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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date 08-24-2016

Subject: **Revised; Flupyradifurone (122304);** Human Health Risk Assessment in Support of Proposed Uses on Kava, Cilantro, Stone Fruit, Group 12-12, Caneberry, Subgroup 13-07A, Quinoa, and Tropical Fruits; Amended Use Requests for Soil Applications to Leafy Vegetables, Group 4 and *Brassica* (Cole) Leafy Vegetables, Group 5; Use on Greenhouse Grown Tomato, Pepper, Cucumber, and Lettuce; Label Amendment to Add Commodities of Tree Nuts, Group 14-12; and Label Amendment to Add Use Directions for Clover Grown for Forage, Fodder, Seed, Straw, and Hay.

PC Code: 122304	**DP Barcode:** D430361
Decision No.: 509944	**Registration No.:** 264-1141, 264-1143, 72155-RAA, 72155-xxx (unregistered product)
Petition No.: 5F8404	**Regulatory Action:** Section 3 registration and amended use requests
Risk Assessment Type: single chemical/aggregate exposure	**Case No.:** NA
TXR No.: not applicable	**CAS No.:** 951659-40-8
MRID No: none	**40 CFR:** §180.679

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered and proposed uses of flupyradifurone. A summary of the findings and an assessment of the human health risk resulting from the registered

and proposed uses are provided in this document. The risk assessment, dietary risk assessment, and residue chemistry data review were provided by William Wassell (RAB 3), the hazard characterization was provided by Whang Phang (RAB 3), the occupational/residential exposure assessment was provided by Kristin Rickard (RAB 3) and the drinking water assessment by Katrina White of the Environmental Fate and Effects Division (EFED).

Table of Contents

1.0 Executive Summary

Flupyradifurone [4-[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]-2(5*H*)-furanone] is an insecticide that is a member of the butenolide class of chemistry effective against a broad range of sucking insects. Its mode of action is classified as a Group 4D insecticide (*i.e.* a nicotinic acetylcholine receptor agonist). Flupyradifurone is thought to bind and stimulate insect nicotinic acetylcholine receptors (nAchRs), leading to paralysis and death. It is registered for foliar, soil drench, and seed treatment for a variety of crops for the control of aphids, whiteflies, leafhoppers, and other insects. Flupyradifurone is taken up by the roots or through the plant tissue and translocated to the plant cells.

Proposed Use: Flupyradifurone may be applied using ground, aerial, or chemigation application equipment to the proposed outdoor agricultural crops; ground, chemigation, or handheld spray equipment to the proposed greenhouse/nursery/landscape ornamental crops; and handheld or ready-to-use spray equipment by residential handlers in residential settings. EPA Reg. No. 264-1141 and 432-RLTL require occupational handlers to wear long-sleeved shirts, long pants, shoes, socks, and chemical-resistant gloves. The proposed restricted-entry interval (REI) is 4 hours for EPA Reg. No. 264-1141 and 432-RLTL.

Bayer CropScience (Bayer) has proposed uses and tolerances for residues of flupyradifurone in or on the following commodities:

Raw Agricultural Commodities/Crop Group	**Proposed Tolerance (ppm)**
Kava, root (as part of Root Vegetables Except Sugar Beets, Crop Subgroup 1B)	0.9
Cilantro, fresh leaves (as part of Leafy Greens, Crop Subgroup 4A)	30
Kava, fresh leaves (translation from Leafy Brassica Greens, Crop Subgroup 5B)	40
Stone Fruit (Crop Group 12-12)	1.5
Caneberry (Crop Subgroup 13-07A)	5.0
Quinoa (as part of Crop Group 15)	3.0
Abiu, Akee apple, Avocado (including Guatemalan, Mexican, and West Indian), Bacury, Banana (including dwarf), Binjai, Canistel, Cupuacú, Etambe, Jatobá, Kei apple, Langstat, Lanjut, Lucuma, Mabolo, Mango (including horse and Saipan), Mangosteen, Paho, Papaya, Pawpaw (common), Pelipisan, Pequi, Pequia, Persimmon (American), Plantain, Pomegranate, Poshte, Quandong, Sapote (including black, green, and white), Sataw, Screw-pine, Star apple, Tamarind-of-the-Indies, and Wild loquat, and cultivars, varieties and hybrids of these commodities[1]	0.6

[1] IR-4 indicates that all of the crops listed are to be included in the "Tropical and Subtropical, Medium to Large Fruit, Smooth, Inedible Peel Subgroup 24B".

It should be noted that The Interregional Research Project No. 4 (IR-4) supports the proposed uses on kava, cilantro, and quinoa. Additionally, IR-4, along with its Canadian partners Agriculture & Agri-Food Canada/Pest Management Centre (AAFC/PMC) have submitted residue data to support the use of flupyradifurone on caneberries, pomegranate, and greenhouse grown cucumbers, lettuce, peppers, and tomatoes.

Additionally, Bayer has submitted amended use requests for flupyradifurone on *Brassica* (cole) leafy vegetables, subgroup 5B and leafy vegetables (except *Brassica*), subgroup 4A to include

soil drench applications. Label amendments to add commodities of tree nuts, group 14-12 to label, and to add previously approved use directions for clover grown for forage, fodder, seed, straw, and hay to the label were also requested.

Bayer has requested the following uses of flupyradifurone applicable to the occupational and residential exposure assessment:

- Proposed outdoor agricultural uses as summarized above.
- Proposed new uses on greenhouse crops: tomato, pepper, cucumber, lettuce (as summarized above); greenhouse and nursery ornamentals and annual flowers; and landscape ornamentals. These uses will be added to the new product label (EPA Reg. No. 432-RLTL) Altus.
- Proposed first new uses of flupyradifurone in residential settings on ornamental plants (gardens, trees, shrubs, flowers) by residential handlers will be added to two new products: FDF 50 SL Concentrate (EPA Reg. No. 72155-RRA) and FDF Ready-to-Use (EPA Reg. No. 72155-XXX).

Bayer has also requested a re-evaluation of the 24-hour REI for girdling and cane-turning grapes in absence of a margin of exposure (MOE) > 400 at the time of the previous exposure review (K. Rury, D413194, 07/31/2014) and an applicable dislodgeable-foliar residue (DFR) study.

Exposure Profile: Based on application rates and label information, only short- and intermediate-term exposure is expected for occupational handlers and post-application workers. Chronic exposure is not expected for the proposed use patterns. Only short-term exposures are expected for residential handlers and residential post-application exposures.

Hazard Assessment: With repeated dosing, reductions in body weight and food consumption were commonly seen in various studies and in all species of test animals (rats, mice, dogs, and rabbits). Flupyradifurone also produced skeletal muscle atrophy/degeneration in dogs at a lower dose level (28 mg/kg/day) relative to other effects. Consequently, the skeletal muscle atrophy/degeneration seen in the 90-day and one-year dog studies formed the basis for chronic dietary exposure and short- and intermediate-term occupational toxicity endpoints. The points of departure (PODs) were 7.8 mg/kg/day and 12 mg/kg/day for chronic dietary exposure and for short- and intermediate-term occupational exposure assessments, respectively.

Flupyradifurone also produced clinical signs (piloerection and pupillary dilatation) indicative of neurotoxicity in the acute neurotoxicity study, and these clinical signs were used to establish the toxicity endpoint with a point of departure of 35 mg/kg/day for acute dietary exposure assessment. The exposure databases are complete or are estimated based on data that reasonably account for potential exposures. Flupyradifurone is classified as "not likely to be carcinogenic to humans."

FQPA Safety Factor Decision: HED presently has sufficient information to evaluate the hazards associated with exposure to flupyradifurone at this time and the FQPA SF has been reduced to 1X. The exposure databases are complete or are estimated based on data that reasonably account for potential exposures. There was no evidence that flupyradifurone induced increased susceptibility in the rat developmental study. There were quantitative susceptibilities

seen in the fetuses of rabbit developmental study and in the pup of the reproduction study, but the PODs used for risk assessment were protective of the increased quantitative susceptibilities in the pups and fetuses.

Residue Chemistry and Drinking Water Assessments: Adequate residue chemistry data have been submitted to support the establishment of tolerances in/on kava, cilantro, fresh leaves, stone fruit, group 12-12, caneberry, subgroup 13-07A, quinoa, and tropical and subtropical, medium to large fruit, smooth, inedible peel, subgroup 24B. Additionally, data were submitted depicting residues of flupyradifurone during processing of plums to prunes. Bayer submitted data to compare foliar application to soil drench applications at transplant (bridging studies). Data were also submitted to support use on greenhouse grown, cucumbers, lettuce, peppers, and tomato. In addition, adequate data are available for the generation of the modeled estimated drinking water concentrations (EDWCs).

***Dietary Risk Estimates (Food + Drinking Water*)**: Acute and chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID, ver. 3.16) which incorporates food consumption data from the United States Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA; 2003-2008). A cancer dietary risk assessment was not conducted as flupyradifurone is classified as not likely to be carcinogenic to humans.

The acute and chronic analysis assumed 100% crop-treated (CT), tolerance-level residues, DEEM (ver. 7.81) default processing factors, empirical processing factors, and modeled water concentrations. The acute dietary (food and drinking water) exposure and risk estimates do not exceed HED's level of concern (LOC) for the U.S. population or any population subgroups. At the 95th percentile of exposure, the resulting acute dietary (food and drinking water) risk estimates utilized 24% of the acute population–adjusted dose (aPAD) for the general U.S. population and utilized 37% of the aPAD for children 1-2 years old, the most highly exposed population subgroup. The chronic dietary (food and drinking water) exposure and risk estimates do not exceed HED's LOC for the U.S. population or any population subgroups. The resulting chronic dietary (food and drinking water) risk estimates utilized 40% of the chronic population-adjusted dose (cPAD) for the general U.S. population and utilized 86% of the cPAD for children 1-2 years old, the most highly exposed population subgroup. Flupyradifurone is classified as "not likely to be carcinogenic to humans"; therefore, a cancer dietary exposure assessment was not performed.

Residential (Non-Occupational) Exposure and Risk Assessment: The combined (dermal and inhalation) residential handler MOEs are not of concern for the proposed uses of flupyradifurone (LOC) = 100). The combined (dermal and inhalation) MOEs range from 47,000 to 590,000. The adult dermal post-application risk estimates for the proposed uses of flupyradifurone in residential areas are not of concern (LOC = 100) and the MOEs range from 290 to 25,000. The child (6 to < 11 years old) dermal post-application risk estimates for the proposed uses of flupyradifurone in residential areas are also not of concern (LOC = 100) and the MOEs range from 430 to 36,000.

Aggregate-Risk Estimates: In accordance with the FQPA, HED considers and aggregates pesticide exposures and risks from dietary (food and water) and residential (dermal, inhalation, and/or incidental oral) sources. Based on the proposed/registered uses, aggregate exposure consists of dietary exposure plus residential exposure. Since the endpoint for short- and intermediate-term dermal, inhalation and oral exposures comes from the same study these exposures should be aggregated. Aggregate short-term MOEs are 170 for adults and 190 for children 6 to <11 years old; therefore, short-term aggregate exposure to flupyradifurone is not of concern.

Occupational Exposure and Risk Assessment: All combined (dermal and inhalation) occupational handler MOEs are not of concern (LOC = 100) with baseline attire or with the PPE specified on the proposed labels (chemical resistant gloves). With baseline attire, combined dermal and inhalation MOEs range from 58 to 550,000. With the attire and PPE specified on the label (gloves), all combined dermal and inhalation MOEs are > 160.

There are no post-application dermal risk estimates of concern for the proposed uses of flupyradifurone on the day of application. The dermal post-application MOEs range from 110 to 32,000 on the day of application using chemical-specific DFR data.
Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for flupyradifurone at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for flupyradifurone.

Evaluation of Proposal to Reduce the REI for Grapes: Bayer has also requested a re-evaluation of the 24-hour REI for girdling and cane-turning grapes in absence of an MOE > 400 and an applicable DFR study at the time of exposure review (K. Rury, D413194, 07/31/2014). Bayer subsequently submitted two DFR studies, which resulted in greater available residues ($\mu g/cm^2$) when adjusted for differences among the proposed application rate and the rate used in the DFR study (0.73 $\mu g/cm^2$) than when using the Agency default of 25% of the application rate (0.51 $\mu g/cm^2$). These residues resulted in MOEs not of concern for girdling and cane-turning of grapes (MOE = 110). Therefore, HED support a revision of the REI for girdling and cane-turning of grapes.

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 Pesticide Handlers Exposure Database (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Residential standard operating procedures (SOPs); and the Agricultural Reentry Task Force (ARTF) database 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[1].

Environmental Justice Considerations: 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."

2.0 HED Recommendations

Provided the petitioner submits a revised Section B/proposed use and a revised Section F/proposed tolerances, HED concludes that the toxicological, exposure, and residue chemistry databases support the establishment of the permanent tolerances listed in Section 2.2.2. Additionally, HED supports a revision of the REI for girdling and cane-turning of grapes based on MOEs not of concern on the day of application.

2.1 Data Deficiencies/Data Needs

Toxicology/ORE: None
Residue chemistry: Revised Section B/proposed use.
Revised Section F/proposed tolerances.

2.2 Tolerance Considerations

References:
Memo, pending, W. Wassell, D430351

2.2.1 Enforcement Analytical Method

An adequate analytical method (Method RV-001-P10-03) which uses high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) to quantitate residues of flupyradifurone and difluoroacetic acid (DFA) in various crops is available for enforcement. Note: DFA was initially identified as a residue of concern for risk assessment, but was subsequently determined to not be of concern. Data concerning DFA are not discussed in this document. The validated limit of quantification (LOQ) is 0.01 ppm for flupyradifurone.

An HPLC/MS/MS method, Method RV-004-A11-05 is adequate as the enforcement method for determination of residues of flupyradifurone and its metabolite DFA in livestock commodities. The validated LOQ for flupyradifurone in/on many commodities is 0.01 ppm.

FDA multiresidue methods (MRMs) are unsuitable to enforce flupyradifurone. The methods are suitable for determination of residues of flupyradifurone only in non-fatty matrices. The methods are not suitable for fatty matrices or matrices that require further clean-up.

[1] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

European MRMs DFG S19 and QuEChERS are unsuitable for the enforcement of tolerances for residues of flupyradifurone and its metabolite (DFA). DFA could not be extracted using the extraction processes described in either of the methods.

2.2.2 Recommended Tolerances

Table 2.2.2.1 is a summary of the proposed and HED-recommended tolerances for residues of flupyradifurone. A revised Section F/proposed tolerances is requested to correct the commodity definition for the individual tropical fruits to Tropical and Subtropical, Medium to Large Fruit, Smooth, Inedible Peel, Subgroup 24B.

Table 2.2.2. Tolerance Summary for Flupyradifurone.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Kava, root (as part of Root Vegetables Except Sugar Beets, Crop Subgroup 1B)	0.9	0.90	*Kava, roots*
Cilantro, fresh leaves (as part of Leafy Greens, Crop Subgroup 4A)	30	30	*Cilantro, fresh leaves*
Kava, fresh leaves (translation from Leafy *Brassica* Greens, Crop Subgroup 5B)	40	40	*Kava, fresh leaves*
Stone Fruit (Crop Group 12-12)	1.5	1.5	*Fruit, stone, group 12-12*
Caneberry (Crop Subgroup 13-07A)	5.0	5.0	*Caneberry, crop subgroup 13-07A*
Quinoa (as part of Crop Group 15)	3.0	3.0	*Quinoa, grain*
Abiu, Akee apple, Avocado (including Guatemalan, Mexican, and West Indian), Bacury, Banana (including dwarf), Binjai, Canistel, Cupuacú, Etambe, Jatobá, Kei apple, Langstat, Lanjut, Lucuma, Mabolo, Mango (including horse and Saipan), Mangosteen, Paho, Papaya, Pawpaw (common), Pelipisan, Pequi, Pequia, Persimmon (American), Plantain, Pomegranate, Poshte, Quandong, Sapote (including black, green, and white), Sataw, Screw-pine, Star apple, Tamarind-of-the-Indies, and Wild loquat, and cultivars, varieties and hybrids of these commodities	0.6	0.60	*Tropical and subtropical, medium to large fruit, smooth, inedible peel subgroup 24B.*

2.2.3 Revisions to Petitioned-For Tolerances

None of the proposed tolerance levels has been altered with the exception of revising the number of significant figures as per current policy; however, since the tropical and subtropical, medium to large fruit, smooth, inedible peel, crop subgroup 24B has been established, the petitioner should propose tolerances for this subgroup instead of the individual commodities. Additionally, corrections to the commodity definitions must be addressed. A revised Section F is required.

2.2.4 International Harmonization

There are no Codex or Mexican maximum residue limits (MRLs) for flupyradifurone. For Canada, the tolerance expression is harmonized. Canadian MRLs for flupyradifurone are established for kava, root and leaves, cilantro, and quinoa. These tolerances/MRLs are harmonized. Canada does not have MRLs for flupyradifurone on stone fruit, caneberry, and tropical fruits.

2.3 Label Recommendations

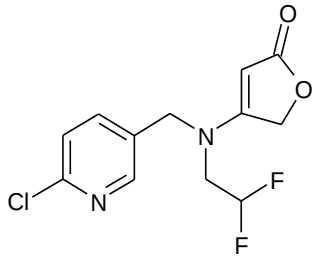
A revised Section B/proposed label is required. Many crops that are normally not rotated, such are fruit crops, berry crops, and tree nuts, are included on the list of crops for immediate plant-back. Crops which are not normally rotated should be removed from the list. Plant-back restrictions are for crops that will be harvested in the same season in which they are planted. Additionally, the proposed labels should be revised to make clear that kava roots are not a member of subgroup 1B, kava leaves are not a member of group 5, and quinoa is not a member of group 15 even though HED allowed translations from the groups/subgroups.

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of flupyradifurone is presented in Table 3.1.1. The physicochemical properties for flupyradifurone are presented in Appendix B.

Table 3.1.1. Flupyradifurone Nomenclature.

Compound	Chemical Structure
	
Common name	Flupyradifurone
Company experimental name	BYI02960
IUPAC name	4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(5*H*)-one
CAS name	4-[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]- 2(5*H*)-furanone
Molecular formula	$C_{12}H_{11}ClF_2N_2O_2$
CAS #	951659-40-8
End-use product/EP	Flupyradifurone TC (98% ai, EPA Reg No. 264-1143) Sivanto 200 SL (1.67 lb ai/gallon or 200 g ai/L soluble-liquid, EPA Reg. No. 264-1141) Altus or Aeron (1.67 lb ai/gallon or 200 g ai/L soluble-liquid, EPA Reg, No. not registered)

3.2 Pesticide Use Pattern/Directions

Proposed Use: Bayer has submitted proposed use directions for Sivanto 200 SL (EPA Reg. No. 664-1141; 1.67 lb ai per gallon formulated as a soluble liquid (SL)) which includes instructions for applications to kava roots (as a root vegetable commodity, subgroup 1B), kava leaves (as a *Brassica* (cole) leafy vegetable commodity, subgroup 5B), cilantro (as a leafy vegetable (except *Brassica*) commodity, subgroup 4A, stone fruit, group 12-12, caneberry subgroup 13-07A, quinoa (as a cereal grains, group 15), and various tropical fruits (listed below). Additionally, amended uses are requested for *Brassica* (cole) leafy vegetables, group 5 and leafy vegetables, except *Brassica*) to add soil applications. Label amendments to add commodities of tree nuts,

group 14-12 to label and to add previously approved use directions for clover grown for forage, fodder, seed, straw, and hay to the label were also requested. The proposed use directions are summarized below. The proposed application scenarios are supported by the available residue chemistry data.

Table 3.2.1. Summary of End-Use Product.

Trade Name	Conc.	Formulation	Label Date	Target Crops	Target Pests
Flupyradifurone TC	98.36%	For formulation into end use products	09/04/2015 (date of petition)	Many	Not listed
Sivanto 200 SL	17.09% 1.67 lb ai/gallon 200 g ai/L	SL	09/04/2015 (date of petition)	Kava, root	Aphids, leafhoppers, whiteflies
				Kava, fresh leaves	Aphids, leafhoppers, green peach aphid
				Cilantro, fresh leaves	Aphids, leafhoppers, whiteflies, green peach aphid
				Stone fruit group 12-12	Aphids, San Jose scale
				Caneberry subgroup 13-07A	Aphids, whiteflies
				Quinoa	Aphids, leafhoppers, whiteflies
				Tropical fruits[1]	Aphids, whiteflies, avocado thrips
Altus [Alternate Brand Names: Aeron]	17.09% 1.67 lb ai/gallon 200 g ai/L	SL	09/04/2015 (date of petition)	Cucumbers	Aphids, leafhoppers, squash bugs, whiteflies
				Lettuce	Aphids, leafhoppers, whiteflies
				Pepper and tomatoes	Aphids, leafhoppers, Colorado potato beetle, psyllid, whiteflies, Chilli trips (suppression), tomato yellow leaf curl virus (suppression)

[1] Tropical fruits are abiu, akee apple, avocado (including Guatemalan, Mexican, and West Indian), bacury, banana (including dwarf), binjai, canistel, cupuacú, etambe, jatobá, kei apple, langstat, lanjut, lucuma, mabolo, mango (including horse and saipan), mangosteen, paho, papaya, pawpaw (common), pelipisan, pequi, pequia, persimmon (American), plantain, pomegranate, poshte, quandong, sapote (including black, green, and white), sataw, screw-pine, star apple, tamarind-of-the-indies, and wild loquat, and cultivars, varieties and hybrids of these commodities.

Table 3.2.2. Summary of Proposed Use Directions.

App. Timing; Type; and Equip.	Formulation	Single App. Rate	Max. # App. per Season	Max. Seasonal App. Rate	PHI (days)	Use Directions and Limitations
Use Directions (Foliar Application) for Kava, Leaves (Added to use directions for *Brassica* (Cole) Leafy Vegetables, Group 5).						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	7	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Maximum number of crop seasons per year is 3. Minimum interval between applications is 7 days. Minimum spray volume 10 gallons per acre (GPA) by ground and 3 GPA by air.
Use Directions (Soil Application) for Kava, Leaves (Added to use directions for *Brassica* (Cole) Leafy Vegetables, Group 5).						

Table 3.2.2. Summary of Proposed Use Directions.						
App. Timing; Type; and Equip.	**Formulation**	**Single App. Rate**	**Max. # App. per Season**	**Max. Seasonal App. Rate**	**PHI (days)**	**Use Directions and Limitations**
Potting hole drench at transplanting or post-transplant drench/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	21.0 to 28.0 fl. oz./A (0.27 to 0.365 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	21	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Maximum number of crop seasons per year is 3. Minimum interval between applications is 7 days. Minimum spray volume 10 GPA by ground and 3 GPA by air.
Use Directions (Soil Application) for Kava, Roots (Added to use directions for Root Vegetables (except Sugar Beet), Subgroup 1B).						
Potting hole drench or post-transplant drench following setting and covering/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	21	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 10 days. Minimum spray volume 10 GPA by ground and 3 GPA by air.
Use Directions (Foliar Application) for Cilantro (Added to use directions for Leafy Vegetables (except *Brassica*), Group 4).						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	1	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Maximum crop seasons per year is 3. Minimum interval between applications is 10 days. Minimum spray volume 10 GPA by ground and 3 GPA by air.
Use Directions (Soil Application) for Leafy Vegetables (except *Brassica*), Group 4.						
Potting hole drench at transplanting or post-transplant drench following setting and covering/applications may be made with ground equipment and by chemigation.	SL (1.67 lb ai/gallon)	21.0 to 28.0 fl. oz./A (0.27 to 0.365 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	21	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Maximum crop seasons per year is 3. Application may be made by chemigation into root zone through low-pressure micro-sprinkler or equivalent equipment. Injection below (3 - 4 inches) the eventual seed-line prior to planting.
Use Directions (Foliar Application) for Stone Fruit, Group 12-12.						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	14	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 10 days. Minimum spray volume 25 GPA by ground and 3 GPA by air. For best results, combine product with a horticultural oil for pre-bloom applications targeting San Jose scale.
Use Directions (Foliar Application) for Caneberry, Subgroup 13-07A.						

Table 3.2.2. Summary of Proposed Use Directions.						
App. Timing; Type; and Equip.	**Formulation**	**Single App. Rate**	**Max. # App. per Season**	**Max. Seasonal App. Rate**	**PHI (days)**	**Use Directions and Limitations**
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	0	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 7 days. Minimum spray volume 30 GPA by ground and 3 GPA by air.
Use Directions (Foliar Application) for Quinoa (Added to use directions for Cereal Grains, Group 15).						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	21 days for grain.	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 7 days. Minimum spray volume 10 GPA by ground and 3 GPA by air. Note: forage, fodder and straw are not normally harvested when quinoa is grown.
Use Directions for Tropical Fruits[1].						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	7 days (pomegranate) 14 days for other listed crops.	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 7 days. Minimum spray volume 10 GPA by ground and 3 GPA by air.
Use Directions for Greenhouse Grown Cucumbers and Lettuce – Foliar or Soil Drench.						
Apply when pest thresholds have been reached/applications may be made with ground equipment, or overhead irrigation. For soil drench application: apply as a soil drench using micro-irrigation, drip irrigation, overhead drip irrigation, or hand-held or motorized calibrated irrigation equipment.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.365 lb ai/A) – as foliar application 21.0 to 28.0 fl. oz./A (0.273 to 0.365 lb ai/A) – as soil drench application	2	28 fl. oz./A (0.365 lb ai/A)	1 day	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum application volume is 50 GPA. Do not make more than 1 application per crop of transplants, regardless of method of application.
Use Directions for Greenhouse Grown Pepper and Tomato – Foliar or Soil Drench.						

Table 3.2.2. Summary of Proposed Use Directions.						
App. Timing; Type; and Equip.	**Formulation**	**Single App. Rate**	**Max. # App. per Season**	**Max. Seasonal App. Rate**	**PHI (days)**	**Use Directions and Limitations**
Apply when pest thresholds have been reached/applications may be made with ground equipment, or overhead irrigation. For soil drench application: apply as a soil drench using micro-irrigation, drip irrigation, overhead drip irrigation, or hand-held or motorized calibrated irrigation equipment.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.365 lb ai/A) – as foliar application 21.0 to 28.0 fl. oz./A (0.273 to 0.365 lb ai/A) – as soil drench application	2	28 fl. oz./A (0.365 lb ai/A)	3 days (peppers) 1 day (tomatoes) 1 day for soil drench application.	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum application volume is 50 GPA. Do not make more than 1 application per crop of transplants, regardless of method of application.
Use Directions for Clover Grown for Forage, Fodder, Seed, Straw, and Hay.						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	14	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 10 days. Minimum spray volume 10 GPA by ground and 3 GPA by air. For use in ID, OR, and WA only.
Use Directions for Tree Nuts, Group 14-12.						
Not specified/ applications may be made with ground equipment, aerial equipment, and by chemigation.	SL (1.67 lb ai/gallon)	7.0 to 14.0 fl. oz./A (0.09 to 0.182 lb ai/A)	Not Specified	28 fl. oz./A (0.365 lb ai/A)	7	Maximum application rate per crop season is 28.0 fl. oz./A (0.365 lb ai/A) regardless of application method. Minimum interval between applications is 14 days. Minimum spray volume 25 GPA by ground and 10 GPA by air.

[1] Tropical fruits are abiu, akee apple, avocado (including Guatemalan, Mexican, and West Indian), bacury, banana (including dwarf), binjai, canistel, cupuacú, etambe, jatobá, kei apple, langstat, lanjut, lucuma, mabolo, mango (including horse and saipan), mangosteen, paho, papaya, pawpaw (common), pelipisan, pequi, pequia, persimmon (American), plantain, pomegranate, poshte, quandong, sapote (including black, green, and white), sataw, screw-pine, star apple, tamarind-of-the-indies, and wild loquat, and cultivars, varieties and hybrids of these commodities.

A revised Section B/proposed use is required. Many crops that are normally not rotated, such are fruit crops, berry crops, and tree nuts, are included on the list of crops for immediate plant-back. Crops which are not normally rotated should be removed from the list as the plant-back restrictions are for crops that will be harvested in the same season in which they are planted.

3.3 Anticipated Exposure Pathways

Based on the proposed/registered application scenarios, flupyradifurone residues may be found in drinking water and crop/livestock commodities. The proposed uses are expected to result in residential exposure. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application.

This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses for flupyradifurone, but also considers the existing registered uses as well, particularly for the dietary exposure assessment.

3.4 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," (http://www.archives/federal-register/executive-orders/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 USDA's NHANES/WWEIA, are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. 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. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

References:
Memo, 08/05/2014, K. Rury *et al*., D407063

Flupyradifurone is an insecticide that is a member of the butenolide class of chemistry effective against a broad range of sucking insects. Its mode of action is classified as a Group 4D insecticide (i.e. a nicotinic acetylcholine receptor agonist). Flupyradifurone is thought to bind and stimulate insect nAchRs leading to paralysis and death. The effects seen in the acute neurotoxicity study are likely related to stimulation of the nAchRs, however there is limited additional evidence in mammalian studies that the pesticidal mode of action is important to mammals.

4.1 Toxicology Studies Available for Analysis

All the required toxicity studies on flupyradifurone have been submitted to support proposed food-use registrations. The toxicology database is acceptable for characterizing flupyradifurone hazard and includes: 28-day oral, 90-day oral, and 28-day dermal studies in rats; 28-day oral and 90-day oral toxicity studies in mice; 28-day-oral and 90-day oral toxicity studies in dogs; a 1-year dietary study in dogs; a carcinogenicity study in mice; a 2-year dietary combined chronic/carcinogenicity in rats; developmental toxicity studies in rats and rabbits; a 2-generation reproduction study in rats; acute and subchronic neurotoxicity studies in rats; a developmental

neurotoxicity study in rats; mutagenicity and genotoxicity studies in bacterial & mammalian model systems; 28-day dietary immunotoxicity studies in rats; metabolism and pharmacokinetic studies in rats with 3 different ^{14}C- labeling positions on flupyradifurone; and *in vivo* and *in vitro* dermal penetration studies on the formulated flupyradifurone. Of the available studies, some subchronic toxicity studies in rats, mice, and dogs contained data on liver enzymes, thyroid hormones, and plasma concentration of flupyradifurone. Two metabolites (DFA and difluoroethyl-amino-furanone) were tested in subchronic oral toxicity studies and in the genotoxicity battery of studies, while two other metabolites ((6-chloro-3-pyridyl) methanol and 6-chloronicotinic acid (6-CNA)) were tested only with bacterial gene mutation assays. Summaries of all toxicology studies are presented in Attachment A.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Absorption, distribution, metabolism, and elimination (ADME) of flupyradifurone were investigated using ^{14}C label at three different positions (pyridinylmethyl label, furanone label, and ethyl label).

Regardless of labeling position, the results showed that following oral administration of a low dose (2 mg/kg) of flupyradifurone to male and female rats, the gastrointestinal absorption of radioactivity was high and accounted for >80% of the administered dose. In most cases, the maximum plasma concentration was reached within 1 or 2 hours after dosing. With the high dose (200 mg/kg), the peak plasma concentration was observed between 2 and 4 hours after dosing. After reaching the peak concentration, the radioactivity levels in plasma declined steadily by several orders of magnitude in all studies independent of sex or labeling position of the test compound. Elimination was very fast, mainly via urine and almost completed after 24 hours. No radioactivity was detected in the expired air after dosing with the pyridinylmethyl- and ethyl- labeled compounds. With administration of [furanone-4-^{14}C] flupyradifurone between 1 and 3% of the administered radioactivity was detected in the expired air.

The absorbed dose was rapidly distributed; at approximately 1 hour after dosing, the concentrations in liver and kidney were significantly higher than in blood, suggesting a preferred clearance from blood and distribution mainly to the organs responsible for metabolism (liver) and excretion (kidney). Very low levels were found in the brain, spinal cord, and renal fat. These results are similar in male and female rats independent of the labeling position. A fast decline of radioactivity concentrations was observed for all organs and tissues in males and females during the entire test period. Concentrations fell for most organs and tissues below 5% of the maximum tissue radioactivity after one day. After seven days, only very low concentrations were found in a few organs and tissues of rats. Basically, male and female rats exhibited very similar absorption, distribution, and elimination patterns. The quantitative whole body autoradiography studies demonstrated that there was no accumulation of radioactivity in any organ of the tested male and female rats.

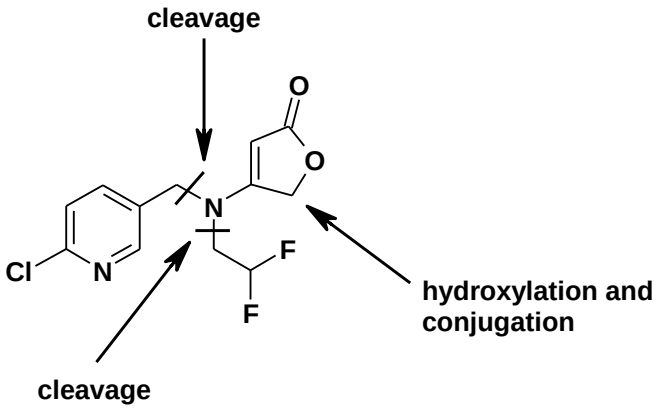
Flupyradifurone was readily metabolized in the rat. Numerous metabolites were formed, most of them being minor. The parent compound represented the predominant part of the radioactivity in urine of male and female rats. In feces of male rats, the metabolite BYI 02960-OH was more

prominent than the parent compound. Two metabolites, 6-chloro-nicotinic acid (BYI 02960-6-CNA) and BYI 02960-hippuric acid were also prominent in male but not in female rats.

The organ metabolism study using the ethyl-^{14}C label showed that, in the 24 hours' samples of plasma, organs, and tissues, DFA was by far the major metabolite accounting for more than 50% of the radioactivity in the tissues. However, DFA accounted for approximately 6% of the administered dose.

The metabolic profiles in urine and feces were very similar for both sexes, but male rats showed a higher rate of metabolite formation as compared to females.

The figure below schematically shows the sites of the molecule which are involved in the metabolic reactions:



The principal metabolic reactions of flupyradifurone in rats could be summarized as follows:

- hydroxylation followed by conjugation with glucuronic acid or sulfate;
- cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl, and BYI 02960-DFA;
- cleavage of the molecule at the pyridinylmethylene bridge forming 6-chlor-nicotinic acid BYI 02960-6-CNA, which was further conjugated with glycine to BYI 02960-hippuric acid and BYI 02960-difluoroethyl-amino-furanone.

4.2.1 Dermal Absorption

There is no dermal absorption study available with technical grade flupyradifurone. However, *in vivo* (rat) and *in vitro* (human and rat skin) dermal penetration studies with the liquid formulation of flupyradifurone are available. The dermal absorption values from the 24 hour measurements from *in vivo* and *in vitro* dermal absorption studies on the most dilute test formulation (0.1 g/L of 200 g/L SL) were used to estimate the human dermal absorption factor (DAF) with the equation: *human DAF = (in vitro human % absorption) x [(in vivo rat % absorption/ (in vitro rat % absorption)]*. The calculated DAF was 7.42% for 24-hour exposure.

4.3 Toxicological Effects

The most sensitive effects seen in the flupyradifurone database were skeletal muscle atrophy/degeneration in dogs, which appear to be the most sensitive tested animal; however, with ¾ body weight scaling, the rat and dogs are equally as sensitive to the effects of flupyradifurone. With dietary administration, reductions in body weight and food consumption were commonly seen in all species of the test animals (rats, mice, dogs, and rabbits). The liver and thyroid were also common targets of flupyradifurone toxicity. The liver effects often consisted of increased liver weight, hepatocellular hypertrophy, liver enzyme increases (cytochrome p450 increases), and decreases in total cholesterol. Some of the liver effects were judged to be adaptive responses while some were correlated with vacuolations and changes in clinical chemistry parameters (increases in alkaline phosphatase (ALP) and alanine aminotranspherase (ALT), and cholesterol level changes indicative of liver effects which were progressed beyond the adaptive stage. The thyroid effects consisted of thyroid follicular cell hypertrophy and were seen mainly in rats. In addition, the thyroid effects were generally found in conjunction with liver effects.

The developmental toxicity data in rats and rabbits showed that flupyradifurone caused delayed bone ossification in the fetal rats and increase incidence of fetal death in rabbits. These effects were seen at the maternal lowest observed adverse effect levels (LOAEL, 150 mg/kg/day) in rat developmental study. No adverse maternal effects were at the highest tested dose (80 mg/kg/day) in the combined data of rabbit developmental studies (main and range finding studies). The increased incidence of fetal death in rabbits was considered to be a quantitative increase in susceptibility in the developing fetuses. However, clear no observed adverse effect levels (NOAELs) were established for both rat and rabbit developmental toxicity studies.

The results of a 2-generation reproduction study showed that flupyradifurone reduced the number of estrus cycles, decreasing the number of implantations in P_2 dams, and decreasing the litter size in the presence of decreased body weight and food consumption in maternal animals. In addition, the body weight of F_2 pups was decreased at a dose (37.8 mg/kg/day) where no effect was seen in the parental animals, and this finding suggested a quantitative increase in susceptibility in the young rat.

Carcinogenicity studies in rats and mice did not yield a compound-related increase in tumor incidence, and the genotoxicity battery did not show flupyradifurone to produce any genotoxicity.

The acute neurotoxicity study showed that flupyradifurone caused increases in the incidence of piloerection and dilated pupils at 50 mg/kg. At the next higher dose level (200 mg/kg) and above, it produced a large number of clinical signs, which are indicative of neurotoxicity. These included lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses, and reduced rectal temperature. However, none of these clinical signs were found in the dietary feeding studies, including the 90-day neurotoxicity study. The effects seen in the acute neurotoxicity study are likely related to stimulation of the nAchRs, however there is limited additional evidence in mammalian studies that the pesticidal mode of action is important to

mammals. The differences in the findings between the acute neurotoxicity study and other studies using dietary administration might be explained by the rapid absorption and excretion. Flupyradifurone was absorbed rapidly in the metabolism study where rats were dosed by gavage. Peak plasma levels were reached within 1-4 hours of dosing depending on the dose, and flupyradifurone was almost completely eliminated approximately 24 hours after administration. With dietary administration, the rodent test animal consumed the compound mostly during the entire night, and the internal flupyradifurone concentration required to produce the effect was probably seldom reached due to metabolism and rapid elimination from the body. As a result, clinical signs were not reported. No neurotoxicity or other adverse effects were seen in 90-day dietary neurotoxicity study in rats at dose levels as high as 174 mg/kg/day.

No immunotoxicity was found in rats tested at the highest dose of 230 mg/kg/day.

The acute toxicity of flupyradifurone was low for all routes (oral, dermal, and inhalation). The rat oral LD_{50} was estimated to be greater than 2,000 mg/kg, with mortalities reported at 2,000 mg/kg, but none at 300 mg/kg (Toxicity Category III). The acute dermal LD_{50} for rats was >2,000 mg/kg (Toxicity Category III). The acute inhalation LC_{50} for rats was >4,671 mg/m^3 (4.67 mg/L), which was the highest achievable concentration (Toxicity Category IV). Flupyradifurone was not irritating to rabbit skin and caused only slight ocular irritation (redness of the conjunctivae) which was reversed within 48 hours.

Several metabolites were found in plants and rat metabolism studies; some of these metabolites were tested in mutagenicity studies and subchronic oral toxicity studies. The results showed that most of the flupyradifurone metabolites had lower toxicity than the parent compound except DFA (BCS-AA56716 see Toxicity Profile Table in Attachment A). The limited data (90-day oral feeding study in rats) showed that DFA produced a different effect from the parent compound, black foci in the glandular part of the stomach which correlated with the histopathology finding of focal glandular erosion/necrosis. In addition, slight decreases in hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and hematocrit were also found. The stomach effects were seen at a LOAEL of 66 mg/kg/day which was lower than a comparable 90-day oral toxicity study of the parent compound in rats (LOAEL = 156 mg/kg/day). It should also be noted that when comparing the NOAEL and LOAEL of this study to a similar study (90-day oral study in dogs) with parent compound, on a molar basis, the NOAELs and LOAELs of DFA and the parent are comparable, however, the effects are different. Furthermore, it should be reiterated that in the rat metabolism study with flupyradifurone, DFA was formed and detected as approximately 6% of the administered dose.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

Based on the currently available toxicity and exposure data, the risk assessment team recommended the FQPA SF be reduced to 1X as supported by a complete toxicological database. Although there are clinical signs which are indicative of neurotoxicity in adult rats and quantitative increases in susceptibility demonstrated by decreased body weights in F_2 rat pups and quantitative and qualitative susceptibility demonstrated by increased incidence of dead rabbit fetuses, there are clear NOAELs for these effects. The NOAEL for offspring toxicity in the 2-generation reproduction study is equivalent to the POD selected for risk assessment while the

NOAELs for neurotoxicity (clinical signs) and rabbit development toxicity are greater than the NOAEL selected as the POD for risk assessment. Therefore, the POD is protective of the effects which are indicative of neurotoxicity and susceptibility in rats and rabbits. There is no uncertainty in the exposure database. Overall, the data support the determination that an additional safety factor is not needed. The details for reducing the FQPA SF are elaborated below.

4.4.1 Completeness of the Toxicology Database

The flupyradifurone toxicology database is adequate to characterize any potential for prenatal or postnatal risk for infants and children, and includes acceptable developmental toxicity studies in the rat and rabbit and a rat reproductive toxicity study, as well as acute and subchronic neurotoxicity studies. HED waived the required subchronic inhalation toxicity study based on flupyradifurone's physical chemical properties, including low vapor pressure; low acute inhalation toxicity (Toxicity Category IV); and the use of a conservative, chronic oral POD that results in screening-level MOEs that do not exceed the target MOE for a waiver of 10X the LOC (TXR#0056903).

4.4.2 Evidence of Neurotoxicity

Although there is evidence that flupyradifurone has neurotoxic effects, EPA has a complete set of neurotoxicity studies (acute, subchronic, and developmental). The effects of those studies are well-characterized and indicate neurotoxic effects that occur at levels above the chronic POD that was selected for risk assessment. The NOAEL for the acute neurotoxicity study is being used for the acute POD. Therefore, there is no need to retain the 10X FQPA SF to account for any uncertainty concerning these effects.

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

There is no evidence that flupyradifurone produces increased susceptibility in in the rat developmental study. There is quantitative susceptibility in the rabbit developmental and rat reproduction studies. In the rabbit developmental study, no maternal effect was seen at the highest tested dose (80 mg/kg/day), while there was an increase in fetal death and decrease fetal body weight at the same dose level. In the rat reproduction study, maternal effect, decrease in body weight, was seen at 137 mg/kg/day, whereas decreases in pup body weight was seen at the next lower dose, 38.7 mg/kg/day or above. These findings are also indicative of an increase in quantitative susceptibility. However, the PODs selected for risk assessment are protective of the quantitative susceptibility seen in the rabbit fetuses and rat pups.

4.4.4 Residual Uncertainty in the Exposure Database

The exposure databases are complete or are estimated based on data that reasonably account for potential exposures. The dietary exposure assessment for flupyradifurone was conservatively based on tolerance-level residues, 100% CT assumptions, as well as conservative ground and surface drinking water modeling estimates. All of the exposure and risk estimates are based on conservative assumptions that do not underestimate risk.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

With oral dosing, ADME of flupyradifurone was rapid. The time of peak plasma concentration was reached within 1-4 hours, depending on the dosage employed. Elimination was almost complete by 24 hours after dosing. The ADME data are consistent with the timing and doses causing effects throughout the database as there was little difference in the values of the LOAELs between the chronic study and subchronic study in either rats (90-day: 156 mg/kg/day; chronic: 120 mg/kg/day) or dogs (90-day: 33 mg/kg/day; chronic: 28 mg/kg/day). The minor differences were due to differences in dose selection. However, in the 1-year dog study, the effects seen at the LOAEL (28 mg/kg/day) were more extensive than that in the 90-day dog study. The 1-year dog study was used to establish the toxicity endpoint and POD for the chronic dietary exposure assessment. For short-term incidental oral exposure assessment and short- and intermediate-term dermal and inhalation assessment, the selection of the POD (12 mg/kg/day) and toxicity endpoint from the 90-day dog study and the 2-generation reproduction study as co-critical is appropriate and is protective of any effects seen in the developmental studies in rats and rabbits. In a similar reasoning, the 90-day dog study is also appropriate for toxicity endpoint selection for short-term dermal and inhalation exposure assessments. The duration of a 90-day dog study also corresponds to the duration of exposure for the intermediate-term dermal and inhalation exposure. The reason for employing the 2-generation reproduction study as a co-critical study in selecting the toxicity endpoint for the dermal, and inhalation exposure assessment is that the pup body weight loss occurred at similar LOAEL as the skeletal muscle atrophy/degeneration in the 90-day dog study. In addition, the pup body weight loss is a clear effect of flupyradifurone on the young animal. The POD (35 mg/kg/day) selected from the acute neurotoxicity study is also protective of any effects seen in the developmental toxicity studies in rats and rabbits. The toxicity endpoints and points of departures are presented in Table 4.5.4.1.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

HED combines exposure from different routes for each population if the same toxic effects are seen for that duration of exposure by each route. Since the same endpoint (skeletal muscle atrophy in the dog, co-critical with the pup body weight decrease) was chosen for both dermal and inhalation risk assessment, these exposures should be combined. Additionally, the chronic dietary endpoint is based on skeletal muscle degeneration. Thus, dermal, inhalation and chronic dietary exposures should be aggregated.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Flupyradifurone is classified as “not likely to be carcinogenic to humans” based on data showing no treatment-related increase in tumour incidence in rat and mouse carcinogenicity studies. No mutagenic concern was reported in the genotoxicity studies.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 is a summary of the toxicological endpoints used in the current assessment.

Table 4.5.4.1: Summary of Toxicity Endpoints and Points of Departure for Use in Dietary, Non-Occupational, and Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure (POD)	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	NOAEL = 35 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	aRfD =0.35 mg/kg/day aPAD = 0.35 mg/kg/day	**Acute neurotoxicity study –rat** LOAEL = 50 mg/kg/day based on increased incidences of piloerection in both sexes and pupil dilation in females on Day 1. At the next higher dose level (200 mg/kg) or above, lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature. Automated measures of motor activity were also reduced in both sexes, compared to controls.
Chronic Dietary (All Populations)	NOAEL = 7.8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	cRfD = 0.078 mg/kg/day cPAD = 0.078 mg/kg/day	**Oral toxicity study-dog (1-year)** LOAEL= 28 mg/kg/day based on minimal to slight, focal to multifocal areas of skeletal muscle degeneration in gastrocnemius and/or biceps femoris muscle.
Oral Short-(1-30 days) and Intermediate-terms (1-6 months)	NOAEL = 12 mg/kg/day	UF_A= 10x UF_H=10x	LOC = 100	**Oral toxicity study-dog (90-day)** LOAEL= 33 mg/kg/day based on skeletal muscle atrophy/degeneration. **2-Generation reproduction study- rat (co-critical study)** NOAEL= 7.7 mg/kg/day. Offspring LOAEL=38.7 mg/kg/day based on pup body weight decrease.
Dermal Short-(1-30 days) and Intermediate-terms (1-6 months)	NOAEL = 12 mg/kg/day DAF = 7.42%[a]	UF_A= 10x UF_H=10x	LOC = 100	**Oral toxicity study-dog (90-day)** LOAEL= 33 mg/kg/day based skeletal muscle atrophy/degeneration. **2-Generation reproduction study- rat (co-critical study)** NOAEL= 7.7 mg/kg/day. Offspring LOAEL=38.7 mg/kg/day based on pup body weight decrease.
Inhalation Short-(1-30 days) and Intermediate-terms (1-6 months)	NOAEL = 12 mg/kg/day	UF_A= 10x UF_H=10x	LOC = 100	**Oral toxicity study-dog (90-day)** LOAEL= 33 mg/kg/day based on skeletal muscle atrophy/degeneration. **2-Generation reproduction study- rat (co-critical study)** NOAEL= 7.7 mg/kg/day. Offspring LOAEL=38.7 mg/kg/day based on pup body weight decrease.
Cancer (oral, dermal, inhalation)	Classification: not likely to be carcinogenic to humans- based on data showing no treatment-related increase in tumors incidence in rat and mouse carcinogenicity studies. No mutagenic concern was reported in the genotoxicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (c = chronic). RfD = reference dose. LOC = level of concern. Dermal absorption factor = DAF. Toxicity via the inhalation route of exposure is assumed to be equivalent to toxicity via the oral route.

[a] This DAF was calculated based on the dermal absorption values from the 24 hours measurements of the most dilute test formulation used in the *in vivo* rat and *in vitro* human and rat skin dermal penetration studies. To estimate the human dermal absorption factor (DAF), the following equation is used: Human DAF = *(in vitro* human % absorption*) x [(in vivo* rat % absorption*/ (in vitro* rat % absorption*)]*.

5.0 Dietary Exposure and Risk Assessment

References:
Memo, pending, W. Wassell, D430351
Memo, pending, W. Wassell, D434938
Memo, 08/05/2014, K. Rury *et al.*, D407063 (PP#2F8101)
ROCKS Memo, 12/19/2013, I. Negrón-Encarnación, D413192

5.1 Metabolite/Degradate Residue Profile

The qualitative nature of flupyradifurone residue in primary crops, livestock, and rotational crops are understood based on the available apple, cotton, rice, tomato, potato, goat, and poultry metabolism studies. All studies were deemed adequate.

The proposed uses under this petition include crops that are typically rotated. The qualitative nature of flupyradifurone residues in rotational crops are understood based on an adequate confined rotational crop data.

Based on these data, the HED Residues of Concern Knowledgebase Subcommittee (ROCKS) concluded that the residues of concern, for tolerance enforcement are flupyradifurone and for risk assessment are flupyradifurone and DFA. Subsequent consultation with the international review partners of the first food use petition (PP#2F8101) led to a decision to include only flupyradifurone as the residue of concern for risk assessment.

Based on the available cotton, eggplant, orange, apple, poultry, and ruminant metabolism studies, the confined rotational crop studies, and the environmental fate data, the residues of concern are summarized in Table 5.1.1.

Table 5.1.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression. [1]			
Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Flupyradifurone, DFA[3]	Flupyradifurone
	Rotational Crop	Flupyradifurone, DFA	Flupyradifurone
	Processed Commodities	Flupyradifurone, DFA	Flupyradifurone
Livestock	Ruminant	Flupyradifurone, DFA	Flupyradifurone
	Poultry	Flupyradifurone, DFA	Flupyradifurone
Drinking Water[2]		Flupyradifurone, DFA, flupyradifurone-succinamide, and flupyradifurone-azabicyclosuccinamide	Not Applicable

[1] Difluoroacetic acid and flupyradifurone may need to be considered in separate risk assessments.
[2] The aqueous photolysis degradates, flupyradifurone-succinamide and flupyradifurone-azabicyclosuccinamide, are recommended for surface water estimates only.
[3] ROCKS recommended flupyradifurone and difluoroacetic acid. Subsequent consultation with the international review partners led to a decision to include only flupyradifurone.

5.2 Food Residue Profile

The number and geographical representation of the submitted field trial data are adequate. In addition, the petitioner submitted adequate plum processing data which indicated that tolerances for residues in/on prunes are not required. In some cases, decisions were made based upon translated data. In all cases, the translated data are adequate in terms of the number and geographical representation of field trials. Bayer has also submitted bridging data for the comparison of foliar use data and soil application data for various commodities. The commodities include cucumber, melon, summer squash, tomato, bell pepper, non-bell pepper, grapefruit, lemon, orange, mandarin orange, and grapes. All studies showed residue levels that were below the established tolerance levels. Additionally, the field trials conducted with soil applications had residues levels that were significantly lower than those of the foliar application studies.

Additionally, IR-4, along with its Canadian partners AAFC/PMC have submitted residue data to support the use of flupyradifurone on caneberries, pomegranate, and greenhouse grown cucumbers, lettuce, peppers, and tomatoes.

5.3 Drinking Water Residue Profile

References:
Memo, 02/28/2014, K. White, D415166

The drinking water residues used in the dietary risk assessment were provided by EFED and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.” EDWCs were calculated for total toxic residues (TTR) consisting of 1) parent plus M47 plus M48 plus unextracted residues (referred to as “TTR-UN”), and 2) parent plus M47 plus M48 (referred to as “TTR”).

EDWCs for the acute assessments were estimated using the Pesticide Root Zone Model-Exposure Analysis Modeling System (PRZM-EXAMS). The EDWC for the chronic assessment

was estimated using PRZM-GW (groundwater). The models used to derive the EDWCs are listed in Table 4. The models and their descriptions are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Table 5.3.1. Tier I EDWCs for Residues of Flupyradifurone Plus M47, M48, and Unextracted Residues.[1]

Source of Drinking Water (Model)	Estimated Drinking Water Concentrations (µg/L)[2]	
	Acute	Annual Average or Post Breakthrough Average
Surface Water (Modified Tier 1 Rice Model)	112	112
Surface water (PRZM/EXAMS)	46.1 (1 season) 47.7 (2 seasons) 52.5 (3 seasons)	13.9 (1 season) 20.1 (2 seasons) 22.3 (3 seasons)
Groundwater (PRZM-GW)	117 (1 season) 23.8 (2 seasons) **352** (3 seasons)	102 (1 season) 208 (2 seasons) **307** (3 seasons)

[1] Refinements can be made to get lower EDWCs Tier II modeling could be conducted to determine EDWC in groundwater.
[2] All values reflect residues of flupyradifurone plus M47, M48, and unextracted residues. Bolded values indicate values used in the acute and chronic assessments.

5.4 Dietary (Food + Drinking Water) Risk Assessment

HED used recommended tolerance-level residues for the proposed and established tolerances, and assumed that 100% of the crops were treated for both the acute and chronic assessments. Empirical processing factors were used for processed commodities of apple (sauce and juice), coffee, citrus oil, cotton (oil), corn (bran, flour, meal, starch, oil), grape (wine, juice), grapefruit (juice), hops (dried cones), limes (juice), lemons (juice), oranges (juice and peel), peanut (butter, oil), pears (juice), potatoes (chips, flakes, cooked), tomatoes (juice, puree, paste), soybeans (oil, milk, flour), and wheat (bran, germ, flour). EDWCs provided by EFED were also included.

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the DEEM-FCID, version 3.16. This software uses 2003-2008 food consumption data from the USDA's NHANES/WWEIA. The analyses were conducted in support of a human health risk assessment to support a section 18 specific emergency exemption for the use of flupyradifurone on sweet sorghum in Kentucky, section 3 requests for kava, cilantro, stone fruit, group 12-12, caneberry, subgroup 13-07a, quinoa, and tropical fruits; amended use requests for soil applications for leafy vegetables, group 4 and *brassica* (cole) leafy vegetables, group 5; use on greenhouse grown tomato, pepper, cucumber, and lettuce; and to add tree nuts, group 14-12 commodities to the label.

The assessments assumed that 100% of the crops were treated with flupyradifurone. EDWCs provided by EFED were also included.

The acute dietary (food and drinking water) exposure and risk estimates do not exceed HED's LOC [i.e., <100% aPAD] for the U.S. population or any population subgroups. At the 95th percentile of exposure, the resulting acute dietary (food and drinking water) risk estimates utilized 24% of the aPAD for the general U.S. population and utilized 37% of the aPAD for children 1-2 years old, the most highly exposed population subgroup.

The chronic dietary (food and drinking water) exposure and risk estimates do not exceed HED's LOC [i.e., <100% cPAD] for the U.S. population or any population subgroups. The resulting chronic dietary (food and drinking water) risk estimates utilized 40% of the cPAD for the general U.S. population and utilized 86% of the cPAD for children 1-2 years old, the most highly exposed population subgroup. Flupyradifurone is classified as "not likely to be carcinogenic to humans"; therefore, a cancer dietary exposure assessment was not performed. The results of the acute and chronic dietary exposure analyses are reported in the Summary Table (Table 5.4.1, below).

Table 5.4.1. Summary of Dietary Exposure (Food Plus Water) Assessment for Flupyradifurone.

Population Subgroup	Acute Dietary[1] (95th Percentile)		Chronic Dietary[2]	
	Dietary Exposure (mg/kg/day)	% aPAD[3]	Dietary Exposure (mg/kg/day)	% cPAD[3]
General U.S. Population	0.082545	24	0.030917	40
All Infants (< 1 year old)	0.099252	28	0.040275	52
Children 1-2 years old	**0.131139**	**37**	**0.066923**	**86**
Children 3-5 years old	0.128509	37	0.055477	71
Children 6-12 years old	0.083362	24	0.035343	45
Youth 13-19 years old	0.064338	18	0.024172	31
Adults 20-49 years old	0.077173	22	0.028260	36
Adults 50+ years old	0.074951	21	0.028337	36
Females 13-49 years old	0.080650	23	0.028412	36

[1] aPAD = 0.35 mg/kg/day.
[2] cPAD = 0.078 mg/kg/day.
[3] % PADs are reported to 2 significant figures. The values for the highest exposed population for each type of risk assessment are bolded.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

References:
Memo, pending, K. Rickard, D430371

This is the first petition requesting residential uses for flupyradifurone. Therefore, the proposed uses have been assessed using HED's 2012 Residential SOPs[2]. These proposed uses will impact the human health aggregate risk assessment for flupyradifurone.

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. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

There are proposed product labels with residential use sites (e.g., EPA Reg. No. 72155-RRA and 72155-XXX) on ornamentals and flowers in residential areas that do not require specific clothing (e.g., long-sleeve shirt/long pants) and/or PPE, and these labels have been considered in the residential handler assessment for flupyradifurone.

[2] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

The quantitative exposure/risk assessment developed for residential handlers is based on the following scenarios:

- mixing/loading/applying liquids to gardens/trees using a manually pressurized handwand;
- mixing/loading/applying liquids to gardens/trees using a hose-end sprayer;
- mixing/loading/applying liquids to gardens/trees using a backpack sprayer;
- mixing/loading/applying liquids to gardens/trees using a sprinkler can;
- mixing/loading/applying ready-to-use formulations to gardens/trees using a trigger spray bottle;
- mixing/loading/applying ready-to-use formulations to gardens/trees using a hose-end sprayer.

Residential Handler Exposure Data and Assumptions: A series of 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 proposed application rates are provided in Table C (Appendix C).

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.

Exposure Duration: Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations: The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs.

Combining Exposures/Risk Estimates:
Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined Dermal + Inhalation dose (mg/kg/day)

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates:
The combined (dermal and inhalation) residential handler MOEs are not of concern for the proposed uses of flupyradifurone (LOC = 100). The combined (dermal and inhalation) MOEs range from 47,000 to 590,000.

Table 6.0.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Exposure Scenario	Level of Concern	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[3]	MOE[4]	Dose (mg/kg/day)[5]	MOE[6]	MOE[7]
Mixer/Loader/Applicator										
Gardens/Trees – Liquids with Manually Pressurized Handwand	100	63	0.018	0.00042 lb ai/gal	5 gal	0.000123	98,000	0.00000047	25,000,000	97,000
Gardens/Trees – Liquids with Hose-End Sprayer		58	0.0014		11 gal	0.000249	48,000	0.0000000809	150,000,000	48,000
Gardens/Trees – Liquids with Backpack Sprayer		130	0.14		5 gal	0.000253	47,000	0.00000368	3,300,000	47,000
Gardens/Trees – Liquids with a Sprinkler Can		58	0.0014		5 gal	0.000113	110,000	0.0000000368	330,000,000	110,000
Gardens/Trees – Ready-to-Use with a Trigger Spray Bottle[8]		85.1	0.061	0.0001275 lb ai/bottle[8]	2 bottles	0.0000201	600,000	0.000000194	62,000,000	590,000
Gardens/Trees – Ready-to-Use with a Hose-End Sprayer		6.26	0.034	0.00068 lb ai/gal	11 gal	0.0000434	280,000	0.00000318	3,800,000	260,000

1 Based on proposed labels (EPA Reg. No. 72155-RRA and 72155-XXX).
2 Based on HED's 2012 Residential SOPs (http://www2.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 (7.42%) ÷ body weight (80 kg).
4 Dermal MOE = dermal NOAEL (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) ÷ body weight (80 kg).
6 Inhalation MOE = inhalation NOAEL (12 mg/kg/day) ÷ inhalation dose (mg/kg/day).
7 Total MOE = NOAEL (12 mg/kg/day) ÷ (dermal dose + inhalation dose)
8 Application rate calculated as follows = 0.000068 lb ai/gal * 1 gal/128 fl. oz. = 0.0000053 lb ai/oz. Product comes in a minimum of a 24 fl. oz. bottle. Therefore, 0.0000053 lb ai/ fl. oz. x 24 fl. oz. = 0.0001275 lb ai/bottle.

6.1 Residential Post-Application Exposure/Risk Estimates

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

- dermal exposures to adults and children (6 to < 11 years old) to gardens, trees and retail plants, and indoor plants.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs. While not the only lifestages potentially exposed for these post-application scenarios, the lifestages that are included in the quantitative assessment are 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.

Application Rate: The proposed application rates are summarized in Table C. (Appendix C).

Exposure Duration: Residential exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

DFR Data: There are two available DFR studies for flupyradifurone; one study on grapes (MRID 496199-10) and one on greenhouse roses (MRID 496186-07). These studies were reviewed by HED and found to be acceptable for risk assessment. The available DFR study on grapes was used to evaluate dermal exposures to outdoor ornamental plants and flowers in residential areas. For the residential post-application assessments, the predicted day 0 residue values (0.357 µg/cm^2) were and adjusted to account for the different application rate used in the study (0.089 lb ai/A) and the proposed application rate (0.59 lb ai/A, which was calculated assuming one gallon treats 50 ft^2, based on information in EPA Reg. No. 72155-RRA).

Residential Post-Application Non-Cancer Exposure and Risk Equations: The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs.

Combining Exposure and Risk Estimates: Only dermal exposures are expected with the proposed residential uses of flupyradifurone. Therefore, these exposures are not combined with any other exposure route.

Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates: The adult dermal post-application risk estimates for the proposed uses of flupyradifurone in residential areas are not of concern (LOC = 100) and the MOEs range from 290 to 25,000. The child (6 to <

11 years old) dermal post-application risk estimates for the proposed uses of flupyradifurone in residential areas are also not of concern (LOC = 100) and the MOEs range from 430 to 36,000.

Table 6.1.1. Residential Post-Application Dermal Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Lifestage	Post-Application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	Dermal MOEs[3] (LOC = 100)
	Use Site	Route of Exposure			
Adult	Gardens	Dermal	0.00068 lb ai/gal or 0.59 lb ai/A	0.041	290
Child (6 to < 11 years old)				0.028	430
Adult	Trees & Retail Plants			0.0037	3,200
Child (6 to < 11 years old)				0.0026	4,700
Adult	Indoor Plants[4]			0.000485	25,000
Child (6 to < 11 years old)				0.000331	36,000

[1] Based on proposed label (EPA Reg. No. 72155-XXX.). However, the proposed application rate was only given in lb ai/fl. oz. per gallon. The area treated was assumed from the proposed EPA Reg. No. 72155-RRA label indicating that one gallon applies enough product to cover 50 ft^2 (0.00068 lb ai/gal x 1 gal/50ft^2 x 43560 ft^2/A = 0.59 lb ai/A.

[2] Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).

[3] MOE = POD (12 mg/kg/day) ÷ dose (mg/kg/day).

[4] Application directions indicate that flupyradifurone may be applied to indoor plants, but outside the home. This assessment was conducted to be protective of this proposed use of flupyradifurone.

6.2 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.2.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for flupyradifurone.

- The recommended residential exposure for use in the adult aggregate assessment reflects dermal post-application exposure to gardens from ready-to-use applications.
- The recommended residential exposure for use in the children 6 to < 11 years old aggregate assessment reflects dermal exposures from post-application exposures gardens from ready-to-use applications.

Table 6.2.1. Recommendations for the Residential Exposures for the Flupyradifurone Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adults	Dermal	0.041	N/A	N/A	**0.041**	290	N/A	N/A	**290**
Child (6 to < 11 years old)		0.028			**0.028**	430			**430**

[1] Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).

[2] MOE = the MOEs associated with the highest residential doses.

6.3 Residential Bystander Post-Application Inhalation Exposure

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 (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 (http://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 flupyradifurone.

A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from these types of applications. However, an inhalation exposure assessment was performed for handlers (i.e., groomers, treaters, etc) and this exposure scenario should be considered protective of any potential low-level post-application inhalation exposure that could result from these types of applications.

6.4 Spray Drift

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for flupyradifurone. The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information). [3] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED considers and aggregates pesticide exposures and risks from dietary (food and water) and residential (dermal, inhalation, and/or incidental oral) sources. Based on the proposed/registered uses, aggregate exposure consists of dietary exposure plus residential exposure. As indicated above, the unrefined acute and chronic dietary risk assessments resulted in exposure estimates which are not of concern to HED.

7.1 Acute Aggregate Risk

The aggregate acute risk estimates include exposure to residues of flupyradifurone in food and water, as there are no residential uses that would be considered in the acute assessment. Refer to Section 5.4 for a summary of the acute dietary (food and drinking water) exposure assessment.

[3] Available: http://www2.epa.gov/reducing-pesticide-drift

The acute risk estimates for the U.S. population and all other population subgroups, resulting from aggregate exposure to flupyradifurone in food and drinking water, are below the Agency's LOC.

7.2 Short-Term Aggregate Risk

There is potential short-term exposure to flupyradifurone via the dietary pathway (which is considered background exposure) and the residential pathway (which is considered the primary pathway). The short-term aggregate exposure assessment for adults includes dietary (food and drinking water) and dermal post-application exposure to gardens from ready-to-use applications. The short-term aggregate exposure assessment for children 6 to < 11 years old includes dietary assessment reflects dermal exposures from post-application exposures gardens from ready-to-use applications. Section 6.2 provides a summary of these scenarios that lead to the highest exposure from residential uses.

The aggregate MOEs for adults and children 6 to <11 years old are 170 and 190, respectively, which are greater than HED's LOC (MOE<100) and not of concern. The dietary exposure assessment is highly conservative, as it assumes tolerance-level residues and 100% crop treated.

Table 7.2. Short-Term Aggregate Risk Estimates

Population	Short-Term Scenario						
	NOAEL 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]
Adults[6]	12	100	0.12	0.028	0.041	0.069	170
Child (6 to < 11 years old)	12	100	0.12	0.035	0.028	0.062	190

[1] LOC is based on UF_A= 10x and UF_H=10x
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure = dermal post-application exposure from use in home gardens (Table 6.2.1).
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure)
[5] Aggregate MOE = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)]
[6] Adult subpopulation of "Females 13-49 years old" was selected from the background (chronic) dietary exposure assessment as the most protective adult subpopulation.

7.3 Intermediate-Term Aggregate Risk

An intermediate-term aggregate risk assessment (1 to 6 months of exposure to flupyradifurone residues from food, drinking water, and residential pesticide uses) is not expected to occur based on the intermittent nature of homeowner applications. Therefore, an intermediate-term aggregate risk assessment was not performed.

7.3 Chronic Aggregate Risk

Chronic exposure is not expected for the residential (dermal and inhalation) exposure pathway. Therefore, the chronic aggregate risk would be equivalent to the chronic dietary exposure

estimate. Refer to Section 5.4. for the chronic dietary (food and drinking water) exposure assessment.

8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flupyradifurone and any other substances and flupyradifurone does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that flupyradifurone has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Characterization

References:
Memo, pending, K. Rickard, D430371

An occupational exposure assessment for flupyradifurone was prepared in as a separate document (reference above). Appendix C provides a summary of the proposed use patterns.

9.1 Occupational Handler Exposure/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 and 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 scenarios outlined in Table 9.1.1.

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: A summary of the proposed uses and application rates is provided in Appendix C.

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 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 Federal Insecticide, Fungicide, and Rodenticide Act (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[4]", 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[5].

Area Treated or Amount Handled: The area treated/amounts handled are summarized in Table 9.1.1.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). For flupyradifurone, based on the proposed uses, short- and intermediate-term exposures could be expected for occupational handlers. However, the dermal and inhalation PODs are the same for short- and intermediate-term exposures; therefore, the assessment is protective of both durations.

Mitigation/Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of 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 flupyradifurone product labels intended for use by occupational handlers (EPA Reg. Nos. 264-1141 and 432-RLTL) direct mixers, loaders, applicators and other handlers to wear long-sleeved shirts, long pants, shoes, socks, and chemical-resistant gloves.

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 D.

Combining Exposures/Risk Estimates: Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined dermal + inhalation dose (mg/kg/day)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates: All combined (dermal and inhalation) occupational handler MOEs are not of concern (LOC = 100) with

[4] Available: http://www2.epa.gov/sites/production/files/2015-09/documents/handler-exposure-table-2015.pdf
[5] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

baseline attire or with the PPE specified on the proposed labels (chemical resistant gloves). With baseline attire, combined dermal and inhalation MOEs range from 58 to 550,000. With the attire and PPE specified on the label (gloves), all combined dermal and inhalation MOEs are > 160.

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 global positioning systems (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.

HED has no data to assess exposures to pilots using open cockpits. The only data available is 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); per the Agency's Worker Protection Standard (WPS) 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.

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
		Baseline (Unless Indicated Otherwise)	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixer/Loader										
Mixing/Loading Liquids for Aerial Application	**Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*	220	0.219	0.183 lb ai/A	60 A	0.00224	5,400	0.000030	400,000	5,300
	Orchard/Vineyards *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]* **Field Crop, Typical** *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]*				350 A	0.0131	920	0.000175	69,000	910
	Field Crop, High Acreage *[CG-16]* & **Forestry** *[Christmas Trees]*				1200 A	0.0448	270	0.000601	20,000	270
Mixing/Loading Liquids for Airblast Application	**Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*	220	0.219	0.183 lb ai/A	20 A	0.000747	16,000	0.000010	1,200,000	16,000
	Orchard/Vineyards *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]*				40 A	0.00149	8,100	0000020	600,000	8,000
Mixing/Loading Liquids for Chemigation Application	**Orchard/Vineyards** *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]* **Field Crop, Typical** *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]* **Field Crop, High Acreage** *[CG-16]*	220	0.219	0.183 lb ai/A	350 A	0.0131	920	0.000175	69,000	910
	Field Crop, Typical – Soil Directed *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]*			0.365 lb ai/A	350 A	0.0261	460	0.00035	34,000	450
	Greenhouse *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables];* **Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*			0.183 lb ai/A	60 A	0.00224	5,400	0.000030	400,000	5,300
Mixing/Loading Liquids for Chemigation Application	**Greenhouse** *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables];* **Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*– **Soil Directed**	220	0.219	0.365 lb ai/A	60 A	0.00447	2,700	0.000060	200,000	2,700

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
		Baseline (Unless Indicated Otherwise)	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixing/Loading Liquids for Groundboom Application	**Field-Grown Ornamental Crops; Orchard/Vineyard** *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]*	220	0.219	0.183 lb ai/A	40 A	0.00149	8,100	0.000020	600,000	8,000
	Nursery *[Ornamentals, Vegetables, Trees, Container Stock];* **Greenhouse** *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables]*				60 A	0.00224	5,400	0.000030	400,000	5,300
	Field Crop, Typical *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]*				80 A	0.00299	4,000	0.0000401	300,000	3,900
	Field Crop, High Acreage *[CG-16]*				200 A	0.00747	1,600	0.00010	120,000	1,600
Applicator										
Applying Sprays via Aerial Equipment	**Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*	*EC:* 2.08	*EC:* 0.0049	0.183 lb ai/A	60 A	0.0000211	570,000	0.000000673	18,000,000	550,000
	Orchard/Vineyard *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]* **Field Crop, Typical** *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]*				350 A	0.00012	98,000	0.00000393	3,100,000	95,000
	Field Crop, High Acreage *[CG-16]* **Forestry** *[Christmas Trees]*				1200 A	0.00042	28,000	0.0000135	890,000	27,000
Applying Sprays via Airblast Equipment	**Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*	1770	4.71	0.183 lb ai/A	20 A	0.00601	2,000	0.000215	56,000	1,900
	Orchard/Vineyard *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]*				40 A	0.0121	990	0.000431	28,000	960
Applying Sprays via Groundboom Equipment	**Field-Grown Ornamental Crops**; **Orchard/Vineyard** *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]*	78.6	0.34	0.183 lb ai/A	40 A	0.000553	23,000	0.0000311	390,000	22,000
	Nursery *[Ornamentals, Vegetables, Trees, Container Stock];* **Greenhouse** *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables]*				60 A	0.00080	15,000	0.0000466	260,000	14,000

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
		Baseline (Unless Indicated Otherwise)	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
	Field Crop, Typical *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]*				80 A	0.00107	11,000	0.0000623	190,000	10,000
	Field Crop, High Acreage *[CG-16]*				200 A	0.00267	4,500	0.000155	77,000	4,300
Flagging for Aerial Applications	**Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*	11	0.35	0.183 lb ai/A	60 A	0.00112	110,000	0.000048	250,000	76,000
	Orchard/Vineyard *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]* **Field Crop, Typical** *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]* **Field Crop, High Acreage** *[CG-16]*				350 A	0.000654	18,000	0.00028	43,000	13,000
Mixer/loader/Applicator										
Mixing/Loading/ Applying with Backpack Sprayers	**Greenhouse** *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables]*	13,200	140	0.00366 lb ai/gal	40 gal	0.00179	6,700	0.000256	47,000	5,900
	Christmas Tree Farm; Nursery *[Ornamentals, Vegetables, Trees, Container Stock];* **Forestry**	58,400	69.1			0.00793	1,500	0.000126	95,000	1,500
	Christmas Tree Farm, Forestry – Soil Directed	8,260	2.58			0.00112	11,000	0.00000473	2,500,000	11,000
	Nursery *[Ornamentals, Vegetables, Trees, Container Stock]*- **Soil Directed**	8,260	2.58	0.0365 lb ai/gal	40 gal	0.0112	1,100	0.0000471	250,000	1,100
	Landscaping *[Trees/Shrubs/Bushes]*; **Landscaping** *[Plants, Flowers]*	58,400	69.1	0.0183 lb ai/gal	40 gal	0.0396	300	0.000633	19,000	300
Mixing/Loading/ Applying with Manually-Pressurized Handwand	**Greenhouse** *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables];* **Christmas Tree Farm**; **Nursery** *[Ornamentals, Vegetables, Trees, Container Stock]*	100,000	30	0.00366 lb ai/gal	40 gal	0.0135	890	0.0000549	220,000	890
	Landscaping *[Trees/Shrubs/Bushes]*; **Landscaping** *[Plants, Flowers]*	100,000	30	0.0183 lb ai/gal		0.0679	180	0.000275	44,000	180
	Orchard/Vineyard *[Stone Fruit, Tree Nuts, Caneberries, Tropical Fruits]*	6050	8.68			0.103	120	0.00199	6,000	120
Mixing/Loading/ Applying with	**Greenhouse** *[Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables]*	3500	120	0.00366 lb ai/gal	1000 gal	0.0119	1,000	0.00549	2,200	690

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
		Baseline (Unless Indicated Otherwise)	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mechanically-Pressurized Handgun	Greenhouse (Ornamentals, Roses, Cut Flowers, Container Stock, Vegetables) – **Soil Directed**	3500	120	0.0365 lb ai/gal	1000 gal	0.0016	7,500	0.000735	16,000	5,100
	Christmas Tree Farm; Nursery (Ornamentals, Vegetables, Trees, Container Stock)	6050	8.68	0.00366 lb ai/gal	1000 gal	0.0205	590	0.000398	30,000	580
	Nursery (Ornamentals, Vegetables, Trees, Container Stock); Field Crop, Typical *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]* - **Soil Directed**			0.0365	1000 gal	0.205	**59**	0.00396	3,000	**58**
		Baseline + *Gloves*: 2050				0.046	170			160
	Landscaping (Trees/Shrubs/Bushes); Field Crop, Typical *[Brassica, Leafy Vegetables, Kava, Taro, Turnip, Cilantro]*	6050	8.68	0.0183 lb ai/gal	1000 gal	0.103	120	0.00199	6,000	120

[1] Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2016); Level of mitigation: baseline, PPE, eng. controls.
[2] Based on proposed labels (EPA Reg. No. 432-RLTL, 264-1141).
[3] Exposure Science Advisory Council Policy #9.1.
[4] 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 (a or gal/day) × DAF (7.42%) ÷ BW (80 kg).
[5] Dermal MOE = dermal NOAEL (12 mg/kg/day) ÷ dermal dose (mg/kg/day).
[6] 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 (a or gal/day) ÷ BW (80 kg).
[7] Inhalation MOE = inhalation NOAEL (12 mg/kg/day) ÷ inhalation dose (mg/kg/day).
[8] Total MOE = NOAEL (12 mg/kg/day) ÷ dermal dose + inhalation dose.

9.2 Occupational Post-Application Exposure/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 may 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 Occupational Post-Application Inhalation Exposure/Risk Estimates

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 FIFRA 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 (http://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 flupyradifurone.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the ARTF. 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.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

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).

The WPS 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)].

9.2.2 Occupational Post-Application Dermal Exposure/Risk Estimates

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. A post-application exposure assessment has not been conducted for the proposed soil-directed uses on fruiting vegetables, cucurbits, citrus, and small vine climbing fruit since the label indicates that the product is to be applied as a drench to the soil and root zone only. Currently, HED has no transfer coefficients or other data to assess post-application dermal exposures to soil by occupational workers. In general, such exposures are considered to be negligible. Therefore, for the soil-directed uses, post-application exposures and risks to occupational workers were not assessed.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. For flupyradifurone, based on the proposed uses, short- and intermediate-term exposures could be expected for occupational handlers. However, the dermal and inhalation PODs are the same for short- and intermediate-term exposures; therefore, the assessment is protective of both durations. Long-term exposures are not expected from the uses in greenhouse because exposures are likely a series of short- or intermediate-term exposures, rather than continuous long-term exposure duration just to flupyradifurone.

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[6]" which, along with additional information about the ARTF data, can be found at the Agency website[7]. Table 9.2.2.2 and Table 9.2.2.3 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites.

Application Rate: The proposed application rates are summarized in Appendix C.

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

Dislodgeable Foliar Residues: As was noted in Section 6.1 (Residential Post-Application Exposure/Risk Estimates), two chemical-specific DFR data sets have been submitted for flupyradifurone on grapes (MRID 49619910) and greenhouse roses (MRID 49618607). Both studies have been reviewed by HED and found to be acceptable for risk assessment. The available DFR data on grapes were used a surrogate for all outdoor/field-grown crops and the DFR data on greenhouse roses were used as a surrogate for all greenhouse-grown ornamental and vegetable crops. The DFR residues (µg/cm^2) were adjusted to account for differences in the proposed application rates and the application rates used in the DFR studies.

[6] Available: http://www2.epa.gov/pesticide-registration/prn-95-3-reduction-worker-protection-standard-wps-interim-restricted-entry
[7] Available: http://www2.epa.gov/pesticide-registration/prn-95-3-reduction-worker-protection-standard-wps-interim-restricted-entry

Occupational Post-Application Non-Cancer Dermal Exposure and Risk Estimate Equations: The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in Appendix D.

Occupational Post-Application Non-Cancer Dermal Risk Estimates: All MOEs are not of concern for the greenhouse uses of flupyradifurone and range from 2,000 to 10,000 on the day of application.

There are no post-application dermal risk estimates of concern for the proposed outdoor uses of flupyradifurone on the day of application. The dermal post-application MOEs range from 110 to 32,000 on the day of application for the outdoor agricultural uses of flupyradifurone.

Table 9.2.2.1. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Greenhouse Uses of Flupyradifurone.

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	DFR/TTR[1] ($\mu g/cm^2$)	Dermal Dose (mg/kg/day)[2]	MOE[3]
Short-Term					
Greenhouse Vegetables	Hand Harvesting, Pinching, Pollination, Scouting, Hand Pruning, Turning, Tying/Training, Propagating, Scouting	1,200	0.69	0.0061	2,000
	Transplanting, Hand Watering	230		0.0012	10,000
Greenhouse Crop (Ornamentals, Non-Bearing Plants)	Hand Harvesting	230	0.73	0.0012	10,000

1 DFR = residues of flupyradifurone from a DFR study on greenhouse roses (MRID 49618607), adjusted to account for differences among the application rates in the study and the proposed rates.
2 Daily dermal dose = [DFR ($\mu g/cm^2$) × transfer coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (7.42%)] ÷ BW (80kg).
3 MOE = POD (12 mg/kg/day) / daily dermal dose.

Table 9.2.2.2. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Outdoor Uses of Flupyradifurone.

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	DFR/TTR[1] ($\mu g/cm^2$)	Dermal Dose (mg/kg/day)[2]	MOE[3]
Short-Term					
Tree Nuts [*Almonds, Hazelnut, Macadamia Nut, Pecan, Pistachio, English Walnut]*	Orchard Maintenance, Poling	100	0.73	0.0054	22,000
	Mechanical Harvesting (Shaking)	190		0.00103	12,000
	Scouting	580		0.00315	3,800
	Transplanting	230		0.0125	9,600
Pome Fruit, Stone Fruit [*Apple, Apricot, Cherry, Nectarine, Peach, Pear, Plum/Prune]*	Scouting, Hand Pruning, Training	580	0.73	0.00315	3,800
	Hand Weeding, Propping, Orchard Maintenance, Bird Control	100		0.00054	22,000
	Hand Harvesting	1400		0.0076	1,600
	Transplanting	230		0.00125	9,600
	Thinning Fruit	3600		0.0195	610
Avocado, Papaya, Pomegranate	Orchard Maintenance, Hand Weeding,	100	0.73	0.00054	22,000
	Scouting, Hand Pruning	580		0.00315	3,800
	Hand Harvesting	1400		0.0076	1,600
	Transplanting	230		0.00125	9,600
Banana	Hand Weeding	100	0.73	0.00054	22,000

Table 9.2.2.2. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Outdoor Uses of Flupyradifurone.

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	DFR/TTR[1] ($\mu g/cm^2$)	Dermal Dose $(mg/kg/day)^2$	MOE[3]
Short-Term					
	Hand Harvesting	1,400		0.0076	1,600
Blackberry, Blueberry (Highbush)	Scouting, Hand Pruning, Hand Weeding, Frost Control, Bird Control, Frost Control	640	0.73	0.00347	3,500
	Hand Harvesting, Tying/Training	1400		0.0076	1,600
	Hand-Set Irrigation	1900		0.01032	1,200
	Transplanting	230		0.00125	9,600
Blueberry (Lowbush)	Hand Harvesting, Scouting	1100	0.73	0.00597	2,000
	Hand Weeding	70		0.00038	32,000
	Hand-Set Irrigation	1900		0.01032	1,200
	Transplanting	230		0.00125	9,600
Broccoli, Cauliflower	Scouting, Hand Harvesting; Hand Weeding, Tying/Training (Cauliflower only)	4200	0.73	0.222	540
	Hand-Set Irrigation	1900		0.101	1,200
	Scouting, Thinning Plants	330		0.017	6,900
	Transplanting	230		0.012	9,800
	Hand Weeding (Broccoli)	1400		0.074	1,600
Brussels Sprouts	Scouting, Hand Harvesting, Hand Weeding, Topping	4200	0.73	0.0228	530
	Hand-Set Irrigation	1900		0.01032	1,200
	Scouting	330		0.00179	6,700
	Transplanting	230		0.00125	9,600
Cabbage; Cabbage	Scouting, Hand Harvesting, Mechanically Assisted Harvesting	1400	0.73	0.0076	1,600
	Hand-Set Irrigation	1900		0.01032	1,200
	Scouting, Thinning Plants	330		0.00179	6,700
	Transplanting	230		0.00125	9,600
	Hand Weeding (Cabbage)	1400		0.0076	1,600
	Hand Weeding (Cabbage, Chinese, Bok Choy; Cabbage, Chinese Napa)	4200		0.02280	530
Christmas Trees	Hand-Set Irrigation	1,900	0.73	0.01032	1,200
	Scouting, Shaping	580		0.00315	3,800
	Hand Weeding, Grading/tagging	100		0.00054	22,000
	Hand Harvesting	1,400		0.0076	1,600
	Transplanting	230		0.00125	9,600
Collards, Leafy Greens, Kale, Leaf Lettuce, Mustard Greens, Parsley, Spinach	Hand-Set Irrigation	1,900	0.73	0.01032	1,200
	Scouting	210		0.00114	11,000
	Hand Harvesting	1,100		0.00597	2,000
	Transplanting	230		0.00125	9,600

Table 9.2.2.2. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Outdoor Uses of Flupyradifurone.					
Crop/Site	**Activities**	**Transfer Coefficient (cm^2/hr)**	**DFR/TTR[1] (µg/cm^2)**	**Dermal Dose (mg/kg/day)[2]**	**MOE[3]**
Short-Term					
	Hand Weeding/Thinning Plants	70		0.00038	32,000
Cranberry	Hand Harvesting (raking), Scouting	1,100	0.73	0.00597	2,000
	Hand Pruning (shears), Hand Weeding	70		0.00038	32,000
	Transplanting	230		0.00125	9,600
Forage Crop	Hand-Set Irrigation	1,900	0.73	0.0132	1,200
	Scouting	1,100		0.00597	2,000
Grape (Wine, Juice)	Scouting, Propagating, Bird Control, Trellis Repair, Hand Pruning, Hand Weeding, Trellis Repair	640	0.73	0.00347	3,500
	Tying/Training, Leaf Pulling	10,100		0.0548	220
	Hand-Set Irrigation	1,900		0.01032	1,200
	Transplanting	230		0.00125	9,600
Grape (Table)	Girdling, Turning	19,300	0.73	0.10478	110
	Hand-Set Irrigation	1,900		0.01032	1,200
	Scouting, Hand Pruning, Hand Weeding	640		0.00347	3,500
	Tying/Training, Hand Harvesting	5,500		0.02986	400
	Transplanting	230		0.00125	9,600
Mango	Hand Harvesting	1,400	0.73	0.00760	1,600
	Thinning Fruit	3,600		0.01954	610
	Hand Pruning, Scouting	580		0.000315	3,800
Nursery Crop (Ornamentals, Non-Bearing Plants)	Hand Harvesting, Hand Pruning, Scouting, Container Moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training	230	0.73	0.0125	9,600
	Hand-Set Irrigation	1,900		0.01032	1,200
Raspberry	Scouting, Hand Pruning	640	0.73	0.00347	3,500
	Hand Harvesting, Tying/Training	1,400		0.0076	1,600
	Hand-Set Irrigation	1,900		0.01032	1,200
	Transplanting	230		0.00125	9,600
Strawberry	Hand Harvesting	1,100	0.73	0.00597	2,000
	Scouting	210		0.00114	11,000
	Hand Weeding, Canopy Management	70		0.00038	32,000
	Transplanting	230		0.00125	9,600
Turnip	Hand Harvesting	1,100	0.73	0.00597	2,000
	Hand-Set Irrigation	1,900		0.01032	1,200
	Scouting	210		0.00114	11,000
	Hand Weeding, Thinning Plants, Hand Weeding	70		0.00038	32,000

1 DFR = residues of flupyradifurone from a DFR study on grapes (MRID 49619910), adjusted to account for differences among the application rates in the study and the proposed rates.
2 Daily dermal dose = [DFR (µg/cm^2) × transfer coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (7.42%)] ÷ BW (80kg).
3 MOE = POD (12 mg/kg/day) / daily dermal dose.

Evaluation of Proposal to Reduce REI for Grapes

References:
Memo, 07/31/2014, K. Rury, D413194
Memo, pending, K. Rickard, D430371

Rationale to Reduce REI Provided by Bayer: Bayer has requested a re-evaluation of the 24-hour REI for girdling and cane-turning grapes in absence of an MOE > 400 at the time of exposure review and an applicable DFR study (MRID 49619911). The waiver policy as later amended automatically waives the 40 CFR §158 data requirements for DFR studies if the MOEs exceed 200. The MOE calculated by HED for grape girdling and cane turning was 170 on Day 0 based on the 25% of the application rate default and reached 200 at 48 hours assuming 10% dissipation per day. To facilitate a final registration decision in the absence of a grape DFR study the Agency proposed, and Bayer accepted, the establishment of the 48-hour REI for grape girdling and cane turning in the absence of a flupyradifurone DFR study in grapes. Therefore, Bayer has provided the Agency with a flupyradifurone grape DFR study to satisfy the data requirement and reduce the REI from 48 hours to 4 hours.

EPA Response: The available DFR study submitted by Bayer showed greater predicted residues on grapes (0.356 µg/cm^2) of flupyradifurone than the Agency default of 25% of the application rate when adjusted for differences among the proposed application rate and the rate used in the DFR study. However, these residues resulted in MOEs not of concern for girdling and cane-turning of grapes (MOE = 110). Therefore, supports a revision of the REI for girdling and cane-turning of grapes.

9.3 Restricted-entry Interval (REI)

Based on the acute toxicity categories for flupyradifurone, the WPS Interim REI for flupyradifurone is 12 hours. REIs may be further reduced if certain criteria are met in accordance with the Pesticide Registration Notice (PRN) 95-3 [Reduction of WPS Interim REIs for Certain Low Risk Pesticides][8]. In PRN 95-3, there are a set of criteria listed for the ai that must be met for chemicals to be eligible for a reduced REI. These criteria include:

1. The ai is in Toxicity Category III or IV based upon data for acute dermal toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation. Acute oral toxicity data were used if no acute dermal data were available. If EPA lacked data on primary skin irritation, acute inhalation, or primary eye irritation of the ai, the Agency reviewed data on that end-point for similar ai's (analogs), and excluded such ai's from consideration for the reduced REI, if the analog is in Toxicity Category I or II for that endpoint.
2. The ai is not a dermal sensitizer (or in the case of biochemical and microbial ai, no known reports of hypersensitivity exist).

[8] Available: http://www2.epa.gov/pesticide-registration/prn-95-3-reduction-worker-protection-standard-wps-interim-restricted-entry

3. The ai is not a cholinesterase inhibitor (NMethyl carbamate and Organophosphate) as these chemicals are known to cause large numbers of pesticide poisonings and have the potential for serious neurological effects.
4. No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the ai. If ai did not have data available for these chronic health effects, EPA considered data on appropriate chemical and biological analogs. Ais that have been classified as carcinogenic in Category B (probable human carcinogen) or Category C with a potency factor, Q* (possible human carcinogen, for which quantification of potential risk is considered appropriate), or are scheduled for the HED's Cancer Peer Review process, were omitted from consideration.
5. EPA does not possess incident information (illness or injury reports) that are ``definitely'' or ``probably'' related to post-application exposures to the ai.

Upon review of the criteria for this ai only, it appears that flupyradifurone is consistent with the criteria in PRN 95-3 that allow for a 4-hour REI.

References:
Memo, pending, W. Wassell, D430351 (Residue Chemistry Summary Document)
Memo, 08/05/2014, K. Rury *et al*., D407063 (Previous Risk Assessment- PP#2F8101)
Memo, pending, W. Wassell, D434938 (Dietary Exposure Assessment)
ROCKS Memo, 12/19/2013, I. Negrón-Encarnación, D413192
Memo, 02/28/2014, K. White, D415166 (EFED Drinking Water Assessment)
Memo, pending, K. Rickard, D430371 (Occupational/Residential Exposure Assessment)
Memo, 07/31/2014, K. Rury, D413194

RDI: RAB3 (07/27/2016)

Appendix A. Toxicology Profile and Executive Summaries.
Appendix B: Physical/Chemical Properties.
Appendix C: Proposed Use Directions for Occupational Residential Exposure Assessments
Appendix D. Summary of Occupational and Residential Non-Cancer Algorithms

Appendix A: Toxicology Profile

A.1 Toxicology Data Requirements

The requirements (40 CFR §158.340) for the proposed food uses of flupyradifurone are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1: Toxicology Data Requirements of Flupyradifurone.

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 (non-rodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	CR	yes*
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (non-rodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (non-rodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Develop. Neurotoxicity	CR	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

*Study waived by HASPOC (TXR# 0056903).

Table A.2.1. Acute Toxicity Profile – Flupyradifurone.				
OPPTS Guideline No.	**Study Type**	**MRID**	**Results**	**Toxicity Category**
870.1000	Acute Oral - rat	48844101	LD_{50} cut off ≥ 2000 mg/kg (HDT) 1/3 death In ACN 2/12 test animals died at 800 mg/kg.	III
870.1200	Acute Dermal- Rabbit	48844104	LD_{50} > 2000 mg/kg.	III
870.1300	Acute Inhalation - Rat	48844105	LC_{50} > 4671 mg/m^3 (4.67 mg/L).	IV
870.2400	Primary Eye Irritation - Rabbit	48844106	Redness of the conjunctivae, reversed within 48 hours (score 2).	IV
870.2500	Primary Dermal Irritation - Rabbit	48844107	Non-irritating.	IV
870.2600	Dermal Sensitization - mouse	48844108	Non-sensitizing.	NA

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
Subchronic toxicity studies			
870.3100 (28-day)	28-day oral toxicity study in rats (gavage)	48844149 (2012) Acceptable /non-guideline 0, 75, 200, 350 mg/kg/day	NOAEL= 75 mg/kg/day. LOAEL = 200 mg/kg/day based on decreased food consumption in females; increases in ALT, creatinine, & triglycerides in females, enlarged and prominent lobulation of the liver in males, diffused follicular cell hypertrophy of the thyroid in male. Cytochrome P-450 was induced.
	28-day oral toxicity study in rats (diet)	48844150 (2012) Acceptable/non-guideline 0, 500, 5000 ppm 0, 33.6, 385 mg/kg/day	NOAEL= 33.6 mg/kg/day. LOAEL = 385 mg/kg/day based on decreases in body weight, and food consumption; decreases in glucose and total bilirubin; and increases in urea nitrogen and total cholesterol; prominent lobulation of the liver, and diffused follicular cell hypertrophy of the liver.
	28-day oral toxicity in mice (diet)	48844151 (2007) Acceptable/non-guideline 0, 300, 600, 1200 ppm M: 0, 40, 78, 166 mg/kg/day F: 0, 47, 98, 192 mg/kg/day	NOAEL = 166/199 mg/kg/day (M/F) (HDT).
	28-day oral toxicity in dogs (diet) (2 dogs/sex/dose)	48844152 (2008) Acceptable/non-guideline 0, 500, 2000, 4000 ppm M: 16, 62, 118 mg/kg/day F: 0, 19, 77, 131 mg/kg/day	NOAEL = 62 mg/kg/day. LOAEL = 118 mg/kg/day based on increased thyroid weights, enlarged thyroid, diffuse follicular dilatation of the thyroid, and decreased food consumption.
870.3100 (90-day)	90-day oral toxicity –rats (diet)	48844111 (2012) Acceptable/Guideline 0, 100, 500, 2500 ppm M: 0, 6.0, 30.2, 156 mg/kg/day F: 0, 7.6, 38.3, 186 mg/kg/day	NOAEL = 38 mg/kg/day. LOAEL = 156 mg/kg/day based on dark colored thyroid associated with follicular cell hypertrophy. Body weight was slightly decreased.
	90-day oral toxicity –mouse (diet)	48844112 (2012) Acceptable/Guideline 0, 100, 500, 2500 ppm M: 0, 15.6, 80.7 407 mg/kg/day F: 0, 18.8, 98.2, 473 mg/kg/day	NOAEL = 81 mg/kg/day. LOAEL = 407 mg/kg/day based on consistent decreases in body weight (>10%), liver effects (↑ ALP and ALT, ↓ in total cholesterol, ↑ in absolute and relative liver weights, ↑ in incidence of moderate diffuse hepatocellular hypertrophy). Kidney effects (changes in clinical chemistry parameters and loss of multifocal/diffuse cortical epithelial cell vacuolation & increases in urea).
870.3150	90-oral toxicity-dogs (diet)	48844114 (2012) 0, 400, 1200, 3600/2400 ppm (on week 9 reduced from 3600 to 2400 ppm due to toxicity of the legs) M: 0, 12, 33, 102/85 mg/kg/day F: 0, 12, 41, 107/78 mg/kg/day	NOAEL = 12 mg/kg/day. LOAEL= 33 mg/kg/day based on skeletal muscle myofiber atrophy/degeneration decreases in body weight towards the end of the study (7-9%).

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
870.3200	28-day dermal toxicity study in rabbits.	48844115 (2012) Acceptable/guideline 0, 50, 150, 500 mg/kg/day	NOAEL= 500 mg/kg/day (HDT). No adverse effect was seen at any test groups.
870.3456	Subchronic inhalation-toxicity study in rats.	Not available.	HASPOC reviewed the data waiver request from the Registrant. A subchronic inhalation study is not required for flupyradifurone at this time (TXR 0056903).
Chronic toxicity studies			
870.4100	Chronic oral toxicity study in dogs. (1-year; diet)	48844121 (2012) Acceptable/Guideline 0, 150, 300, 1000 ppm M: 0, 4.6, 7.8, 28.1 mg/kg/day F: 0, 4.1, 7.8, 28.2 mg/kg/day	NOAEL= 7.8 mg/kg/day. LOAEL= 28 mg/kg/day based on minimal to slight, focal to multifocal areas of skeletal muscle degeneration in gastrocnemius and/or biceps femoris muscle.
870.4300	Combined chronic/ carcinogenicity study in rats.	48844123 (2012) Acceptable/guideline 0, 80, 400, 2000 ppm M: 0, 3.2, 15.8, 80.9 mg/kg/day F: 0, 4.5, 22.5, 120 mg/kg/day Interim sac. at 52 weeks (10/sex/dose).	NOAEL = 15.8 / 22.5 mg/kg/day (M/F). LOAEL = 81/ 120 mg/kg/day (M/F) based on decreases on body weight and body weight gains in females, lens opacity in females, liver effects (macrovacuolation, increased liver weight, eosinophilic/tigroid/mixed foci of hepatocellular alterations increased brown pigmentation), thyroid colloidal alteration and follicular hypertrophy, and lung effects (fomay macrophages and chronic interstitial and perivascular inflammation). In addition, iridial Mydriasis and retinal fundus were also seen.
870.4200	Carcinogenicity study in mice.	48844122 (2012) Acceptable/guideline 0, 70, 300, 1500 ppm M: 0, 10, 43, 224 mg/kg/day F: 0, 12, 53, 263 mg/kg/day Interim sac. at 52 weeks (10/sec/dose)	NOAEL = 43 mg/kg/day. LOAEL = 224 mg/kg/day based on a combination decreases in terminal body weights (slight) and body weight gains. Liver weight increases with associated finding of diffuse hepatocellular vacuolation.
Developmental and reproductive toxicity studies			
870.3700	Developmental toxicity - rabbit. (gavage)	48844117 (2012) (main study) Acceptable/non-guideline 0, 7.5, 15, 40 mg/kg/day 49113601 (2013) Range finding study 0, 15, 40, & 80 mg/kg/day	Combined data from both the main and the range finding study. Maternal NOAEL = 80 mg/kg/day. Maternal LOAEL could not be established. Developmental NOAEL = 40 mg/kg/day. Developmental LOAEL = 80 mg/kg/day based increases in the number of dead fetuses and dead fetus per litter. Reduced fetal body weight (8%).
870.3700	Developmental toxicity –rat (gavage)	48844116 (2012) Acceptable/guideline 0, 15, 50, 150 mg/kg/day	Maternal NOAEL = 50 mg/kg/day. Maternal LOAEL = 150 mg/kg/day based increased incidence of salivation and decreased food consumption. Developmental NOAEL = 50 mg/kg/day. Developmental LOAEL =150 mg/kg/day based on increased incidence of incomplete parietal and hyoid centrum skull bone ossification.
870.3800	2-Generation reproduction study in rats.	48844119 (2011) Acceptable/Guideline 0, 100, 500, 1800 ppm Premating P_1 M: 0, 6.6, 32.5, 117 mg/kg/day F: 7.7, 38.7, 137 mg/kg/day	Parental NOAEL = 38.7 mg/kg/day. Parental LOAEL = 137 mg/kg/day based on decreased body weights. Reproductive NOAEL = 38.7 mg/kg/day. Reproductive LOAEL = 137 mg/kg/day based on reduced number of estrus cycles. Offspring NOAEL = 7.7 mg/kg/day. Offspring LOAEL = 38.7 mg/kg/day based on decreases in pup body weights and pup body weight gains in F_2 pups.
Neurotoxicity studies			

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
870.6200a	Acute neurotoxicity in rats. (gavage)	48844138 (2011) Acceptable / Guideline 0, 20, 35, 50, 200, 800 mg/kg	NOAEL = 35 mg/kg/day. LOAEL = 50 mg/kg/day based on increased incidences of pupil dilation in females on Day 1and piloerection in both sexes. At the next higher dose level (200 mg/kg) or above, the observed effects included lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature. Automated measures of motor activity were also reduced in both sexes, compared to controls.
870.6200b	Subchronic neurotoxicity study in rats.	48844139 (2011) Acceptable / Guideline 0, 100, 500, 2500 ppm M: 0, 5.7, 29.4, 143 mg/kg/day F: 0, 6.9, 34.8, 173 mg/kg/day	NOAEL = 34.8 mg/kg/day. LOAEL = 143 mg/kg/day based on decreased body weight in both sexes. Neurotoxicity was not observed at the doses tested.
870.6300	Developmental neurotoxicity study in rats.	434203011 (2012) Acceptable/guideline 0, 120, 500, 1200 ppm 0, 10.3, 42.4, 102 mg/kg/day	Maternal NOAEL = 102 mg/kg/day (HDT). Offspring NOAEL = 42 mg/kg/day. Offspring LOAEL = 102 mg/kg/day based on statistically significant increases in startle response amplitude.
Metabolism studies: It should be noted that ADME studies with flupyradifurone were conducted using three different labeling positions: ^{14}C in the pyridinlylmethylene bridge, in the 4-position of furanone ring and in the 1 position of the ethyl side chain.			
870.7485	ADME with [pyridinylmethyl-^{14}C] BYI 02960-male Wistar rats	48844141 (2012) Acceptable/guideline Single gavage dose at 2 or 200 mg/kg	The absorption started immediately after dosing with the peak plasma concentration (C_{max}) reached approximately 1 hour after administration in the low dose tests and within approximately 2 to 4 hours in the high dose tests. The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} after 4 – 8 hours in the low dose tests and after 8 – 24 hours in the high dose tests and down to low values around the LOQ in the low dose tests and to approximately 0.5% of C_{max} in the high dose tests by study termination (72 hours). Elimination was rapid, mainly by the renal route and essentially complete by 72 hours post dosing. Female rats exhibited slightly higher renal excretion rates of approximately 86% and 90% of the administered dose compared to approximately 76% of the dose in males. Faecal elimination accounted for approximately 23–26% of the total administered dose in males, and 7–10% in females. At the time of sacrifice, 72 hours after administration, the radioactive residues in organs and tissues were low, and only trace amounts of approx. <0.1 – 0.3% of the total administered dose was detected in the body and in the GIT. The principal metabolic reactions of [pyridinylmethyl-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid to or with sulphate; (2) cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl; and cleavage of the molecule at the pyridinylmethyl bridge forming BYI 02960-6-CNA, which was further conjugated with glycine to BYI 02960-hippuric acid. Parent compound, three major (BYI 02960-OH, BYI 02960-6-CNA and BYI 02960-hippuric acid) and five minor metabolites were isolated from urine and four of them identified by spectroscopic methods.

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	[Pyridinylmethyl-^{14}C] whole body autoradiography-rat	48844142 (2011a) Acceptable/guideline A single gavage dose of 5 mg/kg [pyridinylmethyl-^{14}C]BYI02960 in 0.5% aqueous Tragacanth®.	The data demonstrate that BYI 02960 was readily absorbed from the gastrointestinal tract and distributed throughout the body immediately after administration. In male and female rats, maximum residue levels were reached for nearly all organs and tissues at one hour after administration. At this time, the levels for liver and kidney were significantly higher than in blood, suggesting a preferred clearance from blood and distribution mainly to those organs that are responsible for metabolism (liver) and excretion (kidney), along with several glands. Very low levels were found in the brain, spinal cord and in renal fat. From peak levels, a fast decline of radioactivity concentrations was observed for all organs and tissues in males and females during the whole testing period. In both sexes, concentrations fell for most organs and tissues below 5% of the maximum after one day and below the limit of quantification after seven days post administration. No significant retention of [pyridinylmethyl-^{14}C] BYI 02960 in male and female rats was found.
	ADME with [furanone-4 ^{14}C]-BYI 02960-male Wistar rats	48844143 (2011b) Acceptable/guideline Single gavage dose of 2 mg/kg bw [furanone-4-^{14}C]BYI 02960 in 0.5% aqueous Tragacanth®	[Furanone-4-14C]BYI 02960 was nearly completely absorbed since >79% and >91% of the total dose administered was detected in the urines and the organs of male and female rats, respectively. The absorption started immediately after dosing; peak plasma concentration (C_{max}) was reached approximately 1.5 hours after administration in both sexes. The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} after 8 hours in both sexes and <1% of C_{max} 72h after dosing. Excretion was rapid and mainly by the renal route. The major part of the dose was excreted within 24 hours after treatment. At 168 hours after administration, approximately 0.5% of the dose administered for males and approximately 0.2% for females was still detected in the body. The parent compound was metabolized to approximately 20 metabolites in total, consisting of one major (BYI 02960-OH) and six minor metabolites of an isolated and purified. compound. Parent compound represented the predominant part of the radioactivity in urine but in feces the metabolite, BYI 02960-OH, was more prominent. The principal metabolic reactions of [furanone-4-^{14}C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid or with sulphate; (2) cleavage of the difluoroethyl group forming BYI 02960-desdifluoroethyl; (3) cleavage of the molecule at the pyridinylmethyl bridge forming BYI 02960-difluoroethyl-amino-furanone; and (4) cleavage of molecule at the nitrogen-carbon bond next to the furanone moiety followed by further conversion to C1 and C2 compounds of the natural pool including complete degradation to carbon dioxide.

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	[Furanone-4-^{14}C] whole body autoradiography-rat	48844144 (2011b) Acceptable/Guideline a single gavage dose of 5 mg/kg bw [furanone-4-^{14}C]BYI 02960 in 0.5% aqueous Tragacanth®.	BYI 02960 was readily absorbed from the gastrointestinal tract and distributed throughout the body immediately after administration. At 2 days after dosing, the excretion of radioactivity via urine and feces was almost completed with renal excretion as the predominant route. By 168 hours post dosing approximately 81% in males and 88% in females of the administered dose were recovered in urine and approximately 14% in males and 6% in females in the feces. Approximately 1% (females) to 3% (males) of the dose was exhaled as 14C-carbon dioxide during a sampling period of 48 hours. In male and female rats, maximum radioactivity levels were reached for nearly all organs and tissues at one hour after administration. At this time, the values for liver, kidney, brown fat, myocardium, nearly all glandular and hormonal organs, and the olfactory bulb were higher than that in the blood. After seven days, low radioactive residues were measured in nearly all organs and tissues. No evidence for accumulation or significant retention of [furanone-4-^{14}C]BYI 02960 in male and female rats.
	[Furanone-4-^{14}C] Metabolism in Organs and Tissues--rat	48844145 (2012b) Acceptable/guideline A single gavage dose of 3 mg/kg [furanone-4-^{14}C]BYI02960 in 0.5% aqueous Tragacanth® and sacrificed by exsanguination under anaesthesia at 6 hours post dosing.	Highest radioactivity levels were detected in the liver and kidney which are the main organs responsible for metabolism and urinary excretion. The residue-values for plasma and the other tissues were comparable for both sexes. In the 6 h samples of plasma, organs, and tissues, the parent compound (BYI 02960) was by far the largest component accounting for more than 72% of the total radioactive residues (TRR). For all identified metabolites, the values were less than 12% of the TRR. In the respective urine sample pools, the parent compound was the largest radioactive component (≈ 22% of the dose in males and 38% in females). The metabolism was qualitatively similar in male and female rats. The differences occurred however quantitatively. Metabolism of the parent compound to the different metabolites was significantly higher in males compared to female rats.
	ADME with [Ethyl-1 ^{14}C]-BYI 02960-male Wistar rats	48844146 (2011a) Acceptable/guideline a single gavage dose of 2 mg/kg bw [ethyl-1-^{14}C]BYI02960 in 0.5% aqueous Tragacanth®	[Ethyl-1-^{14}C]BYI02960 was nearly completely absorbed since >85% of the total dose administered was detected in the urine and the body without GIT at sacrifice. The absorption started immediately after dosing; the peak plasma concentration (C_{max}) was reached approximately 1 hour after administration. The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} within 8 hours and to approximately 8% of C_{max} 72h after dosing. Elimination was rapid and mainly by the renal route. The major part of the dose (>87%) was excreted within 24 hours after treatment. Approximately 82% of the total administered dose was excreted in the urine and approximately 14% in the faeces. Only a negligible part of 0.2% of the total administered dose was detected in expired air. At the time of sacrifice, 72 hours after administration, a small proportion of approximately 3% of the total dose administered was still detected in the body without GIT. Parent compound, one major (BYI 02960-OH) and five minor metabolites were identified. The label specific metabolite BYI 02960-DFA was additionally identified (representing ≈5.77% of the administered dose). Parent compound represented the predominant part of the

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.				
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**	
			radioactivity in urine but in faeces samples (≈56% of the administered dose) the metabolite BYI 02960-OH was more prominent. The principal metabolic reactions of [ethyl-1-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid; (2) cleavage of the difluoroethyl group leading to BYI 02960-DFA; and (3) cleavage of the molecule at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone.	
	[Ethyl-1-^{14}C] - Metabolism in organs and tissues-rat	48844147 (2012a) Acceptable/guideline a single gavage dose of 3 mg/kg bw [ethyl-1-^{14}C]BYI02960 in 0.5% aqueous Tragacanth®	The distribution of the radioactivity within the central compartments of the body (e.g. blood, liver, and kidney) was fast for both sexes**.** Radioactivity residues showed a distinctive preference towards the liver and kidney as the main organs responsible for metabolism and urinary excretion. Metabolism of BYI02960 was extensive. Metabolic reactions took place at least at 3 different structural positions of the test compound. The principal metabolic reactions of [ethyl-1-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid, (2) cleavage of the difluoroethyl group leading to BYI 02960-DFA and (3) cleavage of the molecule at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone. In the 24 hours samples of plasma, and organs and tissues BYI 02960-DFA was the by far largest metabolite accounting for more than 50% of the TRR. For all other identified metabolites, the values were less than 10% of the TRR. The percentage-values of the parent compound in these samples ranged from 6 to 38% of the TRR. In the respective urine sample pools, the parent compound was the largest radioactive component (approximately 48% of the dose in males and 77% in females). The metabolism was qualitatively similar in male and female rats. The differences occurred however quantitatively. Metabolism of the parent compound to the different metabolites was significantly higher in males compared to female rats.	
870.7600 (Triple pack)	*In-vivo* Dermal absorption study in rats. 200 g/L Soluble concentrate formulation (SL200)	48844557 (2010) Acceptable Undiluted 200 g/L SL formulation, 0.625 g/L aqueous dilution, or 0.1 g/L aqueous dilution. Exposure time: 8 hours.	Using the 24 hour measuring values, the potential dermal absorptions were: 19.6%, 8.3% and 10.3% for undiluted 200/L SL formulation, 0.625 g/L aqueous dilution, and 0.1 g/L aqueous dilation, respectively.	Based on the 24 – hour measuring dermal absorption values from the in vivo and in-vitro dermal absorption studies with 0.1 g/L aqueous dilution, the *in vivo* human dermal absorption factor was estimated to be 7.42%
	In-vitro dermal penetration studies with rat and human skin. 200 g/L Soluble concentrate formulation (SL200)	48844558 (2010) Acceptable Undiluted 200 g/L SL formulation, 0.625 g/L aqueous dilution, or 0.1 g/L aqueous dilution. Exposure time: 8 hours.	Based on 24-hour measuring interval, the dermal penetration were: **Rat skin**: 0.15%, 5.67%, and 6.61% for 200 g/L concentrate, 0.625 g/L aqueous dilution, and 0.1 g/L aqueous dilution, respectively. **Human skin:** 0.20% 2.01%, and 4.75% for 200 g/L concentrate, 0.625 g/L aqueous dilution, and 0.1 g/L aqueous dilution, respectively. The human DAF was derived as follows: *in vivo* human absorption (% absorbed) = (*in vitro* human % absorption × *in vivo* rat % absorbed) ÷ *in vitro* rat % absorption.	
Immunotoxicity study				

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
870.7800	28-Day Dietary Immunotoxicity Study	48844148 (2011) Acceptable / Guideline 0, 125, 600, 3000 ppm 0, 10, 50, 230 mg/kg/day	Systemic Toxicity NOAEL = 230 mg/kg/day. LOAEL > 230 mg/kg/day. Immunotoxicity NOAEL = 230 mg/kg/day. LOAEL > 230 mg/kg/day. Immunotoxicity was not observed at the doses tested.
Genotoxicity studies			
870.5100 (84-2 a)	Mutagenic potential of Salmonella typhimurium	48844124 (2009a) Acceptable/guideline TA98, TA100, TA102, TA1535, TA1537; (-/+ S9); 0, 16, 50, 158, 500, 1581 and 5000 µg/plate	Negative for mutagenic activity in +/- S9 test systems up to the limit dose (5000 µg/plate).
870.5100 (84-2 a)	Reverse mutation in Salmonella typimurium.	48844125 (2011) Acceptable/guideline TA98, TA100, TA102, TA1535, TA1537 (+/-) S9 0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment 1, and 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment 2. (DMSO).	Negative for mutagenic activity in +/- S9 test systems up to the limit dose (5000 µg/plate).
870.5300	*In vitro* forward gene mutation assay in mammalian cells (hamster V79 Cells) (HPRT mutation assay)	48844128 (2009) Acceptable/guideline 0, 46, 92, 184, 368, 736, 1472 and 2944 µg/mL for 5 hours (±S9) at 37°C.	Negative in the in the V79/HPRT mutation assay (+/-) S9.
870.5375 (84-2)	*In vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells	48844131 (2009) Acceptable/guideline Toxicity assay, 0–3000 µg/mL (the limit dose) with a 4-hour treatment period. Seven concentrations from 0–3000 µg/mL with an 18-hour treatment period.	Negative for the induction of structural and numerical chromosome aberrations in cultured Chinese Hamster V79 cells (+/-) S9.
870. 5395	*In vivo* mouse (Crl:NMRI BR mice, males) micronucleus assy (bone marrow plychromatic erythrycytes)	48844134 (2009b) Acceptable/guidelline 0, 10, 20 and 40 mg/kg by two intra-peritoneal injections 24 hours apart.	Negative for clastogenic and aneugenic activity in the mouse bone marrow micronucleus assay.
	In vivo Micronucleus Assay in Bone Marrow Cells of the Mouse (females)	48844135 (2011) Acceptable/guideline 0, 12.5, 25 and 50 mg/kg by two intra-peritoneal injections 24 hours apart.	Negative for clastogenic and aneugenic activity in the mouse bone marrow micronucleus assay.
Toxicity Studies on Metabolites			
Difluoroacetic acid—(BCS-AA56716)			
	14-Day oral toxicity study-rat (dietary)	48844153 (2011) 0, 500, 2000, & 8000 ppm M: 0, 48, 187 & 745 mg/kg bw/day	NOAEL = 51 mg/kg/day. LOAEL = 187 mg/kg/day based on mean glucose concentration reduced by 41% in males and 48% in females ($p < 0.01$), mean urea concentration was 25%

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
		F: 0. 51, 201 & 800 mg/kg bw/day	higher in females (not statistically significant) in comparison to the controls.
	90-day oral toxicity study-rat (dietary)	48844113 (2012) Acceptable/guideline 0, 200, 1000, 6000 ppm M: 0, 12.7, 66.2, 380 mg/kg/day F: 0, 15.6, 78.7, 472 mg/kg/day	NOAEL = 12.7/15.6 mg/kg/day (M/F). LOAEL = 66.2/78.8 mg/kg/day (M/F) based on a number of findings including reduced body weight approaching 10% on week 13, decreased food consumption, black foci in the glandular part of the stomach with correlated histopathology finding of focal glandular erosion/necrosis. In addition, slight decreases in hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and hematocrit.
	Bacterial reverse mutation (*Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537)	48844126 (2010a) Acceptable/guideline 0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate (+/-) S9	**Negative** for mutagenic activity *Salmonella Typhimurium.* (+/-) S9.
	Mammalian cell gene mutation (Chinese Hamster V79 cell/HPRT)	48844129 (2010a) Acceptable/guideline 0, 30, 60, 120, 240, 480 and 960 µg/mL (+/-) S9	**Negative in (+/-) S9 V79/HPRT mutation assay.**
	In vitro cytogenetics (chromosome aberration assay in Chinese hamster V79 cells)	48844133 (2010b) Acceptable/guideline 0, 240, 480 and 960 µg/mL (+/-) S9	**Negative** for the induction of structural and numerical chromosome aberrations in cultured Chinese Hamster V79 cells (+/-) S9.
BCS-CC98193 (BYI 02960-difluoroethyl-amino-furanone)			
	28-Day oral toxicity study – rat (dietary)	48844109 (2012) Acceptable/Guideline 0, 200, 800, 3000 ppm M: 0, 17, 67, 244 mg/kg/day F: 0,19, 76, 256 mg/kg/day	NOAEL = 244/273 mg/kg/day (M/F) (HDT). No adverse effect was found at all tested dose levels.
	Bacterial reverse mutation *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	48844127 (2010b) Acceptable/guideline 0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment1, and 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment 2 in DMSO.	Negative tested up to the limit dose 5000 µg/plate (+/-) S9.
	Mammalian gene mutation (Chinese Hamster V79 Cells/HPRT)	48844130 (2011) Acceptable/guideline 0, 51.3, 102.5, 205, 410, 820 and 1640 µg/mL (+/-) S9.	Negative in the V79/HPRT mutation assay (+/-) S9.
	In vitro cytogenetics (chromosome aberration assay in Chinese hamster V79 cells)	48844133 (2011a) Acceptable/guideline 0–1636 µg/mL (the limit dose)	Positive **(-S9)** Negative **(+S9)**
	In vivo mouse bone marrow	48844136 (2011b) Acceptable/guideline	Negative for clastogenic or aneugenic activity in the mouse bone marrow micronucleus assay.

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	micronucleus assay	0, 125, 250 and 500 mg/kg by two intra-peritoneal injections 24 hours apart	
	In vivo UDS with rat hepatocytes	48844137 (2011c) Acceptable/guideline 0, 1000 and 2000 mg/kg by a single oral gavage dose.	Negative in unscheduled DNA synthesis at up to the limit dose of 2000 mg/kg bw.
(6-chloro-3-pyridyl)methanol (IM-0)			
	Bacterial reverse gene mutation assay *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and *Escherichia coli* strain WP2*uvrA*	44988432 (1997) Acceptable/guideline 0, 313, 625, 1250, 2500 and 5000 µg/plate. (in DMSO)	Negative up to the limit dose (5000 µg/plate) with (+/-) S9.
6-chloronicotinic acid (IC-0)			
	Bacterial reverse gene mutation assay *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and *Escherichia coli* strain WP2*uvrA*	44988502 (1997b) Acceptable/guideline 0, 313, 625, 1250, 2500 and 5000 µg/plate (in DMSO). (+/-) S9.	Negative up to the limit dose (5000 µg/plate) with (+/-) S9.

Appendix B: Physical/Chemical Properties

Table B.1. is a summary of the physical/chemical properties for flupyradifurone.

Table B. Physicochemical Properties of the Flupyradifurone (99.4% Purity).

Parameter	Value		Reference
Molecular weight (g/mole)	288.68		MRID 48843601
Melting point/range (°C)	69.0		MRID 48843630
pH	6.6 at 24° C		MRID 488436626
Density (g/cm^3)	1.43 g/mL at 20° C		MRID 48843642
Water solubility (g/L at 20°C)	3.2		MRID 48843643
Solvent solubility (g/L at 20°C)	Methanol n-Heptane Toluene Dichloromethane Acetone Ethyl acetate Dimethyl Sulfoxide	>250 0.0005 3.7 >250 >250 >250 >250	MRID 48843656
Vapor pressure (Pa)	9.1 x 10^{-7} at 20°C 1.7 x 10^{-7} at 25°C 2.6 x 10^{-7} at 50°C		MRID 48843650
Dissociation constant (pK_a)	No dissociation occurs in aqueous solutions in the pH range between 1 and 12.		MRID 48843636
Octanol/water partition coefficient Log(K_{OW})	1.2 (pH 4 – 9)		MRID 8843639

Appendix C: Proposed Use Directions for Occupational Residential/Exposure Assessments

Table C. Summary of Directions for Use of Flupyradifurone.

Use Site	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Sivanto™ (EPA Reg. No. 264-1141): Liquid Formulation						
Kava, roots and leaves	See Table 3.2.2					
Cilantro						
Leafy vegetables (except *Brassica*), group 4						
Stone fruit, group 12-12						
Caneberry, subgroup 13-07A						
Quinoa						
Tropical Fruits[1]						
Altus™ (EPA Reg. No. 432-RLTL)						
Greenhouse, Nursery, Landscape Ornamentals[2]	Ground, Aerial, Chemigation, Handheld (Foliar)	0.183	2	0.365	0-14	Apply in 50 – 100 gal/A
	Chemigation, Handheld (Soil Drench)	0.365	1	0.365		NS
Christmas Trees	Ground, Aerial, Chemigation, Handheld	0.183	2	0.365	NS	Aerial minimum application volume: 10 gal/A
Greenhouse Ornamentals/Vegetables[3]	Ground, Chemigation, Handheld (Foliar)	0.183	2	0.365	1-3	Apply in 50 – 100 gal/A
	Chemigation, Handheld (Soil Drench)	0.365	1	0.365		NS
Greenhouse Vegetables and Fruit Transplants – Foliar[4]	See Table 3.2.2					
Greenhouse Vegetables and Fruit Transplants – Soil Directed[5]						
FDF 50 SL Concentrate (EPA Reg. No. 72155-RRA)						
Ornamentals/Vegetables in Residential Areas – Foliar	Handheld	0.0002 lb ai/gal[6]	2	0.0004	*Brassica* and Leafy Vegetables (1) Bushberry (3) Caneberry & Low Growing Berries, Small Fruit Vine Climbing (0) Citrus (1) Cucurbits (1) Fruiting Vegetables (1) Legume Vegetables, Peanuts, Root Vegetables, Tree Nuts, Tuberous and Corm Vegetables (7) Dry Soybean Seed (21), Pome Fruit, Stone Fruit (14)	For outdoor residential use only
Ornamentals in Residential Areas – Soil Directed	Handheld	0.00042 lb ai/gal[6]	1	0.00042	*Brassica* and Leafy Vegetables (21)	For outdoor residential use only

Table C. Summary of Directions for Use of Flupyradifurone.						
Use Site	**Applic. Timing, Type, and Equip.**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
					Cucurbits (21) Fruiting Vegetables (45)	
Flowers	Handheld	0.00013 lb ai/gal[6]	2	0.00026	NS	For outdoor residential use only
FDF Ready-to-Use (EPA Reg. No. 72155-XXX)						
Flowers, Roses, Houseplants (only apply outside), Shrubs	Handheld	0.00068 lb ai/gal[7]	NS	NS	NS	For residential use only. Product container = 24 oz. - 1.3 gal. – Product treats up to 34 medium sized plants. For severe infestations repeat every 7-14 days.

1. Tropical Fruits (abiu, akee apple, avocado (including Guatemalan, Mexican, and West Indian), bacury, banana (including dwarf), binjai, canistel, cupuacú, etambe, jatobá, kei apple, langstat, lanjut, lucuma, mabolo, mango (including horse and saipan), mangosteen, paho, papaya, pawpaw (common), pelipisan, pequi, pequia, persimmon (American), plantain, pomegranate, poshte, quandong, sapote (including black, green, and white), sataw, screw-pine, star apple, tamarind-of-the-indies, and wild loquat, and cultivars, varieties and hybrids of these commodities).
2. Ornamental plants including flowers, foliage plants, shrubs, trees, and groundcovers. Landscape ornamentals include bushberry, caneberry, citrus, low-growing berry, pome fruit, small fruit vine climbing, stone fruit, tree nuts, and tropical fruits.
3. Includes cucumbers, lettuce, peppers, tomatoes.
4. Application rate calculated assuming a greenhouse is 33 x 144 Feet = 4752 ft^2 and contains 640 plants = 5867 plants/A (640 plants ÷ 4752 ft^2 = x plants/43560 ft^2) from: https://extension.tennessee.edu/publications/Documents/pb1609.pdf. Pound ai/A calculated as follows: (0.17 fl. oz./10,000 plants * 1.67 lb ai/gal product) * (1 gal/128 fl. oz.) = 0.0022 lb ai/10,000 plants. 0.0022 lb ai/10,000 plants * 5867 plants/A = 0.0013 lb ai/A.
5. Application rate calculated assuming a greenhouse is 33 x 144 Feet = 4752 ft^2 and contains 640 plants = 5867 plants/A (640 plants ÷ 4752 ft^2 = x plants/43560 ft^2) from: https://extension.tennessee.edu/publications/Documents/pb1609.pdf. Pound ai/A calculated as follows: (0.34 fl. oz./10,000 plants * 1.67 lb ai/gal product) * (1 gal/128 fl. oz.) = 0.0044 lb ai/10,000 plants. 0.0044 lb ai/10,000 plants * 5867 plants/A = 0.0026 lb ai/A.
6. Density of ai in the product was not specified on the proposed product label. Information provided RD/the Registrant indicated that 72155-RRA contains 0.417 lb ai/gal (email dated 5/10/2016 from Jai Rogala).
7. Density of ai in the product was not specified on the proposed product label. Information provided RD/the Registrant indicated that 72155-XXX contains 0.000668 lb ai/gal (email dated 5/10/2016 from Jai Rogala).

Appendix D. Summary of Occupational and Residential Non-Cancer Algorithms

Residential Non-Cancer Handler Algorithms

Turf, Gardens and Trees, Indoor Environments

Dermal and Inhalation Handler Exposure Algorithm: Daily dermal and inhalation exposure (mg/day) for residential pesticide handlers, for a given formulation-application method combination, is estimated by multiplying the formulation-application method-specific unit exposure by an estimate of the amount of ai handled in a day, using the equation below:

$$E = UE * AR * A$$

Residential Non-Cancer Post-Application Algorithms

Gardens and Trees

Post-Application Dermal Exposure Algorithm: Exposure resulting from contacting previously treated gardens and trees while performing physical activities is calculated as shown below. Residential post-application exposure assessment must include calculation of exposure on the day of application. Therefore, though an assessment can present exposures for any day "t" following the application, it must include "day 0" exposure.

$$E = DFR_t * CF1 * TC * ET$$

where:
E = exposure (mg/day); DFR_t = dislodgeable foliar residue on day "t" (µg/cm^2); CF1 = weight unit conversion factor (0.001 mg/µg); TC = transfer coefficient (cm^2/hr); and ET = exposure time (hrs/day).

In the absence of chemical-specific data, DFR_t can be calculated as follows:

$$DFR_t = AR * F_{AR} * (1-F_D)^t * CF2 * CF3$$

where:
DFR_t = dislodgeable foliar residue on day "t" (µg/cm^2); AR = application rate (lbs ai/ft^2 or lb ai/acre); F_{AR} = fraction of ai as dislodgeable residue following application (unitless); F_D = fraction of residue that dissipates daily (unitless); t = post-application day on which exposure is being assessed; CF2 = weight unit conversion factor (4.54 x 10^8 µg/lb); and CF3 = area unit conversion factor (1.08 x 10^{-3} ft^2/cm^2 or 2.47 x 10^{-8} acre/cm^2).

Absorbed dermal dose, normalized to body weight, is calculated as:

$$D = \frac{E * AF}{BW}$$

where:
D = dose (mg/kg-day); E = exposure (mg/day); AF = absorption factor (dermal and/or inhalation); and BW = body weight (kg).

Table C-1: Gardens, Trees, and "Pick-your-own" Farms –Inputs for Residential Post-Application Dermal Exposure					
Algorithm Notation	**Exposure Factor (units)**				**Point Estimate(s)**
AR	Application rate (mass ai per unit area)				0.00068 lb ai/gal or 0.59 lb ai/A
F_{AR}	DFR following application, if chemical-specific is unavailable (fraction)				0.25
F_D	Daily residue dissipation, if chemical-specific is unavailable (fraction)				0.10
TC	Transfer Coefficient (cm^2/hr)	Gardens[a]	Adults		8400
			Children 6 < 11 years old		4600
		Trees, Retail Plants (if applicable)[a]	Adults		1700
			Children 6 < 11 years old		930
		Indoor Plants	Adults		220
			Children 6 < 11 years old		120
ET	Exposure Time (hours per day)	Home activities[b]	Gardens	Adults	2.2
				Children 6 < 11 years old	1.1
			Trees, Retail Plants (if applicable)	Adults	1.0
				Children 6 < 11 years old	0.50
			Indoor Plants	Adults	1.0
				Children 6 < 11 years old	0.50
		"Pick-your-own" Farms (if applicable)	Adults		5.0
			Children 6 < 11 years old		1.9
BW	Body weight (kg)		Adults		80
			Children 6 < 11 years old		32

[a] Transfer coefficient point estimates from a composite distribution assuming equal proportion of time spent conducting various activities. Children 6 < 11 years old TC derived using surface area adjustment.
[b] Activity time point estimates from a composite distribution assuming equal proportion of each respective activity. Time for children 6 < 11 years old derived using hrs/day ratio adjustment.

Occupational Non-Cancer Handler Algorithms: Potential daily exposures for occupational handlers are calculated using the following formulas:

$$E=UE * AR * A * 0.001\ mg/ug$$

where:
E = exposure (mg ai/day); UE = unit exposure (µg ai/lb ai); AR = maximum application rate according to proposed label (lb ai A or lb ai/gal); and A = area treated or amount handled (e.g., A/day, gal/day).

The daily doses are calculated using the following formula:

$$ADD= \frac{E * AF}{BW}$$

where:

ADD = average daily dose absorbed in a given scenario (mg ai/kg/day); E = exposure (mg ai/day); AF = absorption factor (dermal and/or inhalation); and BW = body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each application handler scenario are calculated using a MOE, which is a ratio of the toxicological endpoint to the daily dose of concern. The daily dermal and inhalation dose received by occupational handlers are compared to the appropriate POD (i.e., NOAEL) to assess the risk to occupational handlers for each exposure route. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

where:
MOE = margin of exposure: value used by HED to represent risk estimates (unitless); POD = point of departure (mg/kg/day); and ADD = average daily dose absorbed in a given scenario (mg ai/kg/day).

Occupational Non-Cancer Post-Application Algorithms: Potential daily exposures for occupational post-application workers are calculated using the following formulas:

$$DFR_t = AR * F * (1\text{-}D)^t * \left(4.54E8 \frac{ug}{lb}\right) * \left(2.47E\text{-}8 \frac{A}{cm^2}\right)$$

where:
DFR_t = dislodgeable foliage residue on day "t" (µg/cm^2); AR = application rate (lb ai/acre); F = fraction of ai retained on foliage or 25% (unitless); D = fraction of residue that dissipates daily or 10% (unitless); and t = number of days after application day (days).

$$E = TC * DFR_t * ET * 0.001 \frac{mg}{ug}$$

where:
E = exposure (mg ai/day); TC = transfer coefficient (cm^2/hr); DFR_t = dislodgeable foliar residue on day "t" (µg/cm^2); and ET = exposure time (hours/day).

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

where:
ADD = average daily dose absorbed in a given scenario (mg ai/kg/day); E = exposure (mg ai/day); AF = absorption factor (dermal and/or inhalation); and BW = body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each scenario are calculated using a MOE, which is a ratio of the toxicological endpoint to the daily dose of concern. The daily dermal dose received by occupational post-application workers is compared to the appropriate POD (i.e., NOAEL) to assess the risk to occupational post-application workers. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

where:
MOE = margin of exposure: value used by HED to represent risk estimates (unitless); POD = point of departure (mg/kg/day); and ADD = average daily dose absorbed in a given scenario (mg ai/kg/day).