3, 1.0 mg/kg | The lowest dose at which there was a clear neurologic effect was 0.1 mg/kg (mean slip angles or 2-3° at 2 and 5 hrs with reversal by 7 hrs). The 1.0 mg/kg dose was equivalent to 5 mg/kg of diazepam (mean slip angles or 29-35° at 2 and 5 hrs with reversal by 7 hrs). |
| 870.6200b | Subchronic neurotoxicity screening battery<br>Beta-Cyfluthrin | 44296001 (1997)<br>Acceptable/guideline<br>0, 30, 125, or 400 ppm<br>M: 0, 2.0, 8.0, 27 mg/kg/d<br>F: 0, 2.3, 9.4, 31 mg/kg/d | NOAEL = 8.0 mg/kg/day<br>LOAEL = 27 mg/kg/day based on clinical signs, changes in FOB parameters and possibly decreased body weights, body weight gains, and food consumption |
| 870.6300 | Developmental neurotoxicity<br>Beta-Cyfluthrin | 46054101 (2003)<br>Acceptable/non-guideline<br>0, 30, 125, 200 ppm<br>0, 2.4, 11, 18 mg/kg/d | Maternal NOAEL = 18 mg/kg/day<br>LOAEL = not observed<br>Offspring NOAEL = 11 mg/kg/day<br>LOAEL = 18 mg/kg/day based on decreased body weight, body weight gain; decreased brain weights in females. |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special Study | 7-Day postnatal inhalation study (pups & dams) in mice<br>Cyfluthrin | 44373401 (1997)<br>Acceptable/non-guideline<br>0, 0.006, 0.015, 0.058 mg/L<br>0, 2.5, 6.2, 24 mg/kg/d<br>6 hours/day for 7 consecutive days | Maternal NOAEL = 0.058 mg/L (24.0 mg/kg/day)<br>LOAEL = not determined<br>Offspring NOAEL = 0.006 mg/L (2.48 mg/kg/day)<br>LOAEL = 0.015 mg/L (6.21 mg/kg/day) based on clinical signs and increased spontaneous motor activity in females 4 months after exposure. In adult offspring (both sexes) there was no effect of treatment on brain cortex mAChR density or binding capacity. |
| 870.7485 | Metabolism and pharmacokinetics (Rat)<br>Cyfluthrin | 00131506, 00137549 (1983)<br>Core Minimum<br>Single oral dose: 0.5, 10 mg/kg<br>Single i.v. dose: 0.5, 10 mg/kg<br>15 day oral dose: 0.5 mg/kg/d | Oral dose rapidly and nearly completely absorbed. Peak plasma levels observed about 2 hrs after dosing. > 95-98% dose excreted within 48 hours in urine and feces, virtually none in expired air. About 50% of total urinary recovery by 6-8 hours after dosing, about 90% within 24 hours. At 48 hours, only fat contained levels that exceeded (6-11X) overall mean body level. Levels in brain were lower (15-20X) than overall mean body level. Different dose levels or multiple doses did not affect the above findings significantly. Some sex differences were observed: higher urine/feces ratios in males, and slightly higher organ/tissue levels in females (except for fat tissue). Cyfluthrin is cleaved at the ester bond and then oxidized to 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 unchanged 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. |
| 870.7600 | Dermal penetration – *in vitro*<br>(human and rat)<br>Beta-Cyfluthrin | 49687302 (2004)<br>375, 1232 $\mu g/cm^2$ | Rat skin was more permeable to beta-cyfluthrin than human skin. The permeability in vitro data obtained for beta-cyfluthrin showed a 7.5-fold increased penetration at the high dose and a 12-fold increased penetration at the low dose in rat skin relative to human skin. The stratum corneum had <1% of the doses for human skin and 4-14% for rat skin after 24 hours. The total potentially absorbed dose (calculated as the sum of the total absorbed dose and total dose associated with the skin) was 4.7-14.4% for rat skin, and 0.62-0.91% for human skin. Total radiocarbon recovery was about 94% in human skin and 90-97% in rat skin. |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Dermal penetration – *in vivo* (rat) Beta-Cyfluthrin | 48290901 (2004) 380, 1200 µg/cm$^2$ | Under the conditions of this study, the absorbed plus potentially absorbed dose of beta-cyfluthrin in rats at 24 hours is 14.89% of the applied 1.2 mg/cm2 formulation (1.25 mg/cm2 actual dose) and 19.46% of the applied 0.4 mg/cm$^2$ formulation (0.38 mg/cm$^2$ actual dose). |
| 870.7800 | Immunotoxicity (male rat) | 49020803 (2012) 0, 100, 400, 800 ppm 0, 7.7, 30, 62 mg/kg/d | Systemic NOAEL = 62 mg/kg/day LOAEL was not observed. Immunotoxicity NOAEL = 62 mg/kg/day LOAEL was not observed. |
| 890.1150 | Androgen receptor binding (rat prostate) | 48615601 (2011) Satisfies EDSP Tier 1 Test Order $10^{-10}$ to $10^{-4}$ M | Based on the results from three runs, cyfluthrin is classified as a Non-Binder in the Androgen Receptor Binding Assay. |
| 890.1200 | Aromatase (human recombinant) | 48615602 (2011) Satisfies EDSP Tier 1 Test Order $10^{-10}$ to $10^{-3}$ M | Based on the data from the average response curve, cyfluthrin is classified as a Non-inhibitor of aromatase activity in this assay. |
| 890.1250 | Estrogen Receptor Binding (rat uterus) | 48615603 (2011) Satisfies EDSP Tier 1 Test Order $10^{-10}$ to $10^{-3}$ M | Based on the results from the three runs, cyfluthrin is classified as Not Interactive in the Estrogen Receptor Binding Assay. |
| 890.1400 | *In vivo* Hershberger assay (rat) | 48615605 (2011) Satisfies EDSP Tier 1 Test Order 0, 10, 20 mg/kg/day | Piloerection or increased salivation in one high dose animal during androgen agonist assay; increased salivation in one high dose and one low dose animal in anti-agonist assay. Statistically significant organ weight changes were not seen in two or more of the five androgen sensitive tissues. Cyfluthrin was negative for androgenicity and anti-androgenicity in the Hershberger assay. |
| 890.1450 | Female pubertal (rat) | 48615606 (2011) Satisfies EDSP Tier 1 Test Order 0, 10, 20 mg/kg/day | No treatment-related effects on mean cycle length, percent cycling, percent regularly cycling, or microscopic pathology. At high dose: increased salivation in 5/15 rats; age at VO was delayed ($p<0.01$; 35.73 days treated vs. 33.00 days controls); body weight at VO was increased ($p<0.05$) by 10%; and mean age at first vaginal estrus was delayed (not significant; 36.36 days vs. 34.00 days). |
| 890.1500 | Male pubertal (rat) | 48615606 (2011) Satisfies EDSP Tier 1 Test Order 0, 10, 20 mg/kg/day | No treatment-related effects on attainment of preputial separation, organ weights, hormone (serum T4, TSH, or testosterone) levels, or histopathology parameters at any dose. At the low dose: increased salivation in 1/15 rats on Day 8. At high dose: increased salivation, piloerection, lack of grooming, wasted appearance, uncoordinated movements, and/or tremors in 6/15 animals on at least one occasion. Serum TSH levels were decreased by 37% at high dose compared to controls, although not statistically significant. |

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| Table A.2.3 Acute, Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 890.1550 | Steroidogenesis Assay | 48615607 (2011)<br>Satisfies EDSP Tier 1 Test Order<br>$10^{-10}$ to $10^{-4}$ M | Based on hormone responses in three independent runs, cyfluthrin treatment did not result in statistically significant and reproducible alterations in testosterone or estradiol production. |
| 890.1600 | *In vivo* uterotrophic assay | 48615608 (2011)<br>Satisfies EDSP Tier 1 Test Order<br>0, 5, 10, 20 mg/kg/day | No statistically significant changes were seen in uterine weight in this assay. Cyfluthrin is negative in the uterotrophic assay. |

## Appendix A.3. Cyfluthrin and Beta-Cyfluthrin Inhalation Human-Equivalent Dose (HED) Calculations

### A.3.1 Methodology

Based on the EPA's reference concentration (RfC) guidance document (Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, 1994), the methodology for RfC derivations is an estimate of the quantitative dose-response assessment of non-cancer toxicity for individual inhaled chemicals. This method includes dosimetric adjustments to account for (1) species-specific relationship between exposure concentration and deposited/delivered dose, (2) pharmacokinetic differences between laboratory animals and humans, (3) differences in exposure duration between animal studies and expected human exposure, and (4) physicochemical properties of the chemical. While the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can also be used for shorter inhalation exposures because the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter durations of exposure. The method does not account for pharmacodynamic differences between laboratory animals and humans. Different sets of equations are used if the chemical behaves as a gas or as an aerosol/particle. To provide greater accuracy, the RfC also takes into account the effect of aerosols or gases on the extrathoracic, tracheobronchial, and/or pulmonary respiratory regions as described in the figure below, as well as extrarespiratory (i.e. systemic) effects.

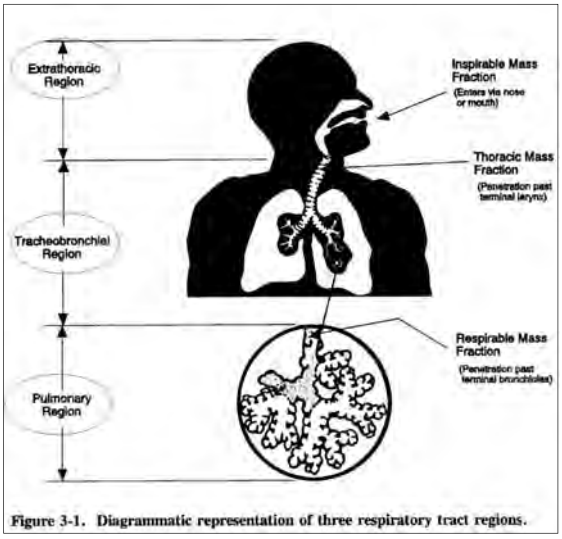


Figure A.3.1: Regions of the human respiratory tract used for HEC calculations (Figure 3-1 of the 1994 RfC methodology document)

Cyfluthrin is an aerosol/particle. Aerosols/particles are assumed to be spherical, relatively insoluble, and non-hygroscopic particles and, thus, physically distinct from gases. For such chemicals, key parameters used in the RfC method include: the inhalation study NOAEL (or LOAEL if a NOAEL is not available), minute ventilation rates ($V_E$) for animals and humans; the chemical's particle size as described by the mass median aerodynamic diameter (MMAD) and geometric standard deviation ($\sigma_g$), and duration (hours/day and days/week) of the expected human exposure scenarios. The NOAEL/LOAEL, MMAD and $\sigma_g$ were determined

experimentally under the conditions of the inhalation toxicity study for cyfluthrin (MRID 00157793) as described in section A.3.2 below. All other parameters use default assumptions described in EPA's RfC guidance (1994).

Derivation of a Human Equivalent Concentration (HEC) for inhaled aerosols/particles is described by the following equation:

$HEC_r = E \times (D_A \div D_H) \times (W_A \div W_H) \times RDDR_r$ Equation 1

HEC: Human equivalent concentration (mg/L)
E: Experimental exposure level (mg/L) or Point of Departure (POD), i.e. NOAEL or LOAEL
D: Number of hours exposed per 24 hours
W: Number of days exposed per 7 days
RDDR: Regional deposited dose ratio
r: Respiratory region (extrathoracic, tracheobronchial, pulmonary or extrarespiratory)
A: Test animals
H: Humans

The regional deposited dose ratio (RDDR) used in the above equation is the ratio between the estimated regional deposited doses (RDD) in test animals and humans. The RDDR is determined by characterizing the particulate exposure, which is in turn defined by the MMAD and the $\sigma_g$. The RDDR is generally described by the following equation:

$RDDR_r = (RDD_{r,A} \div RDD_{r,H}) \times (NF_H \div NF_A)$ Equation 2
$= ((10^{-6} \times C_{i,A} \times V_{E,A} \times F_{r,A}) \div (10^{-6} \times C_{i,H} \times V_{E,H} \times F_{r,H})) \times (NF_H \div NF_A)$
$= (C_{i,A} \div C_{i,H}) \times (V_{E,A} \div V_{E,H}) \times (F_{r,A} \div F_{r,H}) \times (SA_{r,H} \div SA_{r,A})$

$C_i$: Inhaled concentration ($mg/cm^3 = 10^{-6}$ $mg/m^3$)
$V_E$: Minute volume (mL/min)
$F_r$: Fractional deposition in the specific respiratory region
$SA_r$: Surface area of the specific respiratory region

In the above equation, the fractional deposition (F) is determined in part by the MMAD and $\sigma_g$, which describe the particle size distribution. The calculations to derive F are beyond the scope of this document and available in Appendix G of the EPA's RfC guidance document (1994).

Using EPA's route-to-route extrapolation guidance (Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/1998), HEC inhalation units of mg/L can be converted into human equivalent dose (HED) units of mg/kg/day. HEDs can be calculated for different inhalation exposure scenarios. The route-to-route extrapolation is described by the following equation:

$HED_r = HEC_r \times A \times CF \times D_H \times AF$ Equation 3

HED: Human equivalent dose (mg/kg/day)

HEC: Human equivalent concentration (mg/L)
A: Absorption ratio through the respiratory tract as compared to the oral route; assumed to be unity
CF: Human-specific value (L/hr/kg)
$D_H$: Number of hours exposed per 24 hours for humans
AF: Activity factor

The equation above uses a single conversion factor (CF) to account for default body weights and respiratory volumes per unit time. CF equals 11.8 L/hr/kg based on the EPA's RfC guidance document default breathing rate assumed for a typical human (i.e., CF = 13.8 L/min ÷ 70 kg).

A.3.2 Calculations for Cyfluthrin and beta-Cyfluthrin Inhalation Exposure Scenarios

Table A.3.2.1 contains the HEC and HED for potential occupational scenarios, generated using the Equations 1, 2, and 3 described in section A.3.1 above. Since cyfluthrin and beta-cyfluthrin behave as an aerosol/particulate and did not produce adverse effects to the respiratory track (i.e. affects only the extrarespiratory region), HECs were calculated using an RDDR that should be protective of the systemic toxicity (i.e., unkempt fur and lethargy) observed in the 90-day inhalation study. Occupational handler exposure is assumed to be 8 hours/day and 5 days/week. Residential handler and residential outdoor post-application exposures are assumed to be fewer days/week than the duration of available inhalation toxicity studies; however, downward adjustments for exposure duration (comparing animal study versus expected human exposure) are not possible. Residential indoor post-application exposure is assumed to be 2 hours/day and 7 days/week. Residential bystander exposure is assumed to be 24 hours/day and 7 days/week.

Table A.3.2.1 HECs, HEDs and Parameters Used for Calculation for Cyfluthrin and Beta-Cyfluthrin

| Scenario | $D_A$ | $D_H$ | $W_A$ | $W_H$ | RDDR | HEC (mg/L) | A | CF | HED (mg/kg/day) | UF |
|---|---|---|---|---|---|---|---|---|---|---|
| Occupational Handler | 6 | 8 | 5 | 5 | 3.195 | 0.001 | 1.0 | 11.8 | 0.134 | $UF_A$ = 3x<br>$UF_H$ = 10x |
| Residential Handler | 6 | 2 | NA | NA | 3.195 | 0.002 | 1.0 | 11.8 | 0.045 | $UF_A$ = 3x<br>$UF_H$ = 10x |
| Residential Outdoor Post Application | 6 | 2.3 | NA | NA | 3.195 | 0.002 | 1.0 | 11.8 | 0.051 | $UF_A$ = 3x<br>$UF_H$ = 10x |
| Residential Indoor Post Application | 6 | 2 | 5 | 7 | 3.195 | 0.001 | 1.0 | 11.8 | 0.032 | $UF_A$ = 3x<br>$UF_H$ = 10x |
| Residential Bystander | 6 | 24 | 5 | 7 | 3.195 | 0.0003 | NA | NA | NA | $UF_A$ = 3x<br>$UF_H$ = 10x |

$D_A$ = Number of hours exposed per 24 hours for animals. $D_H$ = Number of hours exposed per 24 hours for humans. $W_A$ = Number of days exposed per 7 days for animals. $W_H$ = Number of days exposed per 7 days for humans. RDDR = Regional deposited dose ratio. HEC = Human Equivalent Concentration (mg/L). UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies). A = Absorption ratio through the respiratory tract as compared to the oral route. CF = Human-specific value that accounts for volume respired per unit time. NA = not applicable

A.3.3 Developmental Inhalation Toxicity Study in Rats (MRID 40780401) Executive Summary (as Reviewed by the Agency in 2004)

Two developmental toxicity studies via inhalation (MRID 40780401) were conducted. In the first study, 4 groups of 30 female Bor:WISW (SPF Cpb) rats were inseminated by being housed overnight with males. The presence of sperm in the vaginal smears following mating established gestation day 0. The dams were dynamically exposed head-only to cyfluthrin dissolved in a 1:1 mixture of Lutrol and ethanol at analytical concentrations of 0, 0.0011, 0.0047 or 0.0237 mg/L/day for 6 hours/day on gestation days 6 through 15. A second study was conducted in order to establish a NOAEL for offspring toxicity. In that study, the dams were exposed to analytical concentrations of 0, 0.00009, 0.00025, 0.00059, or 0.0042 mg/L of the test material. The MMAD was 1.23 - 1.45 µm in the first study and 1.29 - 1.53 µm in the second study. An oxygen enriched atmosphere (30%) was provided for the 0.0042 mg/L group to see if the embryotoxic effects seen in the first study at this concentration could be lessened. The rats were observed several times on the exposure days except during the exposures (because of restraint for head-only exposure). They were weighed on gestation days 0, 6, 9, 12, and 20. The dams were sacrificed on day 20 and their pups removed by caesarian section. Their ovaries and uteri were examined for implantations, live young, embryonic and fetal deaths, fetal sex and weights, and external fetal abnormalities.

Combining the results of the two studies, maternal effects were observed at 0.0047 mg/L and above: reduced motility, dyspnea, piloerection, ungroomed coats and eye irritation. The symptoms were mainly observed after the end of exposure in the 0.0047 mg/L concentration group and were largely gone by the next exposure day. At 0.0237 mg/L concentration, the symptoms were observed at greater intensity over the entire exposure period. Effects in the pups were observed at 0.0011 mg/L and above. At 0.0011 mg/L and above, a dose-related increase in the incidence of runts and skeletal anomalies in the sternum were observed. At 0.0047 mg/L and above, biologically significant decreases in pup weights were observed ($p < 0.01$). At 0.0237 mg/L, increases in post-implantation loss, late embryonic deaths and in skeletal anomalies in the extremities were observed as well as microphthalmia.

The maternal NOAEL is 0.0011 mg/L and the maternal LOAEL is 0.0047 mg/L (reduced motility, dyspnea, piloerection, ungroomed coats and eye irritation). The developmental NOAEL is 0.00059 mg/L and the developmental LOAEL is 0.0011 mg/L (increases in the incidence of runts and skeletal anomalies in the sternum).

An ad hoc committee met on 4/22/93 to discuss the developmental toxicity data base for cyfluthrin. At that time, the committee recommended that, because of deficiencies that were mentioned in the review of the study, this study should be re-examined if it is to be used as a regulatory endpoint. Although the study had been graded acceptable, and NOAELs and LOAELs had been established for maternal and developmental toxicity, comments had also been made that developmental anomalies in the study had not been adequately reported. The dams in this study had reflex apnea, although it was poorly characterized.

This study is classified as acceptable guideline and satisfies the guideline requirement for a developmental toxicity study in the rat via inhalation (870.3700, §83-3a).

## A.3.4 Summary of Weight of Evidence (WOE) Considerations for Inhalation Toxicity

| Study (MRID) | Analytical Concentration mg/L (animal equivalent dose mg/kg/day) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.00009 (0.02) | 0.00026/25 (0.07) | 0.00044 (0.12) | 0.00059 (0.16) | 0.00071 (0.19) | 0.0011 (0.29) | 0.0027 (0.71) | 0.0042/38 (1.1/1.0) | 0.0045/47 (1.2) | 0.0060 (1.6) | 0.0235/237 (6.1/6.3) | 0.028 (7.4) | 0.0466 (12) |
| 90 days – cyfluthrin (00157793, 40082901, 40239301) | NOAEL | | | | Unk fur & lethargy ♀[a] after exp wks 6-13<br>BW ↓8% ♂ | | | | Unk fur & lethargy [a] after exp wk 2-5.<br>Slight unk fur & lethargy [a] no exp days wk 6-13.<br>Agitation w/ erect tail [a] after exp wk 6-13.<br>BW ↓15% ♂<br>Urine pH -1.1 ♂ | | | | |
| 28 days – cyfluthrin (41842601) | | | NOAEL | | | | | | | BW ↓10% ♂<br>↓breaths/min | | | Piloerect [a] after exp d 1-28.<br>Slight ↓activity [a] after exp wk 1<br>Slight-moderate hyperactivity [a] after exp start wk 2[b].<br>Slight bradypnea[a] after exp d1-28.<br>BW ↓14% ♂; ↓breaths/min<br>Urine pH [c] -2.1 ♂, -1.2 ♀ |
| 28 days – β-cyfluthrin (41783001) | | NOAEL | | | | | BW ↓10% ♂<br>↓breaths/min | | | | Unk fur & piloerect; "in places" slight ↓motility, but mainly ↑activity; after exp, d 1-28.<br>BW ↓11% ♂;<br>↓breaths/min<br>Urine pH [c] -0.3 ♀ | | |
| Developmental (9 days females only) – cyfluthrin (40780401) | none | none | | NOAEL | | Fetal W ↓7%<br>↑runts & | | BWG -7 g (loss) [d]<br>FetalW ↓5% | 26/30 piloerect d 2-9<br>19/30 eye irritation d 1-9 | | 29/29 piloerect & eye irritation d 1-9<br>27/29 ↓motility d 1-9 | | |

| Study (MRID) | Analytical Concentration mg/L (animal equivalent dose mg/kg/day) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.00009 (0.02) | 0.00026/25 (0.07) | 0.00044 (0.12) | 0.00059 (0.16) | 0.00071 (0.19) | 0.0011 (0.29) | 0.0027 (0.71) | 0.0042/38 (1.1/1.0) | 0.0045/47 (1.2) | 0.0060 (1.6) | 0.0235/237 (6.1/6.3) | 0.028 (7.4) | 0.0466 (12) |
| | | | | | | skeletal alt | | ↑runts & skeletal alterations | 18/30 ↓motility d 1-9<br>5/30 dyspnea d 2-9<br>BWG -8 g (loss) [d]<br>FetalW ↓15%<br>↑runts & skeletal alts | | 20/29 dyspnea d 1-9<br>8/29 unk fur d 3-9<br>BWG -12 g (loss) [d]<br>↑late resorps &<br>↑postimp loss<br>FetalW ↓29%,<br>↑runts & skeletal alts | | |
| 5 days – β-cyfluthrin (4120578) | | NOAEL | | | | | | Unk fur, piloerect | | | Unk fur, piloerect | Unk fur, piloerect, ↓activity, foci in lungs | $LD_{50}$ = 0.082-0.532 |

[a] All clinical signs were observed in 10/10 animals per sex. If sex is not indicated, clinical signs occurred in both sexes. [b] Study report seems to imply this happened from week 2 until the end of study, however this is not clearly indicated. [c] Changes in pH compared to vehicle control are indicated in pH units. [d] For reference, there were 2 control groups and each gained 4.3 g and -2.1 g, respectively.
Unk fur = unkempt fur. BW = body weight. BWG = body weight gain. ↓ = decreased. ↑ = increased. exp = exposure. wk = week. FetalW = fetal weight. resorps = resorptions. postimp = postimplantation. piloerect = piloerection. alt = alterations. ♂ = male. ♀ = female

## Appendix B. Physical/Chemical Properties

| Table 3. Physicochemical Properties of Technical Grade Cyfluthrin | |
|---|---|
| Parameter | Value |
| Melting point/range (°C) | Isomer I: 57 Isomer II: 73-74<br>Isomer III: 65-66 Isomer IV: 101-102 |
| pH | not measurable because of low solubility in water |
| Density (g/mL at 20ºC) | 1.28 |
| Water solubility (µg/L at 20ºC) | Isomer I: 2.2 Isomer II: 1.9<br>Isomer III: 2.2 Isomer IV: 2.9 |
| Solvent solubility (g/L room temperature) | Methylene chloride >200 Toluene >200<br>Hexane 10-20 Isopropanol 20-50 |
| Vapor pressure (20°C) | $1.5 \times 10^{-10}$ mmHg ($1.3 \times 10^{-8}$ Pa) |
| Dissociation constant, $pK_a$ | does not dissociate |
| Octanol/water partition coefficient, Log($K_{OW}$) | Isomer I: 6 Isomer II: 5.9<br>Isomer III: 6 Isomer IV: 5.9 |
| UV/visible absorption spectrum | Absorption maxima: primary: 196 nm, secondary 275 nm |

## Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies, that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.

## Appendix D. Aggregate Risk Calculations

The following equations were used to calculate the risk estimates provided in Table 7.2.b of the Short-Term Aggregate Risk Estimates Section

MOE = NOAEL/Total Exposure

Total Exposure = Background Dietary Exposure + Dermal Exposure + Incidental Oral Exposure
Incidental oral exposure only applies to children 1-2

**Short-term Aggregate Risk for Children 1-2**

For the population subgroups comprised of children, the most highly exposed subgroup was Children 1-2.

The incidental oral (hand-to-mouth) exposure for Children 1-2 is added to the dermal exposure and the background dietary exposure to arrive at the total exposure estimate.

Background Dietary Exposure + Incidental Oral Exposure + Dermal Exposure

= 0.002198 + 0.0002 + 0.0008 = 0.003198 mg/kg/day

Total Aggregate MOE = NOAEL/Total Exposure = 1.17 ÷ 0.003198 = 370

**Total Aggregate MOE for Children 1-2 = 370**

**Short-term Aggregate Risk for All Other Population Subgroups**

The following example for the subgroup Adults 20-49 applies to all other subgroups

The only oral exposure is the background dietary exposure from food and drinking water. This exposure is combined with post-application dermal exposure.

Adults 20-49:

Background Dietary Exposure + Dermal Exposure

= 0.000769 + 0.00091 = 0.001679 mg/kg/day

Total Aggregate MOE = NOAEL/Total Exposure = 1.17 ÷ 0.001679 = 700

**Total Aggregate MOE for Adults 20-49 = 700**

# Appendix E. International Residue Limit Status

## CYFLUTHRIN (8-17-2016)

| Summary of US and International Tolerances and Maximum Residue Limits for Cyfluthrin | | | | |
|---|---|---|---|---|
| **US** | | **Canada** | **Mexico[1]** | **Codex[2]** |
| **Residue Definition:** | | | | |
| 40 CFR 180.436 cyfluthrin (cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2dimethyl-cyclopropane-carboxylate) | | cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate | | cyfluthrin (sum of isomers). The residue is fat soluble. |
| Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg) | | | | |
| Commodity | US | Canada | Mexico[1] | Codex |
| Alfalfa | 5.0 | | | |
| Alfalfa, forage | 5.0 | | | |
| Alfalfa, hay | 13 | | | |
| Almond, hulls | 0.5 | | | |
| Barley, bran | 0.5 | | | |
| Barley, grain | 0.15 | | | |
| Beet, sugar, dried pulp | 1.0 | | | |
| Beet, sugar, roots | 0.10 | | | |
| Brassica, head and stem, subgroup 5A | 2.5 | | | 0.08 cabbages, head 2 cauliflower |
| Brassica, leafy greens, subgroup 5B | 7.0 | | | |
| Buckwheat, grain | 0.15 | | | |
| Carrot, roots | 0.20 | | | |
| Cattle, fat | 2.0 | 5 | | |
| Cattle, meat | 0.10 | 0.4 | | 0.2 (fat) |
| Cattle, meat byproducts | 0.10 | 0.4 | | 0.02 |
| Citrus, dried pulp | 0.3 | | | 2 |
| Citrus, oil | 0.3 | | | |
| Corn, field, grain | 0.05 | | | |
| Corn, pop, grain | 0.05 | | | |
| Corn, sweet, kernel plus cob with husks removed | 0.05 | | | |
| Cotton, hulls | 2.0 | | | |
| Cotton, refined oil | 2.0 | | | 1 (crude) |
| Cotton, undelinted seed | 1.0 | | | 0.7 |
| Egg | 0.01 | 0.01 | | 0.01 (*) |
| Fruit, citrus, group 10 | 0.2 | | | 0.3 |
| Fruit, pome, group 11 | 0.5 | | | 0.1 apple, pear |
| Fruit, stone, group 12 | 0.3 | | | |
| Goat, fat | 2.0 | 5 | | |
| Goat, meat | 0.05 | 0.4 | | 0.2 (fat) |
| Goat, meat byproducts | 0.05 | 0.4 | | 0.02 |
| Grain, aspirated fractions | 150 | | | |
| Grain, cereal, forage, fodder and hay, group 16, forage, except rice | 25 | | | |
| Grain, cereal, forage, fodder and hay, group 16, hay, except rice | 6.0 | | | |

| Summary of US and International Tolerances and Maximum Residue Limits for Cyfluthrin | | | | |
|---|---|---|---|---|
| **US** | | **Canada** | **Mexico[1]** | **Codex[2]** |
| Grain, cereal, forage, fodder and hay, group 16, stover, except rice | 30 | | | |
| Grain, cereal, forage, fodder and hay, group 16, straw, except rice | 7.0 | | | |
| Grape | 1.0 | | | |
| Grape, raisin | 3.5 | | | |
| Grass, forage, fodder and hay, group 17, forage | 12 | | | |
| Grass, forage, fodder and hay, group 17, hay | 50 | | | |
| Hog, fat | 0.5 | 5 | | |
| Hog, meat | 0.01 | 0.4 | | 0.2 (fat) |
| Hog, meat byproducts | 0.01 | 0.4 | | 0.02 |
| Hop, dried cones | 20.0 | | | |
| Hop, vines | 4.0 | | | |
| Horse, fat | 2.0 | 5 | | |
| Horse, meat | 0.05 | 0.4 | | 0.2 (fat) |
| Horse, meat byproducts | 0.05 | 0.4 | | 0.02 |
| Lettuce, head | 2.0 | | | |
| Lettuce, leaf | 3.0 | | | |
| Milk | 0.2 | 0.5 | | 0.01 |
| Milk, fat | 5.0 | 15 | | |
| Millet, grain | 0.15 | | | |
| Mustard greens | 7.0 | | | |
| Nut, tree, group 14 | 0.01 | | | |
| Oat, bran | 0.5 | | | |
| Oat, grain | 0.15 | | | |
| Pea and bean, dried shelled, except soybean, subgroup 6C | 0.15 | | | |
| Pea, dry, seed | 0.15 | | | |
| Pea, southern, succulent | 0.25 | | | |
| Peanut | 0.01 | | | |
| Peanut, hay | 6.0 | | | |
| Pepper | 0.50 | | | 0.2<br>1 chili peppers, dried |
| Pistachio | 0.01 | | | |
| Poultry, fat | 0.01 | 5 | | |
| Poultry, meat | 0.01 | 0.4 | | 0.01 (*) (fat) |
| Poultry, meat byproducts | 0.01 | 0.4 | | 0.01 (*) |
| Radish, roots | 1.0 | | | |
| Rye, bran | 0.5 | | | |
| Rye, grain | 0.15 | | | |
| Sheep, fat | 2.0 | 5 | | |
| Sheep, meat | 0.05 | 0.4 | | 0.2 (fat) |
| Sheep, meat byproducts | 0.05 | 0.4 | | 0.02 |
| Sorghum, grain, grain | 3.5 | | | |
| Soybean, forage | 8.0 | | | |
| Soybean, hay | 4.0 | | | 4 (fodder) |
| Soybean, seed | 0.03 | | | 0.03 (dry) |
| Sugarcane, cane | 0.05 | | | |
| Sugarcane, molasses | 0.20 | | | |

| Summary of US and International Tolerances and Maximum Residue Limits for Cyfluthrin | | | | |
|---|---|---|---|---|
| **US** | | **Canada** | **Mexico[1]** | **Codex[2]** |
| Sunflower, forage | 5.0 | | | |
| Sunflower, seed | 0.02 | | | |
| Teosinte, grain | 0.05 | | | |
| Tomato | 0.20 | | | 0.2 |
| Tomato, dry pomace | 5.0 | | | |
| Tomato, paste | 0.5 | | | |
| Tomato, wet pomace | 5.0 | | | |
| Triticale, grain | 0.15 | | | |
| Turnip, greens | 7.0 | | | |
| Vegetable, cucurbit, group 9 | 0.1 | | | |
| Vegetable, fruiting, group 8 | 0.5 | | | 0.2 egg plant |
| Vegetable, leafy, except brassica, group 4 | 6.0 | | | |
| Vegetable, tuberous and corm, subgroup 1C | 0.01 | | | 0.01 (*) potato |
| Wheat, bran | 0.5 | | | |
| Wheat, grain | 0.15 | | | |
| Wheat, shorts | 0.5 | | | |
| *MRLs with no US equivalent* | | | | |
| Rape seed | | | | 0.07 |
| Spices, fruits and berries | | | | 0.03 |
| Spices, roots and rhizomes | | | | 0.05 |

For the US:

(2) A tolerance of 0.05 ppm is established for residues of the insecticide cyfluthrin (cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate; CAS Reg. No. 69359–37–5) in food commodities exposed to the insecticide during treatment of food-handling establishments where food and food products are held, processed, prepared, or served. Treatments may be made by general surface, spot, and/or crack and crevice applications.

(3) A tolerance of 0.05 part per million is established for residues of the insecticide cyfluthrin (cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate; CAS Reg. No. 68359–37–5) in feed commodities exposed to the insecticide during treatment of feed-handling establishments where feed and feed products are held, processed, prepared, or served. Treatments may be made by general surface, spot, and/or crack and crevice applications.

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[2] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample.

# BETA-CYFLUTHRIN

| Summary of US and International Tolerances and Maximum Residue Limits for Beta-Cyfluthrin | | | | |
|---|---|---|---|---|
| **US** | | **Canada** | **Mexico[1]** | **Codex[2]** |
| **Residue Definition:** | | | | |
| 40 CFR 180.436<br>beta-cyfluthrin, cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate [mixture comprising the enantiomeric pair (*R*)-α-cyano-4-fluoro-3-phenoxybenzyl (1 *S* ,3 *S* )-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1 *R* ,3 *R* )-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate with the enantiomeric pair ( *R* )-α-cyano-4-fluoro-3-phenoxybenzyl (1*S*,3 *R* )-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and ( *S* )-α-cyano-4-fluoro-3-phenoxybenzyl (1 *R* ,3 *S* )-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] | | None | | cyfluthrin (sum of isomers).<br>The residue is fat soluble. |
| Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg) | | | | |
| Commodity | US | Canada | Mexico[1] | Codex[2] |
| Alfalfa | 5.0 | | | |
| Alfalfa, forage | 5.0 | | | |
| Alfalfa, hay | 13 | | | |
| Almond, hulls | 0.5 | | | |
| Barley, bran | 0.5 | | | |
| Barley, grain | 0.15 | | | |
| Beet, sugar, dried pulp | 1.0 | | | |
| Beet, sugar, roots | 0.10 | | | |
| Brassica, head and stem, subgroup 5A | 2.5 | | | 0.08 cabbages, head<br>2 cauliflower |
| Brassica, leafy greens, subgroup 5B | 7.0 | | | |
| Buckwheat, grain | 0.15 | | | |
| Carrot, roots | 0.20 | | | |
| Cattle, fat | 2.0 | | | |
| Cattle, meat | 0.10 | | | 0.2 (fat) |
| Cattle, meat byproducts | 0.10 | | | 0.02 |
| Citrus, dried pulp | 0.3 | | | 2 |
| Citrus, oil | 0.3 | | | |
| Corn, field, grain | 0.05 | | | |
| Corn, pop, grain | 0.05 | | | |
| Corn, sweet, kernel plus cob with husks removed | 0.05 | | | |
| Cotton, hulls | 2.0 | | | |
| Cotton, refined oil | 2.0 | | | 1 (crude) |
| Cotton, undelinted seed | 1.0 | | | 0.7 |
| Egg | 0.01 | | | 0.01 (*) |
| Fruit, citrus, group 10 | 0.2 | | | 0.3 |
| Fruit, pome, group 11 | 0.5 | | | 0.1 apple, pear |
| Fruit, stone, group 12 | 0.3 | | | |
| Goat, fat | 2.0 | | | |
| Goat, meat | 0.05 | | | 0.2 (fat) |
| Goat, meat byproducts | 0.05 | | | 0.02 |
| Grain, aspirated fractions | 150 | | | |
| Grain, cereal, forage, fodder and hay, group 16, forage, except rice | 25 | | | |

| Summary of US and International Tolerances and Maximum Residue Limits for Beta-Cyfluthrin | | | | |
|---|---|---|---|---|
| **US** | | **Canada** | **Mexico[1]** | **Codex[2]** |
| Grain, cereal, forage, fodder and hay, group 16, hay, except rice | 6.0 | | | |
| Grain, cereal, forage, fodder and hay, group 16, stover, except rice | 30 | | | |
| Grain, cereal, forage, fodder and hay, group 16, straw, except rice | 7.0 | | | |
| Grape | 1.0 | | | |
| Grape, raisin | 3.5 | | | |
| Grass, forage, fodder and hay, group 17, forage | 12 | | | |
| Grass, forage, fodder and hay, group 17, hay | 50 | | | |
| Hog, fat | 0.5 | | | |
| Hog, meat | 0.01 | | | 0.2 (fat) |
| Hog, meat byproducts | 0.01 | | | 0.02 |
| Hop, dried cones | 20.0 | | | |
| Hop, vines | 4.0 | | | |
| Horse, fat | 2.0 | | | |
| Horse, meat | 0.05 | | | 0.2 (fat) |
| Horse, meat byproducts | 0.05 | | | 0.02 |
| Lettuce, head | 2.0 | | | |
| Lettuce, leaf | 3.0 | | | |
| Milk | 0.2 | | | 0.01 |
| Milk, fat | 5.0 | | | |
| Millet, grain | 0.15 | | | |
| Mustard greens | 7.0 | | | |
| Nut, tree, group 14 | 0.01 | | | |
| Oat, bran | 0.5 | | | |
| Oat, grain | 0.15 | | | |
| Pea and bean, dried shelled, except soybean, subgroup 6C | 0.15 | | | |
| Pea, dry, seed | 0.15 | | | |
| Pea, southern, succulent | 0.25 | | | |
| Peanut | 0.01 | | | |
| Peanut, hay | 6.0 | | | |
| Pepper | 0.50 | | | 0.2<br>1 chili peppers, dried |
| Pistachio | 0.01 | | | |
| Poultry, fat | 0.01 | | | |
| Poultry, meat | 0.01 | | | 0.01 (*) (fat) |
| Poultry, meat byproducts | 0.01 | | | 0.01 (*) |
| Radish, roots | 1.0 | | | |
| Rye, bran | 0.5 | | | |
| Rye, grain | 0.15 | | | |
| Sheep, fat | 2.0 | | | |
| Sheep, meat | 0.05 | | | 0.2 (fat) |
| Sheep, meat byproducts | 0.05 | | | 0.02 |
| Sorghum, grain, grain | 3.5 | | | |
| Soybean, forage | 8.0 | | | |
| Soybean, hay | 4.0 | | | 4 (fodder) |
| Soybean, seed | 0.03 | | | 0.03 (dry) |

| Summary of US and International Tolerances and Maximum Residue Limits for Beta-Cyfluthrin | | | | |
|---|---|---|---|---|
| **US** | | **Canada** | **Mexico[1]** | **Codex[2]** |
| Sugarcane, cane | 0.05 | | | |
| Sugarcane, molasses | 0.20 | | | |
| Sunflower, forage | 5.0 | | | |
| Sunflower, seed | 0.02 | | | |
| Teosinte, grain | 0.05 | | | |
| Tomato | 0.20 | | | 0.2 |
| Tomato, paste | 0.5 | | | |
| Tomato, pomace | 5.0 | | | |
| Triticale, grain | 0.15 | | | |
| Turnip, greens | 7.0 | | | |
| Vegetable, cucurbit, group 9 | 0.1 | | | |
| Vegetable, fruiting, group 8 | 0.5 | | | |
| Vegetable, leafy greens, except Brassica, group 4 | 6.0 | | | 0.2 egg plant |
| Vegetable, tuberous and corm, subgroup 1C | 0.01 | | | |
| Wheat, bran | 0.5 | | | 0.01 (*) potato |
| Wheat, grain | 0.15 | | | |
| Wheat, shorts | 0.5 | | | |
| *MRLs with no US equivalent* | | | | |
| Rape seed | | | | 0.07 |
| Spices, fruits and berries | | | | 0.03 |
| Spices, roots and rhizomes | | | | 0.05 |

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[2] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample.

## Appendix F. Summary of Registered Uses for Cyfluthrin and Beta-Cyfluthrin

| Table F.1. Summary of Directions for Residential Handler Uses of Cyfluthrin and Beta-cyfluthrin. | | | |
|---|---|---|---|
| **Residential Use** | **Formulation [EPA Reg. No.]** | **Application Rate** | **Application Equipment** |
| Indoor Environment | Dust [3125-456] | 0.001 lb ai/lb dust<br>0.2 lb ai/A | Plunger Duster, Bulb duster, Electric/Power Duster/ Hand crank Duster |
| | Liquid [72155-58] | 0.0098 lb ai/gallon | Manually-pressurized handwand |
| | Ready-to-use [499-485] | 0.004 lb ai/16-oz can | Aerosol Can |
| | Ready-to-use [9688-201] | 0.00834 lb ai/bottle | Trigger-spray bottle |
| | Ready-to-use [4822-481] | 0.001 lb ai/16-oz can | Total-release fogger |
| | Ready-to-use [4822-376] | NS | Bait Station (non-refillable) |
| | Wettable powders [432-1302] | 0.0088 lb ai/gallon | Manually-pressurized handwand |
| | Water-soluble packaging [4822-375] | 0.009 lb ai/gallon<br>0.000005 lb ai/$ft^2$<br>0.22 lb ai/A | Manually-pressurized handwand |
| Lawns/Turf | Granule [71995-46] | 0.13 lb ai/acre | Push-type rotary spreader |
| | | 0.00003 lb ai/$ft^2$ | Belly grinder, spoon, cup, hand dispersal, shaker can |
| | Liquid [499-489] | 0.008 lb ai/gallon<br>0.000004 lb ai/$ft^2$ | Manually-pressurized handwand, Sprinkler can, Backpack |
| | Ready-to-use [72155-40] | 0.00025 lb ai/bottle | Trigger-spray bottle |
| | Ready-to-use [72155-39] | 0.13 lb ai/acre | Hose-end Sprayer |
| | Wettable powder [432-1304] | 0.0022 lb ai/gallon<br>0.0000022 lb ai/$ft^2$ | Manually-pressurized handwand, Sprinkler can, Backpack |
| | Water-soluble packaging [4822-375] | 0.009 lb ai/gallon | Manually-pressurized handwand, Backpack |
| Gardens/Trees | Granule [71995-46] | 0.000003 lb ai/$ft^2$ | Push-type rotary spreader, Spoon, Cup, Hand dispersal, Shaker can |
| | Liquid [71995-45] | 0.00024 lb ai/gallon | Manually-pressurized handwand, Hose-end Sprayer, Backpack, Sprinkler can |
| | Ready-to-use [72155-39] | 0.00024 lb ai/gallon | Hose-end Sprayer |
| | Wettable Powder [432-1304] | 0.00042 lb ai/gallon | Manually-pressurized handwand, Hose-end Sprayer, Backpack, Sprinkler can |
| | Water-soluble packaging [4822-375] | 0.009 lb ai/gallon | Manually-pressurized handwand, Sprinkler can, Backpack |
| Outdoor Fogging/Misting | Ready-to-use [4822-573] | 0.0005 lb ai/can | Aerosol can |

| Table F.2a. Summary of Directions for Occupational (Agricultural, Non-seed Treatment) Uses of Cyfluthrin and Beta-cyfluthrin. | | | |
|---|---|---|---|
| **Formulation [EPA Reg. No.]** | **Application Equipment** | **Rep. Crop Site** | **Max App Rate (lb ai/A)** |
| Granule [264-839] | Aerial, Tractor-drawn Spreader | Field Crop High Acreage/Typical | 0.0073 |
| Liquid [264-745] | Aerial, Chemigation, Groundboom | Field Crop High Acreage/Typical | 0.05 |
| | Mechanically-pressurized handgun | Field Crop Typical | 0.005 lb ai/gallon |
| Liquid [264-770] | Aerial, Airblast, Chemigation, Groundboom | Orchard/Vineyard | 0.1 |
| | Mechanically-pressurized handgun | | 0.004 lb ai/gallon |
| Liquid [59807-18] | Aerial, Airblast, Chemigation, Groundboom, | Nursery, Greenhouse | 0.12 |
| | Injector | | (0.007 lb ai/tree)[1] |
| | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | | 0.0014 lb ai/gallon |
| Wettable Powder [432-1402] | Aerial, Airblast, Groundboom | Nursery, Greenhouse | 0.12[2] |
| | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | | 0.00024 lb ai/gallon |
| Water-soluble Packaging [432-1402] | Aerial, Airblast, Groundboom | Nursery, Greenhouse | 0.12[2] |
| | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | | 0.00024 lb ai/gallon |
| Ready-to-use [499-405] | Total-release Fogger | Greenhouse | 0.016 lb ai/can[3] |

1. HED assumes that the diameter at breast heigh (DBH) is 10 inches. It is unlikely that a tree of this size or larger would be treated regularly, as nurseries typically handle smaller trees/saplings.
2. Crop specific use information may be found below in Table C.2b.
3. The size of the ready-to-use can is not available. HED assumed that the can would be no larger than 16 oz.

| Table F.2b. Summary of Directions for Crop Uses of Cyfluthrin and Beta-cyfluthrin. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Crop** | **Formulation [EPA Reg. No.][1]** | **Application Equipment** | **Rep. Crop Site** | **Max App Rate (lb ai/A)** | **Max. No. App per Year** | **Min. RTI (days)[2]** | **Max. Seasonal App Rate (lb ai/A)** | **PHI (days)[3]** |
| Alfalfa | Liquid [264-745] | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NA | 5 | 0.35 | 7 |
| Corn (Field, pop, seed) | Granule [264-839] | Aerial, Tractor-drawn Spreader | Field Crop Typical, High Acreage | 0.0073 | NS | NS | 0.15 | NS |
| | Liquid [264-745] | Aerial, Chemigation, Groundboom | Field Crop Typical, High Acreage | 0.044 | 4 | 7 | 0.175 | 21 |

| Table F.2b. Summary of Directions for Crop Uses of Cyfluthrin and Beta-cyfluthrin. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Crop** | **Formulation [EPA Reg. No.][1]** | **Application Equipment** | **Rep. Crop Site** | **Max App Rate (lb ai/A)** | **Max. No. App per Year** | **Min. RTI (days)[2]** | **Max. Seasonal App Rate (lb ai/A)** | **PHI (days)[3]** |
| | | Mechanically-pressurized handgun | Field Crop Typical | 0.022 lb ai/gallon | | | | |
| Corn (Sweet) | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.044 | NS | 2 | 0.44 | 0 |
| | | Mechanically-pressurized handgun | | 0.022 lb ai/gallon | | | | |
| Cotton | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.05 | 6 | 3 | 0.3 | 0 |
| Grass[1] | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 5 | 0.176 | 7 |
| Peanut | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 10 | 0.131 | 14 |
| Sorghum | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 10 | 0.131 | 14 |
| Soybean | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 7 | 0.175 | 45 |
| Sugarcane | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 7 | 0.263 | 15 |
| Sunflower | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 7 | 0.131 | 30 |
| Tobacco | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.0044 | 1 | NA | 0.0044 | NA |
| | | Mechanically-pressurized handgun | | 0.0003 lb ai/gallon | | | | |
| Wheat | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.038 | NS | 3 | 0.076 | 30 |
| Brassica Leafy Vegetables | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.05 | NS | 7 | 0.2 | 0 |

| Table F.2b. Summary of Directions for Crop Uses of Cyfluthrin and Beta-cyfluthrin. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Crop** | **Formulation [EPA Reg. No.][1]** | **Application Equipment** | **Rep. Crop Site** | **Max App Rate (lb ai/A)** | **Max. No. App per Year** | **Min. RTI (days)[2]** | **Max. Seasonal App Rate (lb ai/A)** | **PHI (days)[3]** |
| (Crop group 5) | | Mechanically-pressurized handgun | | 0.005 lb ai/gallon | | | | |
| Cucurbits (Crop group 9) | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.044 | NS | 7 | 0.175 | 0 |
| | | Mechanically-pressurized handgun | | 0.0044 lb ai/gallon | | | | |
| Fruiting Vegetables (Crop group 8) | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.044 | NS | 7 | 0.263 | 7 |
| | | Mechanically-pressurized handgun | | 0.0044 lb ai/gallon | | | | |
| Leafy Vegetables (Crop group 4) | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.05 | NS | 7 | 0.2 | 0 |
| | | Mechanically-pressurized handgun | | 0.005 lb ai/gallon | | | | |
| Dried Shelled Legume Vegetables (Crop group 6) | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.05 | NS | 14 | 0.1 | 7 |
| | | Mechanically-pressurized handgun | | 0.005 lb ai/gallon | | | | |
| Pea, Southern | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.033 | NS | 5 | 0.165 | 3 |
| | | Mechanically-pressurized handgun | | 0.0033 lb ai/gallon | | | | |
| Tuberous and Corm Vegetables (Crop group 1C) | | Aerial, Chemigation, Groundboom | Field Crop High Acreage | 0.044 | NS | 5 | 0.263 | 0 |
| Carrot and Radish | | Aerial, Chemigation, Groundboom | Field Crop Typical | 0.044 | NS | 7 | 0.22 | 0 |
| | | Mechanically-pressurized handgun | | 0.0044 lb ai/gallon | | | | |
| Citrus (Crop group 10 | Liquid [264-770] | Aerial, Airblast, Chemigation, Groundboom | Orchard/ Vineyard | 0.1 | NS | 10 | 0.1 | 0 |
| | | Mechanically-pressurized handgun | | 0.004 lb ai/gallon | | | | |

| Table F.2b. Summary of Directions for Crop Uses of Cyfluthrin and Beta-cyfluthrin. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Crop** | **Formulation [EPA Reg. No.][1]** | **Application Equipment** | **Rep. Crop Site** | **Max App Rate (lb ai/A)** | **Max. No. App per Year** | **Min. RTI (days)[2]** | **Max. Seasonal App Rate (lb ai/A)** | **PHI (days)[3]** |
| Grape | | Aerial, Airblast, Chemigation, Groundboom | | 0.07 | NS | 14 | 0.07 | 3 |
| | | Mechanically-pressurized handgun | | 0.003 lb ai/gallon | | | | |
| Hop | | Aerial, Airblast, Chemigation, Groundboom | | 0.05 | NS | 21 | 0.21 | 28 |
| | | Mechanically-pressurized handgun | | NS | | | | |
| Pome Fruit (Crop group 11) | | Aerial, Airblast, Chemigation, Groundboom | | 0.044 | NS | 14 | 0.044 | 7 |
| | | Mechanically-pressurized handgun | | 0.0004 lb ai/gallon | | | | |
| Stone Fruit (Crop group 12) | | Aerial, Airblast, Chemigation, Groundboom | | 0.044 | NS | 14 | 0.088 | 7 |
| | | Mechanically-pressurized handgun | | 0.0009 lb ai/gallon | | | | |
| Tree Nut Crops (Crop group 14) | | Aerial, Airblast, Chemigation, Groundboom | | 0.044 | NS | 6 | 0.044 | 14 |
| | | Mechanically-pressurized handgun | | 0.0004 lb ai/gallon | | | | |

1. Grass: pasture, rangeland, grass for seed, grass for hay, grass in mixed-stands with alfalfa.

| Table F.3. Summary of Directions for Occupational (Agricultural, Seed Treatment) Uses of Cyfluthrin and beta-cyfluthrin. | | | | |
|---|---|---|---|---|
| **Crop** | **Application Equipment** | **Formulation [EPA Reg. No.][1]** | **App Rate (lb ai/lb seed)** | **Use Directions and Limitations** |
| Sugarbeets | Commercial liquid or slurry treaters | L [264-1056] | 0.007 | Not for use in agricultural establishments in on-farm seed treatment applicators used at planting. |

| Table F.4. Summary of Directions for Occupational (Non-Agricultural) Uses of Cyfluthrin and Beta-cyfluthrin. | | | |
|---|---|---|---|
| **Formulation [EPA Reg. No.]** | **Use Site** | **Application Equipment** | **Max. Application Rate** |
| Dust [11556-136] | Poultry/livestock house/horse barn/feed lot | Shaker Can | 0.00001 lb ai/ft$^2$ |
| Dust [3125-456] | Residential Living Spaces (homes, apartments) | Bulb duster | 0.000005 lb ai/ft$^2$ |
| | Foundations/perimeter | Plunger Duster | |
| Dust [47000-143] | Livestock | Shaker can | 0.00046 lb ai/animal |
| | | Dust bag | 0.023 lb ai/bag |

| Table F.4. Summary of Directions for Occupational (Non-Agricultural) Uses of Cyfluthrin and Beta-cyfluthrin. | | | |
|---|---|---|---|
| **Formulation [EPA Reg. No.]** | **Use Site** | **Application Equipment** | **Max. Application Rate** |
| Granule [71995-46] | Mounds/nests | Cup, Hand dispersal, Spoon | 0.135 lb ai/mound |
| Granule [3125-568] | Foundations/perimeter, Landscaping, turf/plants/flowers/trees/shrubs/bushes | Belly grinder, Rotary spreader | 0.17 lb ai/A |
| | | Cup, Hand dispersal, Spoon | 0.000004 lb ai/$ft^2$ |
| Gel/paste [70627-38] | Food handling establishments, Warehouse, Foundations/perimeter, Structural, Residential living spaces, Childcare center/schools/institutions | Injection | NS |
| Liquid [432-1452] | Golf course | Groundboom, Mechanically-pressurized handgun | 0.094 lb ai/A |
| | Landscaping, trees/shrubs/bushes/plants/flowers | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | 0.0004 lb ai/gallon |
| Liquid [72155-58] | Landscaping, turf | Backpack, Manually-pressurized handwand | 0.0008 lb ai/gallon |
| Liquid [11556-145] | Poultry/livestock house/horse barn/feed lot | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | 0.0042 lb ai/gallon |
| Liquid [499-489] | Food handing establishment | Manually-pressurized handwand | 0.008 lb ai/gallon |
| | Landscaping, turf | Mechanically-pressurized handgun | 0.17 lb ai/A |
| Liquid [11556-107] | Livestock | Manually-pressurized handwand, Mechanically-pressurized handgun, Pour-on | 0.009 lb ai/gallon |
| Liquid [3125-420] | Structural | Injector | 0.016 lb ai/$ft^2$ |
| | Structural, Foundations/perimeter | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | 0.04 lb ai/gallon |
| Liquid [432-1303] | Residential living spaces | Manually-pressurized handwand | 0.02 lb ai/gallon |
| Ready-to-use (liquid) [499-485] | Foundations/perimeter, Residential living spaces, Interior landscaping | Trigger-spray bottle | 0.008 lb ai/bottle[1] |
| Ready-to-use (pressurized liquid) [7969-343] | Foundations/perimeter, Interior landscaping, Residential living spaces | Aerosol can | 0.001 lb ai/can |
| Ready-to-use (solid) [11556-106] | Livestock | Ear tag | NS |
| Ready-to-use (solid) [4822-376] | Residential living spaces | Bait station (non-refillable) | NS |
| Wettable Powder [432-1302] | Foundations/perimeter, Landscaping, Mounds/nests, Poultry/livestock house/horse barn/feed lot, Residential living spaces, Structural | Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun | 0.009 lb ai/gallon |
| | Landscaping (turf only) | Backpack, Mechanically-pressurized handgun | 0.19 lb ai/A |

| Table F.4. Summary of Directions for Occupational (Non-Agricultural) Uses of Cyfluthrin and Beta-cyfluthrin. | | | |
|---|---|---|---|
| **Formulation [EPA Reg. No.]** | **Use Site** | **Application Equipment** | **Max. Application Rate** |
| Wettable Powder [432-1338] | Golf course | Groundboom, Mechanically-pressurized handgun | 0.134 lb ai/A |
| Water-soluble Packaging [432-1306] | Landscaping | Backpack, Manually-pressurized handwand | 0.0003 lb ai/gallon |
| | | Mechanically-pressurized handgun | 0.128 lb ai/A |
| Water-soluble Packaging [4822-375] | Foundations/perimeter, Residential living spaces, Structural | Backpack, Manually-pressurized handwand, Mechanically-pressurized hand gun | 0.009 lb ai/gallon<br>0.000009 lb ai/$ft^2$ |

1. The size of the ready-to-use bottle was not available. HED assumed that the bottle would be no larger than 32 fl