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

5

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 31-JUL-2003

SUBJECT: PP#: 0F06164. **Flufenpyr-Ethyl in/on Field Corn, Soybeans and Sugarcane.** Health Effects Division (HED) Risk Assessment. PC Code: 108853. DP Barcode: D270403. Case: 293057. Submission: S582174.

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THRU: Dana Vogel, Acting Branch Senior Scientist
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TO: Joanne Miller/Dianne Morgan, PM Team 23
Herbicide Branch/Registration Division (RD) (7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of the new herbicide flufenpyr-ethyl, ethyl [2-chloro-4-fluoro-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetate], on field corn, soybeans and sugarcane.

A summary of the findings and an assessment of human health risk resulting from the proposed tolerances for flufenpyr-ethyl is provided in this document. The risk assessment and dietary exposure assessment were provided by Jennifer Tyler (RAB1), the residue chemistry data review by George Kramer (RAB1), the hazard characterization by Guruva Reddy (RAB1), the occupational/residential exposure assessment by Mark Dow (RAB1), and the drinking water assessment by Thuy Nguyen of the Environmental Fate and Effects Division (EFED).

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Recommendation for Tolerances

Provided revised Sections B and F with the modifications specified in Section 8.0 of this risk assessment are submitted and a successful Agency petition method validation (PMV) of the analytical enforcement method is reported, the residue chemistry and toxicological databases support the establishment of *conditional registration* and permanent tolerances for the following:

residues of the herbicide flufenpyr-ethyl, acetic acid, [2-chloro-4-fluoro-5-[5-methyl-6-oxo-4-(trifluoromethyl)-1(6H)-pyridazinyl]phenoxy]-ethyl ester, in/on:

Corn, field, grain	0.01 ppm
Soybean, seed	0.01 ppm
Sugarcane, cane	0.01 ppm

the combined residues of the herbicide flufenpyr-ethyl, acetic acid, [2-chloro-4-fluoro-5-[5-methyl-6-oxo-4-(trifluoromethyl)-1(6H)-pyridazinyl]phenoxy]-ethyl ester, and its metabolite, 2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetic acid, free and conjugated in/on:

Corn, field, forage	0.05 ppm
Corn, field, stover	0.05 ppm

HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following data:

- Additional storage stability data for the metabolite S-3153 acid-4-OH in field corn forage and stover.
- Confirmatory method for residues of flufenpyr-ethyl in/on corn, soybean, and sugarcane raw agricultural commodities (RACs).
- If the confirmatory method does not utilize mass-selective detector (MSD), then an interference study will also be required.

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1.0 EXECUTIVE SUMMARY

Flufenpyr-ethyl is a new contact pyridazinone herbicide that controls various broadleaf weeds through inhibition of protophyrinogen oxidase in the chlorophyll biosynthetic pathway, leading to phytotoxic buildup of intermediates and disruption of the cell membrane.

Valent USA Corporation has submitted a petition for the registration of flufenpyr-ethyl formulated as S-3153 Water-Dispersible Granule (WDG) Herbicide (57.5% flufenpyr-ethyl; EPA Reg. No. 59639-XXX) for use on field corn, soybeans and sugarcane; and S-3153/Atrazine WDG Herbicide (1.9% flufenpyr-ethyl and 75% atrazine; EPA Reg. No. 59639-XXX) for use on field corn and sugarcane. In conjunction with the current petition, Valent has requested the establishment of permanent tolerances for residues of the herbicide flufenpyr-ethyl in/on field corn, soybean and sugarcane commodities, and its metabolite S-3153 acid-4-OH, [2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetic acid), in/on field corn forage and stover.

There are currently no established tolerances for residues of flufenpyr-ethyl in/on any plant or livestock commodity. In addition, there are no registered or proposed uses of flufenpyr-ethyl that would result in residential exposure.

Hazard Assessment: Flufenpyr-ethyl has low acute toxicity (Toxicity Category IV) by oral, dermal, and inhalation routes of exposure. It is not an eye irritant (Toxicity Category IV) and not a dermal sensitizer. The mouse is the most sensitive species for flufenpyr-ethyl. The liver was identified as a target organ in the sub-chronic, and carcinogenicity studies in mice. The kidney was also identified as a target organ. However, the kidney lesions are considered equivocal since the effects did not increase in severity, lacked dose-response, and the lesions were not statistically significantly different when compared to controls. Further, the kidney lesions were not repeatable in two 1-generation studies up to 162 and 170 mg/kg/day in males and females, respectively. The mouse carcinogenicity study has the lowest no-observed-adverse-effect-level (NOAEL; 40 mg/kg/day) in the database, based on liver toxicity and mild anemia observed at 402 mg/kg/day [lowest-observed-adverse-effect-level (LOAEL)]. Clear signs of toxicity were only seen in mouse oncogenicity and sub-chronic studies, in which hepatocyte vacuolation and liver cell necrosis were seen at 400 and 907 mg/kg/day, respectively. All other toxicity signs such as urinary incontinence and abdominal staining may be due to increased water consumption resulting in mild diuresis. In addition, the animals in these studies were dosed at the Limit Dose, resulting in an overloading of the system. Flufenpyr-ethyl is not a developmental toxicant up to the Limit Dose in both rat and rabbit developmental toxicity studies. It is also not a reproductive toxicant in the rat the up to the Limit Dose. Flufenpyr-ethyl is classified as "not likely" to be carcinogenic based on lack of evidence of carcinogenicity in mice and rats. Flufenpyr-ethyl is not mutagenic.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision: The HED Hazard Identification Assessment Review Committee (HIARC) met on 4/29/03 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants

and children from exposure to flufenpyr-ethyl according to the February 2002 OPP 10X guidance document. The special FQPA Safety Factor (SF) was reduced to 1x based on toxicological considerations by HIARC (6/8/03; TXR # 0051946), the conservative residue assumptions used in the chronic dietary exposure risk assessment, the completeness of the residue chemistry and environmental fate databases and the lack of the potential for residential exposures (evaluated by the risk assessment team).

Risk assessments were conducted for the following specific exposure scenarios listed below. The chronic reference dose (cRfD) was calculated by dividing the NOAEL by 100 (10X for interspecies extrapolation and 10X for intraspecies variation). Since the special FQPA SF has been reduced to 1X, the chronic population adjusted dose (cPAD) is equal to the cRfD. Since an oral study was selected for all durations of inhalation exposure, a 100% inhalation absorption factor was used in the route-to-route extrapolation. The level of concern for occupational inhalation exposures are for margins of exposure (MOEs) <100.

Exposure Scenario	Dose	Endpoint	Study/Effect
Chronic Dietary	NOAEL = 40 mg/kg/day	cRfD and cPAD = 0.4 mg/kg/day	Carcinogenicity Study in Mice/ Liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males observed at a LOAEL of 401.8 mg/kg/day.
Short-Term Inhalation Intermediate-Term Inhalation Long-Term Inhalation	NOAEL = 40 mg/kg/day	Target MOE = 100 (occupational)	Carcinogenicity Study in Mice/ Liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males observed at a LOAEL of 401.8 mg/kg/day.

Dietary Exposure Estimates: An unrefined deterministic, chronic dietary exposure analysis [using tolerance-level residues, 100% crop treated (CT) information, and modified processing factors for all proposed processed commodities based on guideline processing studies] was conducted using the Dietary Exposure Evaluation Model DEEM-Food Commodity Intake Database (DEEM-FCID™; ver. 1.30) program. The chronic dietary exposure estimates are well below HED's level of concern (<100% cPAD) for the general U.S. population and all population subgroups (<1% cPAD).

Drinking Water Exposure Estimates: Per the recommendations of the HED Metabolism Assessment Review Committee (MARC), EFED provided drinking water estimated drinking water environmental concentration (DWECs) for flufenpyr-ethyl and its degradates (S-3153-acid, S-3153-1-OH, and S-3153-1-OCH_3). Although the MARC recommended the S-3153-1-OCH_3-5'-CH_2OH degradate be included in the drinking water assessment as well, at this time, EFED does not have adequate information to model this degradate. Although a major degradate in the aerobic soil metabolism study (maximum 13.9% of applied), S-3153-1-OCH_3-5'-CH_2OH was only found in the top soil layer of one out of three field studies at the analytical method detection limit level. EFED expects the risk of this degradate to the drinking water resources to be negligible compared to that of the parent and the other three degradates. The Tier 1, FQPA Index Reservoir Screening Tool (FIRST) and Screening Concentration in Ground Water (SCI-GROW) models were used to derive the surface and ground water DWECs, respectively. The chronic

(annual average) surface and ground water DWECs (parent and all degradates of concern) are 2.0 ppb and 0.07 ppb, respectively. All DWEC (parent and all degradates of concern) values are less than the lowest chronic drinking water level of comparison (DWLOC) values of 4,000 ppb (specifically for the infants and children population subgroups). Therefore, the DWECs (parent and all degradates of concern) do not exceed HED's level of concern.

Aggregate Exposure Scenarios and Risk Conclusions: Aggregate exposure risk assessments were performed for the following scenario: chronic aggregate exposure (food + drinking water). An acute aggregate risk assessment was not performed because an endpoint of concern attributable to a single oral dose was not selected for any population subgroup (including infants and children). Short- and intermediate-term aggregate risk assessments were not performed because there are no registered or proposed residential non-food uses. A cancer aggregate risk assessment was not performed because flufenpyr-ethyl is not carcinogenic. **The chronic aggregate exposure and risk estimates do not exceed HED's level of concern.**

Occupational Exposure Estimates: Based on the proposed use patterns, short-term (1-30 days) inhalation exposures are expected for commercial and private (i.e., grower operators) applicators. However, as field corn and soybeans are among the proposed uses, there is a possibility for commercial handlers to have intermediate-term exposure (1-6 months) to flufenpyr-ethyl because these crops are planted over large acreages and are geographically widely distributed across the U.S. Because the short-, intermediate-, and long-term inhalation toxicological endpoints identified by HIARC for use in risk assessment are identical (40 mg a.i./kg bw/day from a mouse carcinogenicity study), the short-term inhalation exposure estimates are adequately protective of all durations of exposure.

The application techniques assessed include mixer-loader, aerial and ground-boom open-cab. No chemical-specific data are available with which to assess potential exposure to pesticide handlers (i.e., mixer/loaders and applicators). Therefore, estimates of exposure are based on study data available in the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, 8/98). All MOEs are >100; and, therefore, do not exceed HED's level of concern. HIARC did not identify dermal toxicological endpoints. In view of the estimated inhalation exposures and risks to handlers, HED expects post-application inhalation exposure to be negligible. Therefore, a post-application exposure assessment was not conducted for this action.

Recommendations for Tolerances: Provided revised Sections B and F with the modifications specified in Section 8.0 of this risk assessment are submitted and a successful Agency PMV of the analytical enforcement method is reported, the residue chemistry and toxicological databases support the establishment of *conditional registration* and permanent tolerances for the following:

> residues of the herbicide flufenpyr-ethyl, acetic acid, [2-chloro-4-fluoro-5-[5-methyl-6-oxo-4-(trifluoromethyl)-1(6H)-pyridazinyl]phenoxy]-ethyl ester, in/on: corn, field, grain at 0.01 ppm; soybean, seed at 0.01 ppm; and sugarcane, cane at 0.01 ppm.
>
> the combined residues of the herbicide flufenpyr-ethyl, acetic acid, [2-chloro-4-fluoro-5-[5-methyl-6-oxo-

4-(trifluoromethyl)-1(6H)-pyridazinyl]phenoxy]-ethyl ester, and its metabolite, 2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetic acid, free and conjugated in/on: corn, field, forage at 0.05 ppm and corn, field, stover at 0.05 ppm

HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following data:

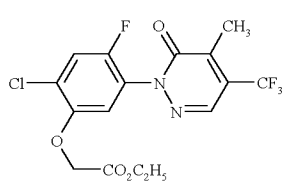
- Additional storage stability data for the metabolite S-3153 acid-4-OH in field corn forage and stover.
- Confirmatory method for residues of flufenpyr-ethyl in/on corn, soybean, and sugarcane RACs.
- If the confirmatory method does not utilize MSD, then an interference study will also be required.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Active Ingredient

Registrant:	Valent USA Corporation	
Common name:	Flufenpyr-ethyl	
Pesticide Type:	Herbicide	
Chemical Class:	Pyridazinone	
Target Pests:	Broadleaf weeds	
Mode of Action:	Inhibition of protophyrinogen oxidase in the chlorophyll biosynthetic pathway, leading to phytotoxic buildup of intermediates and disruption of the cell membrane.	
Formulations:	S-3153 WDG Herbicide	S-3153/Atrazine WDG Herbicide
% a.i.:	57.6%	1.9% flufenpyr-ethyl; 75.0% atrazine
Trade Names:	S-3153 WDG Herbicide	S-3153/Atrazine WDG Herbicide
EPA Reg Nos.:	59639-XXX	59639-XXX
CAS Number:	188490-07-5	
PC Code:	108853	
Chemical name:	ethyl [2-chloro-4-fluoro-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetate	
Empirical Formula:	$C_{14}H_9ClF_4N_2O_4$	
Molecular Weight:	408.74	

2.2 Structural Formula



See Attachment 1 for structures of all pertinent metabolites mentioned in this risk assessment.

2.3 Physical and Chemical Properties

The review of product chemistry data associated with this petition is under the purview of the RD (memo, S. Mathur, 10/29/02, D270192):

Appearance:	Off white powder
Vapor Pressure:	3.76×10^{-7} Pa
Water Solubility:	4.1 ppm
Partition Coefficient (Octanol/Water):	log Po/w = 2.99
Melting Point:	100-101 °C

Note that all property values are given at 20°C unless noted otherwise. Flufenpyr-ethyl is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for flufenpyr-ethyl supports the establishment of permanent tolerances for residues of flufenpyr-ethyl in/on the RACs resulting from the proposed uses.

3.1 Hazard Profile

Flufenpyr-ethyl has low acute toxicity (Toxicity Category IV) by oral, dermal, and inhalation routes of exposure. It is not an eye irritant (Toxicity Category IV) and not a dermal sensitizer. The mouse is the most sensitive species for flufenpyr-ethyl. The liver was identified as a target organ in the sub-chronic, and carcinogenicity studies in mice. The kidney was also identified as a target organ. However, the kidney lesions are considered equivocal since the effects did not increase in severity, lacked dose-response, and the lesions were not statistically significantly different when compared to controls. Further, the kidney lesions were not repeatable in two 1-generation studies up to 162 and 170 mg/kg/day in males and females, respectively. The mouse carcinogenicity study has the lowest NOAEL (40 mg/kg/day) in the database, based on liver toxicity and mild anemia observed at 402 mg/kg/day (LOAEL). Clear signs of toxicity were only seen in mouse oncogenicity and sub-chronic studies, in which hepatocyte vacuolation and liver cell necrosis were seen at 402 and 908 mg/kg/day, respectively. All other toxicity signs such as urinary incontinence and abdominal staining may be due to increased water consumption resulting in mild diuresis. In addition, the animals in these studies were dosed at the Limit Dose, resulting in an overloading of the system. Flufenpyr-ethyl is not a developmental toxicant up to the Limit Dose in both rat and rabbit developmental toxicity studies. It is also not a reproductive toxicant in the rat the up to the Limit Dose. Flufenpyr-ethyl is classified as "not likely' to be carcinogenic based on lack of evidence of carcinogenicity in mice and rats.

Flufenpyr-ethyl has been shown to be negative in *in vitro* bacterial *(salmonella/E.coli)* and mouse lymphoma assays both in the presence and absence of S9 activation. It is not clastogenic in the mouse micronucleus assay.

There is no difference in the metabolic profile of flufenpyr-ethyl attributable to gender or radiolabel position. About 54 - 72% of the administered dose was absorbed and rapidly eliminated in the urine (49 - 72%) and feces (30 - 44%) within 24 to 48 hours. At 7-days post dosing tissue burden was 0.15% and 0.07% in males and females, respectively; and most tissues had less than 0.1 µg eq/g wet tissue. There was no elimination via expired air (< 0.01%). Three major urinary metabolites; S-3153 acid, S-3153 acid-5'-CH_2OH and an unidentified component (UK2) were identified. The S-3153 acid accounted for 52 - 70% of the administered dose. The total unidentified fraction of metabolites represented < 4% of the administered dose. Based on the metabolic profile it was postulated that flufenpyr-ethyl was metabolized primarily via cleavage of the ester linkage to form the major metabolite, S-3153 acid, which accounted for 91 - 96% of the administered dose.

Table 1. Acute Toxicity Profile of Flufenpyr-ethyl Technical Grade Active Ingredient (TGAI).

GDLN	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral	45118902	LD_{50} > 5,000 mg/kg (Limit Test)	IV
870.1200	Acute Dermal	45118906	LD_{50} > 5,000 mg/kg (Limit Test)	IV
870.1300	Acute Inhalation	45152805	LC_{50} > 5.0 mg/L (Limit Test)	IV
870.2400	Primary Eye Irritation	45118909	Minimally irritating, resolved within 24 hrs	IV
870.2500	Primary Skin Irritation	45118909	Non irritating	IV
870.2600	Dermal Sensitization	45118912	Non-sensitizer	N/A

Table 2. Toxicity Profile of Flufenpyr-ethyl Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	45118914 (1997) **Acceptable/guideline** 0, 600, 2,000, 6,000 and 20,000 ppm (Limit Dose) M: 0, 39, 134, 414 and 1434 mg/kg/day F: 0, 47, 154, 467, and 1591 mg/kg/day	NOAEL ≥ 1434/1591 mg/kg/day (M/F) LOAEL not identified

Table 2. Toxicity Profile of Flufenpyr-ethyl Technical.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rodents (rat)	45118915 (1998) **Acceptable/guideline** 0, 1,000, 10,000, and 20,000 ppm (Limit Dose) M: 0, 55, 595 and 1195 mg/kg/day F: 0, 65, 682, and 1378 mg/kg/day	NOAEL ≥ 1195/1378 mg/kg/day (M/F) LOAEL not identified
870.3100 90-Day oral toxicity rodents (mouse)	45118916 (1998) **Acceptable/guideline** 0, 300, 1,000, 3,000, and 7,000 ppm (Limit Dose) M: 0, 37.2, 128.4, 394.8 and 907.6 mg/kg/day F: 0, 45, 155.7, 449.7, and 1088 mg/kg/day	NOAEL = 395 mg/kg/day (M) LOAEL = 908 mg/kg/day, based on increased absolute and relative liver weights and increased incidence of hepatic centrilobular vacuolation in male mice
870.3100 28-Day oral toxicity rodents (mouse)	45118916 (1998) **Acceptable/non-guideline** 0, 300, 1,000, 3,000, and 7,000 ppm (Limit Dose) M: 0, 44.9, 145.0, 447.5 and 1009 mg/kg/day F: 0, 57.1, 210.5, 629.1, and 1212.5 mg/kg/day	NOAEL = 448/629 mg/kg/day (M/F) LOAEL = 1009/1213 (M/F) mg/kg/day, based on increased incidence of hepatic centrilobular vacuolation
870.3150 90-Day oral toxicity in nonrodents (dog)	45118918 (1999) **Acceptable/guideline** M& F: 0,100, 300 and 1000 mg/kg/day (Limit Dose)	NOAEL = 300 mg/kg/day (M/F) LOAEL = 1000 (M/F) mg/kg/day, based on decreased body weight gains, food consumption, and food efficiency and increased incidence of vomiting
870.3200 21-Day dermal toxicity (rat)	45118919 (1999) **Acceptable/guideline** M& F: 0,100, 300 and 1000 mg/kg/day (Limit Dose)	NOAEL = 1000 mg/kg/day (M/F) LOAEL not identified
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental in rodents (rat)	445118925 (1999) **Acceptable/guideline** F: 0, 100, 300, or 1000 mg/kg/day (Limit Dose)	**Maternal** NOAEL ≥ 1000 mg/kg/day LOAEL was not established **Developmental** NOAEL = 1000 mg/kg/day (HDT) LOAEL not identified

Table 2. Toxicity Profile of Flufenpyr-ethyl Technical.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b Prenatal developmental in nonrodents (rabbit)	45118922 (2000) **Acceptable/guideline** F: 0, 100, 300, or 1,000 mg/kg/day (Limit Dose)	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day, based on increased maternal mortality, clinical signs, decreased food consumption and necropsy findings. **Developmental** NOAEL = 1,000 mg/kg/day LOAEL not identified
870.3700b Prenatal developmental in nonrodents (rabbit)	45118923 (2000) **Acceptable/guideline** F: 0, 100, 200, 300, or 1000 mg/kg/day (Limit Dose)	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 200 mg/kg/day, based on increased mortality **Developmental** NOAEL = 1000 mg/kg/day (HDT) LOAEL not identified
870.3800 2-Generation Reproduction and fertility effects (rat)	45119001 & 45119002 (2000) **Acceptable/guideline** 0, 200, 2000, or 20,000 ppm (Limit Dose) F_0 (M/F): 0/0, 14/16, 135/162, or 1463/1672 mg/kg/day F_1 (M/F): 0/0, 17/19, 170/186, or 1766/1914 mg/kg/day	**Parental/Systemic** NOAEL = 1463 - 1914 mg/kg/day LOAEL not identified. **Reproductive** NOAEL = 1463 - 1914 mg/kg/day LOAEL not identified. **Offspring** NOAEL = 1463 - 1914 mg/kg/day LOAEL not identified.
870.3800 1-Generation Reproduction and fertility effects (rat)	45796601(2000) **Acceptable/non-guideline** 0, 20, 50 or 100 ppm (equivalent to 0, 1.1, 3.2, and 6.4 mg/kg/day in males, 0, 1.3, 3.6, and 7.5 mg/kg/day in females)	**Parental/Systemic** NOAEL = 6.4 - 7.5 mg/kg/day LOAEL not identified **Reproductive** NOAEL = 6.4 - 7.5 mg/kg/day LOAEL not identified **Offspring** NOAEL = 6.4 - 7.5 mg/kg/day LOAEL not identified
870.3800 1-Generation Reproduction and fertility effects (rat)	45800701 (2002) **Acceptable/non-guideline** 0, or 2000 ppm (equivalent to 0, or 139.4 mg/kg/day in males, 0, or 151.7 mg/kg/day in females)	**Parental/Systemic** NOAEL = 139.4 - 151.7 mg/kg/day LOAEL not identified **Reproductive** NOAEL = 139.4 - 151.7 mg/kg/day LOAEL not identified **Offspring** NOAEL = 139.4 - 151.7 mg/kg/day LOAEL not identified
870.4300 Combined chronic toxicity/carcinogenicity rodents (rat)	45152807 (2000) **Acceptable/guideline** 0, 100, 1,000, 10,000, or 20,000 ppm (Limit Dose) M: 0, 3.6, 36.5, 375, or 777.8 mg/kg/day F: 0, 4.7, 46.4, 486.4, or 1024.7 mg/kg/day	NOAEL = 778.8/1024.7 mg/kg/day [M/F] LOAEL was not established **No evidence of carcinogenicity**

Table 2. Toxicity Profile of Flufenpyr-ethyl Technical.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200 Carcinogenicity rodents (mouse)	45118920 (1999) **Acceptable/guideline** 0, 350, 3500, or 7000 ppm (Limit Dose) M: 0, 39.9, 401.8 and 814.7 mg/kg/day F: 0, 43.7, 447.9, and 882.8 mg/kg/day	NOAEL = 39.9 - 43.7 mg/kg/day [M/F] LOAEL = 401.8 - 447.9 mg/kg/day [M/F], based on liver toxicity in both sexes and mild anemia in males **No evidence of carcinogenicity**.
870.5100 Bacterial gene mutation assay	MRID 45119003 (1998) **Acceptable/guideline** Four histidine auxotrophic strains (*his*$^-$) of *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) and the tryptophan auxotrophic (*try*$^-$) strain WP2 *uvrA* of *E. coli* were exposed to flufenpyr-ethyl. TA100 strains were exposed (-S9) to 78.1 to 2500 µg/plate and the other 4 strains to 9.77 to 313 µg/plate. All strains were exposed to 156 to 5000 µg/plate + S9.	Flufenpyr-ethyl was tested up to concentrations limited by cytotoxicity. There was no evidence of mutagenicity at any dose levels tested. Positive controls induced appropriate response.

3.2 FQPA Considerations

On 4/29/03, HIARC evaluated the potential for increased susceptibility of infants and children from exposure to flufenpyr-ethyl according to the February 2002 OPP 10X guidance document. HIARC concluded that the toxicology database was complete for FQPA purposes and that there are no residual uncertainties for pre-/post-natal toxicity (Memo, G. Reddy, 6/8/03; TXR NO. 0051946). Based on the on the hazard data, HIARC recommended the special FQPA SF be reduced to 1x. The flufenpyr-ethyl risk assessment team evaluated the quality of the exposure data; and, based these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

- There is no evidence of quantitative and/or qualitative evidence of increased susceptibility of rat and rabbit fetuses to *in utero* exposure to flufenpyr-ethyl. There is no evidence of increased qualitative and/or quantitative evidence of increased susceptibility to flufenpyr-ethyl following pre-natal exposure in a 2-generation reproduction study(s) in rats or 1-generation reproduction studies.
- The toxicological database is complete for FQPA assessment.
- The *chronic* dietary food exposure assessment utilizes tolerance level residues and 100% CT data for all proposed uses. By using these screening-level assumptions, actual exposures/risks will not be underestimated.
- The dietary drinking water assessment utilized modeling results which included conservative assumptions for all degradates of concern (parent and the S-3153-acid, S-3153-1-OH, and S-3153-1-OCH3 degradates). Although the MARC recommended the S-3153-1-OCH_3-5'-CH_2OH degradate be included in the drinking water assessment as well, at this time, EFED does not adequate data to model this degradate. Although a major degradate in the aerobic soil metabolism study (maximum 13.9% of applied), S-3153-1-OCH_3-5'-CH_2OH was only found in the top soil layer of one out of three field studies at the analytical method detection limit level. EFED expects the risk of this degradate to the drinking water resources to

be negligible compared to that of the parent and the other three degradates. Therefore, since conservative assumptions were used in the water models where environmental fate data are lacking, the water exposure assessment will not underestimate the potential risks for infant and children.

- The are no registered or proposed residential uses for flufenpyr-ethyl.

3.3 Dose-Response Assessment

Acute Dietary Endpoint: An endpoint of concern attributable to a single oral dose was not identified for either the general U.S. population (including infants and children) and all population subgroups, or the females 13-50 years old population subgroup for flufenpyr-ethyl; therefore, an acute dietary exposure analysis was **not** performed. There were no endpoints of concern identified in the database including developmental toxicity studies in rats and rabbits. In two separate developmental toxicity studies in rabbits, maternal toxicity (deaths) was observed on or about gestational day (GD) 28, but this was not considered as a single dose effect.

Chronic Dietary Endpoint: The mouse carcinogenicity study was used to select the dose and endpoint for establishing the cRfD of 0.4 mg/kg/day for the general U.S. population. The systemic NOAEL of 40 mg/kg/day was based on liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males observed at the LOAEL of 401.8 mg/kg/day. A 100-fold uncertainty factor (10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the cRfD. This study provides the lowest NOAEL in the database. The study duration and the endpoint is appropriate for this exposure duration and route specific. The special FQPA SF of 1x is applicable for the chronic dietary risk assessment. Thus, the cPAD is 0.4 mg/kg/day.

Carcinogenicity: In accordance with the "*1999 Draft Carcinogen Risk Assessment Guideline*," HIARC, based on the lack of increased tumor incidence, classified flufenpyr-ethyl as "**not likely to be carcinogenic to humans**."

Short- and Intermediate-Term and Incidental Oral Endpoints: Short- and intermediate-term incidental oral endpoints were selected from the rabbit developmental toxicity study. The maternal toxicity NOAEL of 100 mg/kg/day was chosen based on clinical signs (decreased defecation, soft and/or mucoid stools), decreased food consumption and necropsy findings (thickened glandular stomach) observed at the LOAEL of 300 mg/kg/day. Gastric irritation due to the acid pH of flufenpyr-ethyl which could occur following a single or multiple exposures, and may have contributed to the reduced feed consumption as well as gross pathological changes in the glandular stomach. The local effect (stomach lesions) may be responsible for the mortality observed at 300 mg/kg/day and above. Rabbits appear to be the sensitive species by gavage since treatment - related effects in other species (mice, rats, and dogs) were seen only at the Limit Dose. This study and endpoints are appropriate for the population of concern (infants and children) and the route and durations of exposure (1-30 days and 1-6 months).

Dermal Penetration: HIARC concluded quantitation of dermal risk is not required due to lack of systemic toxicity at the limit-dose following repeated dermal exposures as well as lack of concern for developmental toxicity. Quantification of dermal risk is not required, since there was no

toxicity observed via dermal route in a 21-day dermal toxicity study in rats at the Limit Dose. In addition, there are no developmental concerns based on developmental toxicity studies in rats and rabbits. The chronic RfD was established based on liver toxicity seen in a mouse carcinogenicity study. The liver effects (the effects of concern) did not appear to have progressed with duration of exposure based on the results of sub-chronic and chronic toxicity studies. In sub-chronic studies in mice liver effects were observed only at the Limit Dose. Based on the results of sub-chronic and chronic toxicity studies in mice and 21-day dermal toxicity study in the rats, the HIARC concluded that quantitation of dermal risk is not required for any duration. Even though, the developmental toxicity study in the rabbit provides lower NOAEL, the HIARC did not consider this study as appropriate for dermal risk assessment because the primary effects observed in this study appears to be due to gastrointestinal (G.I.) tract irritation which are appropriate only for oral exposure risk assessment.

Dermal Absorption Factor: Not Applicable.

Short-, Intermediate- and Long-Term Dermal Endpoints: Quantification of dermal risk is not required, since there was no toxicity observed via the dermal route in a 21-day dermal toxicity study in rats at the Limit Dose. In addition, there are no developmental concerns based on developmental toxicity studies in rats and rabbits. The chronic RfD was established based on liver toxicity seen in a mouse carcinogenicity study. The liver effects (the effects of concern) did not appear to have progressed with duration of exposure based on the results of sub-chronic and chronic toxicity studies. In sub-chronic studies in mice, liver effects were observed only at the Limit Dose. Based on the results of sub-chronic and chronic toxicity studies in mice and 21-day dermal toxicity study in the rats, HIARC concluded that quantitation of dermal risk is not required for any duration. Even though, the developmental toxicity study in the rabbit provides a lower NOAEL, HIARC did not consider this study as appropriate for dermal risk assessment because the primary effects observed in this study appears to be due to G.I. tract irritation which is appropriate only for oral exposure risk assessment.

Short-, Intermediate-, and Long-Term Inhalation Endpoints: Short-, intermediate-, and long-term inhalation endpoints were chosen from the mouse carcinogenicity study. The systemic NOAEL of 40 mg/kg/day was chosen based on liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males at the LOAEL of 401.8 mg/kg/day. With the exception of an acute inhalation study in which flufenpyr-ethyl was placed in Toxicity Category IV (LC_{50} > 5.0 mg/L), no other inhalation studies are available. Therefore, an oral study was chosen for the inhalation endpoint for all durations. The rabbit study with a lower NOAEL (100 mg/kg/day) was not selected since the endpoint of concern (GI tract irritation) is route specific (oral) and thus not appropriate for inhalation exposure risk assessment. The selected study provides the lowest NOAEL of 40 mg/kg/day in the database, based on the liver toxicity observed at a LOAEL of 401.8 mg/kg/day. The selected study/endpoint is appropriate for the population of concern (general population, including infants and children) and the durations of exposure (1-30 days, 1-6 months and >6 months). Similar effects were also observed in the 90-day and 4 week feeding studies in the mouse; however, at higher doses there was no increased severity. Since the dose

identified is from an oral study, route-to-route extrapolation should be used. Absorption via the inhalation route is assumed to be comparable to oral absorption (i.e., use 100% default inhalation absorption values).

MOE for Occupational Risk Assessments: A MOE of 100 is required for short-, intermediate-, and long-term occupational risk assessments for inhalation routes of exposure. This MOE is based on the conventional uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation).

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for Flufenpyr-ethyl for Use in Human Health Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = None mg/kg/day UF = N/A **Acute RfD** = None	FQPA SF = 1x **aPAD** = acute RfD / FQPA SF = None	A dose and endpoint of concern attributable to a single dose was not available in the database including the developmental toxicity studies.
Acute Dietary (General population including infants and children)	NOAEL = None mg/kg/day UF = N/A **Acute RfD** = None	FQPA SF = 1x **aPAD** = acute RfD / FQPA SF = None	A dose and endpoint of concern attributable to a single dose was not available in the database including the developmental toxicity studies.
Chronic Dietary (All populations)	NOAEL = **40** mg/kg/day UF = **100** **Chronic RfD** = **0.4** mg/kg/day	FQPA SF = 1x **cPAD** = chronic RfD / FQPA SF = **0.4** mg/kg/day	**Carcinogenicity Study - Mice** LOAEL = 401.8 mg/kg/day based on liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males
Short-Term Incidental Oral (1-30 days)	NOAEL = 100 mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	**Developmental Toxicity Study - Rabbit** LOAEL = 300 mg/kg/day, clinical signs, decreased food consumption and necropsy findings.
Intermediate-Term Incidental Oral (1-6 months)	NOAEL=100 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Developmental Toxicity Study - Rabbit** LOAEL = 300 mg/kg/day, clinical signs, decreased food consumption and necropsy findings.
Dermal All Durations	HIARC concluded quantitation of dermal risk is not required due to lack of systemic toxicity at the limit-dose following repeated dermal exposures as well as lack of concern for developmental toxicity.		

Table 3. Summary of Toxicological Dose and Endpoints for Flufenpyr-ethyl for Use in Human Health Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1-30 days)	NOAEL= 40 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study - Mice** LOAEL = 401.8 mg/kg/day based on liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males
Intermediate-Term Inhalation (1-6 months)	NOAEL = 40 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study - Mice** LOAEL = 401.8 mg/kg/day based on liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males
Long-Term Inhalation (>6 months)	NOAEL= 40 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = 100	**Carcinogenicity Study - Mice** LOAEL = 401.8 mg/kg/day based on liver toxicity (hepatocyte necrosis) in both sexes and mild anemia in males
Cancer (oral, dermal, inhalation)	Flufenpyr-ethyl classified as "**not likely to be carcinogenic to humans**"		

[1] UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, flufenpyr-ethyl may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

Flufenpyr-ethyl is being proposed for use on field corn, soybeans and sugarcane. Valent provided copies of the following proposed labels: S-3153 WDG Herbicide (57.5% flufenpyr-ethyl; EPA Reg. No. 59639-XXX) for use on field corn, soybeans and sugarcane; and S-3153/Atrazine WDG Herbicide (1.9% flufenpyr-ethyl and 75% atrazine; EPA Reg. No. 59639-XXX) for use on field corn and sugarcane. Flufenpyr-ethyl is to be applied foliarly by either ground or air equipment (the S-3153/Atrazine mix can be applied by ground equipment only). The proposed application rates, number of applications, application interval, and PHI vary by crop (see Table 4). The proposed use directions for field corn, soybeans and sugarcane are adequate to allow HED an assessment of whether the submitted residue data reflect the maximum residues likely to occur in these crops. The following label deficiencies were noted:

S-3135 WDG Herbicide:

- Based on the results of the confined rotational crop study, PBIs of at least 4 weeks should be specified for all non-labeled crops.
- A minimum RTI of 10 days is specified under "General Restrictions and Limitations" (page 6 of the label); however, under "Sequential Applications" (page 8) a minimum RTI of 14 days is specified. The RTI needs to be clarified to specify a RTI of either 10 or 14 days.
- Field corn needs to be added to "General Information" section (page 6 of the label).
- A restriction against the feeding of soybean hay should be included in the label.

S-3135/Atrazine WDG Herbicide:

- Based on the results of the confined rotational crop study, PBIs of at least 4 weeks should be specified for all non-labeled crops.

A revised Section B with the above changes is requested.

Table 4. Flufenpyr-ethyl Proposed Use Patterns.

App. Timing, Type, and Equip.	Formulation	# App./ year	App. Rate (lb ai/A)		RTI [1] (days)	PHI / PGI [2] (days)	Plantback restrictions
			per app.	per year			
Field Corn							
Ground or Air Postemergent 2-leaf through 10-leaf stage	S-3153 WDG Herbicide [3]	2	0.027	0.054	10 or 14	28 days for the grazing or feeding of corn forage; no specified PHI for corn grain and stover.	In case of crop failure, a 28-day plantback interval (PBI) is specified for soybeans, corn, cotton, grain sorghum, oats, wheat, barley, rice and rye.
Ground Postemergent leaf stage until the corn reaches 12" in height	S-3153/Atrazine WDG Herbicide [4]	2	0.0192	0.0323	10	28 days for the grazing or feeding of corn forage; no specified PHI for corn grain and stover	The following are prohibited: 1) rotating to any crop except corn or sorghum until the year following application; 2) planting sugar beets, tobacco, vegetables, spring seeded small grains, or small seeded legumes and grasses the year following application. In case of crop failure, corn or grain sorghum may be replanted.
Sugarcane							
Ground or Air Postemergent	S-3153 WDG Herbicide [3]	2	0.027	0.054	10 or 14	90	In case of crop failure, a 28-day PBI is specified for soybeans, corn, cotton, grain sorghum, oats, wheat, barley, rice and rye.
Ground Postemergent after 12" in height up to 90 days prior to harvest	S-3153/Atrazine WDG Herbicide [4]	2	0.0355	0.0532	10	PHI = 90 PGI = 28 for the grazing or feeding of sugarcane forage.	Rotating to any crop except corn or sorghum until the year following application and planting sugar beets, tobacco, vegetables, spring seeded small grains, or small seeded legumes and grasses the year following application are prohibited. In case of crop failure, corn or grain sorghum may be replanted.
Soybeans							
Ground or Air Postemergent after first-trifoliate stage	S-3153 WDG Herbicide [3]	2	0.054	0.054	10 or 14	PGI = 45 prohibits the grazing or feeding of green forage to livestock. No restriction listed against the feeding of soybean hay.	In case of crop failure, a 28-day PBI is specified for soybeans, corn, cotton, grain sorghum, oats, wheat, barley, rice and rye.

1 RTI = retreatment interval
2 PHI = preharvest interval; PGI = pregrazing interval
3 S-3153 WDG Herbicide = 57.6% ai. EPA Reg. No. 59639-xxx. May be applied using either ground or aerial equipment in a min. volume of 15 or 7 gallons of water/A, respectively. Each app. should include 1-2 pts/A of either a crop oil concentrate or methylated seed oil or a non-ionic surfactant as an adjuvant. Proportionately less water and herbicide should be used for banded applications.
4 S-3153/Atrazine WDG Herbicide = 1.9% flufenpyr-ethyl and 75.0% atrazine. EPA Reg. No. 59639-xxx. One or two broadcast or banded foliar applications per season. May be applied using ground equipment in a minimum volume of 15 gallons of water/A. Each app. should include 1-2 pts/A of either a crop oil concentrate, methylated seed oil or a non-ionic surfactant as an adjuvant. Proportionately less water and herbicide should be used for banded applications.

4.2 Dietary Exposure/Risk Pathway

The residue chemistry data submitted in support of proposed petitions were evaluated by HED in a memo dated 1/18/02 (G. Kramer, D268664). The drinking water assessment was completed by EFED (Memo in progress, T. Nguyen, D284046). The chronic dietary exposure assessment was completed in a HED memorandum dated 7/29/03 (Memo, J. Tyler, D291079).

4.2.1 Residue Profile

Background: Valent USA Corporation has submitted a petition for the establishment of permanent tolerances for residues of the herbicide flufenpyr-ethyl in/on field corn, soybean and sugarcane commodities, and its metabolite S-3153 acid-4-OH in/on field corn forage and stover. The proposed tolerances for residues of flufenpyr-ethyl *per se* are: field corn, forage at 0.01 ppm; field corn, grain at 0.01 ppm; field corn, stover at 0.01 ppm; soybean, seed at 0.01 ppm; and sugarcane at 0.01 ppm. The proposed tolerances for residues of S-3153 acid-4-OH *per se* are: field corn, forage at 0.04 ppm; and field corn, stover at 0.04 ppm.

There are currently no established tolerances for residues of flufenpyr-ethyl in/on any plant or livestock commodities. As there are no Mexican, Canadian or Codex maximum residue limits (MRLs) established for flufenpyr-ethyl in/on field corn, soybeans and sugarcane, there are no compatibility issues to be reconciled.

Nature of the Residue in Plants and Livestock: Data concerning the metabolism of flufenpyr-ethyl in corn and soybean seed, ruminants, and poultry have been submitted and reviewed in conjunction with the current petition. The results of the aforementioned plant and livestock metabolism studies were presented to the HED Metabolism Assessment Review Committee (MARC) on 6/18/03 (Memo, G. Kramer, *et al.*; D289690). See Attachment 1 for structures of all metabolites pertinent to this risk assessment.

Plants: The nature of the residue in corn and soybean seed is understood. The submitted corn metabolism study is adequate. Additional characterization of bound residues in soybean forage and hay is required before the nature of the residue in these RACs is understood. As the use of forage for feeding is prohibited by the label, data on this RAC are not required. Provided a restriction against the feeding of soybean hay is included on the label, the submitted soybean metabolism study is adequate.

The metabolism of flufenpyr-ethyl was similar in corn and soybeans. Flufenpyr-ethyl is metabolized in corn and soybean by hydrolysis of the ethyl ester to form the S-3153 acid, by defluoronation and subsequent hydrolysis of the ethyl ester to form S-3153 acid-4-OH, or the hydrolysis of the ethyl acetate side chain from the phenyl ring and hydroxylation at the 5′-methyl of the pyridazinyl ring to form S-3153-1-OH-5'-CH_2OH. A minor portion of the S-3153 acid metabolite can be hydroxylated at the 5′-methyl of the pyridazinyl ring to give S-3153-acid-5′-CH_2OH. In soybeans only, a minor portion of the S-3153 acid metabolite undergoes ring cleavage to give 2-chloro-4-fluoro-phenoxyacetic acid. The hydroxylated metabolites S-3153 acid-4-OH, S-3153-1-OH-5'-CH_2OH and S-3153-acid-5′-

CH_2OH can also undergo conjugation.

MARC concluded that parent only is the residue of toxicological concern and the only residue to be included in the risk assessment and tolerance expression for field corn grain, soybean seed, and sugarcane (Memo in progress, G. Kramer, *et al.*; D289691). MARC further concluded that for field corn forage and stover, parent and S-3153 acid-4-OH are the residues of toxicological concern to be used in risk assessment and in the tolerance expression.

Livestock: The nature of the residue in ruminants is understood based on submitted metabolism studies on ruminants (dairy cattle) and poultry (laying hens). The submitted ruminant and poultry metabolism studies are adequate. The metabolism of flufenpyr-ethyl was similar in goats and hens. Flufenpyr-ethyl undergoes hydrolysis of the ethyl ester to form the major metabolite, S-3153-acid. A minor portion of the acid metabolite is then hydroxylated at the 5′-methyl of the pyridazinyl ring to give S-3153-acid-5′-CH_2OH. MARC concluded that parent plus S-3153 acid are the residues of concern for risk assessment and the tolerance expression (if necessary) (Memo in progress, G. Kramer, *et al.*; D289691).

Residue Analytical Methods: The gas chromatography/nitrogen/phosphorus detector (GC/NPD) method (Valent Method RM-36 or RM-36-1) is adequate for determining residues of flufenpyr-ethyl in/on corn RACs and processed commodities, soybean RACs and processed commodities, and sugarcane. The limits of detection (LOD) and quantitation (LOQ) for flufenpyr-ethyl are 0.005 and 0.01 ppm, respectively. The GC/MSD method (Valent Method RM-36-3c) is adequate for determining free and conjugated residues of S-3153 acid-4-OH in/on corn forage and stover and sugarcane. The LOD and LOQ for S-3153 acid-4-OH are 0.01 and 0.02 ppm, respectively.

Method RM-36-1 for determination of flufenpyr-ethyl *per se* and Method RM-36-3c for determination for free and conjugated S-3153 acid-4-OH have been radiovalidated and undergone successful independent laboratory validation (ILV) trials. Both methods were forwarded to the Analytical Chemistry Branch (ACB) for a PMV trial (Memo G. Kramer, 12/14/01; D279236). A confirmatory method for residues of flufenpyr-ethyl in/on corn, soybean, and sugarcane RACs is required. If the confirmatory method does not utilize MSD, then an interference study will also be required. A conclusion on the adequacy of these methods for enforcement of the proposed tolerances will be withheld pending satisfactory method validation (PMV, confirmatory method (RM-36-1 only) and interference study (RM-36-1 only).

Multiresidue Method (MRM): Multiresidue method testing data have been submitted for flufenpyr-ethyl and its metabolite S-3153-acid-4-OH. Acceptable recoveries were obtained with Protocols D and F. These data were forwarded to the Food and Drug Administration (FDA) for review (Memo G. Kramer, 12/14/01; D279240). Acceptable recoveries for the parent compound only were obtained with Protocols D and F.

Storage Stability: The submitted storage stability data are adequate and indicate that flufenpyr-ethyl is stable at -20 C in soybean seeds for at least 28 months, and in corn grain and sugarcane for at least 4 months. Flufenpyr-ethyl is also stable at -20 C in corn forage and

stover for up to 2 months. However, after 3 months of frozen storage, flufenpyr-ethyl declined to 59-76% in corn forage and stover, and by 4 months the recovery of flufenpyr-ethyl declined to 57-66%. The metabolite S-3153 acid-4-OH is stable at -20 C for at least 14 months in corn forage, at least 12 months in corn stover, and at least 13 months in sugar cane.

The available storage stability data adequately support the residue data on soybeans and sugarcane. The data also support the residue data on corn grain and the residue data for flufenpyr-ethyl in/on corn forage and stover. However, 45 of 61 corn stover samples and 33 of 71 corn forage samples were stored frozen for 531-1029 days prior to analysis for the S-3153 acid-4-OH metabolite. Storage stability data for this metabolite are available only for storage intervals up to 427 days. Therefore, additional data are requested demonstrating the frozen storage stability of S-3153 acid-4-OH in forage and stover for up to 2.5 years.

Magnitude of Residues in Plants: Crop field trial data were submitted on field corn, soybean and sugarcane. In the soybean crop field trials, data were acquired on residues of flufenpyr-ethyl. In the sugarcane crop field trial study, data were acquired on both flufenpyr-ethyl and S-3153 acid-4-OH. In the field corn crop field trial study, data were acquired on flufenpyr-ethyl and S-3153 acid-4-OH for forage and stover; and flufenpyr-ethyl in grain.

A summary table of the results of the crop field trial studies can be found in Attachment 2 of this risk assessment. Based on the submitted residue data, detectable residues of flufenpyr-ethyl are not likely to be found in samples of raw commodities following foliar applications. Following a singular foliar application of flufenpyr-ethyl (50% WP) at 0.052-0.055 lb ai/A (1x the proposed seasonal label rate), residues of flufenpyr-ethyl were <0.005 ppm (<LOD) in all soybean, field corn and sugarcane samples harvested at normal maturity. Flufenpyr-ethyl residues were also <0.005 ppm in/on the 10 samples harvested 30-58 DAT in the residue decline study.

Residues of S-3153 acid-4-OH were <0.01 ppm (<LOD) in/on all sugarcane samples; and <0.01 ppm (<LOD) in/on 24 forage samples and 0.01-0.03 ppm in/on 28 forage samples harvested 32-65 DAT, and were <0.01 ppm (<LOD) in/on 45 stover samples and 0.01-0.03 ppm in/on 11 stover samples harvested 58-115 DAT.

Field Corn: The submitted field corn study is adequate, pending submission of additional storage stability data for the metabolite S-3153 acid-4-OH in forage and stover. These data indicate that residues of flufenpyr-ethyl will not exceed the proposed 0.01 ppm tolerance in corn grain, forage, and stover, and residues of S-3153 acid-4-OH will not exceed the proposed 0.04 ppm tolerance in corn forage and stover.

Soybean: The submitted residue data on soybeans are adequate and support the proposed tolerance of 0.01 ppm.

Sugarcane: The submitted sugarcane residue data are adequate and indicate that residues of flufenpyr-ethyl will not exceed the proposed 0.01-ppm tolerance.

The correct tolerance expressions and commodity definitions are listed in Attachment 3. A Revised Section F is required.

Magnitude of Residues in Processed Commodities: The submitted corn and sugarcane processing studies are adequate and indicate that tolerances are not required for flufenpyr-ethyl in corn and soybean processed commodities. Residues of flufenpyr-ethyl were nondetectable (<0.005 ppm) in/on grain samples harvested at normal maturity following a 5x application of flufenpyr-ethyl, and were also <0.005 ppm in all fractions (flour, grits, meal, starch, and oil) processed from the 5x-treated grain. Residues of flufenpyr-ethyl were <0.005 (<LOD) in one sample each of soybean seed, meal, hulls and oil samples processed from soybean seeds treated with flufenpyr-ethyl at 5x and harvested 45 days after application. Tolerances are not required for flufenpyr-ethyl residues in sugarcane processed commodities as residues of flufenpyr-ethyl and its metabolite, S-3153 acid-4-OH, were nondetectable (<0.005 and <0.01 ppm) in all samples from the 1x- and 5x-treated field trials.

Magnitude of Residues in Meat, Milk, Poultry and Eggs (MMPE): Based on data from the available goat and poultry metabolism studies, in which goats and hens were dosed at ~180x and 1000x the maximum theoretical dietary burden (MTDB), respectively, there is no reasonable expectation that quantifiable residues of flufenpyr-ethyl will occur in livestock commodities [40 CFR 180.6(a)(3)]. Therefore, livestock feeding studies and tolerances for livestock commodities are not required at the present time. If the use of flufenpyr-ethyl is expanded in the future to include other livestock feed items, then the need for feeding studies will be reevaluated.

Confined Accumulation in Rotational Crops: The submitted confined rotational crop study is adequate. ^{14}C-Residues were low in rotational crops planted 31, 89 or 221 days following two soil applications of flufenpyr-ethyl totaling 0.053 lb ai/A (1x). Total radioactive residue (TRR) levels were <0.004 ppm in cabbage and carrot tops and roots from the 31- and 89-day PBIs, and were <0.002 in wheat grain from all three PBIs. Only wheat forage from the 31-day PBI (0.013 ppm) and wheat straw from all three PBIs (0.011-0.030 ppm) had ^{14}C-residues in excess of 0.01 ppm. Analysis of these samples detected flufenpyr-ethyl at 8.0% of the TRR (0.001 ppm) in forage and at 1.4-4.7% of the TRR (<0.001 ppm) in straw. The remaining extractable components were composed of multiple polar compounds each accounting for <0.004 ppm. Although no other components were identified in rotational crops due to the low levels of ^{14}C-residues, the chromatographic profile of the extractable ^{14}C-residues was similar to the profiles observed in the primary crop metabolism studies on corn and soybeans. Provided that PBIs of at least 4 weeks are specified for all non-labeled crops, limited field rotational crop studies and tolerances for flufenpyr-ethyl residues in rotational crops are not required for purposes of this petition.

4.2.2 Dietary Exposure Analyses

The flufenpyr-ethyl chronic dietary exposure assessment was conducted using DEEM-FCID™, Version 1.30), which incorporates consumption data from United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food-form is summed with the residue consumption estimates for all other food/food-forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

The results of the chronic assessment are listed in Table 5. DEEM-FCID™ (Ver. 1.30) estimates the dietary exposure for the U.S. population and 28 population subgroups. Based on an analysis of 1994-96, 98 CSFII consumption data which took into account dietary patterns and number of survey respondents, HED determined that the following population groupings were appropriate for regulatory purposes (only the exposure estimates for these populations are reported in this document): U.S. Population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, females 13-49 years old, adults 20-49 years old, and/or adults 50+ years old.

4.2.2.1 Chronic Dietary Exposure Analysis

An unrefined, chronic dietary exposure assessment was conducted for the general U.S. population and various population subgroups. Proposed tolerance-level residues and 100% CT information were used for all proposed commodities. The submitted corn grain, soybean and sugarcane processing studies indicate that flufenpyr-ethyl residues do not concentrate in corn, soybean and sugarcane processed commodities. Therefore, processing factors were set to 1 for all corn, soybean and sugarcane processed commodities.

The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population and all population subgroups (<1% of the cPAD). The chronic assessment was highly conservative, using several upper-end assumptions. Additional refinements, such as inclusion of anticipated residues (ARs) and %CT data, could be made in order to refine the chronic assessment.

Table 5. Summary of Dietary Exposure and Risk for Flufenpyr-ethyl.

Population Subgroup	Chronic Dietary [1]	
	Dietary Exposure (mg/kg/day)	%cPAD
U.S. Population (total)	0.000022	<1
All Infants (< 1 year old)	0.000036	<1
Children 1-2 years old	0.000047	<1
Children 3-5 years old	0.000052	<1

Table 5. Summary of Dietary Exposure and Risk for Flufenpyr-ethyl.

Population Subgroup	Chronic Dietary [1]	
	Dietary Exposure (mg/kg/day)	%cPAD
Children 6-12 years old	0.000039	<1
Youth 13-19 years old	0.000027	<1
Adults 20-49 years old	0.000017	<1
Females 13-49 years old	0.000017	<1
Adults 50+ years old	0.000011	<1

1. Chronic dietary endpoint of 0.4 mg/kg/day applies to the general U.S. population and all population subgroups.

4.3 Water Exposure/Risk Pathway

In a meeting on 6/18/03, the HED MARC met to discuss the flufenpyr-ethyl degradates and metabolites of concern in drinking water (see Attachment 1 for structures of all metabolites pertinent to this risk assessment). Environmental fate data suggest that parent metabolizes quickly in soil aerobically and anaerobically. The major routes of degradation based on the label use pattern will likely be aerobic metabolism in soil (t ½ ≈ 2 days) and anaerobic aquatic metabolism (t ½ < 1 day). Based on aerobic soil metabolism study, major metabolites include: S-3153-acid (maximum of 84%), S-3153-1-OH (maximum of 14 %), S-3153-1-OCH_3 (maximum of 53%), and S-3153-1-OCH_3-5'-CH_2OH (maximum of 17.7% of the applied dose). Based on the available environmental fate data, MARC concluded that the following degradates will likely have similar toxicity to the parent: S-3153-acid, S-3153-1-OH, S-3153-1-OCH3, S-3153-1-OCH3-5'-CH2OH. Therefore, in addition to the parent, these degradates should be included in the drinking water risk assessment (Memo in progress, G. Kramer, *et al.*; D289691).

Therefore, EFED provided, Tier 1 DWECs for ground water (using SCI-GROW) and surface water (using FIRST) for flufenpyr-ethyl and its major soil degradates (S-3153-acid, S-3153-1-OH, and S-3153-1-OCH_3) (see Table 6). At this time, EFED does not have adequate information to model the S-3153-1-OCH_3-5'-CH_2OH degradate (see additional information below). The DWECs were based on two applications of 0.027 lb ai/A each applied at 10-day RTIs, for a total application rate of 0.054 lb ai/A. Both aerial and ground application are permitted for these uses, however aerial application was simulated to derive at the highest level of drift, therefore the highest level of surface water contamination. EFED provided flufenpyr-ethyl surface water estimates for soybeans, sugarcane and field corn. However, due to its high percent cropped area (PCA) value (0.87), the surface DWEC values reported for flufenpyr-ethyl in Table 6 are for sugarcane. Only sugarcane values are reported for the degradates of concern, as they are the most conservative estimates.

The estimated K_{oc} value from the leaching and Adsorption/Desorption studies indicates that flufenpyr-ethyl has some leaching potential. However, since other dissipation routes such as degradation and mineralization are more important and more rapid, the likelihood of flufenpyr-ethyl leaching into ground water could be greatly reduced. In contrast, two of its major metabolites, S-3153-acid and S-3153-1-OH, seem to be more mobile and could have greater ability to reach ground water than the parent. SCI-GROW model results show that S-3153-acid could reach ground water at a higher level than the parent. But in the field studies, neither flufenpyr-ethyl nor these degradates were detected below the 3" soil depth.

The environmental fate data, physical-chemical properties, and surface water modeling results suggest that drift may be the most important route of potential exposure of flufenpyr-ethyl in surface water. However, once in water, flufenpyr-ethyl is prone to hydrolysis, except in acidic aquatic environment, and should not present a major concern to surface water resources. As for the degradates, results from FIRST model predict higher surface water concentrations than for the parent. But it should be noted that there are several levels of uncertainty when modeling the degradates. With an incomplete database, some assumptions were made, including degradates stability in hydrolysis and photolysis, which may be inaccurate based on their molecular formulae, especially with S-3153-acid, where chemical composition suggests higher solubility in water and higher susceptibility to hydrolysis than parent. However, these assumptions are considered conservative, and are likely to result in high DWECs for the degradates.

Table 6. DWECs for Residues of Concern in Drinking Water for Risk Assessment Purposes.

	Tier 1, EECs (ppb)					
	Parent	**S-3153-acid**	**S-3153-1-OH**	**S-3153-1-OCH_3**	**S-3153-1-OCH3-5'-CH2OH**	**Total**
Surface Water - Peak (Acute)	0.065	3.6	0.4	1.5	Not Available	5.6
Surface Water - Annual Average (Chronic)	0.002	1.5	0.04	0.5	Not Available	2.0
Groundwater - Acute and Chronic	<0.01	0.04	<0.01	<0.01	Not Available	<0.07

The assumptions used for estimating the DWECs are listed below. As mentioned above, these assumptions are conservative and likely to result in high DWECs for the degradates.

- Single application rate used in the modeling for each degradate was adjusted from the proposed rate listed in Table 3, proportionally to their maximum concentration relative to the total amount applied and to their molecular weight.
- Although aerial application was simulated, no drift was assumed for the degradates as they were formed in soils, after application. This assumption gives lower surface water values, however non significant, since the application rates are low.

- No solubility data exist for the degradates and their solubility was assumed equal to the parent's. No major impact on the data is expected, as these Tier I screening models are not very sensitive to the change in solubility data.
- No hydrolysis or photolysis data were received for the degradates. Although their chemical formulae indicate higher susceptibility to hydrolysis and photolysis than parent, stability was assumed for all of the modeled degradates, according to the current EFED policies. This assumption would not impact the peak (acute) surface water concentrations, however does result in higher annual average (chronic) values.
- Insufficient data were submitted for S-3153-1-OCH3-5'-CH2OH to estimate its DWECs. Although a major degradate in the aerobic soil metabolism study (maximum 13.9% of applied), this degradate was only found in the top soil layer of one out of three field studies at the analytical method detection limit level. Therefore EFED expects the risk of this degradate to the drinking water resources to be negligible compared to that of the parent and the other three degradates.

4.4 Residential Exposure/Risk Pathway

There are no products containing flufenpyr-ethyl proposed or registered for residential use or that may be applied by commercial applicators to residential sites. Therefore, a residential exposure assessment was not performed.

4.4.1 Non-occupational Off-Target Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for the following scenario: chronic aggregate exposure (food + drinking water). Acute, short- and intermediate-term, and cancer aggregate risk assessments were not performed because an endpoint of concern attributable to a single oral dose was not selected for either the general U.S. population (including infants and children) or the females 13-50 years old population subgroup, there are no registered or proposed residential non-food uses, and flufenpyr-ethyl is not carcinogenic, respectively. Since HED does not have ground or surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxicity endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs.

HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate DWLOCs, the dietary food estimates (from DEEM-FCID™) were subtracted from the PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (US Population and adult male), 60 kg/2L (adult female and youth), and 10kg/1L (infants and children).

For chronic dietary exposure, HED is concerned when estimated dietary risk exceeds 100% of the cPAD.

5.1 Chronic Aggregate Risk Assessment (Food and Drinking Water)

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of flufenpyr-ethyl (food and drinking water) and residential uses. There are no registered and proposed uses of flufenpyr-ethyl that would result in residential exposure. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only.

The unrefined [deterministic assessment using tolerance-level residues, 100% CT information, and modified DEEM™ (version 7.76) processing factors for all proposed processed commodities based on guideline processing studies] chronic dietary exposure estimates are below HED's level of concern for the general U.S. population and all population subgroups (<1% cPAD). The Tier 1, DWECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to flufenpyr-ethyl (parent and all degradates of concern) in drinking water. Therefore, the chronic aggregate risk associated with the proposed use of flufenpyr-ethyl does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 7 summarizes the chronic aggregate exposure estimates to flufenpyr-ethyl residues.

Table 7. Chronic Aggregate Exposures to Flufenpyr-ethyl Residues.

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure[1] (mg/kg/day)	Ground Water DWEC (µg/L)	Surface Water DWEC (µg/L)	Chronic DWLOC[2] (µg/L)
U.S. Population	0.4	0.000022	0.399978	0.07	2.0	14,000
All infants (< 1 year old)	0.4	0.000036	0.399964	0.07	2.0	4,000
Children (1-2 years old)	0.4	0.000047	0.399953	0.07	2.0	4,000
Children (3-5 years old)	0.4	0.000052	0.399948	0.07	2.0	4,000
Children (6-12 years old)	0.4	0.000039	0.399961	0.07	2.0	4,000
Youth (13-19 years old)	0.4	0.000027	0.399973	0.07	2.0	12,000
Adults (20-49 years old)	0.4	0.000017	0.399983	0.07	2.0	14,000

Table 7. Chronic Aggregate Exposures to Flufenpyr-ethyl Residues.

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure[1] (mg/kg/day)	Ground Water DWEC (µg/L)	Surface Water DWEC (µg/L)	Chronic DWLOC[2] (µg/L)
Females (13-49 years old)	0.4	0.000017	0.399983	0.07	2.0	12,000
Adults (50+ years old)	0.4	0.000011	0.399989	0.07	2.0	14,000

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)
[2] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

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

7.0 OCCUPATIONAL EXPOSURE

An occupational exposure assessment for flufenpyr-ethyl was prepared in an HED memorandum (Memo, M. Dow. 7/31/03; D291941). See Table 4 for a summary of proposed new use patterns.

7.1 Occupational Handler

Based on the proposed labeling and new use patterns, HED believes the following pesticide handler activities will result in the highest exposure to flufenpyr-ethyl: 1) mixer/loader (in this case, supporting aerial operations); 2) aerial applicator; and 3) applicator using open-cab, ground-boom equipment. A mixer/loader supporting ground operations was not assessed as the total volume of product handled is likely to be much less than would be for aerial operations.

While it is more likely that private, "grower" handlers may mix, load and apply a pesticide as a single individual, the available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be effected by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring the applicator to wear unnecessary PPE that may be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data are available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based on surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED policy to present estimates of exposure for "baseline" (i.e., single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks) and with other PPE as might be necessary. The S-3153 label directs applicators and other handlers to wear "long-sleeved shirt, long pants, socks plus shoes." The S-3153/Atrazine label directs applicators and other handlers to wear "long-sleeved shirt and long pants, waterproof gloves and socks plus shoes."

Based primarily on the proposed use patterns, commercial and private (i.e., grower operators) pesticide handlers are typically expected to have short-term exposures (i.e., 1-30 days). However, field corn and soybeans are among the proposed uses. Therefore, there is a possibility for commercial handlers to have intermediate-term exposure (1-6 months) to flufenpyr-ethyl because these crops are planted over large acreages and are geographically widely distributed across the U.S. The short-, intermediate-, and long-term inhalation toxicological endpoints identified by HIARC for use in risk assessment are identical (40 mg a.i./kg bw/day from a mouse carcinogenicity study). Therefore, the estimated MOEs presented in Table 8 are adequately protective of all durations of exposure.

Table 8. Estimated Handler Exposure and Risk from the Use of Flufenpyr-ethyl on Field Corn, Sugarcane and Soybean.

Unit Exposure[1] (mg a.i./lb handled)	Application Rate[2]	Units Treated[3] Per Day	Average Daily Dose[4] (mg a.i./kg bw/day)	MOE[5]
Mixer/Loader -Open Pour - Dry Flowable - Supporting Aerial Operation				
Inhalation 0.00077 HC	0.054 lb a.i./A	1200	Inhalation 7.13×10^{-4}	56,000
Applicator - Aerial				
Inhalation 0.000068 MC	0.054 lb a.i./A	1200	Inhalation 6.29×10^{-5}	635,000
Applicator - Ground-boom - Open Cab				
Inhalation 0.00074 HC	0.054 lb a.i./A	200	Inhalation 1.14×10^{-4}	351,000

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. SLNG = Dermal Single Layer Work Clothing **No Gloves**; SLWG = Dermal Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Application Rate. = Taken from proposed labeling for S-3153 WDG Herbicide and W-3153/Atrazine WDG punched received 17 OCT 00.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; Policy No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000;
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg).
5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) (40 mg a.i./kg bw/day) ÷ ADD.

An MOE of 100 is sufficient to protect occupational handlers. All MOEs are greater than 100; therefore, the proposed uses do not exceed HED's level of concern.

7.2 Occupational Post-application Exposure

HIARC did not identify dermal toxicological endpoints. In view of the estimated inhalation exposures and risks to handlers, HED expects post-application inhalation exposure to be negligible. Therefore, assessments of post-application exposure and risk are not necessary; and, therefore, not conducted.

Restricted Entry Interval (REI): Flufenpyr-ethyl is classified in Toxicity Category IV for acute dermal, inhalation, primary eye irritation and primary skin irritation. Therefore, the interim WPS REI of 12 hours is sufficient to protect workers from excessive exposure.

7.3 Incidents

As flufenpyr-ethyl is a new compound, there are no incidents reported.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

- Successful validation of the proposed analytical enforcement method for plants.
- Revised Section F to include the following commodity definitions, tolerances and tolerance expressions:

Tolerance Expression	Commodity Definition	Tolerance (ppm)
residues of the herbicide flufenpyr-ethyl (acetic acid, [2-chloro-4-fluoro-5-[5-methyl-6-oxo-4-(trifluoromethyl)-1(6H)-pyridazinyl]phenoxy]-ethyl ester)	Corn, field, grain	0.01
	Soybean, seed	0.01
	Sugarcane, cane	0.01
combined residues of flufenpyr-ethyl and its metabolite, [2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetic acid, free and conjugated	Corn, field, forage	0.05
	Corn, field, forage	0.05

- Revised Section B to include the following revisions:

S-3135 WDG Herbicide	Based on the results of the confined rotational crop study, PBIs of at least 4 weeks should be specified for all non-labeled crops.
	A minimum RTI of 10 days is specified under "General Restrictions and Limitations" (page 6 of the label); however, under "Sequential Applications" (page 8) a minimum RTI of 14 days is specified. The RTI needs to be clarified to specify a RTI of either 10 or 14 days.
	Field corn needs to be added to "General Information" section (page 6 of the label).
	A restriction against the feeding of soybean hay should be included in the label.
S-3135/Atrazine WDG Herbicide	Based on the results of the confined rotational crop study, PBIs of at least 4 weeks should be specified for all non-labeled crops.

- Additional storage stability data for the metabolite S-3153 acid-4-OH in field corn forage and stover.
- Confirmatory method for residues of flufenpyr-ethyl in/on corn, soybean, and sugarcane RACs.
- If the confirmatory method does not utilize MSD, then an interference study will also be required.

8.2 Toxicology

- None

8.2 ORE

- None.

9.0 ATTACHMENTS

Attachment 1. Summary of Metabolites Discussed in Risk Assessment.
Attachment 2. Summary of Residues from the Crop Field Trials with Flufenpyr-ethyl.
Attachment 3. Summary of Proposed and HED-Recommended Tolerances.

cc: J. Tyler (RAB1), M. Dow (RAB1), G. Reddy (RAB1)
RAB1 Branch (7/16/03), HED RARC (7/24/03), D. Vogel (7/31/03)
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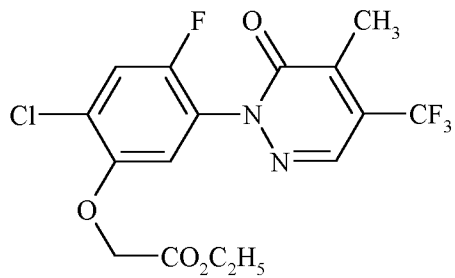
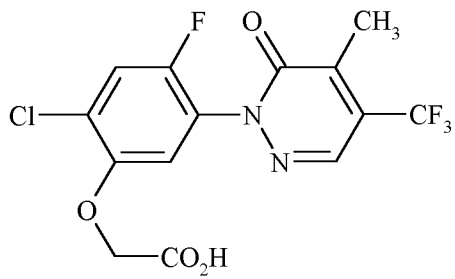
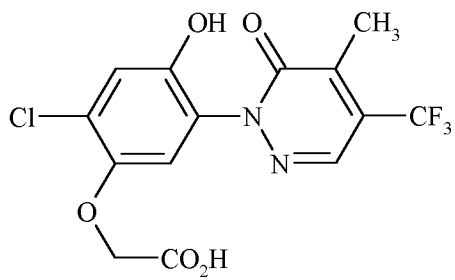
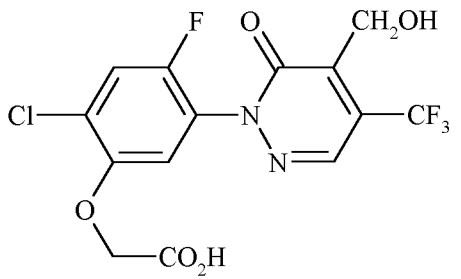
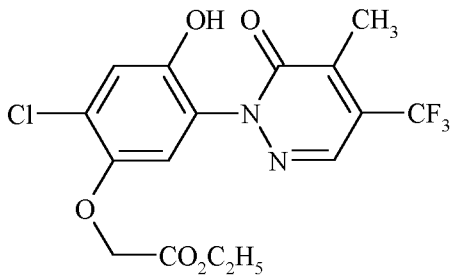
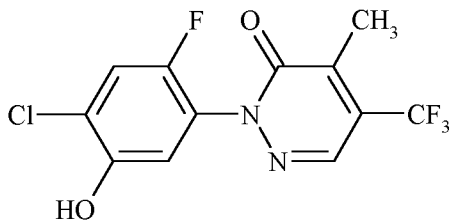
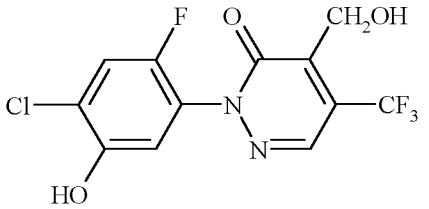
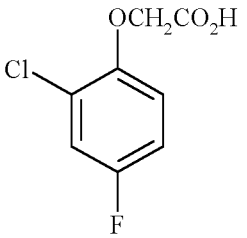
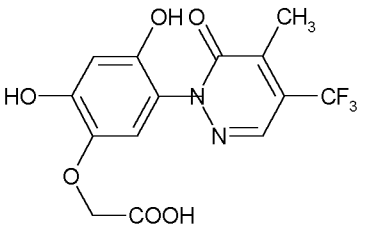
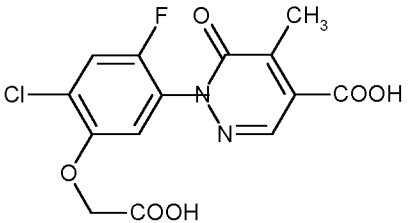
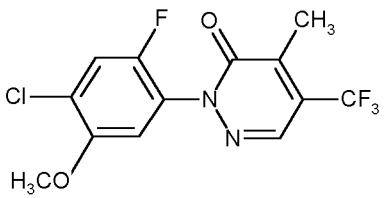
ATTACHMENT 1. Summary of Metabolites Discussed in Risk Assessment.

Common Name (codes) Chemical Name	Structure	Matrices
Flufenpyr-ethyl (V-3153, S-3153) Ethyl [2-chloro-4-fluoro-5-(5-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridazin-1-yl] acetate		Soybean forage, seed, and hay Corn forage and stover Goat milk, kidney, and liver Hen liver
S-3153-acid [2-chloro-4-fluoro-5-(5-methyl-6-oxo-4-trifluoromethyl-1,6-dihydropyridazin-1-yl)phenoxy]-acetic acid		Soybean forage, seed, and hay Corn forage and stover Goat milk, kidney, and liver Hen liver Water
S-3153-acid-4-OH [2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl-1,6-dihydropyridazin-1-yl)phenoxy]- acetic acid		Soybean forage, seed, and hay Corn forage and stover

Common Name (codes) Chemical Name	Structure	Matrices
S-3153-acid-5′-CH_2OH [2-chloro-4-fluoro-5-(5-hydroxymethyl-6-oxo-4-trifluoromethyl-1,6-dihydropyridazin-1-yl)phenoxy]-acetic acid		Soybean forage, seed, and hay Corn forage and stover Goat milk, kidney, and liver Hen liver Water
S-3153-4-OH Ethyl [2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl-1,6-dihydropyridazin-1-yl)phenoxy]-acetate		Soybean forage, seed, and hay Corn forage and stover Water
S-3153-1-OH 2-(4-chloro-2-fluoro-5-hydroxy)phenyl-4-methyl-5-trifluoromethyl-2,3-dihydropyridazin-3-one		Soybean forage, seed, and hay Corn forage and stover Water

Common Name (codes) Chemical Name	Structure	Matrices
S-3153-1-OH-5'-CH_2OH 2-(4-chloro-2-fluoro-5-hydroxy)phenyl-5-hydroxymethyl-4-trifluoromethyl-2,3-dihydropyridazin-3-one		Soybean forage, seed, and hay Corn forage and stover
2-Chloro-4-fluoro-phenoxyacetic acid		Soybean seed
S-3153-acid-4'-COOH 2-[2-chloro-4-fluoro-5-[5-methyl-6-oxo-4-(carboxylic acid)-1,6-dihydropyridazin-1-yl]phenoxy]acetic acid		Water
S-3153-acid-2,4-$(OH)_2$		Water



Common Name (codes) Chemical Name	Structure	Matrices
S-3153-1-OCH$_3$ 2-(4-chloro-2-fluoro-5-methoxy)phenyl-4-methyl-5-trifluoromethyl-2,3-dihydropyridazin-3-one		Water

ATTACHMENT 2. Summary of Residues from the Crop Field Trials with Flufenpyr-ethyl.

Summary of Flufenpyr-ethyl Residues from the Crop Field Trials.						
Crop Matrix	**Applic. Rate (lb ai/A)**	**PHI (days)**	**Residues (ppm)**			
			Min.	**Max.**	**HAFT[1]**	**Mean**
Soybeans (proposed use = 0.054 ai/A total application rate)						
Soybean seed	0.052-0.055	42-46	<0.005	<0.005	<0.005	-
Sugarcane (proposed use = 0.054 lb ai/A total application rate)						
Sugarcane	0.052-0.054	89-91	<0.005	<0.005	<0.005	-
Field Corn (proposed use = 0.054 lb ai/A total application rate)						
Field Corn forage	0.050-0.055	32-65	<0.005	<0.005	<0.005	-
Field Corn stover	0.050-0.055	58-115	<0.005	<0.005	<0.005	-
Field Corn grain	0.050-0.055	58-115	<0.005	<0.005	<0.005	-

[1] HAFT = Highest Average Field Trial.

Summary of S-3153 acid-4-OH Residues from the Crop Field Trials.						
Crop Matrix	Applic. Rate (lb ai/A)	PHI (days)	Residues (ppm)			
			Min.	Max.	HAFT	Mean
Sugarcane (proposed use = 0.054 lb ai/A total application rate)						
Sugarcane	0.052-0.054	89-91	<0.01	<0.01	<0.01	-
Field Corn (proposed use = 0.054 lb ai/A total application rate)						
Field Corn forage	0.050-0.055	32-65	<0.01	0.03	0.03	<0.014
Field Corn stover	0.050-0.055	58-115	<0.01	0.03	0.025	<0.012

ATTACHMENT 3. Summary of Proposed and HED-Recommended Tolerances.

Proposed			HED-Recommended		
Tolerance Expression	**Commodity Definition**	**Tolerance**	**Tolerance Expression**	**Commodity Definition**	**Tolerance**
flufenpyr-ethyl (ethyl (2-chloro-4-fluoro-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetate)	Field corn, forage	0.01	flufenpyr-ethyl (acetic acid, [2-chloro-4-fluoro-5-[5-methyl-6-oxo-4-(trifluoromethyl)-1(6H)-pyridazinyl]phenoxy]-ethyl ester)	Corn, field, grain	0.01
	Field corn, grain	0.01		Soybean, seed	0.01
	Field corn, stover	0.01		Sugarcane, cane	0.01
	Soybean, seed	0.01	combined residues of flufenpyr-ethyl and its metabolite, [2-chloro-4-hydroxy-5-(5-methyl-6-oxo-4-trifluoromethyl–1,6-dihydropyridazin-1-yl)phenoxy]acetic acid, free and conjugated	Corn, field, forage	0.05
	Sugarcane	0.01			
S-3153 acid-4-OH	Field corn, forage	0.04		Corn, field, forage	0.05
	Field corn, stover	0.04			