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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: **September 25, 2012**

SUBJECT: **Fluroxypyr.** Human Health Risk Assessment to Support Proposed New Use on Rice

PC Code: 128968
Decision No.: 456978
Petition No.: 1F7928
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: 48581304, 48581311

DP Barcode: D396339
Registration No.: 62719-285, 62719-577, 62719-xxx
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 69377-81-7
40 CFR: §180.535

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TO: **Kathryn Montague**, RM Team 23
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The Registration Division (RD) requested that the Health Effects Division (HED) conduct a risk assessment for the active ingredient fluroxypyr to estimate the risk to human health that will result from proposed new uses on rice. The attached human health risk assessment addresses exposure and risk associated with the proposed use. The exposures assessed include dietary (food and water), inhalation for occupational workers and residential handlers, toddlers' oral exposure from playing on treated turf, and aggregate exposure and risk for residential handlers and toddlers who play on treated turf. There were no risks of concern identified for any route or duration of exposure.

1.0 Executive Summary

HED has conducted a human health risk assessment for the herbicide, fluroxypyr for the purpose of establishing tolerances for a proposed new use on rice as requested by Dow Agrosciences LLC.

The proposed use directions specify that fluroxypyr is to be applied by broadcast ground and aerial application to the rice field at a maximum single application rate of 0.24 lb ae/A (0.34 lbs ai/A). Two applications per season are permitted with a 60-day preharvest interval (PHI).

The kidney is the target organ for fluroxypyr (and fluroxypyr MHE) following oral exposure to rats, mice, and dogs. There was no evidence of increased susceptibility following *in utero* exposure to the acid and the ester in rats and rabbits, or following pre and/or postnatal exposure to the acid form in rats. Neither developmental toxicity nor reproductive toxicity was observed in rats. In rabbits, developmental toxicity was not observed following exposure to fluroxypyr, but abortions were observed in rabbits following exposure to fluroxypyr MHE at the limit dose. There was no evidence of neurotoxicity or neuropathology in any study. There were no treatment-related effects in an immunotoxicity study in rats. Fluroxypyr is classified "not likely to be carcinogenic to humans" and there is no concern for its mutagenicity potential.

Endpoints for risk assessment were based on kidney effects. Doses selected for risk assessment purposes are summarized below. The FQPA safety factor was reduced to 1X since the toxicity database was considered complete, there were no residual uncertainties for pre-and/or post natal toxicity, no evidence of neurotoxicity or neuropathology was found, and the estimated exposures were not likely to underestimate risk.

An acute dietary risk assessment was not required as there were no effects seen in the database which could be attributable to exposure to a single dose of fluroxypyr. Chronic dietary exposure and risk assessments were conducted assuming 100% crop treated and tolerance level residues for all existing and new uses of fluroxypyr. Modeled drinking water estimated environmental concentrations (EECs) were incorporated into the chronic dietary risk assessment. No chronic dietary risks of concern were identified for the U.S. population or any subgroup. The most highly exposed subpopulation was infants (< 1 year) with an estimated risk equivalent to 3.5% of the chronic population adjusted dose (cPAD). A quantitative dietary cancer risk assessment was not required.

There were no new residential uses requested in this petition. The existing residential uses have been assessed using the new residential SOP (01/01/2012) and all calculated residential MOEs were greater than the target of 100, and therefore, were not of concern to HED.

Human health aggregate risk assessments were conducted for the chronic aggregate exposure (food + drinking water) scenario, as well as the short-/intermediate-term aggregate exposure scenario. Short-, intermediate- and chronic aggregate risks were not of concern.

Occupational handler and post application exposures and risks were evaluated for the proposed new use on rice. MOEs for all scenarios exceeded the target MOE of 100 and were not of concern.

This risk assessment does not rely on any toxicity data from studies in which human subjects were intentionally exposed to a pesticide or other chemical. The ORE assessment used generic exposure data from exposure studies that have been subject to OPP ethics review and have been approved for use in human health risk assessments.

2.0 HED Recommendations

HED has no objection to establishment of the proposed tolerances shown below or to registration of the new use of fluroxypyr on rice.

2.1 Data Deficiencies/Conditions of Registration

There are no data gaps with respect to toxicology, residue chemistry, or occupational exposure for fluroxypyr.

2.2 Tolerance Considerations

Tolerances are established for the residues of the herbicide fluroxypyr, including its metabolites and degradates, under 40 CFR 180.535. Compliance with the established tolerance levels is determined by measuring only the sum of fluroxypyr 1-methylheptyl ester [1-methylheptyl ((4-amino-3, 5-dichloro-6-fluoro-2-pyridinyl)oxy)acetate] and its metabolite fluroxypyr [((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)acetic acid] calculated as the stoichiometric equivalent of fluroxypyr. The established tolerances for plant commodities range from 0.02 ppm (field corn grain, sweet corn K+CWHR, and sorghum grain) to 160 ppm (grass hay) [40 CFR 180.535(a)]. The established tolerances for livestock commodities range from 0.1 ppm (fat, meat, and meat byproducts) to 1.5 ppm (kidney). Time-limited tolerances for combined residues of fluroxypyr 1-MHE and its metabolite fluroxypyr in/on field corn, sweet corn, onion, and sorghum commodities have been established in connection with use of fluroxypyr 1-MHE under Section 18 emergency exemptions [40 CFR 180.535(b)]; time-limited tolerances have past due expiration dates (12/31/05 and 12/31/06), except for onion with an expiration date of 06/30/07.

2.2.1 Enforcement Analytical Method

Adequate GC/ECD (gas chromatography/electron capture detection) analytical methods are available to enforce the proposed plant tolerances. The available methods for plant commodities involve extraction of fluroxypyr residues with acetone, partitioning with hexane, purification using a Florisil column, and analysis of residues by GC/ECD.

2.2.2 International Harmonization

There are no Maximum Residue Limits (MRLs) established by Codex, Canada, or Mexico for any of the proposed commodities in the current registration action (Section 3).

2.2.3 Recommended Tolerances

Permanent tolerances are established under 40 CFR §180.535(a) for the combined residues of fluroxypyr 1-MHE and its metabolite fluroxypyr on a number of plant and livestock commodities. Tolerances are already set on most of the representative crops listed for the cereal grains crop group 15 (sweet corn, field corn, sorghum & wheat), and the forage, fodder, and straw of cereal grains crop group 16 (corn & wheat) except for rice. To support this registration, Dow has submitted field trial data and a processing study for rice. For this petition request, Dow is proposing that permanent tolerances be established for the residues of fluroxypyr in/on the following rice commodities:

Rice .....1.5 ppm
Rice, bran .....3.0 ppm

2.3 Label Recommendations

No label revisions are needed and no recommendations are being made by HED.

2.3.1 Recommendations from Occupational Assessment

No label revisions are needed based on the occupational exposure risk assessments.

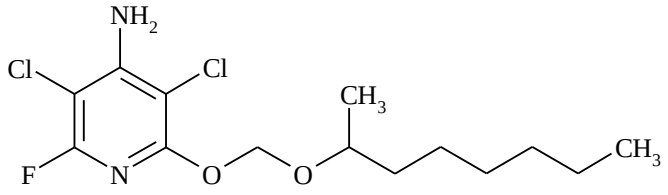
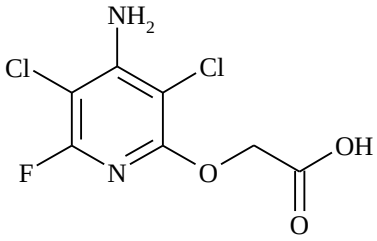
2.3.2 Recommendations from Residential Assessment

No recommendations are needed based on HED's residential exposure and risk assessment.

3.0 Introduction

Fluroxypyr is a member of the pyridinoxy acid class of herbicides. Other chemicals in this class include triclopyr, picloram, and clopyralid. Fluroxypyr induces auxin-type responses in susceptible annual and perennial broadleaf weeds. The pesticide active ingredient is fluroxypyr methylheptyl ester (fluroxypyr MHE). The end-use products are emulsifiable concentrate formulations of fluroxypyr 1-methylheptyl ester (fluroxypyr 1-MHE), with a maximum single application rate of 0.24 lb acid equivalents (a.e.) or 0.34 lb ai/ per acre.

3.1 Chemical Identity

Table 3.1. Fluroxypyr 1-MHE Nomenclature.	
Compound	
Common name	Fluroxypyr 1-methylheptyl ester
Company experimental name	XRM-5316
IUPAC name	1-methylheptyl-4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetate
CAS name	[(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetic acid, 1-methylheptyl ester
CAS #	81406-37-3
End-use product/EP	1.5 lb ae/gal EC formulation (Starane™ Herbicide; EPA Reg. No. 62719-286)
Fluroxypyr, free acid	
Common Name	Fluroxypyr
CAS name	[(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetic acid
CAS #	69377-81-7

3.2 Physical/Chemical Characteristics

Table 3.2. Physicochemical Properties of the Fluroxypyr 1-MHE.	
Parameter	Value
Melting point/range	57.5°C
pH	6.81 in solution containing 90.1 µg/L
Density	1.30 g/mL at 21°C
Water solubility (20 °C)	90.1 µg/L in purified water 294 µg/L in pH 5 buffer 136 µg/L in pH 7 buffer 57.2 g/L in pH 9 buffer
Solvent solubility (20 °C)	6.23 g/100 mL in n-heptane >200 g/100 mL in xylene 377 g/100 mL in methanol 22.0 g/100 mL in n-octanol >300 g/100 mL in acetone
Vapor pressure	2.0 x 10^{-5} kPa at 25 °C 1.0 x 10^{-5} kPa at 20 °C
Dissociation constant	Not applicable
Octanol/water partition coefficient Log(K_{OW})	4.57 at pH 5 5.04 at pH 7 5.31 at pH 9
UV/visible absorption spectrum	Not available

3.3 Pesticide Use Pattern

The herbicide fluroxypyr-1-methylheptyl ester is currently registered for use in or on field corn, sweet corn, sorghum, range and pasture grasses, turf, dry bulb onions, garlic, pome fruits and shallots. Current petition is to establish tolerances for fluroxypyr on rice and rice bran. The most recent risk assessment was performed for the proposed uses of fluroxypyr on pome fruits and shallots (Donna S. Davis, 2007; D344540). Fluroxypyr is registered for use on residential turfgrass and recreational sites, such as golf courses, parks, and sports fields. The summary of purposed use pattern is presented in Table 3.3.

Table 3.3 Summary of Purposed Use Patterns/Formulation Information

Crop	Trade Name	Number of Application per Season	Max Application lb ai/A. per Season	Max. Single Application lb ai/A	PHI
Rice	Starane Ultra™ Herbicide	2	0.57	0.34	60

3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed new use of the herbicide fluroxpypyr on rice. Fluroxpypyr is currently registered for use on field corn, and there are tolerances for residues in crop group 15 (cereal grains) and crop group 16 (forage, fodder and straw of cereal grains) and livestock commodities. Therefore, humans may be exposed to fluroxpypyr in food and drinking water, since the chemical may be applied directly to growing crops and may reach surface and ground water sources of drinking water. While the products containing fluroxpypyr do not appear to be intended for homeowner use, there is the potential for homeowners to purchase and apply the product to their own lawns, and the potential for this exposure has been considered in the risk assessment. In an occupational setting, applicators may be exposed while handling the pesticide prior to application (i.e., mixing/loading), as well as during application. There is the potential for postapplication exposure to workers re-entering treated fields, but since there is no dermal endpoint (toxicity) associated with fluroxypyr, there are no human health concerns for risk by this route of exposure.

Risk assessments have been previously prepared for the existing use of fluroxypyr on residential turf (K. O'Rourke, D328799, 07/06/2006). This risk assessment considers all exposure pathways based on the existing and proposed new use of fluroxypyr.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (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.

4.0 Hazard Characterization and Dose-Response Assessment

The toxicology database is complete. The Fluroxypyr Risk Assessment Team has reviewed the toxicity database and concluded that the doses and endpoints previously selected for risk assessment purposes are consistent with current HED policy and are appropriate for the routes and durations of exposure anticipated from the existing and newly proposed uses of fluroxypyr.

4.1 Toxicology Studies Available for Analysis

The toxicology database on fluroxypyr, which includes studies on both fluroxypyr and fluroxypyr methylheptyl ester) is sufficient for assessing the toxicity and characterizing the hazard of fluroxypyr. The toxicology studies for fluroxypyr and fluroxypyr methylheptyl ester are summarized in Table A.1 in Appendix A. The database includes the following studies.

- Acute/lethality studies (oral, dermal, inhalation, primary eye and dermal irritation, and dermal sensitization) –fluroxypyr and fluroxypyr MHE
- Subchronic oral toxicity studies (rat, mouse, and dog) - fluroxypyr
- Developmental (rat and rabbit) and reproductive (rat) toxicity (oral) studies –fluroxypyr and fluroxypyr MHE
- Dermal (21-day) toxicity (rabbit) study - fluroxypyr MHE
- Chronic oral toxicity studies (rat and dog) - fluroxypyr
- Carcinogenicity (oral) studies [rat (chronic combined) and mouse] - fluroxypyr
- Metabolism study (rat) - fluroxypyr MHE
- Mutagenicity battery - fluroxypyr MHE
- Immunotoxicity study (rat) - fluroxypyr

The studies available for consideration of fluroxypyr toxicity provide a comprehensive database, with routes of administration which are consistent with potential exposure scenarios.

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

Radiolabeled fluroxypyr methylheptyl ester (MHE) was readily absorbed and rapidly eliminated following a single oral dose to male Fischer 344 rats. Approximately 90% of the administered dose was absorbed. Once absorbed, it was extensively metabolized (≈20 metabolites) and rapidly expired as $^{14}CO_2$ or eliminated in the urine, primarily as metabolites. Peak plasma concentrations were attained by 7 hours, and the half-live for the elimination phase was ≈18 hours. Approximately 7% of the administered dose was found in the carcass and ≈0.14% was found in the blood.

4.2.1 Dermal Absorption

No dermal absorption studies are available. A dermal absorption factor is not required since quantification of dermal risk is not required based on lack of toxicity observed in the dermal toxicity study, and the lack of pertinent effects in other toxicity studies not measured in the dermal toxicity study.

4.3 Toxicological Effects

The kidney is the target organ for fluroxypyr following oral exposure to rats, mice, and dogs. In the rat, increased kidney weight, nephrotoxicity, and death were observed in both sexes in the 90-day feeding study, and increased kidney weight and chronic progressive glomerulonephropathy were observed in both sexes in the chronic study. Increased kidney weight was observed in maternal rats in the developmental toxicity study with fluroxypyr, and kidney effects (deaths due to renal failure; increased kidney weight, and microscopic kidney lesions) were observed in both sexes in the 2-generation reproduction study in rats. Although kidney toxicity (early signs of acute tubular nephrosis) was observed in dogs in the 28-day feeding study, no kidney effects or other treatment related toxicity were seen in the chronic feeding study in dogs at the same doses used in the 28-day study. Kidney lesions (increased incidences of renal papillary necrosis and regenerative nephrosis in females) were observed in mice following long-term exposure.

There was no evidence of increased susceptibility (quantitative/qualitative) following *in utero* exposure to the acid and the ester in rats and rabbits, or following pre and/or postnatal exposure to the acid form in rats. Neither developmental toxicity nor reproductive toxicity was observed in rats. In rabbits, developmental toxicity was not observed following exposure to fluroxypyr at dose levels that resulted in maternal death. Abortions were observed in rabbits following exposure to fluroxypyr MHE at the limit dose. There was no evidence of neurotoxicity or neuropathology in any of the studies. An immunotoxicity study in rats found no indication of immunotoxicity. Fluroxypyr is classified "not likely to be carcinogenic to humans", and there is no concern for its mutagenicity potential.

Fluroxypyr has low acute toxicity by the oral and dermal routes of exposure and moderate acute toxicity by the inhalation route of exposure, based on lethality studies. Fluroxypyr (MHE) ester is less acutely toxic than the acid by the oral route of exposure. Neither chemical is irritating to the skin. Fluroxypyr MHE is not a dermal sensitizer; however, it is a mild eye irritant. The

acute toxicity profiles for fluroxypyr and fluroxypyr MHE technical are contained in Attachment 1 of this risk assessment.

The toxicity profile of fluroxypyr and fluroxypyr 1-MHE technical is shown in Attachment 2 of this risk assessment.

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

HED recommends that the 10X FQPA Safety Factor (for the protection of infants and children) be reduced to 1X. An FQPA Safety Factor of 1X is appropriate for the following reasons:

The toxicity database is complete and adequate to assess safety for infants and children. There is no evidence of increased qualitative or quantitative susceptibility in the developmental rat and rabbit studies or in the rat 2-generation reproduction study. These studies have clearly defined NOAEL/LOAELs. Both the neurotoxicity screening battery and the developmental neurotoxicity study have been waived. The exposure assessment will not underestimate children's exposure to fluroxypyr. Further details may be found in the following sections.

4.4.1 Completeness of the Toxicology Database

The toxicology database for fluroxypyr is complete.. Acceptable developmental toxicity studies in rats and rabbits are available for fluroxypyr and fluroxypyr MHE, in addition to an acceptable reproduction study for fluroxypyr in rats. The HED's Hazard and Science Policy Council (HASPOC) determined that the acute and subchronic neurotoxicity studies may be waived.

4.4.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity or neuropathology in the available studies. The salivation and ataxia seen in animals prior to death were considered to be agonal; the salivation in the rat studies occurred following gavage dosing and was attributed to localized irritation; the decreased brain weight in the 90-day rat study was not substantiated in other studies. There is not a concern for developmental neurotoxicity.

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

There is no evidence of increased qualitative or quantitative susceptibility following *in utero* exposure to the acid and the ester in rats and rabbits or following pre and/or postnatal exposure to the acid in rats.

Fluroxypyr is neither a developmental nor a reproductive toxicant in rats. Fluroxypyr has been evaluated for potential developmental effects in the rat and rabbit (gavage administration). Maternal toxicity included death in rats and rabbits. There were no developmental effects in the rat, and while abortions were observed in the rabbit, they occurred only at the limit dose.

The Fluroxypyr Risk Assessment Team reviewed the toxicity database and HIARC recommendations for consistency with current policy and reaffirmed the previous assessment

that the FQPA SF could be reduced to 1X based on the following considerations:

- The toxicological database is considered complete.
- There are no concerns or residual uncertainties for pre- and/or post-natal toxicity.
- There was no evidence of neurotoxicity or neuropathology in the available studies and the neurotoxicity battery (acute and subchronic) and developmental neurotoxicity study requirements have been waived.
- The chronic dietary food exposure assessment utilizes tolerance level residue estimates and assumes 100 % CT for all commodities. This assessment will not underestimate exposure/risk.
- The dietary drinking water assessment utilizes water concentration values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations which will not be exceeded.
- The previous residential exposure assessment was conducted using standard assumptions and is not likely to underestimate exposure.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the fluroxypyr database in regard to dietary (food and drinking water), occupational, and residential exposures. The residue data used for dietary exposure assessment are described in Section 5.4.1 of this document. Further, occupational and residential exposure estimates are based on conservative, health-protective assumptions that also ensure exposures are not underestimated.

4.5 Toxicity Endpoint and Point of Departure Selections

The available hazard database is adequate to characterize any potential for prenatal or postnatal risk for infants and children.

4.5.1 Dose-Response Assessment

The studies used for selecting toxicity endpoints and points of departure (PoDs) for various exposure scenarios are presented in Appendix A.A2. The exposure profile includes all routes and durations of exposure, but based on the proposed use patterns for fluroxypyr, the expected exposure profile will be for chronic dietary, inhalation and incidental oral exposures.

While the description of the toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios is presented in Appendix A, the following outlines the dose-response assessment and a general description of the endpoint selection. A summary of the endpoint and point of departure selections for fluroxypyr is shown in Tables 4.5.4.1 and 4.5.4.2.

***Acute Dietary Endpoint*:** An acute endpoint was not identified. No adverse effects were identified following a single oral dose, and there are no developmental or neurotoxicity concerns noted in the database.

Chronic Dietary Endpoint: The chronic endpoint was selected from the chronic/carcinogenicity study in rats (NOAEL= 100 mg/kg/day; LOAEL= 500 mg/kg/day), based on kidney effects that include increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal function, and an increase in the severity of chronic progressive glomerulonephropathy in both sexes. The NOAEL/LOAEL are supported by the kidney effects observed in male rats in the 2-generation reproduction study (increased kidney weights with corresponding gross and microscopic kidney findings, including papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubule-interstitial nephritis, and dilatations of the tubules). Although a lower NOAEL (50 mg/kg/day) was observed in a 28-day oral toxicity study in dogs (acute tubular necrosis), the finding was not replicated in the chronic dog study at the same dose levels that were tested in the 28-day study, and no other toxicity was observed in the chronic dog study.

Short- and Intermediate-Term Incidental Oral Endpoints:
The incidental oral endpoint was selected from the chronic/carcinogenicity study in rats (NOAEL= 100 mg/kg/day; LOAEL= 500 mg/kg/day), based on kidney effects that include increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal function, and an increase in the severity of chronic progressive glomerulonephropathy in both sexes. This dose/endpoint would address the nephrotoxicity concern for these exposure periods since signs of nephrotoxicity were observed in both sexes of rats after 90 days of exposure. Although a lower NOAEL was observed in the 90-day rat study (80 mg/kg/day), the apparent difference in NOAELs is attributed to dose-spacing (LOAEL 750 mg/kg/day). The 28-day dog study also was not selected due to the low confidence in this study (2 dogs/sex were tested; the results were not replicated in the 1-year dog study; and no other toxicity was observed in the chronic study).

Short- and Intermediate-Term Dermal Endpoints: No dermal endpoint was selected because no dermal or systemic toxicity at the limit dose was observed in the dermal toxicity study in rabbits, and there was no concern for developmental toxicity in rats or rabbits. The developmental toxicity observed in the rabbit occurred at the limit dose. Also, there was no evidence of progression of nephrotoxicity in the rat since the NOAELs/LOAELs were comparable between the subchronic and chronic toxicity studies.

Short- and Intermediate-Term Inhalation Endpoint*:* The most appropriate endpoint for non-occupational and occupational inhalation exposure was determined to be from the chronic oral toxicity study in rats (NOAEL=100 mg/kg/day; LOAEL=500 mg/kg/day), based on kidney effects that include increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal function, and an increase in the severity of chronic progressive glomerulonephropathy in both sexes. Although a point of departure obtained from a study conducted *via* the most relevant route of exposure is preferred for risk assessment, there is no repeat exposure inhalation toxicity study on fluroxypyr. HED waived the requirement for the 28-day inhalation toxicity study, based on a weight of evidence (WOE) approach (TXR No. 0056397) that considered the entire available hazard and exposure information for fluroxypyr.

The level of concern for the relevant non-occupational and occupational exposure scenarios is an MOE of less than 100, based on the standard uncertainty factors for intraspecies variation (10X) and interspecies extrapolation (10X).

Long-Term Dermal and Inhalation Endpoints: No long-term exposure scenarios exist for fluroxypyr.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Dermal exposure was not quantitatively assessed due to a lack of toxicity via the dermal route. Since adults were assessed for potential inhalation exposure while applying fluroxypyr to lawns, this exposure should be combined with background levels in food and water to determine aggregate exposure. For children's residential exposure, only oral postapplication exposure was assessed, and this exposure should be combined with exposure from food and drinking water to determine aggregate exposure. For occupational workers, only inhalation exposure and risk were assessed.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Under the revised 2005 Agency cancer assessment guidelines, fluroxypyr is classified as "not likely to be a human carcinogen." There were no treatment-related increases in the incidence of tumors in either the rat or mouse carcinogenicity studies, both of which were tested at adequate doses.

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

Tables 4.5.4.1 and 4.5.4.2 summarize the points of departure and toxicity endpoints used in the dietary/non-occupational and occupational human health risk assessments, respectively.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Fluroxypyr for Use in Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD/PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (All populations)	No adverse effects were identified following a single oral dose and there are no developmental concerns noted in the database.			
Chronic Dietary (All populations)	NOAEL= 100 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1x	chronic RfD = 1 mg/kg/day chronic PAD= 1 mg/kg/day	**Chronic/Carcinogenicity-Rat** LOAEL = 500 mg/kg/day, based on kidney effects (increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal functions, and increase in severity of chronic progressive glomerulonephropathy in both sexes).
Incidental Oral (Short- and Intermediate Term)	NOAEL= 100 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1x	Residential LOC is for MOE below 100	**Chronic/Carcinogenicity-Rat** LOAEL = 500 mg/kg/day, based on kidney effects (increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal functions, and increase in severity of chronic progressive glomerulonephropathy in both sexes).
Dermal (Short- and Intermediate-term)	Quantification not required since 21-Day dermal rabbit NOAEL = 1000 mg/kg/day, and there are no developmental toxicity concerns.			
Dermal (Long-term)	Long-term dermal exposure is not expected based on the current use pattern.			
Inhalation (All durations)	Oral study NOAEL= 100 mg/kg/day (inhalation and oral toxicity assumed to be equivalent)	UF_A 10x UF_H 10x FQPA SF = 1x	Residential LOC is for MOE below 100	**Chronic/Carcinogenicity-Rat** LOAEL = 500 mg/kg/day, based on kidney effects (increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal functions, and increase in severity of chronic progressive glomerulonephropathy in both sexes).
Cancer (oral)	Classified as a "Not Likely" human carcinogen.			

UF = uncertainty factor, FQPA SF = Food Quality Protection Act 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

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Fluroxypyr for Use in 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**
Inhalation (All durations)	Oral study NOAEL= 100 mg/kg/day (inhalation and oral toxicity assumed to be equivalent)	UF_A 10x UF_H 10x FQPA SF = 1x	Occupational LOC is for MOE below 100	**Chronic/Carcinogenicity-Rat** LOAEL = 500 mg/kg/day, based on kidney effects (increased kidney weights, alterations in clinical chemistry parameters indicative of impaired renal functions, and increase in severity of chronic progressive glomerulonephropathy in both sexes).
Cancer (oral)	Classified as a "Not Likely" human carcinogen.			

UF = uncertainty factor, FQPA SF = Food Quality Protection Act 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

5.0 Dietary Exposure and Risk Assessment

A chronic dietary exposure analysis was performed for the purposes of this human health risk assessment (Fluroxypyr Chronic Dietary (Food and Drinking Water)), (S. Tadayon, D405555, 09/11/12).

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

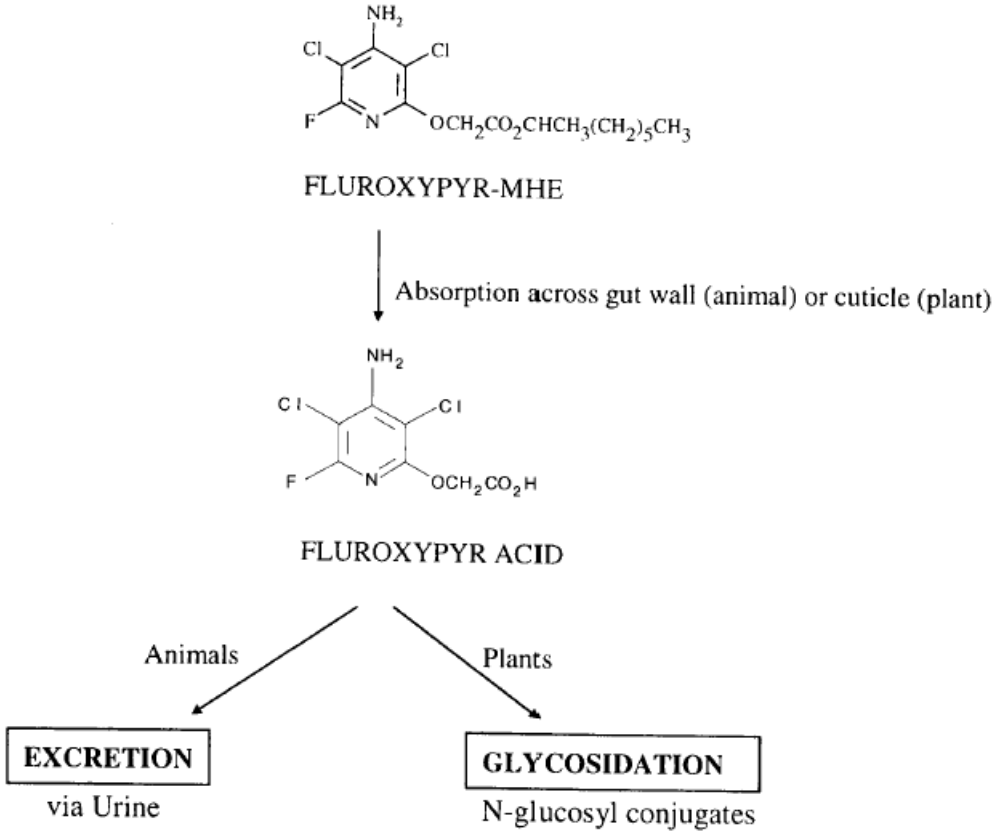
There have been no new data submitted with respect to metabolism in plants and livestock. HED previously concluded that the nature of the residue is adequately understood based on studies in corn, in rotational crops and in livestock. The residue of concern includes the parent fluroxypyr 1-MHE and its acid metabolite, fluroxypyr.

5.1.2 Summary of Environmental Degradation

Degradation of fluroxypyr –MHE and fluroxypyr in environmental fate laboratory studies occurs through base-catalyzed hydrolysis and microbial-medicated metabolism under aerobic conditions. In sterilized buffered water, fluroxypyr –MHE hydrolyzed to the fluroxypyr acid with half lives of 3 and 454 days at PH 9 and 7, respectively. Hydrolysis of fluroxypyr-MHE was not observed in the acidic test system at PH 5. In the aerobic soil metabolism study, microbial degradation of fluroxypyr-MHE appears to follow a biphasic degradation pattern with an initial first order half life of 1-3 weeks in four soils. The rate of metabolism decreased significantly after 2 months. Fluroxypyr and fluroxypyr –MHE degrade rapidly in the aerobic aquatic environment (half life 14 days). Fluroxypyr and fluroxypyr-MHE do not degrade by photolysis in aqueous environments or in soil. Volatility is not a significant rout of dissipation.

5.1.3 Comparison of Metabolic Pathways

The metabolism of fluroxypyr 1-MHE in plants is similar in wheat, onions, and broad-leaved weeds. Metabolism involves cleavage of the ester to the acid, followed by conjugation of the acid. Cleavage of the ether linkage to yield the pyridinol metabolite was insignificant. The primary route of uptake is through the plant cuticle, and other forms of uptake (i.e., via the roots) are less significant. The petitioner presented the metabolic summary for fluroxypyr MHE shown below and taken directly without alteration from MRID 47017103.



In addition to weed metabolites, rice roots may also be exposed to soil degradates of fluroxypyr. An aerobic soil metabolism study demonstrated that fluroxypyr 1-MHE is rapidly hydrolyzed to the acid, though not completely as some of the ester remained more than 5 months after application. Mineralization to CO_2 was a significant route of degradation in the soil. Two soil metabolites were formed: pyridinol and methoxypyridine. The confined rotational crop studies (30-day PBI (plant back interval) with wheat, lettuce and turnips) demonstrated that the two soil metabolites were present at ≤0.01 ppm fluroxypyr acid equivalents in lettuce and turnip tops, and not present in wheat grain. Free or conjugated fluroxypyr acid was the most commonly observed residue and fluroxypyr 1-MHE was not detected at levels >0.01 ppm fluroxypyr acid equivalents.

5.1.4 Residues of Concern Summary and Rationale

The residues of concern for tolerance setting and risk assessment purposes in plants and livestock commodities are fluroxypyr 1-MHE and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr as shown in Table 5.1.4. The rationale for inclusion of these compounds

in the residue of concern is as follows. Fluroxypyr is the major residues in plants. In livestock, very low levels of residue transfer to tissues were seen, and fluroxypyr was the sole residue identified in livestock tissues. Further, the analytical enforcement method includes a hydrolysis step and detects the combined residues of parent and acid, expressed as fluroxypyr equivalents. Lastly, the parent and acid are considered to be of equal toxicity (DP #: D402134, Peter Savoia, 09/11/2012).

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues Included In Risk Assessment	Residues Included In Tolerance Expression
Plants	Primary Crops	Fluroxypyr 1-MHE and Fluroxypyr, free and conjugates	Fluroxypyr 1-MHE and Fluroxypyr, free and conjugates
	Rotational Crops		
Livestock	Ruminant	Fluroxypyr 1-MHE and Fluroxypyr, free and conjugates	Fluroxypyr 1-MHE and Fluroxypyr, free and conjugates
	Poultry & Eggs		
Drinking Water		Fluroxypyr 1-MHE, Fluroxypyr	Not Applicable

5.2 Food Residue Profile

Currently the use of fluroxypyr is limited to application to cereal grains and a new use on rice is proposed in this action. Fluroxypyr is applied post-emergent and consequently, significant residues are seen in forages of grains and rice. The plant metabolism data indicate translocation of residues throughout the plant and field trial data support this, as low, but quantifiable residues are seen in cereal grains and rice. Transfer of residues to livestock through consumption of treated feed items may occur. Low levels are expected in meat, meat by products, and fat. The highest residues are expected in kidney.

5.3 Water Residue Profile

The proposed new use label for application to rice permits a single maximum application of 0.34 lb ai per acre per year and allows for two applications with a maximum total of 0.568 lb ai per acre per year with a minimum retreatment interval (RTI) of ten days. The label also requires a pre-harvest interval (PHI) of 60 days of harvest. This assessment reflects a high-exposure scenario by assuming the maximum application amount of 0.568 lb ai/A (0.64 kg/ha) is used per year.

Tier 1 Rice Model (v1), When using the Tier 1 rice model, EFED assumes pesticide application to a static rice paddy with no inflow from rainfall or outflow from seepage, overflow or evaporation. The only process simulated by the model is partitioning of the applied chemical between the 10-centimeter deep water column and the 1-centimeter deep sediment layer of the paddy. The partitioning is based on the pesticide's K_d. Degradation in the paddy is not calculated by the model so the pesticide is assumed to remain at the initial concentration in the water

indefinitely. Results of the tier 1 rice modeling are presented in Table 5.3. Acute and chronic values are equal because the model does not simulate degradation of the pesticide in the paddy.

Table5.3. Summary of Tier 1 Rice Model EDWC for Use on Rice		
Assessment Type	**Acute EDWC**	**Chronic EDWC**
Tier 1 Rice Model (conc in paddy)	540 µg/L (ppb)	540 µg/L (ppb)

5.4 Dietary Risk Assessment

Memo, S.Tadayon, 09/11/2012, D405555

5.4.1 Description of Residue Data Used in Dietary Assessment

For this analysis existing and recommended tolerance levels were used, as well as 100% crop treated (CT) assumptions for all commodities. DEEM (Version 7.81) default processing factors were used for most processed commodities that do not have individual tolerances. The existing tolerances for livestock commodities were considered adequate (DP #: D405555, S. Tadayon, 09/11/2012.

Drinking water was incorporated directly into the dietary assessment using the maximum chronic concentration for surface water generated by the Rice Model (v1) at 540 ppb.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The chronic dietary exposure assessments based on food and drinking water includes the assumption of 100% crop treated (PCT) for all existing and proposed uses.

5.4.3 Acute Dietary Risk Assessment

There was no appropriate endpoint identified for assessing acute dietary exposure; therefore, no acute dietary risk assessment was performed.

5.4.4 Chronic Dietary Risk Assessment

An unrefined chronic dietary analysis for fluroxypyr was conducted using tolerance level residues and 100% crop-treated (CT) for all existing and proposed crop uses. Fluroxypyr chronic dietary (food + drinking water) exposure estimates using the DEEM-FCID™ software are below HED's level of concern for the U.S. population and each of the population subgroups. Chronic dietary exposure was 1.5% of the cPAD for the general U.S. population. The chronic dietary exposure for the highest reported exposed population subgroup, all infants (<1 year old), was 3.5% of the cPAD. The results of the analysis indicate that chronic risk from the dietary (food + drinking water) exposure to fluroxypyr will not exceed HED's level of concern for the general U.S. population, nor any other population subgroups.

The results of the chronic dietary exposure analysis are reported in the Summary Table 5.4.5.

Table 5.4.5. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Fluroxypyr.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	N/A	N/A	0.01476	1.5	N/A	N/A
All Infants (< 1 year old)			**0.03514**	**3.5**		
Children 1-2 years old			0.03286	3.3		
Children 3-5 years old			0.02411	2.4		
Children 6-12 years old			0.01597	1.6		
Youth 13-19 years old			0.01124	1.1		
Adults 20-49 years old			0.01367	1.4		
Adults 50+ years old			0.01312	1.3		
Females 13-49 years old			0.01349	1.3		

*Population subgroups with the highest exposure are shown in bold.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Memo, M.Lloyd, 09/11/2012, D402132

There are no proposed residential uses in this petition; however, there are existing residential turf uses that have been reassessed in this document to reflect updates to HED's 2012 Residential SOPs along with policy changes for body weight assumptions.

A product containing fluroxypyr (i.e., Vista^{TM}) is registered for application to residential turfgrass and recreational sites such as golf courses, parks, and sports fields. It may be applied to turf at rates ranging from 0.125 to 0.47 lbs ai/A, but may not exceed 0.47 lbs ai/A/yr. The label does not prohibit homeowners from mixing/loading/applying Vista^{TM}.

6.1 Residential Handler Exposure

The residential handler assessment only quantitated the inhalation exposure route because there were no toxicity findings for the dermal route of exposure up to the limit dose, and there are no developmental effects of concern.

The maximum application rate is used for assessing risk estimates for all exposure scenarios (Table 6.1). All risk estimates have MOEs significantly greater than 100 (ranging from 3,800 to 1,500,000) and are not of concern.

Table 6.1. Short-Term Residential Handler Exposure and Risk Estimates for Application of Fluroxypyr on Residential Turf.

Exposure Scenario	Application Rate [a]	Area Treated Daily [b]	Baseline Inhalation Unit Exposure [b]	Baseline Dose [d]	Baseline Inhalation MOE [e]
	lb ai/A	*Acres/gallons*	*mg/lb ai*	*mg/kg/day*	
Manually-pressurized Handwand	0.47	5	0.018	0.0034	30,000
Hose-end Sprayer	0.47	0.5	0.022	0.000065	1,500,000
Backpack	0.47	5	0.14	0.026	3,800

a Application Rates based on maximum application rates of registered residential turf uses for fluroxypyr: Starane Ultra (EPA Reg. No. 6217-577).
b Based on HED's SOPs: Lawns/Turf (January 2012).
c Baseline Inhalation: no respirator.
d Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/gal) x area treated (Acres/day) x absorption factor (%) / body weight (80 kg). No inhalation absorption factor.
e MOE = NOAEL (ST Inhalation NOAEL = 100 mg/kg/day) / daily dose (mg/kg/day). Level of concern = 100.

6.2 Postapplication Exposure

Post-application exposure can result from a number of activities following pesticide applications on turf. Exposure may occur for people of all ages, adults, children 11 < 16 years old, children 6 < 11 years old, and children 1 < 2 years old. These populations are considered the index lifestages for lawns and turf depending on the exposure scenario. Young children 1 to <2 years old may receive incidental oral post-application exposure to fluroxypyr from treated turf. The postapplication exposures for children playing on treated turf resulting in incidental oral exposure as a result of mouthing behaviors were assessed using the new residential lawn/turf SOP (1/1/2012).

Although adults and children performing physical activities on treated turf (e.g. golfing, mowing) may also receive dermal exposure to fluroxypyr residues, a quantitative risk assessment for the dermal route of exposure was not conducted for reasons previously described. In addition, a quantitative postapplication inhalation exposure assessment was not conducted because of the low acute inhalation toxicity (Toxicity Category IV), low vapor pressure (9.27 x 10^{-7} mm Hg) and the relatively low proposed use rate (0.47 lb ai/A). The low application rate and vapor pressure; the inhalation assessment for handlers is protective of potential postapplication exposure and risk.

The MOEs for incidental oral scenarios are summarized in Tables 6.2. The MOEs ranged from 14,000 to 6,500,000 for incidental oral ingestion. All assessed residential exposures and risk estimates resulted in MOEs of > 100; and therefore, are not of concern to HED.

Table 6.2. Children's Short-term Non-Dietary Ingestion Fluroxypyr Exposure and Risk Estimate

Lifestage	Post-Application Exposure Scenario	Dose *mg/kg/day*	MOEs
Emulisiable Concentrate (EC) Liquid Formulation GF-2764 (EPA Reg. No. 62719-577) *3 lb ae/gallon* max single application rate: *0.47 lb ae/A*			
Child 1 to < 2 year old	Hand to Mouth	0.0070	14,000
	Object to Mouth	0.00022	460,000
	Incidental Soil Ingestion	0.000015	6,500,000

Hand-to-Mouth Dose = hand residue loading (mg/cm^2) x fraction of hand mouthed (0.127) x surface area of 1 hand (150 cm^2) x exposure time (1.5 hrs/day) x # of replenishment intervals/hr (4 int/hr) x (1-((1-saliva extraction factor (0.5))^(Number of hand-to-mouth events per hour (13.9 events/hr)/# of replenishment intervals/hr)) / body weight (11 kg).
Object-to-Mouth Dose = object residue loading (µg/cm^2) * unit conversion factor (0.001 mg/µg) * object surface area mouthed / event (10 cm^2/event) * exposure time (1.5 hrs/day) * # replenishment intervals/hr (4 int/hr) * (1-((1- saliva extraction factor (0.50))^(# Object-to-Mouth Events/hr (8.8 events/hr) / # replenishment intervals/hr)) / body weight (11 kg).
Soil Ingestion = soil residue (µg/g) * ingestion rate (50 mg/day) * conversion factor (0.000001 g/µg) / body weight (11 kg).

6.3 Combined Exposure

HED combines risk values resulting from separate exposure scenarios when it is likely they can occur simultaneously based on the use pattern and the behavior associated with the exposed population. In evaluating combined residential uses of fluroxypyr, HED reviewed all residential sources of exposure which consisted of: 1) adult inhalation handler (lawns only) exposure, and 2) child postapplication oral exposure.

Since a dermal endpoint was not selected for fluroxypyr, the only route of exposure for which risks were quantified for adults is through the inhalation route, and therefore, a combined residential exposure assessment is not applicable.

For children, because of the high-end assumptions used in each incidental oral scenario (hand to mouth, object to mouth, and soil ingestion), the exposures from these scenarios are not combined; rather, the highest (typically hand to mouth exposure) is used to assess aggregate risk, as described below. Since dermal and inhalation risks were not quantified, no post-application children's risks were combined.

Table 6.3 identifies the residential scenarios and MOEs for adults and children for use in performing an aggregate exposure assessment as part of the fluroxypyr human health risk assessment. There are no risks of concern.

Table 6.3. Summary of Residential Exposure and Risk Estimates.		
Scenario	**Daily Dose** [1] *mg/kg/day*	**MOE** [2]
Adults		
Residential Handler Inhalation Exposure (Backpack)	0.026	3,800
Children		
Post-Application Incidental Oral Exposure: Hand-to-Mouth (After Liquid Application to Turf)	0.0070	14,000

[1] Daily Dose = See Table 6.1 for adult handler scenarios and Table 6.2 for post-application incidental oral scenarios.
[2] MOE = NOAEL/Daily Dose (mg/kg/day). ST Inhalation = 100; ST Incidental Oral = 100 mg/kg/day. LOC = 100.

6.4 Residential Bystander Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative postapplication inhalation exposure assessment was not performed for fluroxypyr at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV), low vapor pressure (9.27×10^{-7} mm Hg) and the relatively low proposed use rate (0.47 lb ai/A). However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for fluroxypyr. Although a quantitative residential postapplication inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for residential handlers. This exposure scenario is representative of a worse case inhalation exposure and should be considered protective of other postapplication inhalation exposure scenarios.

6.5 Spray Drift

Spray drift is always a potential source of exposure to residents near spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for fluroxypyr. 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 (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, 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 with specific products with significant risks associated with drift.

Although a quantitative residential post-application inhalation exposure assessment was not performed as a result of pesticide drift from neighboring treated agricultural fields, an inhalation exposure assessment was performed for flaggers. This exposure scenario, for which no risks of concern were identified, is representative of a worse case inhalation (drift) exposure and may be considered protective of most outdoor agricultural and commercial post-application inhalation exposure scenarios.

7.0 Aggregate Exposure/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. In the case of fluroxypyr, acute and chronic aggregate risks result from exposure through food and water only. For short-term risks, residential handlers' inhalation exposure and children's incidental oral exposures were combined with background exposure from food and water.

7.1 Acute Aggregate Risk

Acute aggregate risk is equivalent to acute dietary exposure and risk, which is not of concern. Refer to Section 5.4.3.

7.2 Short-Term Aggregate Risk

The residential handler exposure from applying fluroxypyr using a Backpack sprayer and children's postapplication oral exposure (Table 6.3) were combined with the chronic dietary exposure from the mostly highly exposed adult (General US population) and children's (all infants <1 year old) subpopulations (Table 5.4.5), respectively, to determine aggregate exposure and risk as shown in Table 7.2. Despite the numerous conservative assumptions in developing these estimates, the MOEs are above the LOC of 100, and are not of concern.

Table 7.2. Short-Term Aggregate Risk Calculations for Fluroxypyr

Population	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adult (Handler)	100	100	1	0.01473	0.026	0.04073	2500
Child (Postapplication)	100	100	1	0.03514	0.0070	0.04210	2400

[1] The LOC is based on the standard inter- and intra- species uncertainty factors totaling 100. The FQPA Safety Factor has been reduced to 1X.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure (Adult Handler) = Inhalation Exposure (Table 6.1). Residential Exposure (Child Postapplication) = Hand-to-Mouth Exposure (Table 6.2).
[4] Total Exposure = (Avg. Food & Water Exposure + Residential Exposure)
[5] Aggregate MOE = [100/Total Exposure]

7.3 Chronic Aggregate Risk

Chronic aggregate risk is equivalent to chronic dietary exposure and risk, which is not of concern. Refer to Section 5.4.4.

8.0 Cumulative Exposure/Risk Characterization

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

9.0 Occupational Exposure/Risk Characterization

Fluroxypyr may be applied to rice as a foliar spray via groundboom and aerial application. The proposed use pattern is summarized in Table 9.1. Handler exposure is expected to be short- or intermediate-term based on information provided on the proposed label. The personal protective equipment (PPE) label requirements include: long-sleeved shirt, long pants, and shoes plus socks.

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

Mixer/Loaders
1. Mixing/loading liquids to support groundboom applications,
2. Mixing/loading liquids to support aerial applications,

Flaggers
3. Flagging to support aerial application,

Applicators
4. Applying sprays with groundboom equipment, and
5. Applying sprays with aerial equipment.

9.1 Short-/Intermediate-Term Handler Risk

No chemical-specific handler exposure data were submitted in support of the proposed use, and therefore HED relied on the best available surrogate data to complete the occupational handler assessment. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database, and the Outdoor Residential Exposure Task Force (ORETF) database. Some of these data are proprietary (e.g., AHETF data, MRID No. 44339801), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures," are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (http://www.epa.gov/opp00001/science/handler-exposure-table.pdf), which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html.

The proposed product label involved in this assessment directs applicators and other handlers to wear long sleeved shirt and long pants, shoes plus socks, and chemical-resistant gloves. HED typically assesses handler exposure using "baseline" clothing assumptions, and if risks of concern are identified, the use of personal protective equipment (PPE) may be incorporated into the exposure assessment. In the case of fluroxypyr, there is no toxicity via the dermal route, and only inhalation exposures were assessed. No additional PPE (i.e., respirators) were needed to achieve MOEs above the LOC of 100.

Standard assumptions were used with respect to body weight for adult handlers (80 kg), the exposure duration (i.e., short- and intermediate-term), and the area treated for various types of application equipment and application sites. In conjunction with these standard values, HED used the maximum application rates from the proposed label directions. Each of the risks is presented as an MOE, or the ratio of the NOAEL to the calculated daily dose.

Table 9.1 shows the results of HED's exposure and risk assessment for occupational handlers. The MOEs shown in the table are all significantly higher than HED's LOC of an MOE of 100, with the lowest MOE of 90,000 identified for handlers conducting mixing/loading activities for aerial application. Risk associated with this and all other scenarios is not of concern.

Table 9.1. Baseline Short- and Intermediate-Term Occupational Exposures and Risk Estimates for Fluroxypyr Use on Rice.

Exposure Scenario	Application Rate[a] lb ai/A	Area Treated Daily[b] acres	ST/IT Baseline Inhalation UEs[c] µg/lb ai	ST/IT Baseline Inhalation Dose[d] mg/kg/day	ST/IT Baseline Inhalation MOE[e]
Mixer/Loader					
Mixing/Loading Liquids for Groundboom Application	0.34	200	0.219	0.00019	540,000
Mixing/Loading Liquids for Aerial Application	0.34	1200	0.219	0.0011	90,000
Flagger					
Flagging for Aerial Application	0.34	350	0.35	0.000520	190,000

Applicator					
Applying Sprays via Groundboom Equipment	0.34	200	0.34	0.000289	350,000
Applying Sprays via Aerial Equipment	0.34	1200	0.068	0.000346	290,000

a Application Rates based on proposed uses for fluroxypyr (GF-2764 Herbicide, EPA Reg. No. 62719-577).
b Acres Treated Per Day is taken from Exposure Science Advisory Council (ExpoSAC) Policy No. 9.1.
c UEs = Unit Exposures based on PHED Version 1.1, ORETF, or AHETF data. Baseline = no gloves, no respirator.
d Dose (mg/kg/day) = daily unit exposure (µg/lb ai) × application rate (lb ai/acre) × amount handled/day (acres/day) x conversion factor (1 mg/1,000 µg) × absorption factor (%) ÷ body weight (80 kg). No inhalation absorption factor.

e MOE = NOAEL ÷ Dose (mg/kg/day). ST/IT Inhalation NOAEL = 100 mg/kg/day. ST/IT level of concern = 100.

9.2 Short and Intermediate -Term Postapplication Risk

9.2.1 Dermal Postapplication Risk

Agricultural workers performing typical post-application activities (e.g. scouting, hand weeding) may receive exposure to fluroxypyr residues. As no dermal endpoint has been identified, no quantitative dermal postapplication assessment is necessary.

Typically, under WPS for Agricultural Pesticides, active ingredients classified as acute Toxicity Category III or IV for Acute Dermal, Eye Irritation, and Primary Skin Irritation are assigned a 12-hour REI. Based on the quantitative post-application assessment, the 12-hour REI on the proposed label is acceptable for rice.

9.2.2 Inhalation Postapplication Risk

Based on the Agency's current practices, a quantitative postapplication inhalation exposure assessment was not performed for fluroxypyr at this time primarily because it has a low vapor pressure (9.7×10^{-7} mm Hg), it is applied at an application rate of 0.34 lbs ai/A, and it is not projected to be applied via typically high inhalation exposure application equipment (e.g., airblast). However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for fluroxypyr.

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

10.0 References

Residue Chemistry

Fluroxypyr, Section 3 Registration of Fluroxypyr on Rice, Summary of Analytical Chemistry and Residue Data.

Fluroxypyr: Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action to Support New Use on Rice, and for all the Commodities of Crop Group 15 (Cereal Grains).

Occupational and Residential Exposure

Fluroxypyr: Occupational Exposure Assessment for a Proposed New Use on Rice with an Updated Residential Exposure Assessment of All Existing Residential Uses (Turf). Matthew Lloyd, D402132, 09/11/2012.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Available for Fluroxypyr

The toxicological data requirements (40 CFR 158.340) for food uses for fluroxypyr are in Table A1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rat and mouse)	yes	yes
870.3150 Oral Subchronic (dog)	yes	yes
870.3200 21/28-Day Dermal (rat)	yes	yes
870.3250 90-Day Dermal	CR	no
870.3465 28-Day Inhalation	no[A]	no
870.3700a Developmental Toxicity (rat)	yes	yes
870.3700b Developmental Toxicity (rabbit)	yes	yes
870.3800 Reproduction (rat)	yes	yes
870.4100a Chronic Toxicity (rat)	yes	yes
870.4100b Chronic Toxicity (dog)	yes	yes
870.4200a Carcinogenicity (rat)	yes	yes
870.4200b Carcinogenicity (mouse)	yes	yes
870.4300 Chronic/Carcinogenicity (rat)	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 Mutagenicity—Mammalian Erythrocyte Micronucleus.	yes	yes
870.5500 Mutagenicity— Bacterial DNA Damage or Repair Test	yes	no
870.5550 Mutagenicity—Unscheduled DNA Synthesis	yes	no
870.6100a Acute Delayed Neurotoxicity. (hen)	no	---
870.6100b 90-Day Neurotoxicity (hen)	no	---
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes[A]	NA
870.6200b 90 Day Neurotoxicity Screening Battery (rat)	yes[A]	NA
870.6300 Developmental Neurotoxicity (rat)	CR	NA
870.7485 General Metabolism (rat)	yes	yes
870.7600 Dermal Penetration (8-hour), *in vivo* (male rat)	CR	yes
870.7800 Immunotoxicity (rat)	Yes	Yes

[A] waived (HASPOC TXR No. 0056397)

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity of Fluroxypyr Acid and Fluroxypyr 1-Methylheptyl Ester (MHE) Technical				
Guideline No.	**Study Type**	**MRIDs #**	**Results**	**Toxicity Category**
870.1100	Acute Oral - rat	Acid 40354010	LD_{50} = 2405 mg/kg	III
		MHE 40354005	LD_{50} > 5000 mg/kg	IV
870.1200	Acute Dermal – rabbit - rat	Acid 40354010	LD_{50} > 5000 mg/kg	III
		MHE 40354006	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation	Acid 40354011	LD_{50} > 296 mg/m^3	II
		MHE 40354004	LD_{50} > 1.0 gm/m^3	III
870.2400	Primary Eye Irritation - rabbit	Acid 49354010	not applicable	not applicable
		MHE 40354007	mildly irritating	III
870.2500	Primary Skin Irritation- rabbit	Acid 40354010	non-irritating	IV
		MHE 40354008	non-irritating	IV
870.2600	Dermal Sensitization - guinea pig	Acid - none	not applicable	not applicable
		MHE 42137335 & 42540900	not a sensitizer	not applicable

Attachment 2. Toxicity Profile for Fluroxypyr

Table A2. Toxicity Profile of Fluroxypyr Technical (Fluroxypyr acid and Fluroxypyr MHE)		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3150 28-day oral toxicity Dog	MRID 42137340 (1983)/ acceptable/ fluroxypyr acid 98% a.i. 0, 20, 50, 150 mg/kg/day in diet	NOAEL = 50 mg/kg/day LOAEL= 150 mg/kg/day, based on kidney lesions (early signs of acute tubular nephrosis), increased adrenal wts (both sexes), decreased testes wts (males)
870.3100 90-Day oral toxicity rodents (rats)-Fischer 344	MRID 44080316(1991)/ acceptable/ fluroxypyr acid 98.9% a.i. 0, 320, 700, 1000 mg/kg/day	NOAEL = 700 mg/kg/day LOAEL = 1000 mg/kg/day, based on decreased body weight gain & testis weight (males), decreased brain weight (females), and increased kidney weight (both sexes). There were no treatment-related microscopic lesions.
870.3100 90-Day oral toxicity rodents (rats)--Wistar	MRID 42164502 (1987)/ acceptable/ fluroxypyr acid 98.3-98.5% a.i. 0, 80, 750, 1000, 1500 mg/kg/day Mean intake: M 79, 721, 924, 1215; F 81, 755, 969, 1392 mkd	Males NOAEL = 80 mg/kg/day LOAEL = 750 mg/kg/day, based on nephrotoxicity and death Females NOAEL = 750 mg/kg/day LOAEL = 1000 mg/kg/day, based on nephrotoxicity and death

Table A2. Toxicity Profile of Fluroxypyr Technical (Fluroxypyr acid and Fluroxypyr MHE)		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rodents (mice) – SPF ICR	MRID 42137337(1988)/ acceptable/ fluroxypyr acid 99.3% a.i. 0, 200, 500, 2500, 10000 ppm Male: 0, 27, 67, 336, 1342 mg/kg/day Female: 0, 35, 87, 437, 1748 mg/kg/day	NOAEL = 1342 mg/kg/day (males)/1748 mg/kg/day (females) LOAEL not established.
870.3150 90-Day oral toxicity (nonrodents)	NA	NA
870.3200 21-Day dermal toxicity (rabbits)	MRID 42137338(1991)/ acceptable/ fluroxypyr MHE 98.5% a.i. 0, 100, 300, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (HDT) LOAEL not established.
870.3250 90-Day dermal toxicity	NA	NA
870.3465 4-Week inhalation toxicity (rat)	NA	NA
870.3700a Prenatal developmental toxicity (rats) - CD	MRID 40244509 (1983) acceptable/ fluroxypyr acid 99% a.i. GD 6-19 0, 125, 250, 500 mg/kg/day	**Maternal** NOAEL = 250 mg/kg/day LOAEL = 500 mg/kg/day, based on increased kidney weights (one death). **Developmental** NOAEL = 500 mg/kg/day (HDT) LOAEL not established.
870.3700a Prenatal developmental toxicity (rats) –Sprague-Dawley	MRID 44094901 (1994) acceptable/ fluroxypyr MHE 95.8% a.i. GD 6-15 0, 100, 300, 600 mg/kg/day	**Maternal** NOAEL = 300 mg/kg/day LOAEL = 600 mg/kg/day, based on increased maternal deaths (days 4, 6, 7, 7, 8, 8, 10, 10) and decreased body weight gains and food consumption. **Developmental** NOAEL = 600 mg/kg/day (HDT) LOAEL = not established.
870.3700b Prenatal developmental toxicity (rabbits)	MRID 40354013 (1984) acceptable/ fluroxypyr acid 95.8% a.i. 0, 25, 100, 250, 400 mg/kg/day GD 6-19	**Maternal** NOAEL = 250 mg/kg/day LOAEL = 400 mg/kg/day, based on increased maternal deaths. Due to a large number of maternal deaths in this group, a dose level of 250 mg/kg/day was added to the study, and the 400 mg/kg/day dose level was discontinued early (terminated on day 9). **Developmental** NOAEL = 250 mg/kg/day (HDT) LOAEL not established.

Table A2. Toxicity Profile of Fluroxypyr Technical (Fluroxypyr acid and Fluroxypyr MHE)		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b Prenatal developmental toxicity (rabbits)	MRID 44080319 (1996) acceptable/ fluroxypyr MHE 95.8% a.i. 0, 100, 500, 1000 mg/kg/day GD 7-19 (acid equivalent doses: 69, 346, or 693 mg/kg/day)	**Maternal** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day, based on increased abortions (one doe on GD 25). At 1000 mg/kg/day, 3 does aborted (GD 22, GD 25, GD 25) and 1 death GD 20. **Developmental** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day, based on increased abortions (one doe on GD 25). At 1000 mg/kg/day, 3 does aborted (GD 22, GD 25, GD 25) and 1 death GD 20.
870.3800 Reproduction and fertility effects (rats) – Sprague-Dawley	MRID 44080321 (1996) acceptable/ fluroxypyr acid 99% a.i. 0, 100, 500, 750 mg/kg/day (M) 0, 100, 500, 1000 mg/kg/day (F)	**Parental/Systemic** NOAEL = 100 mg/kg/day (males) /500 mg/kg/day (females) LOAEL = 500 mg/kg/day (males)/ 1000 mg/kg/day (females), based on kidney effects (both sexes; increased kidney weight with microscopic findings) and increased deaths (females) due to renal failure. **Reproductive** NOAEL = 750 mg/kg/day (Males)/1000 mg/kg/day (females) (HDT) LOAEL not established. **Offspring** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day, based on decreased pup weight and body weight gain and slightly lower survival.
870.4100a Chronic toxicity (rodents)	NA; see 870.4300	NA
870.4100b Chronic toxicity (dogs)	MRID 40244507(1988) acceptable/ fluroxypyr acid 98%a.i. 0, 20, 50, 150 mg/kg/day	NOAEL = 150 mg/kg/day (HDT) LOAEL not established.
870.4200a Carcinogenicity (rats)	NA; see 870.4300	NA
870.4200b Carcinogenicity (mice)-CD-1	MRID 44080317 (1991) acceptable/guideline fluroxypyr acid 98.9% a.i. 0, 100, 300, 1000 mg/kg/day	NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day, based on decreased body weight and body weight gain (males) and increased kidney lesions (increased incidences of renal papillary necrosis and regenerative nephrosis) in females. No evidence of carcinogenicity.
870.4300 Combined Chronic/carcinogenicity (rats)—Fischer 344	MRID 44080322 (1994) acceptable/guideline fluroxypyr acid 99% a.i. 0, 100, 500, 1000 mg/kg/day	NOAEL =100 mg/kg/day LOAEL = 500 mg/kg/day, based on increased kidney weights and chronic progressive kidney glomerulonephropathy (both sexes). No evidence of carcinogenicity. At 1000 mg/kg/day, 5 male rats died within first 90 days on test.

Table A2. Toxicity Profile of Fluroxypyr Technical (Fluroxypyr acid and Fluroxypyr MHE)		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100 Bacterial reverse mutation	MRID 44080323 (1995) acceptable/ fluroxypyr MHE 95.8% a.i. 100 - 5000 ug/plate	Negative.
870.5300 *In vitro* mammalian cell gene mutation	MRID 44080324 (1996) unacceptable/ fluroxypyr MHE 95.8% a.i. 1.25 - 50 ug/mL	Negative, but did not test a soluble dose.
870.5375 *In vitro* mammalian chromosome aberration (HL)	MRID 44080325 (1996) acceptable/ fluroxypyr MHE 95.8% a.i. 0.42 – 1250 ug/mL	Negative.
870.5395 Mammalian micronucleus (mouse)	MRID 44080326 (1996) acceptable/ fluroxypyr MHE 95.8% a.i. oral gavage of 225, 450 or 900 mg/kg	Negative.
870.6200a Acute neurotoxicity screening battery (rats)	NA	NA
870.6200b Subchronic neurotoxicity screening battery (rats)	NA	NA
870.6300 Developmental neurotoxicity (rats)	NA	NA

870.7485 Metabolism (Fischer 344 rats)	MRID 44080327 (1996) acceptable/ fluroxypyr MHE 99% a.i. Males: 50 mg/kg (labeled) as single oral dose	Total recovery of the administered dose was 105%, with the principal route of excretion being expired $^{14}CO_2$, which contained approximately 61% of the radioactivity for the fluroxypyr MHE. The urine contained approximately 30% and the feces contained 5% of the administered dose. At 48 hours post dose, approximately 7% of the administered dose was recovered in the blood, carcass, and skin. Approximately 52% of the administered dose was absorbed and expired as $^{14}CO_2$ within 12 hours post dose, and an additional 18% of the administered dose was excreted in the urine within 12 hours post dose. Based on the percentage of dose in the expired $^{14}CO_2$, urine, and tissues, approximately 90% of the dose was absorbed. Once absorbed, it was extensively metabolized and rapidly expired as $^{14}CO_2$ and eliminated in the urine with a half-life of 6 hours. Peak plasma concentrations of ^{14}C-radioactivity were attained by 7 hours post dose.
870.7600 Dermal penetration	NA	NA
870.7800 Immunotoxicity (Crl:WI (Han) rats)	MRID 48581311 (2011) Acceptable/guideline fluroxypyr 99.9% Males: 0, 80, 250, 750 mg/kg/day for 29 days	NOAEL = 750 mg/kg/day (highest dose tested; actual dose was 816 mg/kg/day); no treatment-related decrease in primary immune response to SRBCs in male rats; spleen or thymus weights comparable to control.

Appendix B. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; and the Outdoor Residential Exposure Task Force (ORETF) database; are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.