



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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

MEMORANDUM

DATE: 02/24/10

SUBJECT: **Pyraflufen-ethyl:** Human Health Risk Assessment for a Section 3 Registration of New Non-Food Uses on Established Ornamental Turf Lawns (Residential, Industrial, and Institutional), Parks, Cemeteries, Athletic Fields, Golf Courses (Fairways, Aprons, Tees and Roughs), Sod farms, and Similar Turf Areas.

PC Code: 030090

Decision Nos.: 404405 & 404408

Petition No.: N/A

Risk Assessment Type: Single Chemical Aggregate

TXR No.: N/A

MRID No.: N/A

DP Barcodes: 361213 & 361214

Registration Nos.: 71711-7, 71711-25

Regulatory Action: Section 3; New Use; Outdoor-Non-food.

Case No.: N/A

CAS No.: 129630-19-9

40 CFR: 180.585

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The Registration Division (RD) of the Office of Pesticide Programs (OPP) requested that the Health Effects Division (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 pyraflufen-ethyl. A summary of these findings is provided in this document.

Nichino America, Inc. has submitted revisions to their ET® Herbicide product labels proposing the use of the 0.208 lb ai/gal EC (emulsifiable concentrate) and 0.177 lb ai/gal SC (suspension concentrate) formulations of pyraflufen-ethyl on new outdoor non-food uses on established ornamental turf lawns (residential, industrial, and institutional), parks, cemeteries, athletic fields,

golf courses (fairways, aprons, tees and roughs), sod farms, and similar turf areas. Registered turf sites are being expanded to include sports and residential applications and non-crop use sites, like fence yards and ditchbanks. Pyraflufen-ethyl is proposed for residential/homeowner and commercial applicator use for weed control. The proposed use allows application of pyraflufen-ethyl as a spot treatment with low pressure hand sprayer or broadcast application with hose end sprayer.

The existing uses allow application of pyraflufen-ethyl in "non crop areas" such as airports, commercial plants, nurseries, ornamental turf (residential/recreational), roadsides and railroads using lawn hand-gun sprayer, backpack sprayer and low pressure hand-wand sprayer. The existing product was not intended for use by homeowners; product was to be used by professional applicators only.

The hazard characterization/endpoint selection, dietary exposure, and drinking water exposure assessment have not changed since the previous risk assessment (DP#339360, M. Ottley, 04/17/2008) on pyraflufen-ethyl and can be applied directly to this action. This document addresses human-health risk resulting from the proposed expansion of the registered outdoor non-food uses and the currently registered food uses.

The occupational/residential assessment was performed by Kristin Rury. The drinking water assessment was conducted by Jose. L. Melendez. The risk assessment was conducted by Meheret Negussie.

The following risk assessments were conducted to support the proposed uses: short-term incidental oral (children's incidental ingestion), short-term residential (non-occupational) and occupational exposure assessments. In addition, the following aggregate risk assessments were conducted; short-term (residential + chronic food and water), chronic (food and water only) and cancer (food and water + residential). Because a dermal endpoint was not identified (no adverse effects were seen at the limit dose in the dermal toxicity study), dermal exposure was not assessed for non-cancer effects. However, for cancer risk assessment, dermal exposure was added to inhalation exposure for a total exposure calculation (assuming 100% absorption for both). An acute dietary endpoint was not identified.

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1.0 EXECUTIVE SUMMARY

Pyraflufen-ethyl is an herbicide which belongs to the phenyl pyrazole class of chemicals called protox inhibitors. The chemical works by inhibiting an enzyme in a plant's chloroplasts, causing subsequent cell membrane destruction. Pyraflufen-ethyl is currently registered as a defoliant in cotton, a dessicant in potatoes, and to control broad-leaf weeds in field corn, cotton, potatoes, soybeans, wheat, nonbearing crops (tree fruit, tree nut, and vine crops), and non-crop areas (airports, commercial plants, nurseries, and ornamental turf).

Permanent tolerances are established for the combined residues of pyraflufen-ethyl [ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methyl-1*H*-pyrazol-3-yl)-4-fluorophenoxyacetate] and its acid metabolite *E*-1 [2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetic acid] at levels ranging from 0.01 ppm in/on various corn, wheat and soybean commodities to 1.5 ppm in/on cotton gin byproducts [40 CFR§180.585(a)]. No tolerances are established for pyraflufen-ethyl residues in livestock commodities or for inadvertent residues in rotational crops. Time-limited tolerances were established for milk; cattle, meat byproducts; goat, meat byproducts; horse, meat byproducts and sheep, meat byproducts.

Use Profile (Proposed)

Pyraflufen-ethyl may be applied to established ornamental turf lawns (including residential, industrial and institutional), parks, cemeteries, athletic fields, golf courses (including fairways, aprons, tees, and roughs), and similar turf areas for broadleaf weed control. Pyraflufen-ethyl may be applied to cool season grasses (bluegrass, fescue, and ryegrass) and warm season grasses (Bahia grass, common Bermuda grass, centipede grass, St. Augustine grass, and zoysia grass) at a rate of 0.005 lb ai per acre using a pressure sprayer, hose end applicator, groundboom, or similar method. Pyraflufen-ethyl may be applied with spot treatment or via a broadcast application. Up to three applications may be made per year at a maximum seasonal application rate of 0.0188 lb ai per acre with ET 2.0% (EDICT® 2% SC IVM), and one application may be made per year at a maximum seasonal application rate of 0.009 lb ai per acre with ET 2.5% (EDICT® IVM).

Hazard Profile

The toxicology database for pyraflufen-ethyl is of high quality and complete except for acute and subchronic neurotoxicity and immunotoxicity studies which are now included under 40 CFR §158.500 as part of the toxicology data requirements for registration of a pesticide (food and non-food uses). Additionally, because the proposed use pattern will result in repeated inhalation exposure, a 28-day inhalation toxicity study is being required.

Although acute and subchronic neurotoxicity and immunotoxicity studies are needed to complete the database, there are no concerns for immunotoxicity or neurotoxicity based on the results of the existing studies. Further, in the absence of a route specific inhalation toxicity study, a point of departure (POD) for inhalation exposure risk assessment has been extrapolated from an oral study.

The metabolic pathway in plants and animals involves ester hydrolysis and N-demethylation.

Compounds of toxicological significance in rats, plants, and livestock included parent, and metabolites E1 and E9. Other environmental transformation products (E-1, E-2, and E-3), predicted to be present in water, are also considered of toxicological significance.

In the absence of dermal absorption data, dermal absorption is assumed to be 100%.

Pyraflufen-ethyl exhibits relatively low toxicity following single oral, dermal and inhalation exposure. It is moderately irritating to the eye, but is not a skin irritant or a dermal sensitizer. Following repeated short-term and chronic oral doses, the liver, kidney and possibly the hematopoietic system are the target organs for pyraflufen-ethyl in the rat and/or mouse. No adverse toxic effects were noted in the dog following oral exposure or in the rat following dermal exposure. There was no evidence of increased susceptibility following pre-natal exposure to rats and rabbits and pre-and post-natal exposures to rats. Although not mutagenic or carcinogenic in the rat or in female mice, pyraflufen-ethyl is classified as a likely human carcinogen based on increased incidence of hepatocellular tumors (adenomas, carcinomas and/or hepatoblastomas) in male mice.

An acute dietary risk assessment was not conducted as there was no indication of an adverse effect attributable to a single dose. Short-term inhalation and incidental oral risk assessments utilized the most sensitive dose and endpoint in the database, a maternal no observable adverse effect level (NOAEL) of 20 mg/kg/day based on decreased body weight and food consumption observed in the rabbit developmental toxicity study. The chronic dietary risk assessment utilized the most sensitive chronic dose and endpoint in the database, a NOAEL of 20 mg/kg/day based on liver toxicity observed in the 18-month mouse carcinogenicity study. Although neurotoxicity and immunotoxicity studies are needed to complete the database, there are no concerns for neurotoxicity or immunotoxicity based on the results of the existing studies and no need for a database uncertainty factor. The FQPA factor was reduced to 1X because pyraflufen-ethyl showed no evidence of increased susceptibility of the young. The standard 100-fold safety factor for combined human variability and interspecies differences has been applied to the points of departure selected for all non-cancer risk assessment scenarios. A linear low-dose extrapolation (Q_1^* of 3.32×10^{-2} (mg/kg/day)⁻¹) is used for quantification of human cancer risk.

Dietary Risk

Residues of Concern: For both tolerance enforcement and dietary risk assessment, the residues of concern in/on plants (primary and rotational crops) are parent and metabolite E-1 [2-Chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetic acid], and the residues of concern in/on treated livestock commodities are parent, metabolite E-1, and metabolite E-9 [2-chloro-5-(4-chloro-5-difluoromethoxy-1H-pyrazol-3-yl)-4-fluorophenoxyacetic acid]. The residues of concern in drinking water are the parent, metabolites E-1, E-2 [2-Chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenol], and E-3 [4-Chloro-3-(4-chloro-2-fluoro-5-methoxyphenyl)-5-difluoromethoxy-1-methylpyrazole].

Acute Dietary Exposure/Risk: There was no indication of an adverse effect attributable to a single dose; therefore, no acute dietary risk assessment was performed.

Chronic/Cancer Dietary Exposure/Risk: Chronic dietary exposure analyses using DEEM-FCID™ indicate that chronic dietary exposure to the combined residues of pyraflufen-ethyl and metabolite E-1 from food and drinking water are well below HED's level of concern (LOC). Using a partially refined analysis, the estimated chronic dietary exposure is <1% of the cPAD for the general U.S. population and all population subgroups, including children 1-2 years old, the most highly exposed population subgroup. The cancer risk is 2.75×10^{-6} which is also below HED's LOC.

Drinking Water

The drinking water assessment results did not change from the previous assessment (DP# 337845, M. Barrett, 02/29/2008); the highest exposure is still the potato use 0.01789 lb ai/A (compared to 0.00927 lb ai/A for the new use).

Due to its low persistence, pyraflufen-ethyl should not be available for runoff or leaching. However, three metabolites (E-1, E-2, and E-3) were identified as major transformation products and are included in the drinking water assessment. There are no data available on the toxicity of the metabolites; however, since the metabolites are structurally similar to the parent pyraflufen-ethyl, they are assumed to be of equal or lesser toxicity (Metabolism Assessment Review Committee [MARC] Decision memo, 07/19/02 and personal communication with A. Protzel and J. Doherty 9/19/02). Based on the highest application rate, the acute surface water estimated drinking water concentration (EDWC) using the FIRST (FQPA Index Reservoir Screening Tool) model (surface water) is 1247 parts per trillion (ppt) of total residues of pyraflufen-ethyl and its major degradates and the annual average surface water value is 281 ppt. The groundwater screening concentration from SCIGROW (Screening Concentrations in Ground Water) is 1.8 ppt. These values generally represent upper-bound conservative estimates of the total residue concentrations that might be found in surface water and ground water due to the use of pyraflufen-ethyl.

Residential Risk

Residential Handler Exposure: Non-occupational (residential) handlers may be exposed during mixing, loading, and application of pyraflufen-ethyl using a liquid formulation with a low-pressure handwand or garden hose-end sprayer to treat turf. The results indicate that MOEs for inhalation exposure from non-occupational handler scenarios provide a margin of protection substantially greater than HED's LOC (LOC=100).

Residential Postapplication Exposure: Postapplication exposure assessments were performed for children's incidental ingestion of residues of pyraflufen-ethyl on treated turf (hand-to-mouth exposure, object-to-mouth exposure and soil ingestion). Results indicate that MOEs for combined exposure from children's incidental ingestion of pyraflufen-ethyl residues on treated turf were below HED's LOC (i.e. MOEs \geq 100).

Cancer Risk: Cancer risk for adult handler and adult postapplication activities were assessed. For adult cancer risk dermal exposure was added to inhalation exposure for a total exposure calculation (assuming 100% absorption for both). The results indicate that cancer risks for adult handler and post-application exposures do not exceed HED's LOC (10^{-6} range).

Acute Aggregate Risk: No adverse effect attributable to a single exposure (dose) was observed in oral toxicity studies, including the developmental toxicity studies in rats and rabbits. Therefore, an acute reference dose was not established and an acute aggregate risk assessment was not performed.

Short-Term and Intermediate-Term Aggregate Risk: Short-term aggregate risk is based on residential handler exposure, children's incidental oral exposure (from residential postapplication treatment) and dietary exposure (food and drinking water). The anticipated exposure level for children, 1-2 years old (the highest exposed population) is below HED's LOC, with an MOE of 49,000. An intermediate-term aggregate risk assessment was not conducted for adults because exposure duration is expected to be short-term only. In addition, an intermediate-term aggregate risk assessment was not conducted for children (postapplication exposure) because standard assumptions (input values) for intermediate-term exposure are less conservative than those for short-term exposure.

Long-Term Aggregate Risk: For chronic aggregate risk assessment, exposure from food and drinking water were considered. Exposures from residential uses are not expected to occur over the chronic duration. Refer to Chronic Dietary Exposure/Risk.

Aggregate Cancer Risk: Cancer risks were calculated for both adult handler and adult postapplication activities. For the aggregate cancer risk assessment, exposure from residential uses is based on the lifetime average daily dose (LADD), and assumes an exposure period of 5 days per year and 50 years of exposure of a 70-year lifetime. Average food and water-source dietary exposure values were used (based on a Tier 1 analysis). Cancer risk for the US population includes infants and children; therefore, in accordance with HED Policy, children's cancer risk was not reported separately.

HED concludes with reasonable certainty that the aggregate exposure from pyraflufen-ethyl residues in food, drinking water and residential settings will not exceed the Agency's LOC for short-term, long-term or cancer aggregate exposure for any population subgroup.

Occupational Risk

Short- and Intermediate-Term Handler Risk: Occupational handlers may be exposed (short-term and long-term) during mixing, loading and application of pyraflufen-ethyl using hand-held and groundboom equipment for broadcast and spot treatment of turf. Handler non-cancer risk estimates were based on inhalation exposure only (no dermal endpoints were identified based on a lack of dermal toxicity). The results indicate that MOEs for inhalation exposure from all occupational handler scenarios do not exceed HED's LOC (i.e., MOEs \geq 100) at some level of personal protection.

Short- and Intermediate-Term Postapplication Exposure Risk: Dermal toxicity endpoints for postapplication pyraflufen-ethyl exposure were not identified by the HED. Inhalation exposure during postapplication activities is considered negligible for all outdoor pyraflufen-ethyl use scenarios.

Cancer Risk: Cancer risk for adult handler and adult postapplication activities were assessed. Handler cancer risk estimates were based on dermal and inhalation exposures. All exposure

(handler) scenarios with personal protective equipment (PPE) use (as required by the label) resulted in cancer risks below HED's LOC (1.0×10^{-4}). An occupational postapplication assessment for cancer risk was performed for golf course maintenance workers and sod farm workers. Inhalation exposure was considered negligible for postapplication activities. Cancer risks for post-application exposures do not exceed HED's LOC.

Pyraflufen-ethyl is classified as acute toxicity category III for acute dermal and primary eye irritation. It is classified as category IV for primary skin irritation and it is not a dermal sensitizer. Therefore, the interim Worker Protection Standard (WPS) restricted entry interval of 12 hours (as stated on the label) is adequate to protect agricultural workers from post-application exposures to pyraflufen-ethyl.

The minimum level of personal protective equipment (PPE) for handlers is based on acute toxicity for the end-use product. RD is responsible for ensuring that PPE listed on the label is in compliance with the WPS.

Regulatory Recommendations

The proposed residential uses have been assessed and no risks of concern were identified. HED has no objection to registration of this new use pattern provided that the registration be conditional pending submission of the newly required Part 158 toxicology data and well as additional residue chemistry data (see Section 9.0 for details).

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," <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. 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 postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from Pesticide Handlers Exposure Database (PHED) studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies have been determined to require a review of their ethical conduct and have received that review.

2.0 INGREDIENT PROFILE

Pyraflufen-ethyl is a herbicide that is currently registered for use as a harvest aid in cotton and potatoes; for a single preplant or preemergence burndown use in field corn, cotton, deciduous fruit and nut trees and vines, soybeans, and wheat; for postemergence use in cotton; corn (except sweet corn); soybeans; for weed control in non-crop land and uncultivated agricultural areas (nonfood producing); and as a nonselective herbicide for control of broadleaf weeds in non-crop areas, including recreational and residential areas.

2.1 Summary of Registered/Proposed Uses

Pyraflufen-ethyl is a herbicidal active ingredient (ai). The proposed formulated end-use products are labeled under the trade names EDICT® 2% SC IVM, EDICT® 2SC, Venue™, Octane™ 2% SC and Octane™, which contain 2.0% (0.177 lb ai/ gallon) pyraflufen-ethyl, and EDICT® IVM, which contains 2.5% (0.208 lb ai/ gallon) pyraflufen-ethyl.

Pyraflufen-ethyl is proposed for residential/homeowner and commercial applicator use to established ornamental turf lawns (including residential, industrial and institutional), parks, cemeteries, athletic fields, golf courses (including fairways, aprons, tees, and roughs), and similar turf areas for broadleaf weed control. Pyraflufen-ethyl may be applied to cool season grasses (bluegrass, fescue, and ryegrass) and warm season grasses (Bahia grass, common Bermuda grass, centipede grass, St. Augustine grass, and zoysia grass) at a rate of 0.005 lb ai per acre using a pressure sprayer, hose-end applicator, groundboom, or similar method. Pyraflufen-ethyl may be applied with spot treatment or via a broadcast application. Up to three applications may be made per year at a maximum seasonal application rate of 0.0188 lb ai per acre with ET 2.0%, and one application may be made per year at a maximum seasonal application rate of 0.009 lb ai per acre with ET 2.5%.

The proposed use profile is summarized in Table 2.1.

Crop	Product Information	Application Type	Method of Application	Maximum Single Application Rate (lb ai/A)	Maximum Number of Applications	Maximum Seasonal Application Rate (lb ai/A)
Cool Season Grasses (bluegrass, fescue, ryegrass) Warm Season Grasses (Bahia grass, common Bermuda grass,	ET 2% SC herbicide/defoliant EPA Reg. No. 71711-25 Liquid 0.177 lb ai/gallon formulated product	spot treatment, broadcast application, entire lawn	Pressure sprayer, hose-end applicator, or similar	0.005 ^a	3	0.0188 ^c

Table 2.1: Use Profile for Pyraflufen-ethyl For use on established ornamental turf lawns (residential, industrial, and institutional) parks, cemeteries, athletic fields, golf courses (fairways, aprons, tees and roughs), sod farms, and similar turf areas.

Crop	Product Information	Application Type	Method of Application	Maximum Single Application Rate (lb ai/A)	Maximum Number of Applications	Maximum Seasonal Application Rate (lb ai/A)
centipede grass, St Augustine grass, zoysia grass)						
Cool Season Grasses (bluegrass, fescue, ryegrass) Warm Season Grasses (Bahia grass, common Bermuda grass, centipede grass, St Augustine grass, zoysia grass)	ET (2.5%) herbicide/defoliant EPA Reg. No. 71711-7 Liquid 0.208 lb ai/gallon formulated product	spot treatment, broadcast application, entire lawn	Pressure sprayer, hose-end applicator, or similar	0.005 ^b	1	0.009 ^d

a. Application of Spray Concentration: (10 fl oz product/120 fl oz water)*(0.177 lb ai/gal product)*(1 gal/128 fl oz)*(128 fl oz/gal)*(1 fl oz spray concentrate/1000 ft²)*(1 gal/128 fl oz)*(43560 ft²/A)=0.005 lb ai/A

Application of Product: (4 fl oz product/A)*(0.177) lb ai/gal product*(1 gal/128 fl oz) = 0.005 lb ai/A

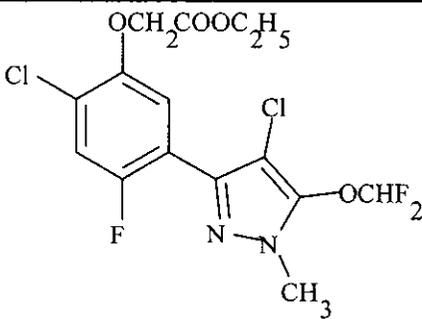
b. Application of Spray Concentration: (8 fl oz product/120 fl oz water)*(0.208 lb ai/gal product)*(1 gal/128 fl oz)*(128 fl oz/1 gal)*(1 fl oz spray concentrate/1000 ft²)*(1 gal/128 fl oz)*(43560 ft²/A)=0.005 lb ai/A

c. lb ai/A from: (2% SC) max 13.6 fl oz product per acre per year*(1gal/128 fl oz)=0.10625 gal product per acre*0.0177 lb ai per gal

d. lb ai/A from: (2.5% EC) max 5.5oz(1gal/128oz)=0.042969 gal product per acre*0.208 lb ai per gal

2.2 Structure and Nomenclature

Table 2.2. Pyraflufen-ethyl Structure and Nomenclature.

Chemical structure	
Empirical Formula	C ₁₅ H ₁₃ Cl ₂ F ₃ N ₂ O ₄
Common Name	Pyraflufen-ethyl
Company Experimental Name	ET-751
IUPAC Name	Ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetate
CAS Name	Ethyl [2-chloro-5-[4-chloro-5-(difluoromethoxy)-1-methyl-1H-pyrazol-3-yl]-4-fluorophenoxy]acetate
CAS Registry Number	129630-19-9
End-use Product (EP)	0.208 lb ai/gal EC (2.5%EC; ET® Herbicide/Defoliant; EPA Reg. No. 71711-7; Label Date 01/29/2009) 0.177 lb ai/gal FIC (2.0%FIC; ET® 2%SC Herbicide/Defoliant; EPA Reg. No. 71711-25; Label Date 01/29/2009)
Chemical Class	Phenylpyrazole herbicide
Known Impurities of Concern	None

2.3 Physical and Chemical Properties

Refer to Section 2.3 Physical and Chemical Properties of the previous risk assessment document (M. Ottley, 04/17/2008, DP# 339360).

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Studies Available

The toxicology database for pyraflufen-ethyl is of high quality and complete except for acute and subchronic neurotoxicity and immunotoxicity studies which are now included under 40 CFR Part §158.500 as part of the toxicology data requirements for registration of a pesticide (food and non-food uses). Additionally, because the proposed use pattern will result in repeated inhalation exposure, a 28-day inhalation toxicity study is being required.

Although acute and subchronic neurotoxicity and immunotoxicity studies are needed to complete the database, there are no concerns for immunotoxicity or neurotoxicity based on the results of the existing studies. Further, in the absence of a route specific inhalation toxicity study, a POD for inhalation exposure risk assessment has been extrapolated from an oral study.

Adsorption, Distribution, Metabolism, and Excretion

Radiolabeled kinetic studies in the rat show that pyraflufen-ethyl is rapidly absorbed in a dose-dependent manner with 56% of the low dose present in urine and bile within 2 days. At 6 hours post-dose, the highest residues were found in the GI tract, liver and excretory organs. There was no evidence of accumulation. Excretion of residues was essentially complete 24 hours after dosing with <1% of the absorbed dose eliminated unchanged.

The metabolic pathway in plants and animals involves ester hydrolysis and N-demethylation. Compounds of toxicological significance in rats, plants, and livestock included parent, and metabolites E1 and E9. Other environmental transformation products (E-1, E-2, and E-3), predicted to be present in water, are also considered of toxicological significance.

In the absence of dermal absorption data, dermal absorption is assumed to be 100%.

Acute, Short- and Long- Term Toxicity

Pyraflufen-ethyl exhibits relatively low toxicity following single oral, dermal and inhalation exposure. It is moderately irritating to the eye, but is not a skin irritant or a dermal sensitizer. Following repeated short-term and chronic oral doses, the liver, kidney and possibly the hematopoietic system are the target organs for pyraflufen-ethyl in the rat and/or mouse. No adverse toxic effects were noted in the dog following oral exposure or in the rat following dermal exposure. There was no evidence of increased susceptibility following pre-natal exposure to rats and rabbits and pre-and post-natal exposures to rats. Although not mutagenic or carcinogenic in the rat or in female mice, pyraflufen-ethyl is classified as a likely human carcinogen based on increased incidence of hepatocellular tumors (adenomas, carcinomas and/or hepatoblastomas) in male mice.

Points of Departure and Uncertainty Factors used for Risk Assessment

An acute dietary risk assessment was not conducted as there was no indication of an adverse effect attributable to a single dose. Short-term inhalation and incidental oral risk assessments utilized the most sensitive dose and endpoint in the database, a maternal NOAEL of 20 mg/kg/day based on decreased body weight and food consumption observed in the rabbit developmental toxicity study. The chronic dietary risk assessment utilized the most sensitive chronic dose and endpoint in the database, a NOAEL of 20 mg/kg/day based on liver toxicity observed in the 18-month mouse carcinogenicity study. Although neurotoxicity and immunotoxicity studies are needed to complete the database, there are no concerns for neurotoxicity or immunotoxicity based on the results of the existing studies and no need for a database uncertainty factor. The FQPA factor was reduced to 1X because pyraflufen-ethyl showed no evidence of increased susceptibility of the young. The standard 100-fold safety factor for combined human variability and interspecies differences has been applied to the points of departure selected for all non-cancer risk assessment scenarios. A linear low-dose extrapolation (Q_1^* of 3.32×10^{-2} (mg/kg/day)⁻¹) is used for quantification of human cancer risk.

3.2 FQPA Considerations

HED recommends that the default 10X FQPA safety factor be reduced to 1X for the following reasons:

- 1) The data base is complete with the exception of acute and subchronic neurotoxicity, immunotoxicity, and inhalation toxicity studies.
- 2) There is no evidence of increased susceptibility of rat or rabbit fetuses following *in utero* exposure in the developmental studies with pyraflufen-ethyl. There is no evidence of increased susceptibility of young rats in the reproduction study with pyraflufen-ethyl and there are no residual uncertainties for pre- and/or postnatal exposure.
- 3) No concerns for neurotoxicity and no need for a DNT.
- 4) There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessment, although somewhat refined, is conservative using tolerance-level residues for most crops and assuming 100% crop treated information. Dietary drinking water exposure is based on conservative modeling estimates. HED Residential SOPs were used to assess post-application exposure to children as well as incidental oral exposure of children (toddlers). These assessments will not underestimate the exposure and risks posed by pyraflufen-ethyl.

3.3 Dose-Response Assessment

HED has evaluated the toxicology database of pyraflufen-ethyl, established reference doses (RfD) and selected the toxicological endpoints for dietary as well as occupational and residential exposure risk assessments. A summary of the endpoints identified for risk assessment is presented below in Table 3.3.1.

Table 3.3.1 Summary of Toxicological Doses and Endpoints for Pyraflufen-Ethyl for Use in Dietary, Residential (Non-Occupational) and Occupational Human Health Risk Assessments.				
Exposure/Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	None	None	None	An endpoint attributable to a single dose was not identified from the available data.
Chronic Dietary (all populations)	NOAEL = 20	UF _A =10x UF _H =10x FQPA SF = 1X	Chronic RfD = 0.20 mg/kg/day cPAD = 0.2 mg/kg/day	Mouse Carcinogenicity LOAEL = 98 mg/kg/day based on liver toxicity
Incidental Oral Short-Term (1-30 days)	Maternal NOAEL = 20 mg/kg/day	UF _A =10x UF _H =10x FQPA SF = 1X	MOE = 100 (residential)	Developmental Toxicity-Rabbit LOAEL = 60 mg/kg/day based on decreases in body weight and food consumption, GI observations, and abortions
Incidental Oral Intermediate-Term (1-6 months)	Maternal NOAEL = 20 mg/kg/day	UF _A =10x UF _H =10x FQPA SF = 1X	MOE = 100 (residential)	Mouse Carcinogenicity LOAEL = 98 mg/kg/day based on liver toxicity at interim sacrifice
Dermal Short-Intermediate- and Long-Term (1-30 days, 1-6 months, and >6 months)	None	None	None	In a 28-dermal toxicity study in rats, no dermal or systemic toxicity was seen at the Limit Dose (1000 mg/kg/day).
Inhalation Short- and Intermediate- (1-30 days, 1-6 months)	Maternal NOAEL = 20 mg/kg/day	UF _A =10x UF _H =10x FQPA SF = 1X	MOE = 100 (occupational) MOE = 100 (residential)	Developmental Toxicity-Rabbit LOAEL = 60 mg/kg/day based on decreases in body weight and food consumption, GI observations, and abortions
Inhalation Long-Term (>6 months)	Maternal NOAEL = 20 mg/kg/day	UF _A =10x UF _H =10x FQPA SF = 1X	MOE = 100 (occupational) MOE = 100 (residential)	Developmental Toxicity-Rabbit LOAEL = 60 mg/kg/day based on decreases in body weight and food consumption, GI observations, and abortions
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" by the oral route. Q ₁ * = 3.32 x 10 ⁻² (mg/kg/day) ⁻¹			

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 (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

HED identified endpoints for chronic dietary exposure assessment (chronic reference dose), short- and intermediate-term incidental oral exposure assessment and short- and intermediate-

term inhalation exposure assessment. Endpoints for short- and intermediate-term dermal exposure assessment were not identified, because in a 28-day dermal toxicity study in rats, no effects were seen at the limit dose (1000 mg/kg/day). Long-term or chronic exposure through dermal or inhalation routes is not expected based on the use pattern (intermittent use).

To quantify cancer risk, the Q_1^* is multiplied by the estimated lifetime average daily doses from occupational or residential exposure. In the absence of dermal absorption data, 100% dermal absorption was assumed, in spite of the fact that the K_{ow} is low, which indicates that dermal absorption is expected to be low. Therefore, cancer risk estimates in this document are considered very conservative. Lifetime average daily dermal and inhalation exposures were summed, because cancer risk is based on total exposure over a lifetime.

3.4 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

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

Pyraflufen-ethyl is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA Sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website:

<http://www.epa.gov/endo/>.

4.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

There are no changes to the dietary exposure/risk; refer to the most recent human health risk assessment DP#339360, M. Ottley, 04/17/2008.

4.1 Pesticide Metabolism and Environmental Degradation

4.1.1. Metabolism in Primary Crops

The qualitative nature of the residue in plants is adequately understood based on the acceptable cotton, potato, and wheat metabolism studies. In plants, pyraflufen-ethyl undergoes ester hydrolysis to form the acid metabolite E-1 and the phenolic derivative, metabolite E-2, and demethylation of the pyrazole ring to form metabolite E-9 (See Appendix A1 for structures). Pyraflufen-ethyl may also undergo further degradation of the phenoxyacetate moiety to form bound polar metabolites and other polar metabolites. Although the cotton metabolism study was originally considered inadequate due to the lower application rate used in the study (0.3x the maximum seasonal rate), the Agency (ChemSAC minutes, 12/3/03) concluded that an additional cotton metabolism study would not be required as increasing the application rate by 3x would be unlikely to make a significant difference in the nature of the residue profile in cotton.

4.1.2. Metabolism in Rotational Crops

A confined rotational crop study on radish, lettuce, and barley was previously submitted reflecting a soil application of [¹⁴C-pyrazole]pyraflufen-ethyl at 0.0127 lb ai/A (0.9x the maximum seasonal rate on cotton). Detectable residues (0.001-0.003 ppm) were observed in 30-day mature radish roots and tops, and barley chaff and straw, 120-day immature radish roots, and 150-day barley forage. No pyraflufen-ethyl was identified on analysis of 30-day radish tops and barley straw; however, metabolites E-1, E-2, and E-3 were tentatively identified in radish tops at <3% TRR each. No residues were identified in barley straw. Pyraflufen-ethyl breaks down in the soil to its metabolites E-1, E-2, and E-3, and uptake of pyraflufen-ethyl and its soil metabolites by rotational crops only occurs at very low levels.

Although the HED originally concluded that the confined rotational crop study was insufficient due to ¹⁴C-labeling in only the pyrazole ring, the Agency (ChemSAC minutes, 12/3/03) concluded that an additional confined rotational crop study with pyraflufen-ethyl radiolabeled in the phenyl ring would not be required, as the metabolic pathways in soil, plants, and animals were similar and there was no evidence of cleavage of the bond between the phenyl and pyrazole rings. The available confined study supports the 30-day plantback interval specified on the label for all crops without primary uses of pyraflufen-ethyl.

4.1.3. Metabolism in Livestock

The qualitative nature of the residue in livestock is adequately understood based on the acceptable ruminant and poultry metabolism studies (radiolabeled in the pyrazole ring only). Pyraflufen-ethyl is metabolized extensively and rapidly in livestock. Pyraflufen-ethyl undergoes ester hydrolysis to form the carboxylic acid derivative, metabolite E-1 and the phenolic derivative, metabolite E-2, and demethylation to form the desmethyl derivative of metabolite E-1, metabolite E-9 (See Appendix A1 for structures). Although the livestock metabolism studies were originally considered insufficient as only the pyrazole ring was labeled, the Agency (Chem SAC minutes, 12/3/03) concluded that additional ¹⁴C-phenyl ring studies would not be required, as the metabolic pathways in soil, plants, and livestock were similar and there was no evidence of cleavage of the bond between the phenyl and pyrazole rings.

4.1.4. Analytical Methodology

Plant Commodities

An adequate gas chromatography/mass spectrometry GC/MS method is available for tolerance enforcement, and substantially similar GC/MS methods were used for data collection in the grass, corn, soybean and wheat field trials and processing studies.

Livestock Commodities

An adequate GC/MS method is available for collecting data on residues of parent and metabolite E-1 (determined as E-15) in livestock commodities. The method has a validated LOQ of 0.01 ppm for each analyte in milk and tissues, for a combined LOQ of 0.02 ppm. The method has undergone a successful independent laboratory validation (ILV) and has been radiovalidated.

Although not relevant to the proposed non-food uses, HED notes that the method does not determine metabolite E-9, which is also a residue of concern in livestock commodities. For the cattle feeding study previously requested for food uses, the data collection method should be modified to also determine metabolite E-9. If HED determines that metabolite E-9 should be included in the permanent tolerance definition for livestock commodities, the method will be reviewed for appropriateness enforcement for metabolite E-9.

Multiresidue Methods

No adequate multiresidue methods testing data have been submitted for pyraflufen-ethyl. Nichino America, Inc. previously submitted a method description and supporting data for an EEC (European) multiresidue enforcement method. This submission was not adequate to fulfill EPA's multiresidue method requirement.

Data are required reflecting recovery of pyraflufen-ethyl and its metabolite E-1 through the FDA multiresidue methods according to Protocols C and D in the Pesticide Analytical Manual, Volume I, Appendix II. Evaluations should be performed with and without Florisil cleanup.

4.1.5. Environmental Degradation

Due to its low persistence, pyraflufen-ethyl should not be available for runoff or leaching. However, three metabolites were identified as major transformation products (E-1, E-2 and E-3). The MARC concluded that the parent, E-1, E-2 and E-3 should all be included in the drinking water assessment. See appendix for metabolite structures. The metabolite E-1 is moderately persistent, making it available for runoff during rain events occurring shortly after application. E-3, the most persistent of three terminal degradates, generally appears at lower concentrations, later in time, and binds more strongly to soils. E-3 should also be available for runoff in rain events accompanied with erosion.

4.1.6. Toxicity Profile of Major Metabolites and Degradates

Pyraflufen-ethyl degrades into similar metabolites in plants, livestock, water and soil. The MARC considered the metabolites and concluded that none of them is likely to be more toxic

than pyraflufen-ethyl itself. While there are no data specific to the toxicity of the metabolites, E-1, E-2 and E-3 are structurally similar to the parent pyraflufen-ethyl and as such are assumed to be of equal or lesser toxicity (MARC Decision memo, 07/19/02 and personal communication with A. Protzel and J. Doherty, 9/19/02). See the appendix of this memo for metabolite structures. The metabolites were included in the risk assessment (E-1 in the food-source dietary assessment and E-1, E-2 and E-3 in the drinking water assessment).

The conclusion that pyraflufen-ethyl metabolites are not expected to be more toxic than the parent compound was confirmed by HED's Derek Analysis program which conducted structure activity analyses on the chemicals in question.

4.1.7. Pesticide Metabolites and Degradates of Concern

The nature of the residue in plants, rotational crops and livestock is adequately understood. The MARC has concluded that the residues of concern in plants and rotational crops include the parent and metabolite E-1 for purposes of tolerance enforcement and risk assessment. Although not relevant to the proposed non-food uses, the MARC has concluded that the residues of concern in livestock commodities for the risk assessment are parent and metabolites E-1 and E-9, and that all three compounds should be measured in livestock feeding studies. HED also previously concluded in connection with food petitions that time-limited tolerances could be established for parent and metabolite E-1 pending results of the requested cattle feeding study. Depending on the results of the requested cattle feeding study, metabolite E-9 may also be included in the future permanent tolerance for livestock commodities.

Environmental fate data indicate that metabolites E-1 and E-2 are the major metabolites (>10% total radioactive residues [TRR]) in photolysis, aerobic soil metabolism, anaerobic aquatic metabolism and aerobic aquatic metabolism studies for parent. E-3 is the major metabolite (>10% TRR) in aerobic soil metabolism resulting from E-2. Although U1 (2-fluoro-5-hydroxy-5-(*N*-methylcarbamoyl)-4-oxo-2-pentenoic acid) was observed at 21% TRR under photolysis in soil, soil photolysis is not a major route of environmental degradation, and with the fact that the application rate is so low (<0.02 lbs ai/A), the MARC concluded that U1 is not a residue of concern in drinking water. Although PD-1 (parent compound with the chlorine on the phenyl ring replaced by hydroxyl) is a major degradate in aqueous photolysis, it is relatively unstable in water based on its short half - life (32.2% at 36 hours to 18.7% at 48 hours). Therefore, the MARC concluded that the residues for risk assessment in drinking water include parent, E-1, E-2, and E-3.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	parent, E-1	parent, E-1
	Rotational Crop	parent, E-1	parent, E-1
Livestock	Ruminant	parent, E-1, E-9	parent, E-1 *

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
	Poultry	parent, E-1, E-9	parent, E-1 *
Drinking Water		parent, E-1, E-2, E-3	Not Applicable

* Metabolite E-9 may be included in permanent tolerance for livestock commodities, depending on the results of the cattle feeding study requested in connection with food uses.

4.1.8. Drinking Water Residue Profile

The drinking water assessment results did not change from the previous assessment (DP# 337845, M. Barrett, 02/29/2008); the highest exposure is still the potato use 0.01789 lb ai/A (compared to 0.00927 lb ai/A for the new use; DP# 361815 and 361816).

Due to its low persistence, pyraflufen-ethyl should not be available for runoff or leaching. However, three metabolites were identified as major transformation products and are included in the drinking water assessment. The metabolite E-1 is moderately persistent, making it available for runoff during rain events occurring shortly after application. E-3, the most persistent of three terminal degradates, generally appears at lower concentrations, later in time, and binds more strongly to soils. E-3 should also be available for runoff in rain events accompanied with erosion. There are no data available on the toxicity of the metabolites. E-1, E-2 and E-3 are structurally similar to the parent pyraflufen-ethyl and as such are assumed to be of equal or lesser toxicity (MARC Decision memo, 07/19/02 and personal communication with A. Protzel and J. Doherty, 9/19/02).

Monitoring data for drinking water estimates are not available. Models were used to calculate drinking water estimates. Upper-bound Tier 1 estimated drinking water concentrations (EDWCs) were calculated for pyraflufen-ethyl and its major residues E-1, E-2, and E-3, calculated using the FIRST model (surface water) and SCIGROW model (ground water). Based on the highest application rate, the acute surface water EDWC value is 1247 ppt of total residues of pyraflufen-ethyl and its major degradates and the annual average surface water value is 281 ppt. The ground water screening concentration from SCIGROW is 1.8 ppt. These values generally represent upper-bound conservative estimates of the total residue concentrations that might be found in surface water and ground water due to the use of pyraflufen-ethyl.

Table 4.1.8. Summary of Estimated Surface Water and Ground Water Concentrations for Pyraflufen-Ethyl and Metabolites.		
	Pyraflufen-ethyl	
	Surface Water Conc., ppt ^a	Groundwater Conc., ppt ^b
Acute (maximum single-day exposure)	1247	1.8
Chronic (non-cancer, one in 10-year average)	281	1.8
^a From the Tier I FIRST (FQPA Index Reservoir Screening Tool) model. Input parameters are based on wheat, soybean, corn, pastures, sod farms, Christmas trees, nurseries, ornamental plantings, non-crop weed control; and for preplant burndown on root and tuber vegetables, cole crops, legumes, fruiting vegetables, cucurbits and small grains ^b From the SCI-GROW model assuming a maximum seasonal use rate of 0.00325 lb ai/A for pasture and range, and 0.00122 lb ai/A for post-emergence use on corn, soybean and wheat, a K _{oc} of approx. 2000.		

4.1.9. Food Residue Profile

Pyraflufen-ethyl is currently registered for use as a harvest aid in cotton and potatoes; for a single preplant or preemergence burndown use in field corn, cotton, soybeans, and wheat; and for postemergence use in cotton. Tolerances are established at levels ranging from 0.01 ppm in/on various corn, wheat and soybean commodities to 1.5 ppm in/on cotton gin byproducts.

The combined residues of pyraflufen-ethyl and metabolite E-1 were below the limit of quantitation (LOQ) in/on potatoes, corn field grain, soybean seeds, and wheat grain. The highest food residue detected was in cottonseed oil.

Processing studies conducted on potatoes, corn field grain, soybean seeds, wheat grain and cotton indicated that residues were nondetectable in all processed commodities.

In cotton and potatoes, foliar application of pyraflufen ethyl as a defoliant/desiccant resulted in higher residue levels in foliage (cotton gin byproducts and potato leaves); residues were significantly lower in cottonseed and were <LOQ in potato tubers. There was no indication of residues concentrating on exterior portion of wheat grain (bran) or soybean seed (hulls).

There are numerous livestock feedstuffs associated with pyraflufen-ethyl uses such as cotton seeds, gin byproducts, meal, and hulls; potato culls and processed waste; grass forage and hay; soybean seed, forage, hay, aspirated grain fractions, meal, and hulls; field corn grain, forage, stover, aspirated grain fractions, and milled byproducts; and wheat grain, forage, hay, straw, aspirated grain fraction, and milled byproducts.

In the cattle feeding study, quantifiable residues of metabolite E-1 were found in kidney samples and detectable residues of metabolite E-1 were found in some milk samples. Combined residues of parent and metabolite E-1 were <LOQ in muscle, fat and liver.

4.1.10 International Residue Limits

There are no MRLs in Codex or Canada.

4.2 Dietary Exposure and Risk

4.2.1 Acute Dietary Exposure/Risk

An acute dietary risk assessment was not performed as no adverse effect attributable to a single exposure (dose) was observed in oral toxicity studies; therefore, pyraflufen-ethyl has no acute toxicological endpoint.

4.2.2 Chronic Dietary Exposure/Risk

Reference: *Pyraflufen-ethyl. Chronic Aggregate (Food and Drinking Water) Dietary Exposure and Risk Assessments for a Section 3 Registration Action to Allow Early Season Postemergence Uses on Corn (Excluding Sweet Corn), Soybeans, and Wheat, DP# 347500, A. Acierto, 3/25/2008.*

The proposed new non-food uses on cool season grasses and warm season grasses do not trigger the need for a new dietary assessment. The dietary risk estimates from the previous dietary assessment (referenced above) is used in the aggregate risk assessment of this document. The chronic dietary (food and drinking water) analysis was conducted for pyraflufen-ethyl, assuming tolerance level residues in the established commodities except corn, cottonseed, potato, soybean and wheat for which ½ of the combined LOQs for the parent and the metabolite were used since all field trial data were <LOQ. All processed commodities derived from the treated corn grain, soybean seeds, and wheat grain had nondetectable residues; therefore, no processing factors were applied to those commodities. An experimental processing factor of 0.6x was used for cotton seed oil. One hundred percent crop treated (%CT) was assumed for all crop commodities. The anticipated residue value in milk was calculated to be 0.007 ppm. This analysis incorporates all current and proposed tolerances for the combined residues of pyraflufen-ethyl and metabolite E-1.

The chronic dietary (food and drinking water) exposure to pyraflufen-ethyl is below HED's LOC (i.e., <100% chronic population adjusted doses [cPAD]) for the general U.S. population and all population subgroups. Using the DEEM-FCID software, dietary exposure is estimated at 0.000083 mg/kg/day for the general U.S. population (<1% of the cPAD) and 0.000333 mg/kg/day (<1% of the cPAD) for children 1-2 years old, the population subgroup with the highest estimated chronic dietary exposure to pyraflufen-ethyl.

Population Subgroup	cPAD (mg/kg/day)	Chronic Dietary		Cancer	
		Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk (Q* = 0.0332)
General U.S. Population	0.2	0.000083	<1	0.000083	2.75x10 ⁻⁶
All Infants (< 1 year old)	0.2	0.000104	<1	NA ²	NA
Children 1-2 years old	0.2	0.000333 ¹	<1		
Children 3-5 years old	0.2	0.000241	<1		

Table 4.2.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Pyraflufen-Ethyl.

Population Subgroup	cPAD (mg/kg/day)	Chronic Dietary		Cancer	
		Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk (Q* = 0.0332)
Children 6-12 years old	0.2	0.000150			
Youth 13-19 years old	0.2	0.000079	<1		
Adults 20-49 years old	0.2	0.000053	<1		
Adults 50+ years old	0.2	0.000048	<1		
Females 13-49 years old	0.2	0.000054	<1		

¹The population subgroup with the highest estimated chronic dietary (food + drinking water) exposure and risk is indicated by bold text.

²NA = not applicable

4.2.3 Cancer Dietary Risk

The cancer dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model (DEEM) software, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1994-1996, 1998. For the cancer assessment, HED's LOC is exceeded when the risk estimate exceeds 3×10^{-6} . Estimated cancer risk is determined for the general U.S. population only. The estimated exposure of the general U.S. population to pyraflufen-ethyl is 8.3×10^{-5} mg/kg/day. Applying the Q_1^* of 0.0332 (mg/kg/day)¹ to the exposure estimate results in a **cancer risk estimate of 2.75×10^{-6}** . Therefore, the lifetime cancer risk to the general U.S. population is below HED's LOC.

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

The chronic dietary exposure analysis is partially refined in that one-half the combined LOQs of the parent and metabolite are used as the residue values rather than the tolerances (for corn, wheat, soybeans, cottonseed and potatoes). However, the assessment assumed that 100% of crops are treated with pyraflufen-ethyl.

5.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION

Reference: *Pyraflufen-ethyl: Occupational and Residential Exposure Assessment for proposed non-food uses of pyraflufen-ethyl on cool season grasses (bluegrass, fescue, and ryegrass) and warm season grasses (Bahia grass, common Bermuda grass, centipede grass, St. Augustine grass, and zoysia grass), DP#361213, K.Rury, 01/14/2010.*

Pyraflufen-ethyl may be used on turf at recreational use sites, and therefore, may result in postapplication exposure to adults and children involved in recreational activities. Exposure to adults and children from the use of pyraflufen-ethyl at recreational use sites are assumed to be

the same as those assessed for residential use sites, and therefore, a separate recreational exposure assessment was not included. Refer to Section 5.1 of this risk assessment for details on assumptions, input variables and risk estimates for residential use sites. Residential turf exposure assessment results in what are considered upper bound risk estimates. Therefore, it is not expected that the upper bound residential exposure scenario would occur on the same day as an upper bound recreational exposure scenario. Therefore, exposures from the residential and recreational scenarios are not aggregated. Rather, the residential risk estimate should serve as an upper bound for both residential and recreational exposure.

5.1 Residential Handler Exposure and Risk

Residential handlers may be exposed from mixing, loading and applying liquid pyraflufen-ethyl for spot treatment and/or broadcast control of weeds on ornamental lawns. Mixing/loading and spot application of a liquid formulation with a low pressure hand sprayer for spot treatment of grasses, and mixing/loading and application via broadcast with a hose end sprayer was assessed. Exposure duration is expected to be short-term only. Dermal exposure is estimated for cancer assessment only because a non-cancer dermal endpoint was not identified. Inhalation exposure is compared to the short-term inhalation endpoint (NOAEL = 20 mg/kg/day). Inhalation absorption is assumed to be equivalent to oral (100%) and a body weight of 60 kg was used, based on an oral developmental study in the rabbit. Cancer risk was determined by multiplying a $Q1^* = 3.32 \times 10^{-2} \text{ mg/kg/day}^{-1}$ by the handler's combined dermal and inhalation exposures; dermal and inhalation exposures were assumed to be 100%. Calculation inputs and results of this assessment are presented in Table 5.1. Short-term inhalation MOEs range from 35,000,000 to 430,000,000. These risks do not exceed HED's LOC. Cancer risks estimated to be in the 10⁻⁸ range also do not exceed HED's LOC.

Table 5.1. Short-Term Exposure and Risk Estimates (MOE) for Homeowner Lawn/Garden Application with Pyraflufen-Ethyl.

Exposure Scenario	Crop or Target	App Rate (lb ai/A) ¹	Acres Treated Daily ²	Dermal Unit Exposure (ug/lb ai)	Inhalation Unit Exposure (ug/lb ai) ³	Dose Baseline Dermal	Dose Baseline Inhalation ⁴	MOE Baseline Inhalation	Total LADD (mg/kg/day)	Cancer Risk
Mixer/Loader/Applicator										
Mixing/Loading and Spot application of Liquid Formulation with Low Pressure Hand Sprayer	Cool Season Grasses, Warm Season Grasses	0.004	0.023	100	30	0.00015	0.000000046	430,000,000	6.0E-07	2.0E-08
Mixing/Loading and Broadcast Application of liquid formulation with (Hose-End Sprayer)	Cool Season Grasses, Warm Season Grasses	0.004	0.5	11	17	0.00037	0.000000057	35,000,000	1.4E-06	4.7E-08

¹ Application rate is based on maximum values found in proposed label: ET (2.5%)(EPA Reg. No. 71711-7) and ET (2%)(EPA Reg. No. 71711-25).

² Area treated is based on the area that can be reasonably treated in a single day based on the application method (standard EPA/OPP/HED values – Policy 12).

³ Inhalation unit exposure values represent no respirator.

⁴ Daily Dose (mg/kg/day) = (Unit Exposure x Application rate x Area treated) / 60 kg.

⁵ Short-Term MOE = NOAEL (20 mg/kg/day) / Daily Dose. The LOC is 100.

⁶ LADD = (Dermal Dose + Inhalation Dose) x average days of exposure (2 days / 365 days) * (50 years / 70 years)

⁷ Cancer Risk Estimates = LADD * Q1*, where Q1* = 3.32E-2 (mg/kg/day)

5.2 Non-occupational (Postapplication) Exposure from Treated Lawns

Toxicity endpoints were chosen by HED for short- and intermediate-term inhalation and oral exposures. Postapplication inhalation exposure is considered to be negligible. However, non-dietary, incidental ingestion of residues from treated turfgrass and contaminated soil are possible for children (hand-to-mouth, object-to-mouth and soil ingestion). While the NOAEL (20 mg/kg/day) is the same for both short- and intermediate-term oral toxicity, the standard assumptions (input values) for intermediate-term exposure are less conservative than those for short-term (e.g., short-term hand-to-mouth events = 20/hr; intermediate-term= 9.5/hr). Therefore, only short-term exposure/risk is assessed as a worst-case for all children's postapplication scenarios. Intermediate-term risk is expected to be lower than that for short-term. Postapplication exposure assessments are summarized in Tables 5.2a, 5.2b, 5.2c and 5.2e. All MOEs for each scenario are above 100, and therefore, are not of concern.

Postapplication dermal exposure is only estimated for adults for use in estimating adult cancer risk. Intermediate-term standard assumptions (input values for transfer coefficients), are used instead of the more conservative short-term assumptions for cancer assessments, because the effect is determined for a life-time of exposure (50 years).

The residential exposure estimates for adult dermal and three children's incidental oral scenarios are assessed for the day of application (day "0") because it is assumed that residential contact with the lawn can occur immediately after application. Chronic exposure is not expected (i.e., these activities are not expected to occur continuously for more than 6 months).

Adult cancer risk from dermal contact with treated lawn (summarized in Table 5.2e) is less than the target risk of 3.0 X E-6, and therefore, does not exceed HED's LOC. Adult golfer cancer risk from dermal contact with treated turf (also summarized in Table 5.2e) does not exceed HED's LOC

Table 5.2a Oral Hand-to-Mouth Exposure and Risk for Children From Treated Lawns.									
Application Rate (AR) (lb ai/A)	Fraction of ai Available (F)	Turf Transferable Residue (TTR) (ug/cm ²)	Exposure Time (hrs/day)	Extraction by Saliva (EX)	Hand Surface Area (SA) (cm ² /event)	Frequency (FQ) (events/hr)	Body Weight (kg)	Daily Dose ⁴ (mg/kg/day)	Short Term MOE
0.004	0.05	0.0022	2	0.5	20	20	15	5.98E-05	330,000
Table 5.2b. Exposure and Risk for Children from Object-to-Mouth (Turfgrass) from Treated Lawns²									
Application Rate (AR) lb ai/A	Fraction of ai available (F)	Grass Residue (GR) (ug/cm ²)	Mouthing Rate (IgR) (cm ² /day)	Body Weight (kg)	Daily Dose ⁴ (mg/kg/day)	Short Term MOE			
0.004	0.2	0.0090	25	15	1.50E-05	1,300,000			
Table 5.2c. Exposure and Risk for Children from Ingestion of Soil from Treated Lawns³									
Application Rate (AR) (lb ai/A)	Fraction of ai Available (F)	Soil Residue (SR) (ug/g)	Ingestion Rate (IgR) (g/day)	Body Weight (kg)	Daily Dose ⁴ (mg/kg/day)	Short Term MOE			
0.004	1	0.030	100	15	2.00E-07	100,000,000			
Table 5.2d. Total Short Term MOE⁵									
270,000									
Table 5.2e. Adult Residential Post Application Exposure and Cancer Risk from Dermal Contact with Treated Lawns.									

	Application Rate (lb ai/A)	Fraction of ai Available	Turf Transferrable Residue (ug/cm)	Exposure Time (hrs/day)	Transfer Coefficient (cm ² /hr)	Body Weight (kg)	Daily Dose ⁴ (mg/kg/d)	LADD ⁶	Cancer Risk ⁷
Residential Contact with Treated Turf	0.005	0.05	0.0028	2	7300	70	0.00058	2.29E-05	7.60E-07
Adult Golfer	0.005	0.05	0.0028	4	500	70	8.01E-05	3.13E-06	1.04E-07

1. Potential Dose Rate (PDR) on Day '0' (mg/kg/day)=TTR*SA*EX*FQ*ET*CF11 (0.001mg/ug) and TTR = AR*F*CF2(4.54E08 ug/lb)*CF3(2.47E-8 acre/cm²)

2. PDR for object to mouth = GR*IgR*CF1 (.001 mg/ug) and GR = AR*F*CF2 (4.54E8 ug/lb)*CF3 (2.47E-8 acre/cm²)

3. PDR for incidental ingestion of soil = SR*IgR*CF1 (1E-6 g/ug) and SR =AR*F*CF2(4.54E8 ug/lb)*CF3(2.47E-8 acre/cm²)*CF4(0.67 cm³/g soil)

4. Daily Dose = unit exposure*Application Rate*Area treated/body weight

5. Total MOE=[1/(Oral Hand-to-Mouth Dose+Object-to-mouth Dose+Ingestion of Soil Dose)]*NOAEL (20 mg/kg/day)

6. LADD= (Inhalation Dose)*average days of exposure (1)/year x 50 years of expected exposure/(365 days/year x 70 year lifetime)

7. Cancer Risk = LADDxQ1*; where Q1*=3.32E-2 (mg/kg/day)

6.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

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

6.1 Acute Aggregate Risk

No adverse effect attributable to a single exposure (dose) was observed in oral toxicity studies, including the developmental toxicity studies in rats and rabbits. Therefore, an acute reference dose was not established and an acute aggregate risk assessment was not conducted.

6.2 Short- and Intermediate-Term Aggregate Risk

The short-term aggregate risk assessment estimates risks likely to result from 1- to 30-day exposure to pyraflufen-ethyl residues from food, drinking water, and residential pesticide uses. High-end estimates of residential exposure are used in the short-term assessment, while average values are used for food and drinking water exposure (i.e., chronic exposures).

The same endpoints were identified for short-term incidental oral and inhalation risk assessment. Therefore, this assessment will combine dietary/incidental oral exposure with inhalation exposure.

Short-term aggregate risk is based on residential handler exposure, children's incidental oral exposure (from residential postapplication treatment) and dietary exposure (food and drinking water). The anticipated exposure level for children, 1-2 years old (the highest exposed population) is below HED's LOC, with an MOE of 49,000.

An intermediate-term aggregate risk assessment was not conducted for adults because exposure duration is expected to be short-term only. In addition, an intermediate-term aggregate risk assessment was not conducted for children (postapplication exposure) because standard assumptions (input values) for intermediate-term exposure are less conservative than those for short-term exposure.

Estimated aggregate (food + water + residential) exposure to adults and children from pyraflufen-ethyl residues is below HED's LOC.

Population	Short- or Intermediate-Term Scenario					
	NOAEL Mg/kg/day	LOC ¹	Max Allowable Exposure ² mg/kg/day	Average Food & Water Exposure mg/kg/day	Residential Exposure ³ mg/kg/day	Aggregate MOE (food and residential) ⁴
Adult Male	20	100	0.2	0.000083	0.00000057	240,000
Adult Female	20	100	0.2	0.000083	0.00000057	240,000
Children, 1-2 years old	20	100	0.2	0.000333	0.000075	49,000

¹ Interspecies variability = 10x, Intraspecies variability = 10x, FQPA Factor = 1x

² Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC

³ Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Dermal Exposure is not a concern since no effects were observed at the Limit Dose in a 28-day dermal study.

⁴ Aggregate MOE = [NOAEL/(Avg Food & Water Exposure + Residential Exposure)]

6.3 Chronic Aggregate Risk

Chronic exposure from the residential pathway is not anticipated based on the current/proposed use pattern. The chronic aggregate risk (food and drinking water) is below HED's LOC (i.e., <100% cPAD for the general U.S. population and all population subgroups). Using the DEEM-FCID software, dietary exposure is estimated at 0.000083 mg/kg/day for the general U.S. population (<1% of the cPAD) and 0.000333 mg/kg/day (<1% of the cPAD) for children one - two years old, the population subgroup with the highest estimated chronic dietary exposure to pyraflufen-ethyl. See Section 4.2.2 for details.

6.4 Aggregate Cancer Risk

The aggregate cancer risk assessment for the general U.S. population takes into account exposure estimates from dietary consumption of pyraflufen-ethyl from food, residential and drinking water sources. Exposures from residential uses are based on the lifetime average daily dose and assume an exposure period of 5 days per year and 50 years of exposure in a lifetime (70 years). Average food+water source dietary exposure was used. Estimated cancer risk for the general U.S. population includes infants and children; therefore, in accordance with HED Policy, a children's cancer risk estimate was not reported separately.

HED's LOC is for risk estimates that exceed 10^{-6} . The range that HED generally accepts as "negligible risk" may be as great as 3×10^{-6} or greater. The aggregate cancer risk estimate for pyraflufen-ethyl is 2.9×10^{-6} . Therefore, aggregate cancer risk estimate from pyraflufen-ethyl residues in food and drinking water are below HED's LOC for the general U.S. population.

Population	Q*	Negligible Risk Level	Chronic Food & Water Exposure mg/kg/day	Residential Exposure (LADD) mg/kg/day	Aggregate Cancer Risk (food, water and residential) ¹
U.S. Pop	0.0332	3×10^{-6}	0.000083	4.5×10^{-6}	2.9×10^{-6}

¹ Aggregate $MOE_{Cancer} = Q^* \times [Chronic\ Food\ \&\ Water\ Exposure + Residential\ Exposure\ (Lifetime\ Average\ Daily\ Dose)]$.

7.0 CUMULATIVE RISK

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 for pyraflufen-ethyl and any other substances, and pyraflufen-ethyl does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA assumed that pyraflufen-ethyl does not have 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 OPP 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/>.

8.0 OCCUPATIONAL EXPOSURE AND RISK

Pyraflufen-ethyl may be applied to established ornamental turf lawns (including residential, industrial and institutional), parks, cemeteries, athletic fields, golf courses (including fairways, aprons, tees, and roughs), and similar turf areas to control broadleaf weeds. Pyraflufen-ethyl may be applied to cool season grasses (bluegrass, fescue, and ryegrass) and warm season grasses (Bahia grass, common Bermuda grass, centipede grass, St. Augustine grass, and zoysia grass) at a rate of 0.005 lb ai per acre using a pressure sprayer, hose end applicator, groundboom or similar method. Up to three applications may be made per year at a maximum seasonal application rate of 0.0188 lb ai per acre with ET 2.0%, and one application may be made per year at a maximum seasonal application rate of 0.009 lb ai per acre with ET 2.5%.

8.1 Occupational Handler

There is a potential for exposure to pyraflufen-ethyl during mixing, loading and application activities. An exposure/risk assessment using applicable endpoints selected by HED was performed. Handler's exposure and risk were estimated for the following scenarios:

- Mixing and loading liquid formulation
- Mixing and loading for lawn care operator handgun sprayer
- Mixing and loading to support groundboom application
- Applying with a Hand Gun

- Applying with a groundboom
- Mixing/Loading/Applying with low pressure handwand sprayer
- Mixing/Loading/Applying with a handgun sprayer

Appendix A.3 provides a summary of exposures and non-cancer and cancer risks to occupational pesticide handlers.

A MOE of 100 is adequate to protect occupational pesticide handlers from short-term and intermediate-term exposures to pyraflufen-ethyl. The proposed use patterns do not exceed HED's LOC for non-cancer risks. Intermediate-term exposures are not expected. However, the intermediate-term inhalation NOAEL is also 20 mg ai/kg bw/day. Therefore, the estimates of short-term risk are adequate to describe the risks from intermediate-term exposures should they occur.

Cancer risk estimates for workers of greater than 1.0×10^{-4} are of concern to HED. When cancer risk estimates to workers are less than 1.0×10^{-4} , but greater than 1.0×10^{-6} at baseline protection, additional mitigation is assessed that would result in a cancer risk estimate more closely approaching 1.0×10^{-6} (i.e., additional PPE and clothing or engineering controls). In Appendix A.3, it can be seen that only the estimated cancer risk for workers in baseline clothing, engaged in open mixing/loading liquids to support aerial application causes concern to HED (i.e., the risk is greater than 1.0×10^{-4}). With the addition of gloves, this activity results in an estimated cancer risk that does not cause HED concern.

8.2 Occupational Postapplication

Dermal toxicity endpoints for postapplication pyraflufen-ethyl exposure were not identified by the Hazard Assessment Review Committee (HIARC). Inhalation exposure is considered negligible for postapplication activities with treated sites. Pyraflufen-ethyl does not pose a dermal hazard; however, an occupational postapplication assessment for cancer risk was conducted for golf course maintenance and sod farm workers. The results indicate that all cancer risks for post-application exposure for golf course maintenance workers were not of concern to the Agency. Results of the assessment are summarized in Table 8.2.

Scenario	TTR (ug/cm ²) ^a	Transfer Coefficient (cm ² /hr)	Exposure Time (ET) (hrs/day)	Daily Dose ^b	LADD ^c	Cancer Risk ^d
Golf course turf, recreational and home lawn maintenance (mowing, aerating, scouting, fertilizing, etc.)	0.00025	3,400	8	0.00011	4.66E-06	1.55E-07
Sod Transplanting, hand weeding, hand harvesting	0.00025	6,800	8	0.00023	9.32E-06	3.09E-07

a. Default TTR value based on standard assumption of 5% of application rate (0.005x.05) for fraction of ai initially available from the application rate

b. Daily Dose: $[(TTR \text{ (ug/cm}^2) \times TC \text{ (cm}^2/\text{hr)} \times 100\% \text{ dermal absorption} \times \text{mg}/1000 \text{ ug} \times \text{ET (hrs/day)})] / [BW \text{ (60kg)}]$

c. LADD (Lifetime Average Daily Dose) = $(\text{daily dose}) \times (100\% \text{ absorption}) \times (30 \text{ days}/365 \text{ days}) \times (35 \text{ years}/70 \text{ years})$

d. Cancer Risk = $Q1 \times (3.32E-2) \times LADD \text{ (mg/kg/day)}$

8.3 Restricted Entry Interval (REI)

Pyraflufen-ethyl is classified as Acute Toxicity Category III for acute dermal toxicity and for primary eye irritation. It is classified as Toxicity Category IV for acute inhalation toxicity and primary skin irritation. It is not a dermal sensitizer. Therefore the interim worker protection standard (WPS) re-entry interval (REI) of 12 hours is adequate to protect agricultural workers from post-application exposures to pyraflufen-ethyl as might result from the proposed new use pattern.

9.0 DATA NEEDS/LABEL RECOMMENDATIONS

9.1 Toxicology

875.1300 Inhalation Exposure

- Since the proposed use pattern will result in repeated inhalation exposure, a 28-day inhalation toxicity study is being required. Pyraflufen-ethyl may qualify for a waiver from the requirement of the 28-day inhalation toxicity study (see SOP 2002.01- HED Standard Operating Procedure: Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies, 08/15/02).

870.6200 Acute and Subchronic Neurotoxicity Studies

- Acute and subchronic neurotoxicity studies are now required under the revised 40 CFR §158.340 guidelines.

Guideline Number: 870.6200
Study Title: Neurotoxicity Screening Battery
Rationale for Requiring the Data
Acute and subchronic neurotoxicity studies with pyraflufen-ethyl were not conducted, pyraflufen-ethyl showed no indication of neurotoxicity in the provided studies and there was no evidence of neurotoxicity in open literature searches, however, the submitted studies did not examine neurotoxicity endpoints. These data are now required under the revised CFR 158.340.
Practical Utility of the Data
How did the Agency make its re-registration decision without this data?
For many chemicals, the amount of toxicity data that is available for pyraflufen-ethyl would be considered to be a complete toxicity database. In fact, the Agency was able to select doses and endpoints for conducting a risk assessment from the available studies. However, the toxicity database for pyraflufen-ethyl does not include any neurotoxicity studies and there is uncertainty of the neurotoxicity potential of pyraflufen-ethyl as none of the submitted studies measured neurotoxicity endpoints.
How will the data be used?
After the review and evaluation of the acute and subchronic neurotoxicity studies, it is possible that Agency could choose a dose and endpoint from either the acute or

subchronic neurotoxicity study for the deriving the acute RfD.

How could the data impact the Agency's future decision-making?

If a dose can be selected for the acute RfD, then the pyraflufen-ethyl acute dietary risk assessment would need to be conducted. At present there were no effects observed in oral toxicity studies including developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure). The risk would then be identified for the acute RfD.

870.7800 Immunotoxicity Study

- An immunotoxicity study in rats and/or mice is now required under the revised 40 CFR §158.340 guidelines.

<p>Guideline Number: 870.7800 Study Title: Immunotoxicity</p>
<p>Rationale for Requiring the Data</p>
<p>This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).</p> <p>The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.</p>
<p>Practical Utility of the Data</p>
<p>How will the data be used?</p> <p>These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).</p> <p>How could the data impact the Agency's future decision-making?</p> <p>If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments</p>

for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

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

9.2 Residue Chemistry

Tolerance Expression – Compliance/Measurement Policy

HED recommends for modification of the tolerance expressions for pyraflufen-ethyl according to the new compliance/measurement policy (*Interim Guidance on Tolerance Expressions*, Steve Knizner, May 27, 2009) as follows:

Note to PM: HED recommends that the tolerance definition entry in 40 CFR 180.585 be revised as follows: (a) **General.** Tolerances are established for residues of the herbicide, pyraflufen-ethyl, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methyl-1H-pyrazol-3-yl)-4-fluorophenoxyacetate and its acid metabolite, E-1, 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methyl-1H-pyrazol-3-yl)-4-fluorophenoxyacetic acid, calculated as the stoichiometric equivalent of pyraflufen-ethyl, in or on the commodity.

Permanent tolerances for livestock commodities and full registration can be granted when the remaining deficiencies as noted below are resolved.

860.1340 Residue Analytical Methods

- If HED determines that metabolite E-9 should also be included in the tolerance definition for livestock commodities, a tolerance enforcement method for the determination of metabolite E-9 in livestock commodities will be required.

860.1360 Multiresidue Methods

- Data are required reflecting recovery of pyraflufen-ethyl and metabolite E-1 through the FDA Protocols C and D with and without the use of Florisil cleanup. **These data requirements remain outstanding.**
- If HED determines that metabolite E-9 should also be included in the tolerance definition for livestock commodities, data will be required reflecting recovery of metabolite E-9 through the FDA multiresidue methods.

860.1480 Meat, Milk, Poultry and Eggs

- An additional cattle feeding study must be conducted to determine residues of E-9 in milk and cattle tissues. The new feeding study should be conducted at 1x, 3x, and 10x the RBDB of 1.70 ppm for dairy cattle, and residues of all three residues of concern (parent, metabolite E-1 and metabolite E-9) should be determined in milk and tissues.
- Although inadequate, the existing feeding study indicates that tolerances should be established for selected livestock commodities. Therefore, time-limited tolerances for livestock commodities will be established using data from the existing study. The time-limited tolerance expression for livestock commodities will include parent and metabolite E-1, expressed in terms of parent.
- Residue data from the available cattle feeding study indicate that the time-limited tolerances should be established at the method LOQ (0.02 ppm) for the combined residues of pyraflufen-ethyl and metabolite E-1 in milk and meat byproducts from cattle, goats, horses and sheep. Tolerances for other livestock commodities are not required at the present time.

860.1650 Submittal of Analytical Reference Standards

- If HED determines that metabolite E-9 should also be included in the tolerance definition for livestock commodities, the petitioner will need to send an analytical reference standard for metabolite E-9 to the National Pesticide Standards Repository.

REFERENCES:

Pyraflufen-ethyl: Occupational and Residential Exposure Assessment for proposed non food uses of pyraflufen-ethyl on cool season grasses (bluegrass, fescue, and ryegrass) and warm season grasses (Bahia grass, common Bermud agrass, centipede grass, St. Augustin egrass, and zoysia grass), K .Rury, 01/14/2010, DP#361213.

Tier I Drinking Water Assessment, for the Registration of the New Non-Food Uses of Pyraflufen-ethyl on Established Ornamental Turf Lawns (Residential, Industrial, and Institutional), Parks, Cemeteries, Athletic Fields, Golf Courses (Fairways, Aprons, Tees, and Roughs), Sod Farms, and Similar Turf Areas; J. Meléndez, 08/07/2009, DP#s 361815, 361816.

Pyraflufen-ethyl: Human Health Risk Assessment for Pyraflufen-ethyl: Proposed New Use on Pasture and Rangeland Grasses (PP#7F7190) and Amendment to Allow Early Season Postemergence Broadcast Uses to Corn (excluding sweet corn), Soybeans, and Wheat and Proposed Increased Tolerances on Soybean Forage and Hay (PP#1F6248) M. Ottley, 04/17/2008, DP# 339360.

Pyraflufen-ethyl. Chronic Aggregate (Food and Drinking Water) Dietary Exposure and Risk Assessments for a Section 3 Registration Action to Allow Early Season Postemergence Uses on Corn (Excluding Sweet Corn), Soybeans, and Wheat; A. Acierto, 03/25/2008, DP# 347500.

PP#1F06248 human health risk assessment for pyraflufen-ethyl on cotton and potatoes, DP# 286618, M. Rust, 11/06/2002.

APPENDIX

Appendix A1 Nomenclature

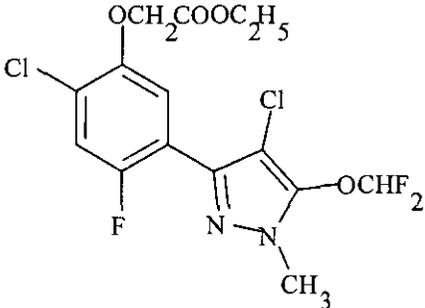
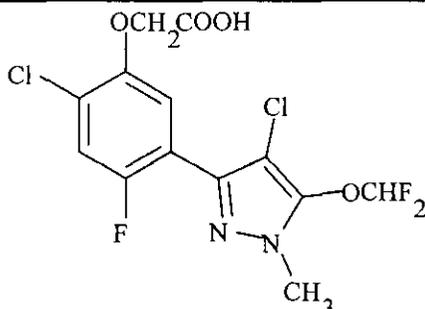
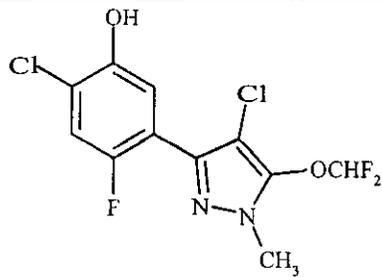
Table A1. Chemical Structures of Pyraflufen-Ethyl and its Metabolites.	
Chemical structure	
Common name	Pyraflufen-ethyl
PC Code	030090
Company experimental name	ET-751
IUPAC name	Ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetate
CAS name	Ethyl [2-chloro-5-[4-chloro-5-(difluoromethoxy)-1-methyl-1H-pyrazol-3-yl]-4-fluorophenoxy]acetate
CAS registry number	129630-19-9
Chemical structure	
Common name	Pyraflufen
PC Code	030091
Company experimental name	Metabolite E-1; Pyraflufen-ethyl plant and livestock metabolite of concern
Chemical name	2-Chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetic acid
CAS name	[2-chloro-5-[4-chloro-5-(difluoromethoxy)-1-methyl-1H-pyrazol-3-yl]-4-fluorophenoxy]acetic acid
CAS registry number	129630-17-7
Chemical structure	
Company experimental name	Metabolite E-2; drinking water metabolite of concern
Chemical name	2-Chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenol

Table A1. Chemical Structures of Pyraflufen-Ethyl and its Metabolites.	
Chemical structure	
Company experimental name	Metabolite E-3; drinking water metabolite of concern
Chemical name	4-Chloro-3-(4-chloro-2-fluoro-5-methoxyphenyl)-5-difluoromethoxy-1-methylpyrazole
Chemical structure	
Company experimental name	Metabolite E-9; Pyraflufen-ethyl livestock metabolite of concern
Chemical name	2-Chloro-5-(4-chloro-5-difluoromethoxy-1H-pyrazol-3-yl)-4-fluorophenoxyacetic acid

Appendix A2 Toxicity Profiles

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100 81-1	Acute Oral	45327615	LD ₅₀ > 5000 mg/kg	IV
870.1200 81-2	Acute Dermal	45327613	LD ₅₀ > 2000 mg/kg	III
870.1300 81-3	Acute Inhalation	45282821	LC ₅₀ > 5.03 mg/L	IV
870.2400 81-4	Primary Eye Irritation	45327614	moderate irritation	III
870.2500 81-5	Primary Skin Irritation	45282823	no irritation	IV
870.2600 81-6	Dermal Sensitization	45282824	non-sensitizing	N/A

Guideline Number and Study Type	Results
870.3100 13-Week Feeding in Rats; 1994; Dose Levels: 0, 200, 1000, 5000 or 15,000 ppm (representing 0, 17.8, 85.6, 455.5 and 1489.4 mg/kg/day (M); 0, 19.4, 95.4, 499.0 and 1502.9 mg/kg/day (F); 10 rats/sex/group	NOAEL = 5000 ppm (456-499 mg/kg/day). LOAEL = 15,000 ppm (1489-1503 mg/kg/day) based on clinical signs, death, effects on erythrocytes, changes in clinical chemicals for liver function and splenomegaly
870.3150 13-Week Feeding Study in Dogs-capsule; 1996; Dose Levels: 0, 40, 200 or 1000 mg/kg/day 4 dogs/sex/group	NOAEL = 1000 mg/kg/day. LOAEL not established. No effects observed.
870.3200 28-Day Dermal Toxicity in Rats; (2000); Dose Levels: 0, 100, 300 or 1000 mg/kg/day; 10 rats/sex/group; Application: 6-7 hr/day, 7 days/week for 29 days	NOAEL = 1000 mg/kg/day. LOAEL not established. No effects observed.
870.3700a Developmental Toxicity Study in Rats; 1995; Dose Levels: 0, 100, 300 or 1000 mg/kg/day; 22 females/sex/group	Maternal NOAEL > 1000 mg/kg/day. Maternal LOAEL not determined; no effects observed. Developmental NOAEL > 1000 mg/kg/day. Developmental LOAEL not determined; no effects observed.

<p>870.3700b Developmental Toxicity in Rabbits; 1996; Dose Levels: 0, 20, 60 or 150 mg/kg/day; 15 females/group</p>	<p>Maternal NOAEL = 20 mg/kg/day. Maternal LOAEL = 60 mg/kg/day based on mortality.</p> <p>Developmental = 60 mg/kg/day. Developmental LOAEL = 150 mg/kg/day based on increased incidence of abortion.</p>
<p>870.3800 2-Generation Reproduction Study in Rats; 1996; Dose Levels: 0, 100, 1000 or 10, 000 ppm (representing 0, 6.84, 70.8 and 721 mg/kg/day (F₀[M]); 0, 7.78, 80.1 and 813 mg/kg/day (F₀[F]); 0, 8.10, 82.3 and 844 mg/kg/day (F₁[M]); 0, 9.06, 91.2 and 901 mg/kg/day (F₁[F]) 24 rats/sex/group</p>	<p>Parental NOAEL = 1000 ppm (70.8-82.3 mg/kg/day [M]; 80.1-91.2 [F]). Parental LOAEL = 10,000 ppm (721-844 and 813-901 mg/kg/day) based on decreased bwt and bwt gains of F₀ and F₁(M) and F₁(F), gross and microscopic liver lesions of (M) and (F)-both generations.</p> <p>Reproductive NOAEL > 10,000 ppm (721-844 and 813-901 mg/kg/day). Reproductive LOAEL not determined. No effects observed.</p> <p>Offspring NOAEL = 1000 ppm (70.8-82.3 mg/kg/day [M]; 80.1-91.2 [F]). Offspring LOAEL = 10, 000 ppm (721-844 and 813-901 mg/kg/day) based on decreased bwt and bwt gains of the F₁ and F₂ pups.</p>
<p>870.4100a/870.4200 2-year Feeding Study/Carcinogenicity in Rats; 1996; Dose Levels: 0, 80, 400, 2000 or 10,000 ppm (representing 0, 3.4, 17.2, 86.7 and 468.1 mg/kg/day (M); 0, 4.4, 21.8, 11.5 and 578.5 mg/kg/day (F) 70 rats/sex/group</p>	<p>NOAEL = 2000 ppm (86.7 mg/kg/day (M); 111.5 mg/kg/day (F). LOAEL = 10,000 ppm (468.1 mg/kg/day(M); 578.5 mg/kg/day (F) based on decreased bodyweight (bwt) and bodyweight gain in males and microcytic anemia, liver lesions and kidney toxicity (both sexes); possible increase pheochromocytomas in females</p>
<p>870.4100a/870.4300 78-Week Carcinogenicity Study in Mice; 1996; Dose Levels: 0, 200, 1000 or 5000 ppm (representing 0, 20.99, 109.7 and 546.8 mg/kg/day (M); 0, 19.58, 98.3, and 523.7 mg/kg/day (F) 60 mice/sex/group</p>	<p>NOAEL = 200 ppm (20.99 mg/kg/day (M); 19.58 mg/kg/day (F). LOAEL = 1000 ppm (109.7 mg/kg/day (M); 98.3 mg/kg/day (F) based on liver toxicity, hepatocellular tumors at 5,000 ppm; possibly hemangioma/ hemangioasarcoma.</p>
<p>870.4100b 52-Week Feeding in Dogs-capsule; 1996; Dose Levels: 0, 40, 200 or 1000 mg/kg/day 4 dogs/sex/group</p>	<p>NOAEL > 1000 mg/kg/day. LOAEL not determined; no effects observed.</p>

Appendix A3 Additional Exposure Assessment Data

Table A3 Exposure and Risk Estimates (MOE) for Occupational Application of Pyraflufen-Ethyl.														
Exposure Scenario	Crop or Target	App Rate (lb ai/A) ¹	Acres Treated Daily ²	Dermal Unit Exposure (mg/lb ai)	PPE-G Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (ug/lb ai) ³	Dose Baseline Dermal ⁴	PPE Dermal Dose ⁴	Dose Baseline Inhalation ⁴	MOE Baseline Inhalation	LADD ⁶ (mg/kg/day)	LADD PPE ⁷ (mg/kg/day)	Baseline Cancer Risk ⁸	PPE Cancer Risk ⁹
Mixer/Loader														
Mixing and Loading Liquid Formulation (PHED)	Cool Season Grasses, Warm Season Grasses	0.005	10	2.9	0.023	1.2	0.0024	0.000019	0.0000010	20,000,000	9.94E-05	8.29E-07	3.30E-06	2.75E-08
Mixing and Loading a Lawn Care Operator Handgun (PHED)		0.005	100	2.9	0.023	1.2	0.024	0.00019	0.000010	2,000,000	9.94E-04	8.29E-06	3.30E-05	2.75E-07
Mixing and Loading to Support Groundboom Application (PHED)		0.005	80	2.9	0.023	1.2	0.019	0.00015	0.0000080	2,500,000	7.95E-04	6.63E-06	2.64E-05	2.20E-07
Applicator														
Applying with Hand Gun (PHED)	Cool Season Grasses, Warm Season Grasses	0.005	5	N/A	0.34	1.4	N/A	0.00014	0.00000058	34,000,000	N/A	5.85E-06	N/A	1.94E-07
Applying with Groundboom - Open Cab (PHED)		0.005	80	0.014	0.014	0.74	0.000093	9.33E-05	0.0000049	4,100,000	4.04E-06	4.04E-06	1.34E-07	1.34E-07
Mixer/Loader/Applicator														
Mixing/Loading and Application of Liquid Formulation with Low Pressure Hand Sprayer (ORETF)	Cool Season Grasses, Warm Season Grasses	0.005	5	0.45	0.245	0.15	0.00019	0.00010	0.000000063	320,000,000	1.88E-04	4.20E-06	6.23E-06	1.39E-07

Table A3 Exposure and Risk Estimates (MOE) for Occupational Application of Pyraflufen-Ethyl.

Exposure Scenario	Crop or Target	App Rate (lb ai/A) ¹	Acres Treated Daily ²	Dermal Unit Exposure (mg/lb ai)	PPE-G Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (ug/lb ai) ³	Dose Baseline Dermal ⁴	PPE Dermal Dose ⁴	Dose Baseline Inhalation ⁴	MOE Baseline Inhalation	LADD ⁶ (mg/kg/day)	LADD PPE ⁷ (mg/kg/day)	Baseline Cancer Risk ⁸	PPE Cancer Risk ⁹
Mixer/Loader														
Mixing/Loading and Application of liquid formulation Hose End Sprayer (PHED)		0.005	5	N/A	0.34	9.5	0.00014	0.00014	0.0000040	5,100,000	1.42E-04	6.00E-06	4.71E-06	1.99E-07

4 Daily Dose (mg/kg/day) = (Unit Exposure x Application rate x Area treated) / 60 kg.
 5 Short-Term MOE = NOAEL (20 mg/kg/day) / Daily Dose. The LOC is 100.
 6 LADD= (Dermal Dose+Inhalation Dose) x average days of exposure (30/365) x (35 years/70 years)
 7 LADD =(Dermal PPE Dose+Inhalation Dose) x average days of exposure (30/365) x (35 years/70 years)
 8 Cancer Risk Estimates = LADD x Q1*, where Q1*=3.32E-2 (mg/kg/day)
 9 Cancer Risk PPE Estimates = LADD PPE x Q1*, where Q1*=3.32E-2 (mg/kg/day)



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R181067

Chemical Name: Pyraflufen-ethyl

PC Code: 030090

HED File Code: 14000 Risk Reviews

Memo Date: 2/24/2010

File ID: 00000000

Accession #: 000-00-0134

HED Records Reference Center

2/26/2010