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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 26-JUN-1998

SUBJECT: PP#6F04772. **Fluroxypyr** in/on Barley, Oats, Wheat. **HED Risk Assessment.**
DP Barcode: D232215 Chemical #: 128959, 128968
PRAT Case # : 288019 Submission #: S510931
Class: Herbicide

FROM: Myron Ottley, William Donovan, Brenda Tarplee
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Health Effects Division (7509C)

THROUGH: Melba Morrow, Branch Senior Scientist
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TO: Joanne Miller, Product Manager
Daniel Kenny, Reviewer
Registration Division (7505C)

Dow Agrosciences LLC has submitted a petition requesting a permanent tolerance in support of Section 3 registration for its herbicide 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] in or on barley, oats and wheat (EPA File Symbol 707-RGN). The recommended permanent tolerances for the combined residues of fluroxypyr 1-methylheptyl ester and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr are listed below:

Wheat, oats, and barley, grain	0.5 ppm
Wheat, oats, and barley, straw	12 ppm
Wheat, oats, and barley, forage	12 ppm

Wheat, oats, and barley, hay	20 ppm
Aspirated grain fractions	0,6 ppm
Meat, fat, milk and meat byproducts (except kidney)	0.1 ppm
Kidney	0.5 ppm

No permanent tolerances have been established for residues of fluroxypyr or its metabolites in/on raw agricultural or animal commodities.

A summary of the findings and an assessment of human risk resulting from the proposed use of fluroxypyr 1-methylheptyl ester and fluroxypyr are provided in this document. The hazard assessment was provided by Myron Ottley of RAB1; the product and residue chemistry data review by William Donovan of RAB1; the dietary risk assessment by Brian Steinwand of CEB1; the drinking water exposure assessment by William Effland of EFED; the occupational exposure assessment by Brenda Tarplee of RAB1.

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I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue data submitted by Dow Elanco/Dow Agrosciences Company in accordance with the Federal, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158, to support pending registration containing the active ingredient (ai) fluroxypyr for control of annual and perennial broadleaf weeds and volunteer potatoes in small grains (barley, oats and wheat), fallow cropland and non-cropland. HED has identified **no residential exposure issues** at this time.

Toxicity. Fluroxypyr was reviewed by the Hazard ID Review Committee (report dated 28-JAN-1998). The Committee selected doses and endpoints for acute dietary, chronic dietary (RfD), occupational and residential exposure risk assessments, assessed the carcinogenic potential and addressed the sensitivity of infants and children from exposure to fluroxypyr as required by the Food Quality Protection Act (FQPA). The following dose/endpoints were selected:

- Acute dietary, NOEL = 100 mg/kg/day. Risk assessment is required.
- Chronic dietary, RfD = 0.50 mg/kg/day (NOEL = 50 mg/kg/day; Uncertainty factor =100).
- Short-term dermal, (systemic) NOEL = 100 mg/kg/day. Risk assessment is required.
- Intermediate-term dermal, NOEL = 100 mg/kg/day. Risk assessment is required. An oral dose was selected, thus, a dermal absorption factor of 100% should be used in dermal risk assessment.
- Long-term dermal. Not applicable. Risk assessment is not required.
- Inhalation, NOEL = 100 mg/kg/day. Risk assessment is required.
- Additional factors required to address sensitivity to infants and children: 3x, due to increased susceptibility.
- No data gaps. However, due to incomplete data reporting and evaluation regarding an oncogenicity study, the Hazard ID Assessment Review Committee (document dated 01 Dec, 1997) determined that the Registrant must 1) submit the appropriate historical control data and 2) evaluate the thyroid glands from all animals at 100 mg/kg/day in the rat study (MRID 44080322).

Risk Assessment. The Margin of Exposure (MOE) is a measure of how closely the anticipated exposure comes to the NOEL and is calculated as a ratio of the NOEL to the exposure (NOEL/exposure = MOE). The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. The 100 uncertainty factor is to take into account interspecies extrapolation and intraspecies variability. For fluroxypyr, however, HED's level of concern is for MOEs that are below 300 for acute dietary exposure, because a 3x factor is added to address increased susceptibility issues.

Acute dietary (food + water) risk estimates do not exceed HED's level of concern for the U.S. population and for infants and children. Chronic dietary (food + water) risk for the U.S. population and for infants and children do not exceed HED's level of concern.

The calculations of risk from dermal and inhalation occupational exposures indicate that the MOEs are greater than 300 for all the exposure scenarios that were considered. For the subject

short term risk assessment MOEs of 300 for dermal exposures and inhalation exposures are considered acceptable. These calculations indicate that worker risk from short term exposures to fluroxypyr do not exceed HED's level of concern. Long-term occupational exposure is not expected. HED does not have concern for potential risks from post-application exposures at this time.

This chemical has been classified by the HED Hazard Identification Review Committee (document dated 28-JAN-1998) as a Not Likely Human Carcinogen, based on the lack of evidence of carcinogenicity in mice and rats at doses that were judged to be adequate to assess the carcinogenic potential. There was no apparent concern for mutagenicity (no mutagenic activity).

The toxicological data base is adequate to support the permanent tolerances submitted for the herbicide fluroxypyr on barley, wheat and oats. Contingent on the satisfactory resolution of the chemistry deficiencies listed in Section 7 (Data Requirements) of this document, the chemistry data base also supports the permanent tolerances submitted for fluroxypyr 1-MHE on barley, wheat and oats.

II. BACKGROUND

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 end-use product is Starane™ EC herbicide, an emulsifiable concentrate formulation of 26.2% fluroxypyr 1-MHE, which is 1.5 lb. acid equivalents (a.e.)/gal (18.2%). The proposed use on barley, oats, and wheat is intended for post-emergence control of sulfonylurea resistant kochia and other broadleaf weeds. Starane™ EC was first introduced to the cereal markets of Europe in 1984.

Temporary tolerances were previously established for residues of fluroxypyr 1-MHE and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr on barley, oats, and wheat in support of an experimental use permit (PP#2G04066). Also, a Section 18 exemption for the use of fluroxypyr 1-MHE on wheat, barley, field corn, and sweet corn in the state of Washington has been granted (ID #98WA0017).

III. SCIENCE ASSESSMENT

A. PHYSICAL AND CHEMICAL PROPERTIES ASSESSMENT

1. Identification of Active Ingredient and Structural Formulae

Chemical Name: ((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)acetic acid, 1-methylheptyl ester

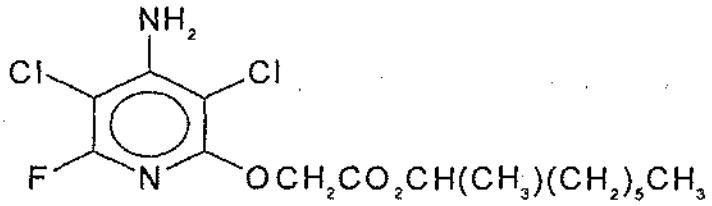
Common Name: Fluroxypyr 1-methylheptyl ester

PC Code Number: 128968

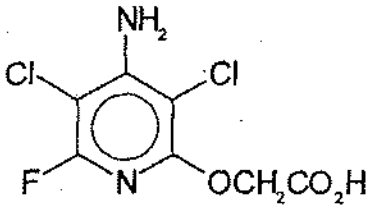
CAS Registry No.: 81406-37-3

Molecular Formula: $C_{15}H_{21}Cl_2FN_2O_3$

Molecular Weight: 367.3



Fluroxypyr 1-methylheptyl ester



Fluroxypyr

2. Physical and Chemical Properties

Table 1. Physical and Chemical Properties of fluroxypyr 1-Methylheptyl Ester	
Physical State	Solid
Color	Gray olive
Melting Point	57.5°C
Odor	Musty, slightly chlorine
Density	1.30 g/mL at 21°C
Solubility	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 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	2.0×10^{-5} kPa at 25°C 1.0×10^{-5} kPa at 20°C
Octanol/Water Partition Coefficient	$\log_{10} K_{ow} = 5.04$ at pH 7
pH	6.81 in a solution containing 90.1 mg/L
Oxidation/Reduction	No obvious chemical incompatibility
Flammability	Non-flammable
Explodability	Not potentially explosive

B. HUMAN HEALTH RISK ASSESSMENT

I. Hazard Assessment

Toxicology data are used by HED to assess the hazards to humans and domestic animals. The data are derived from a variety of acute, subchronic and chronic toxicity tests,

developmental/reproductive tests, and test to assess mutagenicity and pesticide metabolism. Registration eligibility decisions require that HED have sufficient information to select the appropriate endpoints for performing a human health risk assessment. This requires a toxicological data base that is not only complete, but of acceptable quality.

The toxicology profile for fluroxypyr is summarized in Table 1.1. The toxicology data base on fluroxypyr is complete.

Table 1.1: Toxicology Profile

Guideline	Study Type	MRID #	Required	Satisfied
81-1	Acute oral - rat	42935014	yes	yes
81-1	Acute oral - mouse	42935011	yes	yes
81-2	Acute dermal - rat	42935019	yes	yes
81-3	Acute Inhalation - rat.	42935020	yes	yes
81-4	primary eye irritation - rabbit	42935021	yes	yes
81-5	primary dermal Irritation - rabbit	42935022	yes	yes
81-6	Dermal Sensitization - g.pig	43000203	yes	yes
81-7	acute delayed neurotoxicity - hen		no	--
81-8	acute neurotoxicity - rat		yes	yes
82-1	subchronic feeding - rat	42935024	yes	yes
82-1	subchronic feeding - mouse	42935023	yes	yes
82-1	subchronic feeding - dog	42935025 43000204	yes	yes
82-2	21-day dermal - rabbit		yes	yes
82-5	subchronic neurotoxicity - rat		yes	yes
83-1(a)	chronic toxicity - rat	42935031	yes	yes
83-1(b)	chronic toxicity - dog	43000205	yes	yes
83-2	carcinogenicity - mouse	42935026	yes	yes
83-3(a)	developmental toxicity - rat	43000206	yes	yes
83-3(b)	developmental toxicity - rabbit	42935028	yes	yes
83-4	2-generation reproduction - rat	42935030	yes	yes

Guideline	Study Type	MRID #	Required	Satisfied
83-5	chronic/oncogenicity - rat	42935031	yes	yes
84-2	gene mutation	42935032 42935033 42935034 42935035	yes	yes
84-2	chromosomal aberration	43000208	yes	yes
84-2	other genotoxic effects	43000207 43000209	yes	yes
85-1	metabolism		yes	yes
85-2	dermal penetration		no	--
86-1	domestic animal safety		no	--

a. Acute Toxicity

Adequacy of data base for acute toxicity (Series 81-1 to 81-6): The data base for acute toxicity is considered complete. No additional studies are required at this time. Acute toxicity values and categories for fluroxypyr Technical are summarized in Table 1.2.

Table 1.2 Acute Toxicity - Fluroxypyr

Study	Type	Species	MRID #	Results	Tox. Cat
81-1	Acute oral	rat	42935014	LD50 = 50-100 mg/kg	II
81-1	Acute oral	mouse	42137329	LD_{50} (M) 2408 mg/kg LD_{50} (F) >3000 mg/kg	III
81-2	Ac. dermal	rat	4237330	LD_{50} > 2000 mg/kg	III
81-3	Ac. Inhal.	rat	42137331	LD_{50} > 3.04 mg/l	IV
81-4	ocular Irritation	rabbit	42137332	slight/marked irritant	II
81-5	dermal Irritation	rabbit	42137333	slight irritant	IV

Study	Type	Species	MRID #	Results	Tox. Cat
81-6	Dermal Sensitization	G.Pigs	42137334	positive dermal sensitizer	N/A

Fluroxypyr produces significant toxicity to the eye, and is a dermal sensitizer.

b. Subchronic Toxicity

Adequacy of data base for subchronic toxicity (Series 82): The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

82-1 90-day Feeding - Rat (MRID 42164502)

In a 90-day feeding study Wistar rats (10/sex/group) were administered fluroxypyr (98.5% a.i.) in the diet at 0, 80, 750, 1000 or 1500 mg/kg/day for 13 weeks.

Significant nephrotoxicity and deaths were observed at 1000 and 1500 mg/kg/day in both sexes, and in males at 750 mg/kg/day. Death was due to renal papillary necrosis. Also observed were signs of ill health, emaciation, decreased food intake, increased kidney weight, histopathological lesions and decreased renal function. Histological changes were observed in the adrenals in both sexes at 1000 and 1500 mg/kg/day. **In males the NOEL for this study is 80 mg/kg/day, and the LOEL is 750 mg/kg/day based on kidney effects and death. In females the NOEL is 750 mg/kg/day, with the LOEL at 1000 mg/kg/day based on kidney effects and death.**

This study satisfies the guideline requirement (82-1) for a subchronic feeding study in rodents.

82-1 90-day Feeding - Mouse (MRID 42137337)

In a 90-day feeding study SPF ICR (Crj:CD-1) mice (12/sex/group) were administered fluroxypyr (99.3% a.i.) in the diet at levels of 0, 200, 500, 2500 or 10000 ppm (males: 0, 26.7, 67.7, 330 or 1342 mg/kg/day; females: 0, 32.5, 81.7, 418, or 1748 mg/kg/day) for 13 weeks.

Under the conditions of the study, no significant effects were observed at any dose level. **The NOELs are therefore 1342 and 1748 mg/kg/day in males and females, respectively, the highest dose level tested, and above the 1000 mg/kg limit dose. A LOEL could not be established.**

This study satisfies the guideline requirement (82-1) for a subchronic feeding study in rodents.

82-1 28-Day Feeding - Dog (MRID 42137340)

In a range finding feeding study Beagle dogs were administered Fluroxypyr [98.0% a.i.] in the diet at levels of 0, 50, 150 or 450 mg/kg/day for 28 days.

Dogs at 500 mg/kg/day exhibited ataxia and hind limb weakness as well as decreases in body weight and food consumption and were sacrificed on days 16/17 of the study. Histopathology showed moderate acute tubular nephrosis and a slight to moderate acute gastroenteritis. Some early signs of acute tubular nephrosis were also seen in both sexes of dogs at 150 mg/kg/day.

The NOEL for the study was 50 mg/kg/day, the LOEL was 150 mg/kg/day based on histopathological lesions in the kidneys, decreased testes weights, and increased adrenal weights in both sexes.

82-2 21-Day Dermal - Rabbit (MRID 42137338)

In a 21-day dermal study fluroxypyr (98.5% a.i.) was administered to New Zealand white rabbits (5/sex/group) at levels of 0, 100, 300, or 1000 mg/kg/day for three weeks. Administration was 6 hr/day to an area approx. 10 x 15 cm (10% of body surface area).

No dermal or systemic toxicity was observed at any dose level. **The NOEL for males and females is therefore 1000 mg/kg/day. A LOEL could not be established.**

This study satisfies the guideline requirement (82-2) for a 21-day dermal toxicity study.

c. Chronic Toxicity/Oncogenicity

Adequacy of data base for chronic toxicity and oncogenicity (Series 83-1, 83-2, 83-5): The data base for chronic toxicity and oncogenicity is considered complete. No additional studies are required at this time.

83-5 Combined Chronic/Carcinogenicity Study - Rat

In the combined chronic toxicity/carcinogenicity study in rats, (MRID 44080322) fluroxypyr [99.0% a.i.] was administered to 50 Fischer 344 rats/sex/dose via the diet at dose levels of 0, 100, 500, and 1000 [females only] mg/kg/day for 24 months [10 rats/sex/dose for 12 months].

At the high-dose level, there was an increase in death of both sexes, and the males at this dose level were terminated on day 118 [6 deaths prior to day 112] following erratic body-weight gains, changes in clinical chemistry findings indicative of impaired renal function, and a thin

appearance. The high-dose females had a 42% mortality rate, with 48% of the deaths attributed to renal failure. Body-weight gain during the first 90-day interval was decreased [79% of control] in males at the high dose but comparable to control for females. Overall body-weight gain of the high-dose females was decreased [69% of control] compared to the control. Food consumption was not adversely affected overall. There were no consistent findings in hematology, clinical chemistry, or urinalysis parameters monitored, although the changes noted on several occasions were consistent with kidney effects and/or nutritional condition of the rat. Kidney weight was increased at the 500 mg/kg/day dose level in males and at all three dose levels in females, although the increase at the low-dose level appears to be within that of the historical control. Gross and microscopic lesions characteristic of renal toxicity [decreased size, papillary necrosis, and roughened surface] were observed in the high-dose males sacrificed on day 118. At study termination, chronic progressive glomerulonephropathy [CPG] of a severe or very severe degree was slightly increased in males at 500 mg/kg/day when compared to the low-dose and control males and was slightly higher than the historical control. In females at study termination, increased severity of renal CPG was observed at the 500 and 1000 mg/kg/day dose levels, compared to the control and low-dose groups. Other changes observed [decreased body fat, gastric erosion/ulcers of glandular mucosa] were considered secondary changes due to the nutritional state of the rat. Histologically, hyperplasia of the pelvic epithelium, papillary necrosis, and tubular nephrosis were observed at the 500 mg/kg/day in males and at 1000 mg/kg/day in females at study termination. There was no apparent increase in the incidence of kidney tumors in either sex. With the exception of an increased incidence of parafollicular cell adenomas [single only] in males at 500 mg/kg/day, at the doses tested, there was no apparent treatment-related increase in any tumor type in either sex. **The LOEL is 500 mg/kg/day, based on increased kidney weight in both sexes, increased incidence of atrophy, adipose tissue [mesenteric tissues] in males and an increase in the severity of chronic progressive glomerulonephropathy in the kidney in both sexes. The NOEL is 100 mg/kg/day. Deaths occurred at 1000 mg/kg/day in males within the first 90 days on test [2 by day 28 and 3 more by day 56].**

This guideline [§83-5] combined chronic toxicity/ carcinogenicity study in the rat is Acceptable.

83-2 Carcinogenicity Study - Mouse

In the carcinogenicity study in mice, (MRID 44080317) fluroxypyr [98.92% a.i.] was administered to 60 CD-1 mice/sex/dose via the diet at dose levels of 0, 100, 300, and 1000 mg/kg/day for 18 months.

There were no adverse effects on survival or clinical signs in either sex. A slight decrease in body weight was observed in the high-dose males [93% of control value at study termination] and decreased body-weight gains [overall gain 80%/92% (males/females) of control] were observed at the high-dose level in both sexes. Food consumption was not adversely affected by treatment. There were no adverse effects observed on any of the monitored hematology or ophthalmoscopy parameters in either sex. At the terminal sacrifice, there was a slight increase in

the incidence of distended gall bladder [both macroscopically and microscopically] in both sexes at the high-dose level and a slight increase in the number of mice of both sexes with kidneys that were considered decreased in size. Organ weights, including the kidneys, were comparable among the groups in both sexes. Microscopically, there was a significant increase in the incidence of renal papillary necrosis and regenerative nephrosis [severe grade only] in the high-dose females. There was no apparent treatment-related increase in the incidence of any tumor type in either sex. **The LOEL is 1000 mg/kg/day, based on decreased body weight/gain in males and an increased incidence of kidney lesions in females. The NOEL is 300 mg/kg/day.**

This guideline [§83-2] carcinogenicity study in the mouse is Acceptable.

83-1b Onc-Year Chronic Feeding - Dog

In a one-year chronic feeding study (MRID 40244507), fluroxypyr [98.0% a.i.] was administered to Beagle dogs (4/sex/group) in the diet at 0, 20, 50 or 150 mg/kg/day for 12 months.

No adverse effects were observed at any dose level. No abnormalities in hematology, clinical chemistry or urinalysis. No abnormal findings were made at necropsy, nor were there any significant changes in food consumption or body weight. **The NOEL for this study is 150 mg/kg/day, the highest dose level tested. The LOEL could not be established.**

This one-year chronic study in the dog is considered Acceptable

d. Developmental Toxicity

Adequacy of data base for Developmental Toxicity (Series 83-3): The data base for developmental toxicity is considered complete. No additional studies are required at this time.

83-3a Developmental Toxicity - Rat

1. In a developmental toxicity study (MRID 40244509) Crl COBS CD (SD) Br pregnant rats (six/dose group) were administered fluroxypyr (99% a.i.) at oral dose levels of 0, 125, 250, or 500 mg/kg/day in 1% methyl cellulose on days 6 through 19 of gestation.

Clinical signs such as salivation and brown facial staining were observed at 250 and 500 mg/kg/day; a 10% increase in mean kidney weight was observed at 500 mg/kg/day, along with renal pelvic dilatation. No adverse effects were observed on food consumption, body weight gain, live young, embryonic deaths, implants, corpora lutea, pre- or post-implantation loss, litter weight or mean fetal weight. In pups, reduced skeletal ossification was observed at the 500 mg/kg/day. No other significant effects were observed on the conceptus. **The maternal NOEL is 125 mg/kg/day, and the LOEL is 250 mg/kg/day based on clinical signs. The**

developmental NOEL is 250 mg/kg/day, the LOEL is 500 mg/kg/day based on reduced ossification.

This study is classified as Acceptable.

2. In a developmental toxicity study (MRID 44094901) fluroxypyr methylheptyl ester [95.8% a.i.] was administered to 28 naturally-mated female Sprague-Dawley CD® [SD] BR rats/group via gavage at dose levels of 0 [Mazola® corn oil], 100, 300, and 600 mg/kg/day from days 6 through 15 of gestation.

Fluroxypyr administration resulted in 8 deaths [following 4, 6, 7, 7, 8, 8, 10, 10 days of dosing] at the high-dose level and decreased body-weight gain [77% of control] and food consumption during the dosing period at this dose level also. Clinical signs observed in those dying on test included staining of the skin/fur in the ano-genital area, lethargy, hypothermia, labored breathing, irregular gait, pale appearance]. Excessive salivation was observed only in the treated dams, and although the incidence increased with dose, it is not clear whether this is a direct systemic effect of the test material or due to residual amounts of the test material in the buccal cavity from the dosing procedure. There were no treatment-related effects on gross pathologic alterations or absolute and relative liver and kidney weights at any dose level. Comparable pregnancy rates were observed among the groups, and there were no abortions, premature deliveries, or dams with 100% intrauterine deaths [except one mid-dose dam]. All dams had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses among the groups. There were no dead fetuses. Fetal body weights and sex ratio were comparable among the groups, and there were no external malformations, visceral malformations or variations, or skeletal malformations that could be attributed to treatment. The overall incidence of fetuses and litters with fetuses with one or more ossification variation was comparable among the groups; but there was an increase in the incidence of incompletely ossified cervical vertebral transverse processes [mid- and high-dose levels, not dose-related] and incompletely ossified pubes at the high-dose level compared to the concurrent and historical controls. These increases occurred at a dose level that resulted in severe maternal toxicity [death]. **The maternal NOEL is 300 mg/kg/day, the LOEL is 600 mg/kg/day, based on deaths and decreased body-weight gain and food consumption. The developmental toxicity NOEL is 300 mg/kg/day, and the LOEL is 600 mg/kg/day, based on an increase in two ossification variations [incompletely ossified cervical vertebral transverse processes and pubes].**

This guideline [§83-3(a)] prenatal developmental toxicity study in the rat is classified Acceptable.

83-3b Developmental Toxicity - Rabbit

In a developmental toxicity study (MRID 44080319) fluroxypyr methylheptyl ester [95.8% a.i.] was administered to 20 naturally-inseminated New Zealand female rabbits/group via gavage at

dose levels of 0 [vehicle METHOCEL*A4M], 100, 500, and 1000 mg/kg/day from days 7 through 19 of gestation.

Fluroxypyr administration resulted in maternal toxicity at the high-dose level, as evidenced by an increased incidence of abortions. Body weight was comparable among the groups, but body-weight gains were decreased at the mid- and high-dose levels [not dose-related] mainly during the dosing period, which may be attributed to palatability. Corrected maternal body weight was comparable among the groups. Comparable pregnancy rates were observed among the groups, and there were no premature deliveries or does with 100% intrauterine deaths. All does had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses among the groups. Both pre- and post-implantation losses were comparable among the groups. Fetal body weight was slightly decreased [97% of control] at the high-dose level compared to the concurrent control, but this may be attributed to the increased number of fetuses per doe at this dose level. There were no external, skeletal, or visceral anomalies or variations that could be attributed to treatment, and there was no treatment-related increase in visceral or skeletal malformations. Although there was an apparent increase in the incidence of a minor anomaly, retrocaval ureter, at the mid- and high-dose levels, its toxicological significance is doubtful. **The maternal/developmental LOEL is 1000 mg/kg/day, based on an increased incidence of abortions. The maternal NOEL is 500 mg/kg/day.**

This guideline [§83-3(b)] prenatal developmental toxicity study in the rabbit is classified Acceptable.

In a prenatal developmental toxicity study (MRIDs 40354013 and 42137341), pregnant New Zealand White rabbits received oral (gavage) administration of fluroxypyr (unspecified purity) in 0.5% carboxymethylcellulose (5 mL/kg) at dose levels of 0, 25, 100, or 400 mg/kg/day during gestation days 6 through 19. Due to a large number of maternal deaths in the 400 mg/kg/day 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

For maternal toxicity, the NOEL was 250 mg/kg/day and the LOEL was 400 mg/kg/day based on maternal deaths. For developmental toxicity, the NOEL was 100 mg/kg/day and the LOEL was 250 mg/kg/day, based on increased postimplantation loss.

This guideline [§83-3(b)] prenatal developmental toxicity study in the rabbit is classified Acceptable.

e. **Reproductive Toxicity**

Adequacy of data base for Reproductive Toxicity (Series 83-4: The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

83-4 Two generation reproduction study in rats

In a 2-generation reproduction study (MRID 44080321), fluroxypyr [99.0% a.i.] was administered to 30 Sprague-Dawley rats/sex/dose via the diet at dose levels of 0, 100, 500, and 750 mg/kg/day [males] and 0, 100, 500, and 1000 mg/kg/day [females] during the pre-mating period of 10 weeks [F1 generation]/12 weeks [F2 generation]. There was one litter [F1] in the first generation and two litters [F2A and F2B] in the second generation.

Treatment-related deaths due to renal failure occurred in both sexes at the high dose in both generations {1 P1 male [day 100], 2 P1 females [days 48 & 71], 1 P2 male [day 112], 1 P2 female [day 50]}. Males of both generations displayed lower body weights [P1 (91-94% of control); P2 (89-93% of control)] and body-weight gains [P1 (93%)/P2 (91% of control] during the dosing period and overall. Body weight and body-weight gain were comparable among the P1 females throughout the dosing period, but the P2 females displayed lower body weight [88-94% of control] and body weight gain [91% of control] during the dosing period. Food consumption was comparable among the P1 rats of both sexes during the dosing period, but decreased food consumption was noted in the P2 rats of both sexes. The effects observed increased progressively with time of exposure. During gestation, body weights were comparable among the P1 dams, and progressively lower than the controls at the high-dose level for the P2 dams during both gestation periods [1st 88-92% of control/2nd 86-91% of control]. Body-weight gains were progressively lower than the controls with each subsequent gestation period [P1 86%/1st P2 82%/2nd P2 74% of control]. During lactation, all dams of both generations displayed body weights that were initially lower than control values but by day 21 of lactation were comparable to the control values. Body-weight gains during lactation were greater than the controls at the mid- and high-dose levels [dose-related] for both generations and both litters of the P2 generation, and this effect increased progressively with time of exposure. There were increases in kidney weight with corresponding gross and microscopic findings [papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubulo-interstitial nephritis, and dilatation of the tubules] at the high-dose level in both sexes [both generations] and to a lesser degree in the mid-dose males [second generation]. Decreased absolute liver weight was observed in the high-dose males of both generations and in the high-dose females in the second generation, which was attributed to the nutritional status, lower body weights, and decreased abdominal fat of these rats. Reproductive indices [mating performance, fertility, gestation length, time to mating, and the pup sex ratio] of both generations were not adversely affected by exposure to fluroxypyr up to the limit dose in females and 750 mg/kg/day in males. Pup survival [F2A 94.5% vs 98.9%/F2B 92.1% vs 99.7% high dose vs control] and consequently litter sizes were decreased slightly in the F2A and F2B litters at the high-dose level. The author attributed the decrease to a few dams with compromised heath, as evidenced by their decreased amount of body fat and moderate to severe renal disease, although this was not very apparent from the data as presented. There were no apparent effects observed on pups at the mid- or low-dose level. F1 pup body weight at the high-dose level was

comparable to the control during lactation, but body-weight gain was initially [day 1-4] lower than the control [♂♂ 81%,♀♀ 88% of control]. Decreased body weight was observed throughout lactation in both the F2A [♂♂ 85%-91%/♀♀ 86%-92% of control] and F2B pups [♂♂ 86%-92%/♀♀ 89%-94% of control; P2 89-93% of control]. Decreased body-weight gain was observed throughout lactation for both the F2A and F2B pups, but the magnitude of the decrease was greatest initially [days 1-4]. Overall, body-weight gain during lactation was only slightly lower than the control for both the F2A [♂♂ 90%/♀♀ 92% of control] and F2B [♂♂ 92%/♀♀ 94% of control] pups. **The NOEL for maternal/paternal toxicity is 500/100 mg/kg/day], and the LOEL is 1000/500 mg/kg/day], based on death in females and increased kidney weight with corresponding gross and microscopic findings [papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubulo-interstitial nephritis, and dilatation of the tubules] in both sexes. The reproductive NOEL is 1000/750 mg/kg/day], the highest dose tested. The neonatal NOEL is 500 mg/kg/day, and the LOEL is 1000 mg/kg/day, based on decreased pup body weight/body-weight gain and slightly lower survival.**

This guideline [§83-4; OPPTS 870.3 2-generation reproduction study in rats is classified Acceptable.

f. Neurotoxicity

Adequacy of data base for neurotoxicity (Series 81-8, 82-5): This chemical is not an OP and hen studies were not performed or required. Specific neurotoxicity was not observed in any of the subchronic or chronic studies. Therefore, neurotoxicity testing was not required at this time.

g. Mutagenicity

Adequacy of data base for mutagenicity (Series 84): The data base for Mutagenicity is considered adequate. Based on the available mutagenicity studies, there are no concerns for mutagenicity at this time.

A total of nine studies were available for review; five with the acetic acid form of **fluroxypyr** and four with the **fluroxypyr methylheptyl ester.** The studies on the methylheptyl ester were submitted to support the bridging of data between the two forms of fluroxypyr since the ester is rapidly hydrolyzed to the acid.

A. Fluroxypyr

1. Gene Mutations

In a Salmonella typhimurium reverse gene mutation assay, fluroxypyr was not mutagenic up to a cytotoxic dose (10,000 µg/plate +S9) (MRID No. 40354014).

In a Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay) fluroxypyr was negative up a cytotoxic concentration (2000 µg/mL +/-S9) (MRID No. 40244511).

In a L5178Y $TK^{+/-}$ mouse lymphoma forward gene mutation assay , there were increases in the mutation frequency (MF) compared to concurrent controls at a severely cytotoxic dose (2400 µg/mL) and at a moderately cytotoxic dose (2000 µg/mL) without S9 activation. In the presence of S9 activation, increases in the MF occurred at the highest dose tested (2400 µg/mL) with only 1% cell survival; dose-related increases in the MF were also seen at 1400-2000 µg/mL with the percentage of cell survival ranging from 50 to 24%. The findings are considered marginal since the MFs for treated cultures, while higher than the concurrent controls, rarely exceeded the generally accepted background MF range for mouse lymphoma cells (MRID No. 40354015).

2. Chromosome Aberrations

An *in vitro* chromosome aberration assay in CHO cells was negative for damage to structural chromosomes up to doses causing moderate cytotoxicity (500 and 1000 µg/mL +/-S9). There was, however, marginal and nondose-related evidence of polyploidy under nonactivated and S9-activated conditions (MRID No. 40354016).

3. Other Mutagenic Mechanisms

In an *in vitro* unscheduled DNA synthesis (UDS) assay in human embryonic lung fibroblasts, cell line no. 2002 was negative up to nonactivated and S9-activated doses causing precipitation and moderate cytotoxicity (500-3333 µg/mL) (MRID No. 40354018).

B. Fluroxypyr Methylheptyl Ester

1. Gene Mutations

In a *Salmonella typhimurium/Escherichia coli* reverse gene mutation assay, independent trials were negative up to insoluble doses with or without S9 activation (≥2500 µg/plate) (MRID No. 44080323).

In a Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay, independent trials were negative up to cytotoxic concentrations without S9 activation (≥30 µg/mL -S9). In the presence of S9 activation, the test was also negative over the entire dose range investigated (100-1200 µg/mL) in two trials. However, all test material doses were insoluble under S9-activated conditions; therefore, this portion of the assay is currently considered Unacceptable but can be upgraded if the Sponsor adequately explains the rationale for not testing a soluble dose (MRID No. 44080324).

2. Chromosome Aberrations

In an *in vitro* chromosome aberration assay with rat lymphocytes, independent trials were negative up to cytotoxic concentrations (≥270 µg/mL +/-S9) (MRID No. 44080325).

In an *in vivo* bone marrow micronucleus assay, negative results were obtained in CD-1 (ICR) male and female mice receiving single oral gavage administrations of 225-900 mg/kg. Lethality and other clinical signs of toxicity were noted at 900 mg/kg. There was, however, no evidence of bone marrow cytotoxicity at any dose (MRID No. 44080326).

C. Conclusions:

The available studies indicate that **fluroxypyr** was not mutagenic in bacteria. By contrast, a mutagenic response was uncovered in the forward gene mutation assay with mouse lymphoma cells but not with CHO cells. There was also no evidence of clastogenicity *in vivo* using CHO cells. Hence the marginal positive result seen in the mouse lymphoma assay was not confirmed in a second mammalian cell line and the test material was negative for UDS *in vitro*.

Fluroxypyr methylheptyl ester was also not mutagenic in bacteria or clastogenic either *in vitro* or *in vivo*. However, the S9-activation portion of the mammalian cell gene mutation assay was classified as Unacceptable.

Although the findings from the Acceptable studies with **fluroxypyr methylheptyl ester** tend to support bridging, a final decision will not be made until the Sponsor adequately explains the rationale for not testing a soluble dose in the mammalian cell gene mutation assay with the ester.

h. Metabolism

Adequacy of data base for metabolism (Series 85-1): The data base for metabolism is considered to be complete. No additional studies are required at this time.

In a metabolism study (MRID 44080327), fluroxypyr ^{14}C-methylheptyl ester [95.8 % a.i. unlabeled; radiochemical purity 99%; labeled on the methylheptanol portion of the molecule] or ^{14}C- methylheptanol [98.9% unlabeled; radiochemical purity 97.5%] was administered to 5 [plasma]/3 [balance] male Fischer 344 rats/group in single oral [equimolar] doses of 50 mg fluroxypyr methylheptyl ester/kg body weight or 17.7 mg methylheptanol/kg body weight. The total recovery of the administered dose was 105% and 104%, with the principal route of excretion being expired $^{14}CO_2$, which contained ≈61% and 63% of the radioactivity for the fluroxypyr MHE and methylheptanol balance groups, respectively. The urine contained ≈30% and 27% and the feces contained 5% and 7% of the administered dose for the fluroxypyr MHE and Methylheptanol groups, respectively. At 48 hours post dose, ≈7% of the administered dose was recovered in the blood, carcass, and skin of both groups. The overall rates and routes of elimination were comparable between the groups. Each was extensively absorbed and rapidly

eliminated. Approximately 52% and 54% of the administered fluroxypyr MHE and Methylheptanol, respectively, 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 the dose in the expired $^{14}CO_2$, urine, and tissues, ≈90% of the dose was absorbed by the rats in each case. Once absorbed, both were extensively metabolized [20-22 metabolites] and rapidly expired as $^{14}CO_2$ and eliminated in the urine with a half-life of 6 hours. fluroxypyr MHE displayed a slower absorption rate than Methylheptanol, but once absorbed, the pharmacokinetic parameters were similar. Peak plasma concentrations of ^{14}C-radioactivity were attained by 7 and 10 hours post dose, and the half-lives for the elimination phase were ≈18.2 and 17.4 hours for fluroxypyr MHE and Methylheptanol, respectively. It was stated that the percentage of radioactivity recovered in the tissues and carcass [≈7%] suggests ^{14}C-incorporation into the carbon pool that may account for the longer half life in plasma as compared to the urinary half-life of 6 hours. Average area under the curve values were 140 µg eq hr/g and 163 µg eq hr/g for the fluroxypyr MHE and Methylheptanol groups, respectively. Clearance values were comparable for these groups also [2.1 and 1.8 mL/min kg]. These pharmacokinetic parameters indicate no difference in kinetics of Methylheptanol, based on whether it is labeled alone or as part of the fluroxypyr MHE molecule. Urine profiles were similar and indicated extensive metabolism [20-22 metabolites]. Unchanged fluroxypyr MHE was not detected in any of the samples, and the author stated that this "is consistent with the majority of the dose metabolized to CO_2." **The data indicate that the fluroxypyr MHE bond is readily hydrolyzed and that the methylheptyl ester portion of fluroxypyr is bioequivalent to Methylheptanol.**

This metabolism study in the rat is classified Acceptable.

I. Dermal Absorption

No dermal absorption studies are available at this time.

Dermal Absorption Factor: A dermal absorption factor of 100% should be used for correcting oral dosing to dermal dosing.

2. Dose Response Assessment

The HED Hazard Identification Assessment Review Committee met on 06 Jan, 1998 to select appropriate endpoints for acute dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) for Fluroxypyr.

a. Special Sensitivity to Infants and Children.

EPA generally defines the level of appreciable risk as exposure that is greater than 1/100 of the no observed effect level in the animal study appropriate to the particular risk assessment. This 100-fold uncertainty (safety) factor/margin of exposure (safety) is designed to account for inter-species extrapolation and intra-species variability. FFDCA section 408 provides that EPA shall

apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base (resulting in a total factor of 1000) unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

On 06 Jan, 1998, the Hazard Identification Committee evaluated the chemical fluroxypyr for FQPA considerations. The following discussion represents the information that was considered and the following conclusions were drawn by the Committee.

i. Adequacy of data: An acceptable two-generation reproduction study in rats (MRID 44080321) and acceptable prenatal developmental toxicity studies in rats (MRID 44094901) and rabbits (MRID 44080319) have been submitted to the Agency, meeting basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. The Committee determined that, based on a weight-of-the-evidence review of the available data, a developmental neurotoxicity study with Fluroxypyr in rats was not recommended at this time. There are no data gaps for the assessment of the effects of fluroxypyr on developing animals following *in utero* and/or early postnatal exposure.

ii. Susceptibility Issues: The Committee determined that the data as described below, with **developmental toxicity** studies **in rats and rabbits with both fluroxypyr** and **fluroxypyr 1-methylheptyl ester** and a **two-generation** reproduction study **with fluroxypyr**, are sufficient to assess the effects on infants and children for both forms of the chemical.

In the prenatal developmental toxicity studies in rats and rabbits with **fluroxypyr methylheptyl ester,** and in the prenatal developmental toxicity study in rats and the two-generation reproduction study in rats with **fluroxypyr** , there was no indication of increased susceptibility of the young animals to pre- and/or postnatal exposure. However, in the prenatal developmental toxicity study in rabbits with **fluroxypyr**, developmental toxicity was observed in the absence of maternal toxicity; this is an indication of increased susceptibility following prenatal exposure to fluroxypyr. Confidence in this finding is somewhat diminished by the fact that the incidence is only slightly above historical control range, and because it is not known if statistical evaluations of these data were performed.

iii. Uncertainty Factor: The Committee determined that for fluroxypyr, the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be reduced to 3 x.** This conclusion was based on the following factors. 1) the developmental toxicity study in rats showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures, 2) the two- generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, and 3) the toxicology data base is complete (i.e., no data gaps).

However, the Committee determined that a UF of 300 is required because in the prenatal developmental toxicity study in rabbits, there is an indication of additional susceptibility

following prenatal exposure to **fluroxypyr** since the developmental NOEL was less than the maternal NOEL. The confidence in these data, however, were minimized by the fact that the value is only slightly above the historical control, and because no statistical significance was indicated. Additionally, susceptibility to the offspring was not observed in any of the other prenatal developmental toxicity studies examined, and there is always the possibility that maternal toxicity may have been present (as kidney pathology) but that the relevant endpoint was not examined.

iv. **Recommendation for a Developmental Neurotoxicity Study**: The Committee determined that, based on a weight-of-the-evidence review of the available data, a developmental neurotoxicity study in rats with fluroxypyr is not required. The following information was considered in arriving at this decision. There was no evidence of developmental anomalies, including abnormalities in the development of fetal nervous system, in the developmental toxicity studies with both **fluroxypyr** and **fluroxypyr methyhexyl ester** at doses up to and including 600 mg/kg/day in rats 1000 mg/kg/day (Limit-Dose) in rabbits. Also, no evidence of neurotoxicity was observed in the overall data base. The decrease in absolute brain weight in female rats in the subchronic dietary study appeared to be an isolated finding, since the same effect was not observed in the chronic study, nor in males after short or long-term treatment.

b. **Reference Dose (RfD)** The Hazard ID Assessment Review Committee (document dated 28 Jan, 1998) **assigned an RfD of 0.50 mg/kg/day** using a NOEL of 50 mg/kg/day and an uncertainty factor of 100; NOEL established from a four-week range-finding feeding study in the dog; LOEL = 150 mg/kg/day based on histopathological lesions in the kidneys, decreased testes weights, and increased adrenal weights in both sexes (MRID 42137340).

Comments about Study and Endpoint: The Hazard ID Assessment Review Committee noted that although renal toxicity was seen at 150 mg/kg/day in the 28-day study, it was not seen in the 1-year study (MRID No. 4024450) at the same dose (150 mg/kg/day) in the same species (dogs). Also in the 28-day study, dogs at 500 mg/kg/day exhibited ataxia and hind limb weakness as well as decreases in body weight and food consumption and were sacrificed on days 16/17 of the study. Histopathology showed moderate acute tubular nephrosis and a slight to moderate superacute gastroenteritis. Some early signs of superacute tubular nephrosis were also seen in both sexes of dogs at 150 mg/kg/day. The Committee was unclear as to this discrepancy between the results of these two studies in dogs specifically when the kidneys were shown to be the target organ for Fluroxypyr-induced toxicity as demonstrated in several studies discussed below. Therefore, the Committee selected the dose (NOEL) and the endpoint (renal toxicity) from the 28-day study for the establishment of the RfD.

c. **Carcinogenic Classification and Risk Quantification**
Cancer Classification and Basis: Based on the lack of evidence of carcinogenicity in mice (MRID 44080317) and rats (MRID 44080322) at doses that were judged to be adequate to assess the carcinogenic potential, Fluroxypyr was classified as a "**not likely**"

human carcinogen by the Hazard ID Assessment Review Committee (document dated 01 Dec, 1997) according to EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996). However, due to incomplete data reporting and evaluation, the Committee determined that the Registrant must 1) submit the appropriate historical control data and 2) evaluate the thyroid glands from all animals at 100 mg/kg/day in the rat study (MRID 44080322).

d. Dermal Absorption

A dermal absorption study was not available for review. Therefore an absorption factor of 100% will be assumed.

e. Other Toxicological Endpoints

i. **Acute Dietary (one-day)**

In a prenatal developmental toxicity study (MRIDs. 40354013 and 42137341), pregnant New Zealand White rabbits received oral (gavage) administration of fluroxypyr (unspecified purity) in 0.5% carboxymethylcellulose (5 mL/kg) at dose levels of 0, 25, 100, or 400 mg/kg/day during gestation days 6 through 19. Due to a large number of maternal deaths in the 400 mg/kg/day group, a dose level of 250 mg/kg/day was added to the study, and the 400 mg/kg/day dose levels was discontinued early. For maternal toxicity, the NOEL was 250 mg/kg/day and the LOEL was 400 mg/kg/day based on maternal deaths. For developmental toxicity, the NOEL was 100 mg/kg/day and the LOEL was 250 mg/kg/day, based on increased postimplantation loss.

Dose and Endpoint for Risk Assessment: Developmental NOEL of 100 mg/kg/day based on increased postimplantation loss at 250 mg/kg/day (LOEL).

Comments about Study and Endpoint: The postimplantation loss is presumed to occur after a single exposure (dose). Appropriate endpoints attributable to a single exposure (dose) for this population were not seen in oral toxicity studies including maternal toxicity in the developmental toxicity studies in rats and rabbits. The Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be reduced to 3 x.** For acute dietary risk assessment, **a Margin of Exposure (MOE) of 300 is required.** This includes the conventional 100x for inter- and intra-species variation, and 3 x for FQPA.

This risk assessment is **required for females 13+ only,** since the endpoint is based on an *in utero* effect. An appropriate endpoint attributable to single-dose exposure for the general population or other population subgroups is not available at this time. The available data, which include developmental studies in rats and rabbits, a 3-month feeding rat study and a 28-day mouse feeding study, did not demonstrate toxicity which can be observed following one exposure only.

ii. **Chronic Dietary [Reference Dose (RfD)]**

In a 4-week range finding study (MRID 42137340), groups of beagle dogs (2/sex/dose) were fed diets containing fluroxypyr (98%) at dose levels of 0, 20, 50 , 150 or 500 mg/kg/day for 4 weeks. At week 3, dogs at 500 mg/kg/day received their dose via capsule. No mortality occurred in the control, 20, 50 or 150 mg/kg/day levels. No treatment-related effects were seen at 20 or 50 mg/kg/day. All dogs at 500 mg/kg/day that were sacrificed on Day 16/17 of study. All dogs at 500 mg/kg/day exhibited ataxia, tachycardia and weakness of the hind legs prior to sacrifice. Alterations seen in several clinical chemistry parameters in both sexes of dogs at 500 mg/kg/day were consistent with the clinical state of the dogs, as well as kidney effects. Both the absolute and relative weights of the kidneys were increased in both sexes of rat at 500 mg/kg/day, and there was a dose-related increase in adrenal weight (absolute and relative) in both sexes at this dose. Males at this dose exhibited a dose-related decrease in absolute and relative testes weights. At 150 mg/kg/day increased adrenal weights and decreased testicular weights were seen. All dogs at 500 mg/kg/day exhibited acute tubular nephrosis (slight to moderate) with cloudy swelling and hydropic degeneration, and some tubules showed initial signs of coagulation necrosis in a patchy distribution. Dogs at this dose also showed slight to moderate superacute gastroenteritis. At 150 mg/kg/day, minimal thickening of the glomerular basement membrane (parietal sheet of Bowman's capsule) and a focal increased eosinophilia of some proximal tubules was observed.

Dose and Endpoint for Risk Assessment: NOEL = 50 mg/kg/day based on histopathological lesions in the kidneys, decreased testes weights and increased adrenal weights in both sexes at 150 mg/kg/day (LOEL).

Comments about Study and Endpoint: The Committee noted that although renal toxicity was seen at 150 mg/kg/day in the 28-day study, it was not seen in the 1-year study (MRID No. 4024450) at the same dose (150 mg/kg/day) in the same species (dogs). Also in the 28-day study, dogs at 500 mg/kg/day exhibited ataxia and hind limb weakness as well as decreases in body weight and food consumption and were sacrificed on days 16/17 of the study. Histopathology showed moderate acute tubular nephrosis and a slight to moderate superacute gastroenteritis. Some early signs of superacute tubular nephrosis were also seen in both sexes of dogs at 150 mg/kg/day. The Committee was unclear as to this discrepancy between the results of these two studies in dogs specifically when the kidneys were shown to be the target organ for fluroxypyr-induced toxicity as demonstrated in several studies discussed below. Therefore, the Committee selected the dose (NOEL) and the endpoint (renal toxicity) from the 28-day study for the establishment of the RfD. An Uncertainty Factor of 100 was applied to account for inter-(10 x)-and intra-(10 x) species variation.

This risk assessment is required.

iii. Occupational and Residential Exposure (Dermal)

Short-Term (1 - 7 days) Dermal

In a prenatal developmental toxicity study (MRIDs. 40354013 and 42137341), increased post pregnant New Zealand White rabbits received oral (gavage) administration of fluroxypyr (unspecified purity) in 0.5% carboxymethylcellulose (5 mL/kg) at dose levels of 0, 25, 100, or 400 mg/kg/day during gestation days 6 through 19. Due to a large number of maternal deaths in the 400 mg/kg/day group, a dose level of 250 mg/kg/day was added to the study, and the 400 mg/kg/day dose levels was discontinued early. For maternal toxicity, the NOEL was 250 mg/kg/day and the LOEL was 400 mg/kg/day based on maternal deaths. For developmental toxicity, the NOEL was 100 mg/kg/day and the LOEL was 250 mg/kg/day, based on implantation loss.

Dose and Endpoint for Risk Assessment: Developmental NOEL of 100 mg/kg/day based on increased postimplantation loss at 250 mg/kg/day (LOEL)

Comments about Study and Endpoint: Although a 21-day dermal toxicity study with **fluroxypyr methylheptyl ester (98.5%)** in New Zealand White rabbits with a NOEL of $\geq$ 1000 mg/kg/day is available, the developmental NOEL from an oral study with **fluroxypyr** in the same species (rabbits) was selected for this risk assessment because 1) of the concern for developmental effects seen in the oral study with the acid which was not studied with the ester, 2) developmental effects are not evaluated in the dermal toxicity study (i.e., the consequence of these effects can not be ascertained for the dermal route of exposure; and 3) the concern for exposure by pregnant occupational workers. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments, to convert to oral equivalents.

This risk assessment is required.

Intermediate-Term (7 days to several months) Dermal

In a prenatal developmental toxicity study (MRIDs. 40354013 and 42137341), increased post pregnant New Zealand White rabbits received oral (gavage) administration of fluroxypyr (unspecified purity) in 0.5% carboxymethylcellulose (5 mL/kg) at dose levels of 0, 25, 100, or 400 mg/kg/day during gestation days 6 through 19. Due to a large number of maternal deaths in the 400 mg/kg/day group, a dose level of 250 mg/kg/day was added to the study, and the 400 mg/kg/day dose levels was discontinued early. For maternal toxicity, the NOEL was 250 mg/kg/day and the LOEL was 400 mg/kg/day based on maternal deaths. For developmental toxicity, the NOEL was 100 mg/kg/day and the LOEL was 250 mg/kg/day, based on implantation loss.

Dose and Endpoint for Risk Assessment: Developmental NOEL of 100 mg/kg/day based on increased postimplantation loss at 250 mg/kg/day (LOEL)

Comments about Study and Endpoint: Although a 21-day dermal toxicity study with **fluroxypyr methylheptyl ester (98.5%)** in New Zealand White rabbits with a NOEL of ≥ 1000 mg/kg/day is available, the developmental NOEL from an oral study with **fluroxypyr** in the same species (rabbits) was selected for this risk assessment because 1) of the concern for developmental effects seen in the oral study with the acid which was not studied with the ester, 2) developmental effects are not evaluated in the dermal toxicity study (i.e., the consequence of these effects can not be ascertained for the dermal route of exposure; and 3) the concern for exposure by pregnant occupational workers. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments.

This risk assessment is required.

Long Term (Several Months to Life-time) Dermal

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: Based on the current use pattern (one use per year), long-term dermal exposure is not anticipated. Therefore, a dose and endpoint was not identified.

This risk assessment is NOT required.

iv. **Inhalation Exposure (Any-Time period)**

Executive Summary: Except for an acute inhalation toxicity study, the results on which fluroxypyr is placed in Toxicity Category IV (LC_{50} = >3.4 mg/L), no other studies are available via this route. Therefore, the HIARC selected the oral NOEL of 100 mg/kg/day from the developmental toxicity study in rats for Short-and Intermediate-Term for inhalation risk assessments. This dose and endpoint was selected because of the lack of inhalation studies suitable for these time period and the concern for fetal effects seen via the oral route and the concern for exposure by pregnant occupational workers. Since an oral dose was selected, inhalation exposure should be included in the risk assessment as follows:

Step I. The inhalation exposure component (i.e.,mg/L) using a 100% absorption rate (default value) should be *converted to an equivalent oral dose* (mg/kg/day)

Step II. The dermal exposure component (i.e., mg/kg/day) using a 100 % dermal absorption rate should be *converted to an equivalent oral dose.* This dose should then be combined with the converted oral dose in Step I.

Step III The combined dose from Step II should then be *compared to the oral NOEL* of 100 mg/kg/day for Short-and Intermediate-Term exposure s to calculate the MOE's. Based on the current use pattern, Long-Term inhalation risk assessment is not required.

This risk assessment is required.

v. **Margin of Exposure for Occupational/Residential Exposures:**

For Short and Intermediate-Term dermal and inhalation exposure risk assessment, a MOE of 100 is required. No FQPA considerations apply here.

3. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Source)

i. Directions for Use

The petitioner provided the proposed labeling for this Section 3 registration of Starane™ EC for use on small grains, fallow cropland and non-cropland for selective post-emergence control of annual and perennial weeds. The proposed use patterns are described below.

Crop Uses (Wheat, Barley, and Oats)
Apply Starane™ EC for post-emergence control of kochia, including sulfonylurea resistant kochia, and other broadleaf weeds infesting wheat, barley, or oats. Apply to actively growing wheat, barley, or oats, from the 2 leaf crop growth stage up to and including flag leaf emergence. Apply when weeds are actively growing, but before weeds are 8 inches tall or vining. Only weeds emerged at the time of treatment will be controlled. Apply 2/3 pint (2 oz. acid equivalents (a.e.)) of Starane™ EC per acre. Do not allow livestock to graze treated areas or harvest treated forage within 7 days of application. Do not make more than one application per season closer than 14 days before cutting of hay or 40 days before harvesting of grain and straw.

HED requests a revised Section B/label which clarifies the last sentence above to ensure the use of just one application per year: "Do not make more than one application per year; this application must not occur within 14 days of hay cutting or 40 days of grain and straw harvesting". Also, a plant back interval of 120 days is needed.

Fallow Cropland and Non-Cropland
Apply Starane™ EC as a single broadcast treatment by ground or aerial equipment to control or suppress susceptible broadleaf weeds. Do not apply less than 3 gallons per acre by air or less than 8 gallons per acre by ground equipment. Do not exceed 40 gallons per acre total spray volume. Starane™ EC may be applied alone or in tank-mix combination with other registered herbicides. Apply 2/3 to 1 1/3 pint (2 to 4 oz. a.e.) per acre. Use lower rates to control light to

moderate infestations and under good growth conditions. Use higher rates for moderate to heavy infestations and to compensate for less than ideal growth conditions.

HED requests a revised Section B/label which specifies one application per year to fallow cropland and non-cropland. A plant back interval of 120 days is needed for fallow cropland.

ii. **Nature of the Residue - Plants**

DowElanco has submitted data from previous studies (MRID 40244528 and 42137344) investigating the metabolism of ^{14}C-labeled fluroxypyr 1-MHE in wheat. The data contained in MRID 40244528, an outdoor study, was reviewed by R.A. Loranger (memo of 31-DEC-1987 concerning PP#7G3541). For the purposes of the temporary tolerances in that study, the residue of concern was defined as fluroxypyr in both its free and conjugated forms. In the memo, it was noted that for a permanent tolerance, additional characterization of water soluble residues would be needed, including a search for 4-amino-3,5-dichloro-6-fluropyridin-2-ol. Data in support of an Experimental Use Permit (EUP) was contained in MRID 42137344, a greenhouse study, which was reviewed by G.J. Herndon (memo of 30-SEP-1992 concerning PP#2G04066). In this memo, it was noted that the predominant metabolic route for fluroxypyr MHE in wheat appears to be ester hydrolysis to form fluroxypyr, followed by conjugation into various fluroxypyr-based moieties (at least some of which appear to be various glycosylated fluroxypyr residues). Thus, for the experimental use, the residue of concern in wheat, barley and oats was fluroxypyr MHE and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr. This memo also states that for a permanent tolerance, the registrant should attempt to further elucidate the residue in wheat straw. However, DowElanco declined to do so on the grounds that further efforts towards identifying the structures of the conjugates of fluroxypyr in wheat straw would not provide significant insight into understanding the pathway of degradation of fluroxypyr in wheat and would not change the identity of the residue of concern (G.J. Herndon, 26-JUN-1996 memo).

Both wheat metabolism studies involved foliar application of ^{14}C-labeled fluroxypyr 1-MHE, and yielded similar results. The initial deposits on plant leaf surfaces were equivalent to 6.2 and 33 ppm fluroxypyr from the applications of 4.3 and 8.6 oz a.e./acre, respectively. These deposits were easily removable with solvent washes and comprised of virtually all fluroxypyr 1-MHE. In the outdoor study, there was a substantial reduction in the level of ester associated with the leaves and an increase in both fluroxypyr and polar compounds. Most of the radioactivity associated with the plant was solvent-extractable only after homogenization, indicating that it was not a surface deposit. In comparison, the greenhouse study showed that fluroxypyr 1-MHE was more persistent and readily removable in surface washes.

At harvest, the concentrations of residues in the grain and straw fractions were 0.025 and 2.1 ppm, respectively, for a 4.3 oz a.e./acre treatment and 0.055 and 5.5 ppm, respectively, for a 8.6 oz a.e./acre treatment. Progressively more polar and hydrolytic extraction techniques showed that the residue at harvest comprised either fluroxypyr or conjugates that would release

fluroxypyr when subjected to acid or base hydrolysis or enzyme digestion. A ^{14}C-labeled peak with an HPLC retention time similar to that of 4-amino-3,5-dichloro-6-fluoro-2-pyridinol (pyridinol) was detected at <1% of the total ^{14}C residue in both wheat forage and straw. No positive identification of this compound was made. Assuming this tentative assignment is correct, the pyridinol metabolite does not appear to be present in significant quantities.

The nature of the residue in wheat appears to be adequately understood. Metabolism of fluroxypyr 1-MHE proceeds through ester hydrolysis to form fluroxypyr, followed by conjugation into various fluroxypyr-based moietics. The residue of concern is fluroxypyr 1-methylheptyl ester and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr (HED Metabolism Assessment Review Committee, 21-APR-1998).

iii. Nature of the Residue - Animals

Poultry

DowElanco submitted data from a study (MRID 42137345) investigating the metabolism of ^{14}C-labeled fluroxypyr in laying hens. This study was reviewed previously by G.J. Herndon (memo of 30-SEP-1992 concerning PP#2G04066). Three replicate groups of five laying hens each were orally dosed with ^{14}C-fluroxypyr for 10 consecutive days. The laying hens used were 28 weeks old and beginning their first laying cycle. Twenty hens were split into four groups of five hens each. One group served as a control and received placebo doses. The other three groups received treated doses equivalent to about 10 ppm per day (22X the maximum theoretical dietary burden (MTDB) in poultry). Eggs were collected once each day and separated into yolks and whites. Excreta were collected once a day. Within 24 hours of the last dose, all hens were sacrificed. The following samples were collected and analyzed: blood, skin, breast muscle, thigh muscle, liver, heart, fat, gizzard, abdominal egg yolks, and kidneys. All samples were homogenized using various techniques and either counted directly by liquid scintillation counting (LSC), or combusted, with the resulting ^{14}C counted by LSC.

Very little of the radioactivity administered was transferred to the tissues or eggs of the hens. The highest level of radioactivity found in any of these fractions was 0.019 ppm of fluroxypyr equivalents (in one of the kidney samples, the other two were both < 0.007 ppm). The plant and animal metabolism guidance document (memo of D. Edwards and E. Zager, 16-JUL-1992) states that if the total activity in a crop/animal part is 10 ppb or less, no differentiation of the radioactivity will be required. Thus, HED will not require any additional characterization or identification at this time. No measurable residues are expected in poultry and eggs from these proposed uses; this use falls in category 3 of Section 180.6(a) with respect to residues in poultry and eggs.

The nature of the residue in poultry has been adequately defined for the proposed uses on wheat, barley, and oats. The residue of concern is fluroxypyr 1-methylheptyl ester and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr (HED Metabolism Assessment Review Committee, 21-APR-1998).

Ruminants

DowElanco submitted two studies (MRID 42137346 and 44080351) investigating the metabolism of ^{14}C-labeled fluroxypyr in lactating goats. In the first study (MRID 42137346), three lactating goats were given capsules containing ^{14}C-fluroxypyr orally for 4 consecutive days. Two of these goats were dosed at a daily rate of about 100 ppm (3.0X the MTDB assuming the same diet for dairy cattle and goats), while the third was dosed at rate of about 340 ppm (10.3X the MTDB assuming the same diet for dairy cattle and goats). This study was reviewed previously by G.J. Herndon (memo of 30-SEP-1992 concerning PP#2G04066). This study was conducted prior to the GLP rule, and was not conclusive about the origin of trace amounts of 4-amino-3,5-dichloro-4,6-difluropyridine and 2-amino-3,5-dichloro-4,6-difluropyridine. In addition, the goat metabolism samples were held up to 18 months between sample collection and analysis.

In the more recent study (MRID 44080351), one goat was orally dosed with 395 ppm/day ^{14}C-fluroxypyr for three consecutive days, approximately 20X the maximum theoretical dietary exposure for goats (assuming the same diet for dairy cattle and goats). Milk, urine, and feces were collected daily, and the goats were sacrificed within 24 hours of the last dose. This study was in full compliance with GLP and all samples were analyzed within 62 days after animal sacrifice. Radiochemical analysis of the edible tissues demonstrated relatively low concentrations of fluroxypyr: the highest concentration in tissues was found in kidneys at 0.67 ppm. Liver, fat, and muscle contained fluroxypyr equivalents of 0.067, 0.036, and 0.018 ppm, respectively. Milk samples contained a peak concentration of 0.509 ppm. The relatively low residue levels in milk and edible tissues, combined with the quantitative recovery of the test substance in the excreta, suggests that the residues of fluroxypyr do not concentrate in the goats. There was no evidence of any significant conjugation of the residues in any of the samples analyzed. HPLC and TLC analysis indicated that no significant metabolites of fluroxypyr were formed in the goat during the study; thus, the only significant residue was fluroxypyr.

The nature of the residue in ruminants has been adequately defined for the proposed uses on wheat, barley, and oats. The residue of concern is fluroxypyr 1-methylheptyl ester and its metabolite fluroxypyr, free and conjugated, all expressed as fluroxypyr (HED Metabolism Assessment Review Committee, 21-APR-1998).

iv. Residue Analytical Methods

Plants

DowElanco submitted a validation study (MRID 44080352) for the determination of residues of fluroxypyr and fluroxypyr 1-MHE as the acid equivalent in the grain, forage, straw, and hay of wheat, barley, and oats by capillary gas chromatography with mass selective detection (GC/MSD). For grain, analytical method GRM 96.02 was validated over the concentration range of 0.01 - 1.0 ppm with a validated limit of quantitation (LOQ) of 0.01 ppm. For forage, straw, and hay, the method was validated over the concentration range of 0.05 - 10.0 ppm with a validated LOQ of 0.05 ppm.

The method employs a 60% acetone/40% 0.25 N hydrochloric acid solution to extract residues of fluroxypyr and fluroxypyr 1-MHE from the sample matrices. An aliquot of the extract is basified

with sodium hydroxide to hydrolyze any fluroxypyr 1-MHE to the free acid. The sample is concentrated to remove the acetone, acidified with hydrochloric acid and then hydrolyzed at 90°C for two hours. Following hydrolysis, the sample is diluted with water and purified using a C18 solid-phase extraction (SPE). The eluate from the C18 SPE is extracted with 1-chlorobutane, the 1-chlorobutane evaporated to dryness, and the residue reconstituted and derivatized with acidified 1-propanol. Following derivatization, the 1-propanol is evaporated from the derivatizing solution, and the 1-propyl ester derivative (fluroxypyr PE) is partitioned from an aqueous sodium chloride solution into isooctane containing fluroxypyr 1-butyl ester (fluroxypyr BE) as an internal standard. A portion of the isooctane extract is then analyzed by GC/MSD. Quantitation of fluroxypyr residues was based on the peak area ratio of the fluroxypyr propyl ester ion at m/z 296 to that of the fluroxypyr butyl ester ion at m/z 310. Confirmation of the presence of fluroxypyr was based on the peak area ratio of the fluroxypyr propyl ester ions at m/z 298 to m/z 296.

Recovery values of fluroxypyr from samples of grain fortified over the concentration range of 0.01 to 1.0 ppm averaged 95 ± 6%. Recovery values of fluroxypyr from samples of forage fortified over the concentration range of 0.05 to 10.0 ppm averaged 99 ± 4%. Recovery values of fluroxypyr from samples of straw fortified over the concentration range of 0.05 to 10.0 ppm averaged 101 ± 3%. Recovery values of fluroxypyr from samples of hay fortified over the concentration range of 0.05 to 10.0 ppm averaged 96 ± 4%.

Successful independent laboratory validation of the residue method GRM 96.02 was reported in a study (MRID 44080353) submitted by DowElanco. Grain was fortified at 0.010 and 0.050 ppm and analyzed for residues of fluroxypyr by GC/MSD. Forage, straw, and hay were fortified at 0.05 and 0.25 ppm and analyzed for residues of fluroxypyr by GC/MSD. Recovery averaged 92 ± 14%, 94 ± 9%, 100 ± 2%, and 94 ± 4% for grain, forage, straw, and hay, respectively.

An EPA method validation is needed for method GRM 96.02 on wheat before it can be deemed acceptable for enforcement purposes. A request for EPA method validation has been made (memo of W. Donovan, 25-MAR-1998).

Animals

DowElanco submitted a validation study (MRID 44080354) for the determination of residues of fluroxypyr and fluroxypyr 1-MHE as the acid equivalent in ruminant tissues and milk by GC/MSD. For all substrates, the method GRM 96.03 was validated over the concentration range of 0.01 - 1.0 ppm with a validated limit of quantitation (LOQ) of 0.01 ppm.

Recovery values of fluroxypyr from samples of muscle fortified over the concentration range of 0.01 to 1.0 ppm averaged 101 ± 9%. Recovery values of fluroxypyr from samples of liver fortified over the concentration range of 0.01 to 1.0 ppm averaged 96 ± 6%. Recovery values of fluroxypyr from samples of kidney fortified over the concentration range of 0.01 to 1.0 ppm averaged 98 ± 8%. Recovery values of fluroxypyr from samples of fat fortified over the concentration range of 0.01 to 1.0 ppm averaged 96 ± 7%. Recovery values of fluroxypyr from samples of milk fortified over the concentration range of 0.01 to 1.0 ppm averaged 99 ± 7%.

An EPA method validation is needed for method GRM 96.03 for ruminant tissues and milk before it can be deemed acceptable for enforcement purposes. A request for EPA method validation has been made (memo of W. Donovan, 25-MAR-1998).

v. Multiresidue Methods

Fluroxypyr has been tested through the FDAs Multiresidue Methodology, Protocols C, D, and E. The results have been published in the FDA Pesticide Analytical Manual, Volume I (see MRID 44080359).

vi. Storage Stability Data

Dow Elanco submitted data from a study (MRID # 44094904) investigating the stability of fluroxypyr on wheat forage, hay, grain and straw during frozen storage. Table 3.1 summarizes the results, which demonstrate no significant degradation of fluroxypyr.

Table 3.1. Summary of Storage Stability Data for Fluroxypyr on Wheat Matrices.

Days of Storage	Average % Recovery			
	Forage	Hay	Grain	Straw
0	94	100	98	97
34/41[a]	97	96	85	100
98/105[b]	104	99	82	96
258/265[c]	106	98	98	90

[a] Grain and straw were stored 34 days, forage and hay for 41 days.
[b] Grain and straw were stored 98 days, forage and hay for 105 days.
[c] Grain and straw were stored 258 days, forage and hay for 265 days.

The petitioner also references a study reported by DowElanco Europe demonstrating the stability of fluroxypyr during frozen storage in immature plants or straw for 18 months and in grain for 12 months.

Adequate storage stability data have been submitted. The data are adequate to conclude that decline in frozen storage does not occur during the interval that the field samples were stored: a maximum of 208, 300, 258, and 272 days for forage, hay, grain, and straw, respectively.

vii. Crop Field Trials

Dow Elanco submitted residue data for fluroxypyr on wheat, barley and oats (MRID # 44094904, 44080356, and 44080357).

Wheat

A total of 21 wheat field trials were conducted in 11 states (California, Illinois, Minnesota, Mississippi, North Carolina, North Dakota, Oklahoma, South Dakota, Texas, Washington, and Wisconsin) in 1995 (MRID 44094904). The crop field trials were conducted in EPA regions II (1), IV (1), V (5), VI (1), VII (5), VIII (6), X (1), and XI (1). The number of field trials and geographical representation are adequate.

In the trials, one application of fluroxypyr 1-MHE was made to all test sites at approximately 4 oz a.e./acre (same as the maximum intended use rate of 4 oz a.e./acre), and in a spray volume rate of 20 - 40 gal/acre. Actual application rates were 3.9 - 4.6 oz a.e./acre. The applications were made with small plot sprayers or backpack sprayers and were made at approximately flag leaf wheat growth stage (Feekes 8-10).

Table 3.2 presents the levels of fluroxypyr residues found in wheat forage and hay, while Table 3.3 shows the results for wheat grain and straw. These data indicate that the proposed tolerances for wheat forage, hay, grain and straw of 10, 20, 0.5, and 10 ppm, respectively, are reasonable with the following labeling restrictions: 1) 7-day forage grazing restriction for livestock, 2) 14-day hay grazing restriction for livestock, 3) 40 day PHI for grain and 4) 40 day PHI for straw.

Table 3.2. Residues of Fluroxypyr in Wheat Forage and Hay.

Forage				Hay			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
CA1W	7	4.1	2.7 - 3.8 (3.2)	SD1W	7	4.0	15.9 - 22.7 (19.6)
MN1W	7	4.0	2.8 - 3.2 (3.0)	SD2W	7	4.0	10.8 - 12.3 (11.6)
MN2W	7	4.0	3.2 - 5.1 (4.4)	MN3W	14	4.0	10.6 - 12.6 (11.6)
MS1W	7	4.0	5.9 - 6.5 (6.2)	NC1W	14	4.1	9.2 - 13.4 (10.8)
NC1W	7	4.1	4.0 - 4.6 (4.3)	TX2W	19	4.1	10.7 -13.5 (12.3)
ND1W	7	4.6	2.4 - 3.0 (2.7)	ND3W	20	4.4	6.1 - 6.4 (6.2)
ND2W	7	4.6	3.3 - 4.6 (4.0)	WI1W	20	4.2	1.2 - 1.8 (1.5)
ND3W	7	4.4	2.9 - 3.4 (3.1)	MN2W	21	4.0	3.4 - 13.4 (10.6)
OK1W	7	4.0	3.4 - 3.8 (3.6)	MN1W	22	4.0	4.2 - 4.3 (4.2)
OK2W	7	3.9	5.3 - 6.0 (5.7)	ND1W	22	4.6	2.4 - 2.9 (2.7)
SD1W	7	4.0	2.6 - 6.3 (3.9)	ND2W	22	4.6	3.7 - 3.8 (3.7)
SD2W	7	4.0	3.2 - 4.8 (4.0)	WA1W	22	4.0	5.5 - 8.4 (6.6)
TX1W	7	4.0	6.7 - 7.2 (6.9)	MS1W	26	4.0	5.4 - 8.2 (6.9)
TX2W	7	4.1	3.4 - 4.2 (3.8)	OK3W	27	4.1	11.7 - 15.8 (13.7)

TX3W	7	4.0	7.7 - 8.4 (8.0)	CA1W	28	4.1	6.4 - 7.9 (7.2)
TX4W	7	4.0	4.1 - 5.4 (4.8)	TX4W	29	4.0	3.4 - 4.5 (4.0)
WA1W	7	4.0	3.5 - 3.7 (3.6)	TX3W	30	4.0	5.9 - 7.6 (6.6)
WI1W	7	4.2	4.3 - 4.4 (4.4)	OK2W	33	3.9	7.0 - 7.2 (7.1)
OK3W	7	4.1	5.5 - 6.0 (5.7)	TX1W	33	4.0	5.5 - 6.1 (5.8)
MN3W	8	4.0	4.5 - 4.5 (4.5)	OK1W	35	4.0	2.9 - 3.0 (2.9)
				IL1W	36	4.1	6.0 - 7.4 (6.7)

[1] Site ID coded as XXnY, where XX is the state postal abbreviation, n is the site number in the state, and Y is the crop identifier (B = barley, O = oats, W = wheat).
[2] Preharvest interval.
[3] Ounces of acid equivalents per acre.
[4] Range of values measured in ppm, average value in parenthesis.

Table 3.3. Residues of Fluroxypyr on Wheat Grain and Straw.

Grain				Straw			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
SD1W	40	4.0	0.02 - 0.02 (0.02)	SD1W	40	4.0	3.1 - 4.1 (3.6)
SD2W	41	4.0	0.03 - 0.03 (0.03)	SD2W	41	4.0	3.2 - 5.5 (4.3)
MN3W	43	4.0	0.03 - 0.04 (0.03)	MN3W	43	4.0	1.3 - 1.3 (1.3)
ND2W	45	4.6	0.01 - 0.01 (0.01)	ND2W	45	4.6	0.3 - 0.5 (0.4)
WI1W	46	4.2	0.02 - 0.03 (0.02)	WI1W	46	4.2	0.9 - 0.9 (0.9)
MN2W	47	4.0	0.03 - 0.03 (0.03)	MN2W	47	4.0	1.3 - 1.4 (1.3)
ND3W	47	4.4	0.01 - 0.02 (0.02)	ND3W	47	4.4	1.4 - 1.7 (1.5)
TX4W	52	4.0	0.01 - 0.01 (0.01)	TX4W	52	4.0	2.3 - 4.1 (3.4)
NC1W	55	4.1	0.03 - 0.03 (0.03)	NC1W	55	4.1	1.4 - 1.8 (1.6)
TX2W	55	4.1	0.09 - 0.10 (0.10)	TX2W	55	4.1	5.6 - 6.0 (5.8)
WA1W	55	4.0	0.04 - 0.05 (0.05)	WA1W	55	4.0	4.0 - 4.6 (4.4)
MN1W	56	4.0	0.02 - 0.02 (0.02)	MN1W	56	4.0	0.9 - 1.0 (0.9)
ND1W	56	4.6	0.01 - 0.01 (0.01)	ND1W	56	4.6	0.9 - 1.0 (1.0)
TX1W	57	4.0	0.03 - 0.05 (0.04)	TX1W	57	4.0	3.7 - 5.9 (5.3)

CA1W	58	4.1	0.04 - 0.07 (0.06)	CA1W	58	4.1	6.9 - 10.8 (8.9)
IL1W	58	4.1	0.01 - 0.01 (0.01)	IL1W	58	4.1	0.4 -0.5 (0.4)
OK3W	62	4.1	0.03 - 0.04 (0.03)	OK3W	62	4.1	2.2 - 2.2 (2.2)
OK1W	63	4.0	0.02 - 0.02 (0.02)	OK1W	63	4.0	0.9 - 1.0 (0.9)
MS1W	65	4.0	0.04 - 0.07 (0.05)	MS1W	65	4.0	1.9 - 1.9 (1.9)
OK2W	68	3.9	0.01 - 0.02 (0.01)	OK2W	68	3.9	0.7 - 0.8 (0.8)
TX3W	69	4.0	0.01 - 0.02 (0.01)	TX3W	69	4.0	2.1 - 3.4 (2.7)

[1] Site ID coded as XXnY, where XX is the state postal abbreviation, n is the site number in the state, and Y is the crop identifier (B = barley, O = oats, W = wheat).
[2] Preharvest interval.
[3] Ounces of acid equivalents per acre.
[4] Range of values measured in ppm, average value in parenthesis.

To demonstrate the decline pattern of fluroxypyr residues on wheat forage, samples were taken from two sites (IL and MN) on the day of fluroxypyr 1-MHE application, and at 1, 2, and 3 weeks after application. An exponential nonlinear regression function was used to fit the equation for first-order decay to the mean fluroxypyr concentration in forage: $C_t = C_0 * e^{(-kt)}$, where C_t is the mean concentration of fluroxypyr at time t, C_0 is the mean concentration of fluroxypyr at t = 0, and k is the first-order rate constant. The first-order half-life was then calculated as $t_{1/2} = 0.693/k$, where regression analysis provided the rate constant k and the coefficient of determination R^2. Thus for wheat forage the field half-life of fluroxypyr was estimated at 22 days ($R^2 = 0.969$) and 30 days ($R^2 = 0.981$) for the IL and MN field samples, respectively.

HED concludes that tolerances of 0.5, 12, 20, and 12 ppm for fluroxypyr residues in wheat grain, forage, hay and straw, respectively, are appropriate.

Barley
A total of 12 barley field trials were conducted in 8 states (California, Minnesota, North Carolina, North Dakota, Oregon, South Dakota, Utah, and Washington) in 1995 (MRID 44080356). The crop field trials were conducted in EPA regions II (1), V (3), VII (4), IX (1), X (1), and XII (2). The number of field trials and geographical representation are adequate.

In the trials, one application of fluroxypyr 1-MHE was made to all test sites at approximately 4 oz a.e./acre (same as the maximum intended use rate of 4 oz a.e./acre), and in a spray volume rate of 20-40 gal/acre. Actual application rates were 3.9 - 4.6 oz a.e./acre. The applications were made with small plot sprayers or backpack sprayers and were made at approximately flag leaf growth stage (Feekes 8-10) for barley.

Table 3.4 presents the levels of fluroxypyr residues found in barley forage and hay, while Table 3.5 shows the results for barley grain and straw. These data indicate that the proposed tolerances for barley forage, hay, grain and straw of 10, 20, 0.5, and 10 ppm, respectively, are reasonable with the following labeling restrictions: 1) 7-day forage grazing restriction for livestock, 2) 14-day hay grazing restriction for livestock, 3) 40 day PHI for grain and 4) 40 day PHI for straw.

Table 3.4. Residues of Fluroxypyr on Barley Forage and Hay.

Forage				Hay			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
CA1B	7	4.1	4.1 - 4.3 (4.2)	SD1B	7	3.9	23.6 - 27.7 (25.6)
MN1B	7	4.0	3.6 - 3.7 (3.6)	SD2B	7	4.0	15.5 - 15.9 (15.7)
NC1B	8	4.0	3.6 - 3.7 (3.6)	MN2B	14	3.9	9.4 - 9.8 (9.6)
ND1B	8	4.2	1.4 - 1.4 (1.4)	MN3B	14	4.0	3.5 - 4.5 (3.9)
ND2B	7	4.0	2.5 - 2.8 (2.6)	NC1B	14	4.0	11.4 - 12.5 (12.0)
OR1B	7	4.0	6.5 - 6.9 (6.7)	CA1B	20	4.1	7.2 - 11.3 (8.9)
SD1B	7	3.9	6.8 - 7.1 (7.0)	MN1B	22	4.0	7.8 - 9.8 (8.7)
SD2B	7	4.0	6.6 - 7.1 (6.9)	ND1B	22	4.2	4.1 - 4.2 (4.2)
UT1B	7	3.9	3.1 - 3.5 (3.3)	ND2B	22	4.6	2.7 - 3.2 (3.0)
WA1B	7	4.0	4.9 - 6.1 (5.3)	OR1B	29	4.0	13.0 - 13.6 (13.4)
MN2B	7	3.9	3.3 - 3.9 (3.6)	UT1B	33	3.9	3.2 - 4.0 (3.6)
MN3B	7	4.0	2.6 - 2.7 (2.7)	WA1B	35	4.0	11.7 - 14.3 (12.9)

[1] Site ID coded as XXnY, where XX is the state postal abbreviation, n is the site number in the state, and Y is the crop identifier (B = barley, O = oats, W = wheat).
[2] Preharvest interval.
[3] Ounces of acid equivalents per acre.
[4] Range of values measured in ppm, average value in parenthesis.

Table 3.5. Residues of Fluroxypyr on Barley Grain and Straw.

Grain				Straw			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
SD1B	40	3.9	0.02 - 0.02 (0.02)	SD1B	40	3.9	3.7 - 4.1 (3.9)
SD2B	41	4.0	0.05 - 0.05 (0.05)	SD2B	41	4.0	2.3 - 3.2 (2.6)
MN2B	43	3.9	0.07 - 0.13 (0.12)	MN2B	43	3.9	2.3 - 2.3 (2.3)

Grain				Straw			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
ND2B	45	4.6	0.03 - 0.03 (0.03)	ND2B	45	4.6	1.6 - 2.0 (1.8)
MN3B	46	4.0	0.09 - 0.10 (0.10)	MN3B	46	4.0	1.8 - 2.4 (2.1)
OR1B	52	4.0	0.02 - 0.03 (0.02)	OR1B	52	4.0	4.7 - 5.1 (4.9)
NC1B	55	4.0	0.35 - 0.37 (0.36)	NC1B	55	4.0	0.8 - 1.1 (1.0)
MN1B	56	4.0	0.01 - 0.02 (0.01)	MN1B	56	4.0	0.5 - 0.9 (0.7)
WA1B	58	4.0	0.05 - 0.06 (0.05)	WA1B	58	4.0	3.3 - 3.6 (3.5)
ND1B	60	4.2	0.01 - 0.01 (0.01)	ND1B	60	4.2	1.0 - 1.1 (1.0)
UT1B	62	3.9	0.01 - 0.02 (0.01)	UT1B	62	3.9	0.5 - 0.6 (0.5)
CA1B	73	4.1	0.10 - 0.18 (0.14)	CA1B	73	4.1	4.5 - 5.0 (4.7)

[1] Site ID coded as XXnY, where XX is the state postal abbreviation, n is the site number in the state, and Y is the crop identifier (B = barley, O = oats, W = wheat).
[2] Preharvest interval.
[3] Ounces of acid equivalents per acre.
[4] Range of values measured in ppm, average value in parenthesis.

HED concludes that tolerances of 0.5, 20, and 12 ppm for fluroxypyr residues in barley grain, hay, and straw, respectively, are appropriate. No tolerance level is needed for barley forage.

Oats
A total of 16 oat field trials were conducted in 11 states (California, Illinois, Minnesota, Mississippi, North Carolina, North Dakota, Oklahoma, South Dakota, Texas, Washington, and Wisconsin) in 1995 (MRID 44080357). The crop field trials were conducted in EPA regions I (1), II (1), V (9), VI (1), VII (3), VIII (1). The number of field trials and geographical representation are adequate.

In the trials, fluroxypyr 1-MHE was applied to all test sites at approximately 4 oz a.e./acre (same as the maximum intended use rate of 4 oz a.e./acre), and in a spray volume rate of 20-40 gal/acre. Actual application rates were 3.9 - 4.6 oz a.e./acre. The applications were made with small plot sprayers or backpack sprayers and were made at approximately flag leaf growth stage (Feekes 8-9) for oats.

Table 3.6 presents the levels of fluroxypyr residues found in oat forage and hay, while Table 3.7 shows the results for oat grain and straw. These data indicate that tolerances for oat forage, hay, grain and straw of 12, 20, 0.5, and 12 ppm, respectively, are reasonable with the following labeling restrictions: 1) 7-day forage grazing restriction for livestock, 2) 14-day hay grazing restriction for livestock, 3) 40 day PHI for grain and 4) 40 day PHI for straw. These tolerances

are what DowElanco proposed except that we have increased the forage and straw values from 0 to 12 ppm.

Table 3.6. Residues of Fluroxypyr on Oat Forage and Hay.

Forage				Hay			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
1L1O	7	3.9	3.1 - 3.1 (3.1)	SD1O	7	4.0	22.4 - 31.5 (25.8)
1L2O	7	3.9	4.4 - 4.4 (4.4)	SD2O	7	3.9	12.7 - 14.9 (14.2)
MN1O	7	4.0	1.9 - 2.0 (2.0)	MN3O	14	4.0	5.2 - 6.1 (5.5)
MN2O	7	3.9	2.6 - 2.7 (2.7)	MN4O	14	3.9	3.3 - 4.5 (4.0)
NC1O	7	4.0	2.7 - 5.1 (4.1)	NC1O	14	4.0	14.4 - 19.8 (17.5)
ND1O	7	4.2	1.2 - 1.2 (1.2)	WI1O	20	4.0	1.6 - 1.7 (1.6)
ND2O	7	4.6	1.7 - 2.0 (1.8)	WI2O	20	3.9	1.6 - 2.1 (1.8)
OH1O	7	4.0	1.9 - 2.5 (2.2)	MN2O	21	3.9	10.1 - 10.3 (10.2)
OK1O	7	3.9	3.6 - 4.1 (3.8)	PA1O	21	4.0	5.5 - 8.9 (7.1)
OK2O	7	3.9	9.1 - 10.7 (10.1)	MN1O	22	4.0	3.3 - 5.2 (4.4)
PA1O	7	4.0	2.9 - 3.3 (3.1)	ND1O	14	4.2	2.6 - 3.2 (2.9)
SD1O	7	4.0	4.4 - 6.1 (5.2)	ND2O	22	4.6	2.2 - 2.8 (2.5)
SD2O	7	3.9	6.6 - 7.7 (7.0)	OH1O	27	4.0	3.5 - 4.1 (3.7)
WI1O	7	4.0	3.0 - 3.1 (3.0)	OK1O	27	3.9	6.8 - 7.6 (7.2)
WI2O	7	3.9	2.9 - 3.4 (3.1)	1L1O	28	3.9	6.1 - 6.2 (6.1)
MN3O	8	4.0	2.6 - 3.3 (2.9)	IL2O	28	3.9	4.0 - 7.5 (5.7)
MN4O	8	3.9	2.0 - 2.2 (2.1)	OK2O	32	3.9	6.0 - 7.3 (6.7)

[1] Site ID coded as XXnY, where XX is the state postal abbreviation, n is the site number in the state, and Y is the crop identifier (B = barley, O = oats, W = wheat).
[2] Preharvest interval.
[3] Ounces of acid equivalents per acre.
[4] Range of values measured in ppm, average value in parenthesis.

Table 3.7. Fluroxypyr residues on oat grain and straw.

Grain				Straw			
Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]	Site ID[1]	PHI[2]	oz ae/A[3]	Range (AFT)[4]
SD1O	40	4.0	0.22 - 0.35 (0.28)	SD1O	40	4.0	3.2 - 4.1 (3.6)
SD2O	41	3.9	0.06 - 0.10 (0.08)	SD2O	41	3.9	3.8 - 4.1 (3.9)
MN3O	43	4.0	0.04 - 0.04 (0.04)	MN3O	43	4.0	0.8 - 0.8 (0.8)
OK1O	43	3.9	0.02 - 0.05 (0.03)	OK1O	43	3.9	1.2 - 1.3 (1.2)
ND2O	45	4.6	0.03 - 0.03 (0.03)	ND2O	45	4.6	1.1 - 1.2 (1.2)
OH1O	45	4.0	0.02 - 0.02 (0.02)	OH1O	45	4.0	0.7 - 0.7 (0.7)
MN4O	46	3.9	0.04 - 0.05 (0.04)	MN4O	46	3.9	0.9 - 1.2 (1.0)
WI1O	46	4.0	0.03 - 0.06 (0.05)	WI1O	46	4.0	1.2 - 1.4 (1.3)
WI2O	46	3.9	0.06 - 0.06 (0.06)	WI2O	46	3.9	1.3 - 1.4 (1.4)
MN2O	47	3.9	0.04 - 0.05 (0.04)	MN2O	47	3.9	1.4 - 1.4 (1.4)
OK2O	47	3.9	0.02 - 0.02 (0.02)	OK2O	47	3.9	0.4 - 0.6 (0.5)
PA1O	48	4.0	0.03 - 0.03 (0.03)	PA1O	48	4.0	1.7 - 2.5 (2.0)
IL1O	49	3.9	0.03 - 0.03 (0.03)	IL1O	49	3.9	< 0.05
IL2O	49	3.9	0.02 - 0.03 (0.02)	IL2O	49	3.9	1.5 - 2.9 (2.1)
MN1O	56	4.0	0.02 - 0.02 (0.02)	MN1O	56	4.0	0.7 - 0.7 (0.7)
ND1O	60	4.2	0.02 - 0.02 (0.02)	ND1O	60	4.2	0.7 - 0.8 (0.7)

[1] Site ID coded as XXnY, where XX is the state postal abbreviation, n is the site number in the state, and Y is the crop identifier (B = barley, O = oats, W = wheat).
[2] Preharvest interval.
[3] Ounces of acid equivalents per acre.
[4] Range of values measured in ppm, average value in parenthesis.

To demonstrate the decline pattern of fluroxypyr residues on oat forage, samples were taken from one site on the day of fluroxypyr 1-MHE application, and at 1, 2, and 3 weeks after application. An exponential nonlinear regression function was used to fit the equation for first-order decay to the mean concentration in forage: $C_t = C_0 * e^{(-kt)}$, where C_t is the mean concentration of fluroxypyr at time t, C_0 is the mean concentration of fluroxypyr at t = 0, and k is the first-order rate constant. The first-order half-life was then calculated as $t_{1/2} = 0.693/k$, where regression analysis provided the rate constant k and the coefficient of determination R^2. Thus for oat forage the field half-life of fluroxypyr is estimated to be 22 days, with a R^2 of 0.527.

HED concludes that tolerances of 0.5, 12, 20, and 12 ppm for fluroxypyr residues in oat grain, forage, hay, and straw, respectively, are appropriate.

viii. Processed Food/Feed

DowElanco submitted data from a study (MRID 44080358) investigating the potential for concentration of fluroxypyr residues in the processed commodities of wheat.

Fluroxypyr 1-MHE was applied as a ground postemergent spray to plots of spring wheat at a site in Belgrade, Montana at 9 oz a.e./acre (2.25X the label rate) or 15 oz a.e./acre (3.75X the label rate). The lower treatment rate was intended as a backup to the higher rate. However, no difficulties were encountered with wheat samples from the plot treated at 3.75X, so all the results reported apply to samples from this plot. Samples of combine-threshed wheat grain were collected at normal harvest (104 days after treatment). All samples (including controls) were frozen on the day of harvest and shipped frozen to Texas A&M for processing. After obtaining a moisture content of 10 to 12%, samples were aspirated to separate the grain dust. The cleaned seed was then further processed into bran, middlings, shorts, low grade flour and patent flour. Samples were frozen after processing and shipped frozen to DowElanco for analysis.

All samples were analyzed within 133 days of harvest. The fractions of bran, middlings, shorts, low grade flour, and patent flour were analyzed within 49 days of processed fraction generation, while grain dust samples were analyzed within 103 days of generation. The results are summarized below:

Table 3.8. Fluroxypyr residues in wheat processed fractions.

Substrate[a]	Rate (oz a.e./acre)	Fluroxypyr (ppm)[a]
Wheat grain	15	0.066
Bran	15	0.053
Low grade flour	15	ND[b]
Middlings	15	0.010
Shorts	15	0.018
Patent flour	15	<0.01[c]
Dust >2540	15	0.26
Dust >2030	15	0.23
Dust >1180	15	0.46
Dust >850	15	0.63
Dust >425	15	0.42
Dust <425	15	0.32

[a] Average of replicate determinations.
[b] ND = Not Detected, less than the limit of detection, 0.005 ppm.
[c] <0.01 = Value between limit of detection (0.005 ppm) and limit of quantitation (0.01 ppm).

For the processed fractions of bran, middlings, shorts, and flour, fluroxypyr residue levels were lower than those found in wheat grain, **demonstrating that fluroxypyr residues do not concentrate in these processed food commodities of wheat grain. However, data are needed for wheat germ.**

The pre-milling fraction of dust showed concentration ranging from 3.5 to 9.5X the residue found in wheat grain, with the highest residue level appearing in the dust fraction between 850 and 1180 μm at 0.63 ppm. Taking into account the observation that at least 50% of commercial grain dust has a particle size of < 400 μm (E. Saito and E. Zager memo, "Aspirated Grain Fractions (Grain Dust): A Tolerance Perspective", 07-JUN-1994), we calculate an average concentration factor of 5.7X. Applying this concentration factor to the maximum wheat grain residue level in the crop field trial data (0.10 ppm) gives a result of 0.57 ppm. **Thus, a tolerance of 0.6 ppm for aspirated grain fractions should be adequate.**

ix. Meat, Milk, Poultry, and Eggs

Grain, forage, straw, and hay from wheat, barley, and oats are cattle feed items (except barley forage). In addition, aspirated grain fractions and milled byproducts are also cattle feed items. DowElanco submitted data from a dairy cow feeding study (MRID 40244538) to examine the residues present when fluroxypyr was fed in the diet at 20, 200 and 1000 ppm. The maximum theoretical dietary burden (MTDB) for dairy and beef cattle can be assessed by considering the values in Table 3.9 below:

Table 3.9. Data for Calculation of Maximum Theoretical Dietary Burden for Beef and Dairy Cattle.

Feedstuff for barley, oats or wheat	% Dairy Cattle Diet	% Beef Cattle Diet	% Dry Matter	Proposed Tolerance (ppm)
grain	40	50	88 - 89	0.5
forage	0 - 60	0 - 25	25 - 30	10
hay	60	25	88 - 90	20
straw	10	10	88 - 90	10
aspirated grain fractions	0 - 20	0 - 20	85	0.5
milled byproducts	0 - 50	0 - 40	88	0.5

The maximum theoretical dietary burden is estimated from a dairy cattle diet composed of the highest residue feedstuff fed at the maximum % dairy cattle diet corrected for lowest percentage

of dry matter in the feedstuff range. These conditions occur with a dairy cattle diet of 60% forage, corrected for 25% dry matter, and 40% hay, corrected for 88% dry matter. The maximum exposure is then 38 ppm:

MTDB = (% Forage/%DM Forage) X Recommended forage tolerance + (% Hay/%DM Hay) X Recommended hay tolerance

MTDB = (60%/25%) X 12 ppm + (40%/88%) X 20 ppm = 38 ppm

Applying the same type of calculation to beef cattle gives a MTDB of just 19 ppm. Since dairy cattle can have a higher dietary burden than beef cattle, the worst case scenario is represented by dairy cattle. Comparing the MTDB to the feeding levels in the feeding study provides an indication of the appropriate tolerance levels as shown in Table 3.10:

Table 3.10. Fluroxypyr Residue Levels Found in Animal Commodities at Different Feed Dose Levels.

Dose, ppm (in feed)	Maximum Fluroxypyr Levels in Dairy Cattle Tissues and Milk, ppm				
	Muscle	Fat	Kidney	Liver	Milk
0	<0.05	<0.05	<0.05	<0.05	<0.05
20	<0.05	<0.05	0.08	<0.05	<0.05
38	<0.05[a]	0.05[a]	0.12[a]	0.05[a]	0.06[a]
200	<0.05	0.07	0.63	0.08	0.15
1000	<0.05	0.14	2.12	0.10	0.49

[a] Interpolated values assuming a linear relationship between dose and residue level.

The proposed tolerances for meat, fat, milk, and meat byproducts (except kidney) of 0.1 ppm and for kidney of 0.5 ppm are adequate. Based on the poultry metabolism study (MRID 42137345), no tolerances are needed on poultry or eggs.

x. Water, Fish, and Irrigated Crops

Fluroxypyr is not registered for direct use on potable water or aquatic food and feed crops; therefore, no residue chemistry data are required under these guideline topics.

xi. Food Handling Establishments

Fluroxypyr is not registered for use in food-handling establishments; therefore, no residue chemistry data are required under this guideline topic.

xii. Confined Accumulation in Rotational Crops

A confined accumulation in rotational crops study (MRID 44080350) with fluroxypyr 1-MHE was conducted for DowElanco by PTRL-East, Inc., in Lexington, Kentucky. Fluroxypyr, ^{14}C-radiolabeled in the 2 and 6 ring carbons, was applied to sandy loam soil at rate of 8.8 oz a.e./acre, equivalent to an exaggeration rate of 2.2X the label use rate for fallow cropland and 4.4X the rate for wheat, barley, and oats. Wheat, lettuce, and turnip crops were planted in the treated soil at 30, 120, and 365 days after treatment (DAT). Corn was also planted at 365 days. The crops were grown to maturity and harvested. Total ^{14}C-fluroxypyr equivalent residue in soil and plant samples was determined by combustion to $^{14}CO_2$ and subsequent liquid scintillation counting (LSC).

Identification and characterization of the radioactive residue involved extraction of the plant samples with appropriate solvents and analysis by HPLC and TLC. Retention times of the resulting peaks were compared to those of radiolabeled and non-radiolabeled standards. The peaks were fractionated and submitted to LSC for quantitative information on the degradates. TLC was employed as a secondary method for degradate identification. Unextractable radioactive residues in plant matrices were characterized by cell wall fractionation. Most of this plant-bound material was incorporated into cellulose, hemicellulose, lignin and starch.

The highest residues were found in the 30-DAT crops and ranged from 0.02 ppm in the turnip foliage and wheat grain to 0.43 ppm in wheat straw (Table 3.11). The 120-DAT and 365-DAT crops contained lower radioactive residues with the highest residue levels being 0.08 ppm in the 120-DAT wheat chaff, and 0.06 ppm in the 365-DAT wheat straw. The majority of the radioactive residues were extractable from crop fractions and were characterized as free fluroxypyr and polar conjugates or degradates. Fluroxypyr 1-MHE was not detected in any crop sample, except for the 30-DAT turnip foliage and root (<0.01 ppm). Fluroxypyr was the free residue most frequently observed. Other known metabolites were the methoxypyridine and the pyridinol. None of these free metabolites was observed at residue levels exceeding 0.01 ppm after the 120-DAT rotational interval sampling. Two major radioactive components observed in the 30-DAT rotational interval were Unknowns 1 and 6. Each was observed at greater than 0.04 ppm in the 30-DAT rotational interval samples, but were less than or equal to 0.01 ppm by the 365-day sampling. Further characterization work showed that Unknown 6 and a large part of Unknown 1 were conjugates of fluroxypyr. The registrant provided evidence that Unknown 6 was the N-glucosyl conjugate of fluroxypyr also observed in a separate nature of the residue study of fluroxypyr 1-MHE applied directly to wheat.

Table 3.11. Total Radioactive Residues of ^{14}C-Labeled Fluroxypyr Equivalents in Rotational Crops from Soil Treated at a Rate of 8.8 oz a.e./acre with Fluroxypyr 1-MHE.

Sample Description	Total Residue Level (ppm)
30-DAT	
Day 77 Lettuce Foliage	0.04
Day 83 Immature Wheat	0.09

Sample Description	Total Residue Level (ppm)
Day 91 Turnip Foliage	0.02
Day 91 Turnip Root	0.08
Day 156 Wheat Straw	0.43
Day 156 Wheat Chaff	0.22
Day 156 Wheat Grain	0.02
120-DAT	
Day 168 Lettuce Foliage	0.01
Day 202 Immature Wheat	0.05
Day 215 Turnip Foliage	0.01
Day 215 Turnip Root	0.06
Day 289 Wheat Grain	0.02
Day 289 Wheat Chaff	0.08
Day 289 Wheat Straw	0.05
365-DAT	
Day 414 Immature Wheat	0.04
Day 418 Lettuce Foliage	0.01
Day 428 Turnip Foliage	<0.01
Day 428 Turnip Root (whole)	0.01
Day 428 Turnip Root (peeling)	0.03
Day 428 Peeled Turnip Root	0.01
Day 467 Wheat Straw	0.06
Day 467 Wheat Grain	0.01
Day 467 Wheat Chaff	0.03
Day 467 Corn Fodder	0.02
Day 467 Corn Grain	<0.01

The EPA Residue Chemistry Test Guidelines suggest that for confined rotational crop studies, the treatment rate should be 1X and the appropriate rotational crop restriction can be set at the shortest interval where no TRR is ≥0.01 ppm, provided the registrants are willing to include this interval on the label. The present study employed an exaggerated rate of 4.4X for wheat, barley,

and oats, and 2.2X for fallow cropland. The registrant proposes a plant back interval of 30 days. However, the data show a significant reduction in TRR from 30 to 120 DAT, with a further small decline in TRR at 365 DAT.

Taking into account the exaggerated rate used, the nature of the residue analysis, and the observation that no free metabolites were observed at residue levels exceeding 0.01 ppm after the 120-DAT rotational interval sampling, a plant back interval of 120 days is requested. This interval is also needed for fallow cropland. Both of these plant back intervals were judged appropriate by the HED Chemistry Science Advisory Council (08-APR-1998).

In addition to the crop residues presented above, the registrant provided HPLC characterization of the extractable residues in soil samples. These results show detectable quantities of fluroxypyr 1-MHE, fluroxypyr, the 2-pyridinol metabolite, and the 2-methoxy metabolite. The first half-life of the total radioactive residue was approximately 22 days, while the second half-life was approximately 120 days. Table 3.12 below provides the detailed data for each metabolite monitored.

Table 3.12. HPLC Characterization of the Extractable Residues in Soil Samples During Study.

Soil Sample (DAT)	Total Residue/ Extracted (ppm)[a]	Fluroxypyr 1-MHE		Fluroxypyr		2-Pyridinol		2-Methoxy	
		% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
0	0.62/0.58	9.8	0.057	24.1	0.14	9.1	0.053	49.2	0.287
30	0.25/0.21	8.5	0.018	20.2	0.042	7.8	0.016	46.8	0.097
83	0.21/0.18	7.4	0.013	7.7	0.014	5.9	0.011	63.5	0.113
120	0.16/0.15	9.3	0.014	1.2	0.002	1.8	0.003	83.2	0.127
202	0.14/0.11	7.2	0.008	0.0	0.000	1.2	0.001	68.4	0.073
215	0.12/0.09	10.0	0.009	0.8	0.001	1.0	0.001	57.8	0.050

[a] The first value given is the total residue present; the second value is the total residue extracted in ppm.

These results clearly show that the predominant residue in soil is the 2-methoxy metabolite, and help explain the results of the analysis of the 120-DAT turnip root, where 0.046 ppm (75%) of the TRR was attributed to the 2-methoxy metabolite. Moreover, the TRR in the peelings was three times as high as in the rest of the turnip root, suggesting that most of the residue was adsorbed/absorbed from the soil rather than produced metabolically by the plant.

xiii. Field Accumulation in Rotational Crops - Not applicable.

xiv. Reduction of Residues - Anticipated Residues - Not applicable.

xv. International Harmonization of Tolerances

There are no CODEX, Canadian, or Mexican tolerances for fluroxypyr residues on wheat, barley or oats. Therefore, international harmonization is not an issue at this time.

b. Dietary Exposure (Drinking Water Source)

The Environmental Fate and Effects Division (EFED) provided a Tier 1 drinking water assessment of fluroxypyr (William Effland, Environmental Risk Branch 2, memo dated 23-DEC-1997). This assessment utilized the GENEEC and SCI-GROW2 screening models to provide estimates of ground and surface water contamination from fluroxypyr formulated as fluroxypyr 1-MHE. In terrestrial and aquatic environments, fluroxypyr 1-MHE is rapidly hydrolyzed to fluroxypyr, which has herbicidal activity.

i. Ground Water

Using available fate parameters and assuming a label application rate of one application at 0.25 lbs ae/acre/year, the estimated ground water concentration from fluroxypyr using SCI-GROW2 was 0.025 μg/L.

The drinking water exposure from the ground water screening model, SCI-GROW2, yields a peak Estimated Environmental Concentration (EEC) of 0.025 ppb in ground water. There may be exceptional circumstances under which ground water concentration could exceed the SCI-GROW2 estimates. However, such exceptions should be quite rare since the SCI-GROW2 model is based exclusively on maximum ground water concentrations from studies conducted at sites and under conditions which are most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW2 are based on the largest 90-day average recorded during the sampling period. The concentration of 0.025 μg/L can be considered as both the acute and chronic values (see EPA memo dated 24-NOV-1997, "Interim Guidance for Conducting Water Exposure and Risk Assessments").

ii. Surface Water

The GENEEC version 1.2 model was used to estimate surface water concentrations for fluroxypyr resulting from its use on wheat, oats, and barley. Surface water concentrations ranged from a peak of 11.2 μg/L to a 56 day average of 3.9 μg/L. This estimate is based on one application at a maximum application rate of 0.25 lbs ae/acre. The GENEEC values represent upper-bound estimates of the concentrations that might be found in surface water due to fluroxypyr use.

c. Dietary Risk Assessment and Characterization

i. Chronic Risk

The chronic dietary exposure analysis from food sources was conducted using the reference dose (RfD) of 0.50 mg/kg/day. The RfD is based on the NOEL of 50 mg/kg/day in male and female dogs from the four week range finding study in dogs (MRID 42137340), and an uncertainty factor of 100. The fluroxypyr chronic DRES run was performed on 16-JUN-1998.

In conducting this chronic dietary risk assessment, EPA has made very conservative assumptions: 100% of wheat, oats, and barley RACs having fluroxypyr tolerances will contain fluroxypyr residues and those residues will be at the level of the established tolerance. This results in an overestimate of human dietary exposure. Thus, in making a safety determination for this tolerance, EPA is taking into account this conservative exposure assessment.

The recommended fluroxypyr tolerances (including the necessary Section 18 tolerances) result in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percentages of the RfD:

Table 3.13. Summary of Results from Chronic DRES Analysis.

Subgroups	%RfD
U.S. Population (48 states)	0.41
Nursing Infants (< 1 year old)	0.39
Non-Nursing Infants (< 1 year old)	1.6
Children (1-6 years old)	1.1
Children (7-12 years old)	0.69
Hispanics	0.48
Non-Hispanic Whites	0.42
Non-Hispanic Others	0.43
Males (13-19 years old)	0.46

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants and children; and (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states).

ii. Carcinogenic Risk

The carcinogenic potential of fluroxypyr has been evaluated by the Hazard ID Committee (06-JAN-1998) and, in accordance with the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (10-APR-1996), classified fluroxypyr a "not likely" human carcinogen based on the lack of evidence of carcinogenicity in mice and rats (male and female).

iii. Acute Dietary Risk

The endpoint selected by the Hazard ID Committee (06-JAN-1998) for assessment of acute dietary risk is 100 mg/kg/day (NOEL), based on rabbit developmental toxicity studies (MRID 40354013 and 42137341). Thus, this risk assessment is required for the females (13+) population subgroup. The fluroxypyr acute DRES run was performed on 30-MAR-1998.

This acute dietary (food) risk assessment used the Theoretical Maximum Residue Contribution (TMRC). Resulting exposure values and MOEs (MOE = NOEL ÷ Exposure) are shown below.

Table 3.14. Summary of Results from Acute DRES Analysis.

Population Subgroup	NOEL (mg/kg/day)	High-end Exposure (mg/kg/day)	MOE
Females (13+ years)	100	0.002	50000

The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for the interspecies extrapolation and the intraspecies variability. For infants and children, an MOE of 300 is appropriate to take into account the additional 3X uncertainty factor identified by the Hazard Identification Assessment Review Committee (28-JAN-1998).

iv. Drinking Water Risk - Acute and Chronic

HED followed OPP's "Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments" issued on 24-NOV-1997. Thus, the GENEEC model and the SCI-GROW2 model were run to produce estimates of fluroxypyr concentrations in surface and ground water, respectively. The primary use of these models is to provide a coarse screen for sorting out pesticides for which OPP has a high degree of confidence that the true levels of the pesticide in drinking water will be less than the human health drinking water levels of concern (DWLOCs). A human health DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that chemical from food, water, and non-occupational (residential) sources.

$$DWLOC_{acute} = \frac{[\text{water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

$$\text{where water exposure (mg/kg/day)} = \frac{\text{NOEL (mg/kg/day)}}{\text{MOE}} - \text{food exposure (mg/kg/day)}$$

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

where chronic water exposure (mg/kg/day) = [RfD - (chronic food + residential exposure) (mg/kg/day)]

The $DWLOC_{chronic}$ is the concentration in drinking water as part of the aggregate chronic exposure that occupies no more than 100% of the RfD. The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female), and 10 kg/1L (child).

Table 3.15. Comparison of DWLOCs to Screening Model Estimates of fluroxypyr in Drinking Water for Acute and Chronic Scenarios.

Population Subgroup	Acute Scenario[1]				Chronic Scenario[2]			
	NOEL mg/kg/day	DWLOC μg/L	Ground Water SCI-GROW2 EEC in μg/L	Surface Water GENEEC EEC in μg/L	RfD mg/kg/day	DWLOC μg/L	SCI-GROW2 EEC in μg/L	GENEEC[3] EEC in μg/L
U.S. Population	NA[4]	NA	NA	NA	0.50	17400	0.025	1.3
Females (13+, nursing)	100	9940	0.025	11.2	0.50	14900	0.025	1.3
Children (1-6 yrs.)	NA	NA	NA	NA	0.50	4950	0.025	1.3

[1] Assuming a MOE of 300 for U.S. population, females (13+, nursing), and children (1-6 yrs.).
[2] DRES TMRCs in mg/kg/day: U.S. population = 0.002073, females (13+, nursing) = 0.001839, children (1-6 yrs.) = 0.005290.
[3] The average EEC for surface water of 3.9 ppb ÷ 3 = 1.3 ppb.
[4] NA = Not applicable.

For chronic (non-cancer) exposure to fluroxypyr in surface and ground water, the drinking water levels of concern are 17400 μg/L for U.S. population, and 4950 μg/L for children (1-6 yrs.). To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to fluroxypyr in drinking water. DWLOCs were then calculated using default body weights and drinking consumption figures.

Estimated maximum concentrations of fluroxypyr in surface and ground water are 11.2 and 0.025 ppb, respectively. Estimated average concentrations of fluroxypyr in surface and ground water are 1.3 ppb (after adjustment for the highly conservative nature of the GENEEC model [20-NOV-1997 memo, M. Stasikowski and J. Merenda]) and 0.025 ppb, respectively. The estimated average concentrations of fluroxypyr in surface and ground water are less than OPP's

level of concern for fluroxypyr in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of fluroxypyr in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

d. Statement of the Adequacy of the Dietary Exposure Database to Assess Infants' and Children's Exposures

The dietary (food and water) exposure database for fluroxypyr is adequate to assess infants' and children's exposure.

4. Occupational and Residential Exposure and Risk Assessment/Characterization

a. Occupational and Residential Exposure

I. Summary of Use Patterns and Formulations

Fluroxypyr, 1-methylheptyl(4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyl)acetate, is a selective herbicide for post-emergence control of annual and perennial broadleaf weeds and volunteer potatoes in small grains, fallow cropland, and non-cropland. Starane™ EC herbicide is an emulsifiable concentrate formulation of fluroxypyr containing 26.2% active ingredient (18.2% fluroxypyr acid equivalent) manufactured by DowElanco.

For wheat, barley, and oats, Starane™ EC is applied to actively growing weeds by groundboom or aerial equipment at a rate of 2.0-4.0 ounces a.e. per acre. One application per season is allowed and must made be no less than 14 days before cutting of hay or 40 days before harvesting of grain and straw.

Starane™ EC may also be applied to fallow cropland and non-cropland, including industrial manufacturing sites and rights-of-way (such as electrical power lines, communication lines, pipelines, roadsides and railroads) as a single broadcast treatment, alone or in tank-mix combination with other herbicides.

Currently there are no proposed residential uses for fluroxypyr.

Table 4.1 Summary of Use Pattern and Formulation

Parameter	Comments
Crop(s)	Wheat, Barley, Oats not under seeded with a legume.
Use Pattern(s)/Site(s)	Selective post-emergence herbicide for annual and perennial broadleaf weeds and volunteer potatoes.

Table 4.1 Summary of Use Pattern and Formulation	
Parameter	**Comments**
Application Method(s)	Aerial and groundboom equipment.
Application Rate(s)	2-4 oz a.e./A per use season.
Maximum Number of Applications	One application per season.
Percent Absorption	100% dermal absorption assumed. 100% inhalation absorption assumed.
Average Acreage of Application per Day (Y. NG,BEAD)	Aerial: 350 Acres Groundboom: 200 Acres Rights-of-Way: 40 Acres
Manufacturer	DowElanco

ii. Handler Exposures & Assumptions

Table 4.2 Handler Exposures & Assumptions	
Factors	**Quantities/Units**
Mixer/loader body weight	60 kg (HED Default Value for Reproductive Endpoints of Concern)
Maximum Application rate(s)	2-4 oz a.e./A = 0.05lb a.e./A per use season
Acres treated per day	Aerial: 350A (HED Default) Groundboom: 200A (Based on Typical Farm Size - wheat) Rights-of-Way: 40 A (HED Default)
Mixer/loader unit exposure from PHED, V1.1 (All liquids; Open mixing and loading; with long pants, long-sleeved shirt, and gloves). Dermal: High Confidence Run Inhalation: High Confidence Run	Dermal - 23µg/lb ai handled Inhalation - 1.2µg/lb ai handled Total - 24µg/lb ai handled
Aerial Applicator unit exposure from PHED, V1.1 (Aerial fixed-wing; Closed cab; Liquid application; with long pants, long-sleeved shirt, and no gloves). Dermal: Medium Confidence Run Inhalation: Medium Confidence Run	Dermal - 5.0µg/lb ai handled Inhalation - 0.068µg/lb ai handled Total - 5.1µg/lb ai handled

Table 4.2 Handler Exposures & Assumptions	
Factors	**Quantities/Units**
Groundboom Applicator unit exposure from PHED, V1.1 (Groundboom application; Open cab; with long pants, long-sleeved shirt, and gloves). Dermal: Medium Confidence Run Inhalation: High Confidence Run	Dermal - 14µg/lb ai handled Inhalation - 0.74µg/lb ai handled Total - 15µg/lb ai handled
Rights-of-Way Applicator unit exposure from PHED, V1.1 (Liquid application; with long pants, long-sleeved shirt, and gloves). Dermal: Low Confidence Run (inadequate number of replicates) Inhalation: High Confidence Run	Dermal - 395µg/lb ai handled Inhalation - 3.9µg/lb ai handled Total - 400µg/lb ai handled
Required Clothing and Personal Protective Equipment (PPE), per label.	Long-sleeved shirt and long pants; chemical-resistant gloves such as Barrier Laminate or Viton; shoes plus socks; and protective eyewear.

iii. Post-Application Exposures & Assumptions

Wheat, barley, and oats are all mechanically harvested resulting in low post-application exposure. Worker exposure to fluroxypyr is possible during scouting of crops for insect, weed, and disease problems, however, this potential exposure is adequately addressed by the Worker Protection Standard requirements (REI and PPE).

iv. Mixer/Loader/Application Exposure Assessments

Table 4.3 Mixer/Loader/Application Exposure Assessments

Job Function	Average Daily Dose (mg ai/kg bw/day)	Short & Intermediate-Term MOEs[1]
Aerial Mixer/loader	0.007	14000
Aerial Applicator	0.0015	67000
Groundboom Mixer/Loader	0.004	25000
Ground boom Applicator	0.0025	40000
Rights-of-Way Sprayer	0.013	7500

[1] MOE = NOEL/ADD (where NOEL = 100mg/kg/day)

The exposure estimates in Table 4.3 are based on the handler assumptions listed in Table 4.2 and are calculated as follows:

$$\text{Daily Dermal Exposure (mg/kg/day)} = \frac{\text{PHED Unit Exposure } (\mu g/lb\ ai) * \text{Max. Appl. Rate (lb ai)} * \text{Acres Treated}}{\text{body wt (kg)}}$$

v. Post-Application Exposure Assessment

The petitioner did not provide post-application exposure data for fluroxypyr. Post-application exposure is expected to be minimal, however, since wheat, barley, and oats are mechanically harvested. Although worker exposure to fluroxypyr is possible during scouting of crops for insect, weed, and disease problems; this potential exposure is adequately addressed by the Worker Protection Standard requirements (REI and PPE).

b. Occupational and Residential Risk Assessment/Characterization

i. Risk from Dermal and Inhalation Exposures

Using these exposure assumptions for short and intermediate-term risk assessment, it is concluded that the MOEs that will result from the handling and application of fluroxypyr to wheat, barley, and oats and to non-cropland areas, do not exceed HED's level of concern for occupationally exposed workers.

Chronic exposure is not expected for use of fluroxypyr on wheat, barley, and oats; therefore a chronic risk assessment is not required.

Currently there are no proposed residential uses for fluroxypyr; therefore a residential risk assessment is not required.

ii. Risk from Post-Application Exposures

Post-application exposure is expected to be minimal since wheat, barley, and oats are mechanically harvested. Worker exposure to fluroxypyr is possible during scouting of crops for insect, weed, and disease problems, however, this potential exposure is adequately addressed by the Worker Protection Standard (REI and PPE) requirements.

iii. Restricted Entry Interval

Based on the Tox Category (II), the appropriate REI is 24 hours. The proposed label for Starane™ EC is in compliance with the REI of 24 hours.

Clothing and Personal Protective Equipment (PPE) required for early entry to treated areas include: Coveralls; Chemical-resistant gloves such as Barrier Laminate or Viton; Shoes plus socks; and Protective eyewear.

iv. Incident Reports

Five (5) reports concerning fluroxypyr are cited in the incidents section of the REFS database(09-FEB-1998). These entries are part of a 1994-95 United Kingdom report of incidents with glyphosate, 2,4-D, and other pesticides, however, and are not specific to fluroxypyr.

v. Data Requirements

No residential uses are currently proposed, therefore, there are no data requirements at this time.

5. Aggregate Exposure and Risk Assessment/Characterization

a. Acute Aggregate Exposure and Risk

As indicated in Section 3c.iii., from the acute dietary (food only) risk assessment, a high-end exposure estimate for fluroxypyr was calculated for females 13+ years, the subgroup of concern. The MOE was greater than 300. Therefore, HED concludes with reasonable certainty that residues of fluroxypyr in food do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

Similarly, as indicated in Section 3c.iv., from the chronic drinking water risk assessment, the maximum estimated concentrations of fluroxypyr in surface and ground water are less than HED's levels of concern in drinking water as a contribution to acute aggregate exposure. Therefore, HED concludes with reasonable certainty that residues in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

b. Short- and Intermediate- Term Aggregate Exposure and Risk

Fluroxypyr is not currently registered for any residential uses. Therefore, a risk assessment for short- and intermediate- term aggregate risk is not required.

c. Chronic Aggregate Exposure and Risk

For the U.S. population, 1.2% of the RfD is occupied by dietary (food) exposure. Fluroxypyr is not currently registered for residential uses, thus, no chronic residential exposure is anticipated. The estimated average concentrations (EECs) of fluroxypyr for the U.S. population and for children (1-6 years old) in surface and ground water are less than OPP's levels of concern for fluroxypyr in drinking water as a contribution to chronic aggregate exposure when considering the uses proposed by this action.

6. Other Food Quality Protection Act (FQPA) Considerations

a. Cumulative Risk

Fluroxypyr is a member of the pyridinoxy acid class of herbicides. Other chemicals in this class include triclopyr, picloram, and clopyralid. These are considered hormone herbicides that translocate in both the phloem and xylem, diplaying soil and foliar activity (G.W. Ware, The Pesticide Book, 1994). Further, other pesticides may have common toxicity endpoints with fluroxypyr.

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments. There are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether fluroxypyr has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that fluroxypyr has a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether fluroxypyr shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for fluroxypyr need to be modified or revoked.

b. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect

produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. **Determination of Safety**

US Population, Infants, and Children

Fluroxypyr has been classified as a "not likely" human carcinogen, based on a lack of evidence of carcinogenicity in mice (MRID 44080317) and rats (MRID 44080322) at dose levels judged to be adequate to assess the carcinogenic potential. Thus, a cancer risk assessment is not required.

Occupational exposure (short- and intermediate-term) estimates do not exceed HED's levels of concern. Fluroxypyr will not be used over several months; thus, chronic exposure assessment is not required. Fluroxypyr does not have residential uses; therefore, no residential risk assessment is required.

Chronic aggregate dietary (food + water) risk estimates do not exceed HED's level of concern. Furthermore, acute dietary risk does not exceed HED's level of concern

7. Data Requirements

a. Toxicology

No additional data are required for this use at this time. However, due to incomplete data reporting and evaluation regarding an oncogenicity study, the Hazard ID Assessment Review Committee (document dated 01 Dec, 1997) determined that the Registrant must 1) submit the appropriate historical control data and 2) evaluate the thyroid glands from all animals at 100 mg/kg/day in the rat study (MRID 44080322).

b. Chemistry

i. Successful EPA method validation for plant and animal commodities must be completed before any of the tolerances discussed in this document may be established.

ii. The petitioner should submit data in support of the processed food/feed study to show if fluroxypyr residues concentrate in wheat germ.

iii. The petitioner should submit revised labels as discussed in Section 3(a)I of this document.

c. Occupational and Residential Exposure

No additional data are required for this use at this time.

cc: M.S. Ottley, W. Donovan, B. Tarplee
RDI: Team (25-JUN-1998)
Caswell File

Attachments:
1. Drinking Water Screening Exposure Assessment for Fluroxypyr, 23-DEC-1997
2. Chronic (16-JUN-1998) and Acute (30-MAR-1998) DRES analysis for Fluroxypyr.
3. HED Hazard ID Assessment and Revisions memo, with supplemental rabbit developmental toxicity DER.

Attachment

ONE

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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: December 23, 1997

TO: Daniel Kenny
Herbicide Branch - PM23
Registration Division (7505C)

FROM: William R. Effland, Ph.D.
Environmental Scientist
Environmental Risk Branch II
Environmental Fate and Effects Division (7507C)

THROUGH: Elizabeth M.K. Leovey, Ph.D.
Branch Chief
EFED/ERB II

RE: Drinking Water Screening Exposure Assessment for Fluroxypyr
(PC Code: 128959; DP Barcode: 241115)

SUMMARY

This memorandum describes the water resources screening assessment for fluroxypyr "acid" (4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetic acid) formulated as fluroxypyr-1-methylheptyl ester (fluroxypyr-MHE). In terrestrial and aquatic environments, fluroxypyr-MHE is rapidly hydrolyzed to fluroxypyr acid which has herbicidal activity. Fluroxypyr acid is further degraded (although less rapidly) via microbial-mediated metabolism to 4-amino-3,5-dichloro-6-fluoro-pyridin-2-ol ("pyridinol" degradate) and 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine ("methoxypyridine" degradate). In aerobic environments, fluroxypyr acid and the pyridinol and

methoxypyridine degradates are ultimately metabolized to carbon dioxide (totaled 46.8-76.2% of the applied radioactivity in the aerobic soil study).

The assessment discusses the screening modeling results for both surface water and ground water media and includes an Environmental Fate Assessment for fluroxypyr. Water resource monitoring data are not available for fluroxypyr-MHE or fluroxypyr acid. Data reported in Table 1 presents the maximum acute and chronic surface water concentrations estimated from GENEEC Version 1.2 modeling. For surface water resources, the maximum acute estimated environmental concentration (EEC) was 11.2 µg/L and the maximum chronic EEC was 3.9 µg/L when fluroxypyr was modeled at 0.25 lbs acid equivalents/A/yr using aerial application. Results of the Groundwater Screening Assessment using SCI-GROW2 estimated the acute and chronic EEC for groundwater to be 0.025 µg/L. The modeling inputs are shown in Tables 2 and 3.

Table 1. Surface Water EECs (µg/L) using GENEEC Version 1.2

Maximum EEC	Mean 4-Day EEC	Mean 21-Day EEC	Mean 56-Day EEC
11.2	10.4	7.1	3.9

Environmental Fate Assessment

Degradation of fluroxypyr-MHE in environmental fate laboratory studies occurs through base-catalyzed hydrolysis and microbial-mediated 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 to 3 weeks in four soils. The rate of metabolism decreased significantly after 2 months. Degradation of fluroxypyr-MHE yields fluroxypyr acid (the herbicidal agent), 4-amino-3,5-dichloro-6-fluoro-pyridin-2-ol (pyridinol metabolite), 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine (methoxypyridine metabolite) and CO2. The aerobic aquatic metabolism half-life was estimated to be 14 days.

Fluroxypyr acid is considered mobile based on Freundlich Kads values ranging from 0.11-1.9 ml/g in four test soils (silt loam, sandy loam, loam, and silty clay textures). These soil/water partitioning coefficients indicate fluroxypyr will occur principally in the aqueous phase of soil/water systems.

Table 2. Ground Water Exposure Assessment using SCI-GROW2

MODEL INPUT VARIABLE	INPUT VALUE

Application Rate (lbs. ai/A)	0.25
Maximum No. of Applications	1
Koc	68 (median; n = 4)
Aerobic Soil Metabolic Half-life (days)	14 (mean; n = 4)

Table 3. Surface Water Exposure Assessment using GENEEC (v.1.2)

MODEL INPUT VARIABLE	INPUT VALUE
Application Rate (lbs ai/A)	0.25
Maximum No. of Applications	1
Koc	50 (minimum reported value)
Aerobic Soil Metabolic Half-life (days)	23 (maximum of 4 reported values)
Is the pesticide wetted-in?	No
Depth of Incorporation (in.)	0.0
Spray Drift	Aerial (5%).
Solubility (mg/L)	0.90
Aerobic Aquatic Metabolic Half-life (days)	14
pH 7 Hydrolysis Half-life (days)	stable (454 days)
Photolysis Half-life (days)	0 (stable)

Attachment

TWO

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Fluroxypyr Caswell #128959 CAS No. 128959 A.I. CODE: 128959 CFR No.	4 week Feeding - dog NOEL= 50.0000 mg/kg 0.00 ppm LEL= 150.0000 mg/kg 0.00 ppm ONCO: not classified	histopathological lesions kidney inc. adrenal weights decreased testes wts	ADI UF -->100 OPP RfD= 0.500000 EPA RfD= 0.500000	No data gaps	HED reviewed 4/23/98

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM) NEW	PENDING	PUBLISHED
15005AA	CORN,SWEET	98WA017	0.050000		
24001AA	BARLEY	9710019		0.100000	
24001AA	BARLEY	6F04772		0.400000	
24002EA	CORN,GRAIN-ENDOSPERM	98WA017	0.050000		
24002HA	CORN,GRAIN-BRAN	98WA017	0.050000		
24002SA	CORN SUGAR	98WA017	0.050000		
24003AA	OATS	9710019		0.100000	
24003AA	OATS	6F04772		0.400000	
24007AA	WHEAT-ROUGH	9710019		0.100000	
24007AA	WHEAT-ROUGH	6F04772		0.400000	
24007GA	WHEAT-GERM	9710019		0.100000	
24007GA	WHEAT-GERM	6F04772		0.400000	
24007WA	WHEAT-FLOUR	9710019		0.100000	
24007WA	WHEAT-FLOUR	6F04772		0.400000	
50000SB	MILK-NON-FAT SOLIDS	9710019		0.050000	
50000SB	MILK-NON-FAT SOLIDS	6F04772		0.050000	
50000FA	MILK-FAT SOLIDS	9710019		0.050000	
50000FA	MILK-FAT SOLIDS	6F04772		0.050000	
50000SA	MILK SUGAR (LACTOSE)	9710019		0.050000	
50000SA	MILK SUGAR (LACTOSE)	6F04772		0.050000	
53001BA	BEEF-MEAT BYPRODUCTS	9710019		0.050000	
53001BA	BEEF-MEAT BYPRODUCTS	6F04772		0.050000	
53001BB	BEEF(ORGAN MEATS)-OTHER	9710019		0.050000	
53001BB	BEEF(ORGAN MEATS)-OTHER	6F04772		0.050000	
53001DA	BEEF-ORIEO	9710019		0.050000	
53001DA	BEEF-ORIEO	6F04772		0.050000	
53001FA	BEEF(BONELESS)-FAT (BEEF TALLOW)	9710019		0.050000	
53001FA	BEEF(BONELESS)-FAT (BEEF TALLOW)	6F04772		0.050000	
53001KA	BEEF(ORGAN MEATS)-KIDNEY	9710019		0.300000	
53001KA	BEEF(ORGAN MEATS)-KIDNEY	6F04772		0.200000	
53001LA	BEEF(ORGAN MEATS)-LIVER	9710019		0.050000	
53001LA	BEEF(ORGAN MEATS)-LIVER	6F04772		0.050000	
53001MA	BEEF(BONELESS)-LEAN (W/O REMOVEABLE FAT)	9710019		0.050000	
53001MA	BEEF(BONELESS)-LEAN (W/O REMOVEABLE FAT)	6F04772		0.050000	
53002BA	GOAT-MEAT BYPRODUCTS	9710019		0.050000	
53002BA	GOAT-MEAT BYPRODUCTS	6F04772		0.050000	
53002BB	GOAT(ORGAN MEATS)-OTHER	9710019		0.050000	
53002BB	GOAT(ORGAN MEATS)-OTHER	6F04772		0.050000	
53002FA	GOAT(BONELESS)-FAT	9710019		0.050000	
53002FA	GOAT(BONELESS)-FAT	6F04772		0.050000	

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Fluroxypyr Caswell #128959 CAS No. 128959 A.I. CODE: 128959 CFR No.	4 week feeding - dog NOEL= 50.0000 mg/kg 0.00 ppm LEL= 150.0000 mg/kg 0.00 ppm ONCO: not classified	histopathological lesions kidney inc. adrenal weights decreased testes wts	ADI UF -->100 OPP RfD= 0.500000 EPA RfD= 0.500000	No data gaps	HED reviewed 4/23/98

FOOD CODE	FOOD NAME	PETITION NUMBER	NEW	TOLERANCE (PPM) PENDING	PUBLISHED
53002KA	GOAT(ORGAN MEATS)-KIDNEY	9710019		0.300000	
53002KA	GOAT(ORGAN MEATS)-KIDNEY	6F04772		0.200000	
53002LA	GOAT(ORGAN MEATS)-LIVER	9710019		0.050000	
53002LA	GOAT(ORGAN MEATS)-LIVER	6F04772		0.050000	
53002MA	GOAT(BONELESS)-LEAN (W/O REMOVEABLE FAT)	9710019		0.050000	
53002MA	GOAT(BONELESS)-LEAN (W/O REMOVEABLE FAT)	6F04772		0.050000	
53003AA	HORSE	9710019		0.050000	
53003AA	HORSE	6F04772		0.050000	
53005BA	SHEEP-MEAT BYPRODUCTS	9710019		0.050000	
53005BA	SHEEP-MEAT BYPRODUCTS	6F04772		0.050000	
53005BB	SHEEP(ORGAN MEATS)-OTHER	9710019		0.050000	
53005BB	SHEEP(ORGAN MEATS)-OTHER	6F04772		0.050000	
53005FA	SHEEP(BONELESS)-FAT	9710019		0.050000	
53005FA	SHEEP(BONELESS)-FAT	6F04772		0.050000	
53005KA	SHEEP(ORGAN MEATS)-KIDNEY	9710019		0.300000	
53005KA	SHEEP(ORGAN MEATS)-KIDNEY	6F04772		0.200000	
53005LA	SHEEP(ORGAN MEATS)-LIVER	9710019		0.050000	
53005LA	SHEEP(ORGAN MEATS)-LIVER	6F04772		0.050000	
53005MA	SHEEP(BONELESS)-LEAN (W/O REMOVEABLE FAT	9710019		0.050000	
53005MA	SHEEP(BONELESS)-LEAN (W/O REMOVEABLE FAT	6F04772		0.050000	
53006BA	PORK-MEAT BYPRODUCTS	9710019		0.050000	
53006BA	PORK-MEAT BYPRODUCTS	6F04772		0.050000	
53006BB	PORK(ORGAN MEATS)-OTHER	9710019		0.050000	
53006BB	PORK(ORGAN MEATS)-OTHER	6F04772		0.050000	
53006FA	PORK(BONELESS)-FAT (INCLUDING LARD)	9710019		0.050000	
53006FA	PORK(BONELESS)-FAT (INCLUDING LARD)	6F04772		0.050000	
53006KA	PORK(ORGAN MEATS)-KIDNEY	9710019		0.300000	
53006KA	PORK(ORGAN MEATS)-KIDNEY	6F04772		0.200000	
53006LA	PORK(ORGAN MEATS)-LIVER	9710019		0.050000	
53006LA	PORK(ORGAN MEATS)-LIVER	6F04772		0.050000	
53006MA	PORK(BONELESS)-LEAN (W/O REMOVEABLE FAT)	9710019		0.050000	
53006MA	PORK(BONELESS)-LEAN (W/O REMOVEABLE FAT)	6F04772		0.050000	

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS DATE: 06/16/98 PAGE: 1

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Fluroxypyr Caswell #128959 CAS No. 128959 A.I. CODE: 128959 CFR No.	4 week feeding - dog NOEL= 50.0000 mg/kg 0.00 ppm LEL= 150.0000 mg/kg 0.00 ppm ONCO: not classified	histopathological lesions kidney inc. adrenal weights decreased testes wts	ADI - UF -->100 OPP RfD= 0.500000 EPA RfD= 0.500000	No data gaps	NEO reviewed 4/23/98

POPULATION SUBGROUP	TOTAL THRC (MG/KG BODY WEIGHT/DAY) CURRENT THRC*	NEW THRC**	NEW THRC AS PERCENT OF RFD	DIFFERENCE AS PERCENT OF RFD	EFFECT OF ANTICIPATED RESIDUES ARC	%RFD
U.S. POPULATION - 48 STATES	0.000000	0.002073	0.414686	0.414686		
U.S. POPULATION - SPRING SEASON	0.000000	0.001968	0.393678	0.393678		
U.S. POPULATION - SUMMER SEASON	0.000000	0.002041	0.408182	0.408182		
U.S. POPULATION - FALL SEASON	0.000000	0.002151	0.430267	0.430267		
U.S. POPULATION - WINTER SEASON	0.000000	0.002133	0.426685	0.426685		
NORTHEAST REGION	0.000000	0.002154	0.430873	0.430873		
NORTH CENTRAL REGION	0.000000	0.002161	0.432185	0.432185		
SOUTHREN REGION	0.000000	0.001873	0.374578	0.374578		
WESTERN REGION	0.000000	0.002184	0.436837	0.436837		
HISPANICS	0.000000	0.002392	0.478378	0.478378		
NON-HISPANIC WHITES	0.000000	0.002085	0.417063	0.417063		
NON-HISPANIC BLACKS	0.000000	0.001835	0.367041	0.367041		
NON-HISPANIC OTHERS	0.000000	0.002172	0.434324	0.434324		
NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.001972	0.394468	0.394468		
NON-NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.007770	1.554069	1.554069		
FEMALES (13+ YEARS, PREGNANT)	0.000000	0.001453	0.290570	0.290570		
FEMALES 13+ YEARS, NURSING	0.000000	0.001839	0.367819	0.367819		
CHILDREN (1-6 YEARS OLD)	0.000000	0.005290	1.058017	1.058017		
CHILDREN (7-12 YEARS OLD)	0.000000	0.003473	0.694549	0.694549		
MALES (13-19 YEARS OLD)	0.000000	0.002310	0.462020	0.462020		
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.000000	0.001757	0.351434	0.351434		
MALES (20 YEARS AND OLDER)	0.000000	0.001433	0.286512	0.286512		
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)	0.000000	0.001169	0.233761	0.233761		

*Current THRC does not include new or pending tolerances.
**New THRC includes new, pending, and published tolerances.

TOLERANCE ASSESSMENT SUMMARY FOR Fluroxypyr DATE: 06/16/98
CASWELL #128959

ANALYSIS FOR POPULATION SUB-GROUP: U.S. POPULATION - 48 STATES

EXISTING TOLERANCES (PUBLISHED ONLY)		
RESULT IN A TMRC OF:	0.000000	MG/KG/DAY
THE EXISTING TMRC IS EQUIVALENT TO:	0.000	% OF THE ADI.
PROPOSED NEW TOLERANCES (CURRENT PETITION ONLY)		
RESULT IN A TMRC OF:	0.000028	MG/KG/DAY
THESE NEW TOLERANCES WILL OCCUPY:	0.005	% OF THE ADI.
IF THE NEW TOLERANCES (CURRENT PETITION ONLY)		
ARE APPROVED THE RESULTANT TMRC WILL BE:	0.000028	MG/KG/DAY
THE NEW TMRC WILL OCCUPY	0.005	% OF THE ADI.
OTHER PENDING TOLERANCES EXCLUDING THE		
CURRENT NEW PETITION HAVE A TMRC OF:	0.002047	MG/KG/DAY
THIS TMRC WILL OCCUPY	0.409	% OF THE ADI.
IF ALL PENDING TOLERANCES (INCLUDING THE		
CURRENT NEW PETITION) ARE GRANTED		
THE RESULTANT TMRC WILL BE:	0.002074	MG/KG/DAY
THE TOTAL TMRC WILL OCCUPY	0.415	% OF THE ADI.

ANALYSIS FOR POPULATION SUB-GROUP: NON-NURSING INFANTS (< 1 YEAR OLD)

EXISTING TOLERANCES (PUBLISHED ONLY)		
RESULT IN A TMRC OF:	0.000000	MG/KG/DAY
THE EXISTING TMRC IS EQUIVALENT TO:	0.000	% OF THE ADI.
PROPOSED NEW TOLERANCES (CURRENT PETITION ONLY)		
RESULT IN A TMRC OF:	0.000069	MG/KG/DAY
THESE NEW TOLERANCES WILL OCCUPY:	0.014	% OF THE ADI.
IF THE NEW TOLERANCES (CURRENT PETITION ONLY)		
ARE APPROVED THE RESULTANT TMRC WILL BE:	0.000069	MG/KG/DAY
THE NEW TMRC WILL OCCUPY	0.014	% OF THE ADI.
OTHER PENDING TOLERANCES EXCLUDING THE		
CURRENT NEW PETITION HAVE A TMRC OF:	0.007702	MG/KG/DAY
THIS TMRC WILL OCCUPY	1.540	% OF THE ADI.
IF ALL PENDING TOLERANCES (INCLUDING THE		
CURRENT NEW PETITION) ARE GRANTED		
THE RESULTANT TMRC WILL BE:	0.007771	MG/KG/DAY
THE TOTAL TMRC WILL OCCUPY	1.554	% OF THE ADI.

1DETAILED ACUTE ANALYSIS INCLUDING AR'S: ALL STATISTICS BASED ON USERS' DAILY CONSUMPTION 14:02 Monday, March 30, 1998 22

NAME: FLUROXYPYR STUDY RDV NOEL SF STUDY TYPE SPECIES EFF. LEV. CORE GRADE DOC. NO.
*CASWELL NO: 128A8C CFR NO: CFR A *
*CAS NO: SHAUGHNESSY NO: 128959 B *
*STATUS CODES: C *
*RDV INFO: The LD value used in this analysis is 0.001 MG/KG of BODY WEIGHT/DAY *
FILE INFO: No Tolerance Data Are Used--Without User Modifications. AR DATA: No User Modifications

-U.S. POP.--48 STATES

ESTIMATES BASED ON	ESTIMATED % OF POTENTIAL PERSON DAYS THAT ARE USER-DAYS	MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY MG/KG BODY WEIGHT/DAY	AS PERCENT OF RDV
TOLERANCES:	0.00	0.000000	0.00
ANTICIPATED RESIDUES:	99.62	0.000820	82.05

0 ESTIMATED % OF POPULATION USER-DAYS WITH RESIDUE CONTRIBUTION EXCEEDING X TIMES THE RDV, FOR X=

	0	.2	.4	.6	.8	1	1.2	1.4	1.6	1.8	2	3	4	5	10	15	20
TOLERANCES:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ANTICIPATED RESIDUES:	100	89	66	46	33	25	19	15	12	10	8	3	1	0	0	0	0

0INFANTS(<1 YEAR)

ESTIMATES BASED ON	ESTIMATED % OF POTENTIAL PERSON DAYS THAT ARE USER-DAYS	MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY MG/KG BODY WEIGHT/DAY	AS PERCENT OF RDV
TOLERANCES:	0.00	0.000000	0.00
ANTICIPATED RESIDUES:	90.80	0.003349	334.94

0 ESTIMATED % OF POPULATION USER-DAYS WITH RESIDUE CONTRIBUTION EXCEEDING X TIMES THE RDV, FOR X=

	0	.2	.4	.6	.8	1	1.2	1.4	1.6	1.8	2	3	4	5	10	15	20
TOLERANCES:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ANTICIPATED RESIDUES:	100	97	94	91	90	88	86	84	80	77	74	51	34	19	1	0	0

0CHILDREN(1-6 YRS)

ESTIMATES BASED ON	ESTIMATED % OF POTENTIAL PERSON DAYS THAT ARE USER-DAYS	MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY MG/KG BODY WEIGHT/DAY	AS PERCENT OF RDV
TOLERANCES:	0.00	0.000000	0.00
ANTICIPATED RESIDUES:	99.88	0.002141	214.12

0 ESTIMATED % OF POPULATION USER-DAYS WITH RESIDUE CONTRIBUTION EXCEEDING X TIMES THE RDV, FOR X=

	0	.2	.4	.6	.8	1	1.2	1.4	1.6	1.8	2	3	4	5	10	15	20
TOLERANCES:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ANTICIPATED RESIDUES:	100	99	98	96	91	86	80	72	64	56	48	19	7	2	0	0	0

1DETAILED ACUTE ANALYSIS INCLUDING AR'S: ALL STATISTICS BASED ON USERS' DAILY CONSUMPTION 14:02 Monday, March 30, 1998 23

		STUDY	RDV	NOEL	SF	STUDY TYPE	SPECIES	EFF. LEV.	CORE GRADE	DOC. NO.
*NAME: FLUROXYPYR		A								*
*CASWELL NO: 128ABC	CFR NO: CFR	B								*
*CAS NO:	SHAUGHNESSY NO: 128959	C								*
*STATUS CODES:										*
*RDV INFO: The LD value used in this analysis is 0.001			MG/KG of BODY WEIGHT/DAY							*
*FILE INFO: No Tolerance Data Are Used--Without User Modifications.									AR DATA: No User Modifications	*

-FEMALES(13+ YRS)

	ESTIMAYED % OF POTENTIAL	MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY	
ESTIMATES BASED ON	PERSON DAYS THAT ARE USER-DAYS	MG/KG BODY WEIGHT/DAY	AS PERCENT OF RDV
TOLERANCES:	0.00	0.000000	0.00
ANTICIPATED RESIDUES:	99.61	0.000489	48.92

0 ESTIMATED % OF POPULATION USER-DAYS WITH RESIDUE CONTRIBUTION EXCEEDING X TIMES THE RDV, FOR X=

	0	.2	.4	.6	.8	1	1.2	1.4	1.6	1.8	2	3	4	5	10	15	20
TOLERANCES:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ANTICIPATED RESIDUES:	100	84	53	29	15	7	4	2	1	1	0	0	0	0	0	0	0

0MALES(13+ YRS)

	ESTIMATED % OF POTENTIAL	MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY	
ESTIMATES BASED ON	PERSON DAYS THAT ARE USER-DAYS	MG/KG BODY WEIGHT/DAY	AS PERCENT OF RDV
TOLERANCES:	0.00	0.000000	0.00
ANTICIPATED RESIDUES:	99.85	0.000605	60.54

0 ESTIMATED % OF POPULATION USER-DAYS WITH RESIDUE CONTRIBUTION EXCEEDING X TIMES THE RDV, FOR X=

	0	.2	.4	.6	.8	1	1.2	1.4	1.6	1.8	2	3	4	5	10	15	20
TOLERANCES:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ANTICIPATED RESIDUES:	100	91	65	40	24	14	8	5	3	2	1	0	0	0	0	0	0

General U.S. Population

Exposure = RDV x X
= 0.001 x 5
High End Exposure = 0.005

MOE = Noel ÷ Exposure
= 100 mg/kg/day ÷ 0.005 mg/kg/day
MOE = 20000

Infants (< 1 year)

Exposure = RDV x X
= 0.001 x 15
High End Exposure = 0.015

MOE = Noel ÷ Exposure
= 100 mg/kg/day ÷ 0.015 mg/kg/day
MOE = 6666

Children (1-6 years)

Exposure = RDV x X
= 0.001 x 10
High End Exposure = 0.01

MOE = Noel ÷ Exposure
= 100 mg/kg/day ÷ 0.01 mg/kg/day
MOE = 10000

Females (13+ Years):

Exposure = RDV x X
= 0.001 x 2
High End Exposure = 0.002

MOE = Noel ÷ Exposure
= 100 mg/kg/day ÷ 0.002 mg/kg/day
MOE = 50000

Males (13+ Years):

Exposure = RDV x X
= 0.001 x 3
High End Exposure = 0.003

MOE = Noel ÷ Exposure
= 100 mg/kg/day ÷ 0.003 mg/kg/day
MOE = 33333

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128ABC 15005AA10  0.0500 CORN, SWEET
128ABC 15005AA21  0.0500
128ABC 15005AA31  0.0500
128ABC 24001AA21  0.1000 BARLEY
128ABC 24003AA21  0.1000 OATS
128ABC 24003AA22  0.1000 OATS
128ABC 24003AA23  0.1000 OATS
128ABC 24007AA10  0.1000 WHEAT-ROUGH
128ABC 24007AA21  0.1000 WHEAT-ROUGH
128ABC 24007AA22  0.1000 WHEAT-ROUGH
128ABC 24007AA23  0.1000 WHEAT-ROUGH
128ABC 24007GA10  0.1000 WHEAT-GERM
128ABC 24007GA22  0.1000 WHEAT-GERM
128ABC 24007HA10  0.5000 WHEAT-BRAN
128ABC 24007HA21  0.5000 WHEAT-BRAN
128ABC 24007HA22  0.5000 WHEAT-BRAN
128ABC 24007WA10  0.1000 WHEAT-FLOUR
128ABC 24007WA21  0.1000 WHEAT-FLOUR
128ABC 24007WA22  0.1000 WHEAT-FLOUR
128ABC 24007WA25  0.1000 WHEAT-FLOUR
128ABC 50000D810  0.0500 MILK-NON-FAT
SOL
128ABC 50000D821  0.0500 MILK-NON-FAT
SOL
128ABC 50000D851  0.0500 MILK-NON-FAT
SOL
128ABC 50000FA10  0.0500 MILK-FAT
SOLIDS
128ABC 50000FA21  0.0500 MILK-FAT
SOLIDS
128ABC 50000FA51  0.0500 MILK-FAT
SOLIDS
128ABC 50000SA21  0.0500 MILK SUG
(LACT)
128ABC 50000SA51  0.0500 MILK SUG
(LACT)
128ABC 53001BA21  0.0500 BEEF-MEAT
BYP
128ABC 53001BA26  0.0500 BEEF-MEAT
BYP
128ABC 53001BB21  0.0500 BEEF-OTH
ORGAN
128ABC 53001BB51  0.0500 BEEF-OTH
ORGAN
128ABC 53001DA21  0.0500 BEEF-DRIED
128ABC 53001FA10  0.0500 BEEF-FAT
128ABC 53001FA21  0.0500 BEEF-FAT
128ABC 53001FA22  0.0500 BEEF-FAT
128ABC 53001FA23  0.0500 BEEF-FAT
128ABC 53001FA24  0.0500 BEEF-FAT
128ABC 53001FA25  0.0500 BEEF-FAT
128ABC 53001KA21  0.3000 BEEF-KIDNEY
128ABC 53001LA25  0.0500 BEEF-LIVER
128ABC 53001LA31  0.0500 BEEF-LIVER
128ABC 53001MA10  0.0500 BEEF-LEAN
128ABC 53001MA21  0.0500 BEEF-LEAN
128ABC 53001MA22  0.0500 BEEF-LEAN
128ABC 53001MA23  0.0500 BEEF-LEAN
128ABC 53001MA24  0.0500 BEEF-LEAN
128ABC 53002BA00  0.0500 GOAT-MEAT
BYP
128ABC 53002BB00  0.0500 GOAT-OTH
ORGAN
128ABC 53002FA23  0.0500 GOAT-FAT
128ABC 53002FA25  0.0500 GOAT-FAT
128ABC 53002KA00  0.3000 GOAT-KIDNEY
128ABC 53002LA00  0.0500 GOAT-LIVER
128ABC 53002MA23  0.0500 GOAT-LEAN
128ABC 53002MA25  0.0500 GOAT-LEAN
128ABC 53003AA00  0.0500 HORSE
128ABC 53005BA21  0.0500 SHEEP-MEAT
BYP
128ABC 53005BB21  0.0500 SHEEP-OTH
ORGAN
128ABC 53005FA21  0.0500 SHEEP-FAT
128ABC 53005KA21  0.3000 SHEEP-KIDNEY
128ABC 53005LA00  0.0500 SHEEP-LIVER
128ABC 53005MA21  0.0500 SHEEP-LEAN
128ABC 53005MA31  0.0500 SHEEP-LEAN
128ABC 53006BA21  0.0500 PORK-MEAT
BYP
128ABC 53006BB21  0.0500 PORK-OTH
ORGAN
128ABC 53006BB26  0.0500 PORK-OTH
ORGAN
128ABC 53006FA10  0.0500 PORK-FAT
128ABC 53006FA21  0.0500 PORK-FAT
128ABC 53006FA23  0.0500 PORK-FAT
128ABC 53006FA25  0.0500 PORK-FAT
128ABC 53006FA26  0.0500 PORK-FAT
128ABC 53006KA21  0.3000 PORK-KIDNEY
128ABC 53006LA21  0.0500 PORK-LIVER
128ABC 53006LA25  0.0500 PORK-LIVER
128ABC 53006MA21  0.0500 PORK-LEAN
128ABC 53006MA25  0.0500 PORK-LEAN
128ABC 53006MA26  0.0500 PORK-LEAN
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Attachment

THREE

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 19-MAY-1998

SUBJECT: PP#6F04772. **Fluroxypyr** in/on Barley, Oats, Wheat. **HED Hazard Assessment and Revisions**
DP Barcode: D232215 Chemical #: 128959, 128968
PRAT Case # : 288019 Submission #: S510931
Class: Herbicide

FROM: Myron Ottley, Ph.D. and William Dykstra, Ph.D.
Registration Action Branch I
Health Effects Division (7509C)

THROUGH: Melba Morrow, D.V.M. Branch Senior Scientist
Registration Action Branch I
Health Effects Division (7509C)

TO: Jess Rowland, M.S.
Executive Secretary
Hazard Identification Committee
Health Effects Division (7509C)

ISSUES/CONCLUSIONS

1. Upon re-evaluation of the developmental toxicity study in rabbits (MRID 44080319, attached), it is confirmed that there was a significant increase in post-implantation loss at the high dose level (250 mg/kg/day), and that this loss was largely due to early resorptions. This finding suggests that a single treatment of fluroxypyr can

produce an adverse effect, and validates use of this study in assessing acute endpoints.

2. At the Risk SARC held on 23-April-1998, it was determined that while it was appropriate to apply an additional 3X uncertainty factor to cover FQPA concerns (females 13+) in Acute Dietary exposure, it was unnecessary to add the 3X factor to the RfD as was recommended by the Hazard ID Committee (cf. HED Doc. No. 012464, 28-Jan-1998), because the developmental endpoint from which the 3X factor stems, applies only to females 13+ and not the general population. It is recommended, therefore, that the official Hazard ID report be amended to reflect this change.

3. On page six of the Hazard ID Committee report (cf. HED Doc. No. 012464, 28-Jan-1998) under the section "Chonic Dietary Risk Assessment", it was stated that although this study shows increased susceptibility to developing offspring, the FQPA factor should be 3X and not 10X. Reevaluation of the study does not change the conclusion that 3X is the appropriate factor. The Risk SARC also concurred with this conclusion.

cc: PP#6F04772, M.S. Ottley, W. Dykstra, M. Morrow, O. Odiott

EPA Reviewer: Myron S. Ottley, Ph.D. Myron S. Ottley, Date 5/13/98
Team 2, Registration Action Branch I (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. William Dykstra, Date 5/13/98
Team 2, Registration Action Branch I (7509C)

DATA EVALUATION RECORD--
Supplemental

STUDY TYPE: Prenatal Developmental Study - rabbit; OPPTS 870.3700 §83-3(*b*)

DP BARCODE: D232215 SUBMISSION CODE:S510931
P.C. CODE: 128959, 128968 TOX. CHEM. NO.:

TEST MATERIAL (PURITY): fluroxypyr methylheptyl ester (95.8% a.i.)

SYNONYMS: None

CITATION: Tesh, JM; Ross, FW; Wightman TJ. 02-February-1984. Dowco 433. Effects of oral administration upon pregnancy in the rabbit. Life Science Research Eye, Suffolk England. Report No. 84/DCC006/025, 02-February-1984. MRID 44080319. Unpublished.

SPONSOR: Dow Chemical Europe

EXECUTIVE SUMMARY:

This DER is a supplement to the original DER (HED Doc. 006688), and contains information not included in the original document.

In a developmental toxicity study (MRID 44080319) fluroxypyr methylheptyl ester (95.8% a.i.) was administered to 29 female New Zealand White rabbits/dose by gavage at dose levels of 0, 25, 100, 250 or 400 mg/kg/day from days 6 through 19 of gestation.

There were no treatment-related effects in mortality, clinical signs, body weight, food consumption, or cesarean parameters at the three lower dose levels. The highest dose level (400 mg/kg/day) caused severe maternal toxicity, resulting in the termination of that group, and exclusion of those results from the study. **The maternal LOEL is >250 mg/kg/day. The maternal NOEL is 250 mg/kg/day (HDT).**

Developmental toxicity was observed in the form of increased post-implantation loss at the high-dose level, due to increases in early and late resorptions. This increase (20.9% vs. 11.1% in controls) was determined by HED to be statistically significant. In addition, the increase is just outside the range of historical values (1.0% - 20.5%), and it is well above the historical mean

(10.5%), thus strengthening the case for its toxicological significance. Also observed at the HDT (250 mg/kg/day) was a 6% decrease (7.9 vs. 8.4 in controls) in live fetuses/litter. **The developmental LOEL is 250 mg/kg/day, based on post-implantation loss. The developmental NOEL is 100 mg/kg/day.**

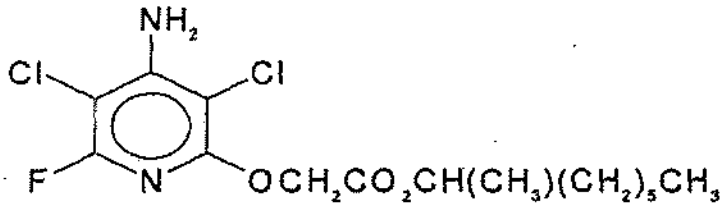
The developmental toxicity study in the rabbit is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Dow 433
   Description: To be provided by sponsor
   Lot/Batch #: J.3199; 433-T-0683-16
   Purity: To be provided by sponsor
   CAS #:



Fluroxypyr 1-methylheptyl ester

2. Vehicle: Carboxymethyl cellulose 0.6% w/v
   Lot/Batch #: Not provided
   Purity: Not provided

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age at mating: 18 - 24 wks
   Weight at mating: 1.56 - 4.65 g
   Source: C & J Morton Ltd., Essex, England

Housing: singly in galvanized steel cages
Diet: Beta Rabbit Standard diet ad libitum
Water: tap, ad libitum
Environmental conditions:
Temperature: 64 - 69 °F
Humidity: 72 ± 14%
Air changes: 17 - 20/hr
Photoperiod: 14 hrs dark/ 10 hrs light
Acclimation period (P): three weeks minimum.

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: 28-Jun-1983; end: 15-Dec-1983

2. Mating: females were artificially inseminated with pooled semen from New Zealand White bucks of established fertility. Following insemination, each female was injected i.v. with 25 i.u. luteinizing hormone to ensure successful ovulation. The day of insemination was designated Day 0 of gestation.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. Assignment was random to four treatment groups in order of insemination so that females inseminated on one day were evenly distributed among groups.

TABLE 1 Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	29
Low (LDT)	25	29
Mid (MDT)	100	29
High**	400	5
High (HDT)	250	29

** High dose terminated after treatment of one batch of animals, on day nine, with sponsor's concurrence, in view of the unlikely survival of animals until the end of dosing.

4. Dose selection rationale:
In a preliminary study, four pregnant rabbits/group were administered Dow 433 suspended in carboxymethyl cellulose by oral gavage at dosage levels of 0, 300, and 1000 mg/kg/day. Severe toxicity was observed at the high dose level, including 50% mortality, which resulted in termination of that dose level and introduction of a 500 mg/kg/day dose level. Toxicity in the 500 mg/kg/day group included increased respiration rate, muscular weakness, and unsteadiness/incoordination. In addition, mean values for postimplantation loss, and fetal and placental weights, were depressed in this group; one maternal death occurred but was not considered by the investigators to be treatment related. Based on these results, it was concluded that the HDT for the principal study should be in the 300 - 500 mg/kg/day range. The study directors therefore chose 0, 25, 100 and 400 mg/kg/day as the dose levels to be used. However, shortly after commencement of dosing at 400 mg/kg/day (gd 9), severe toxicity was observed which prompted the immediate replacement of this treatment group with a 250 mg/kg/day group. RAB1 does not consider the time lag for the replacement group to compromise the integrity of the findings.

5. Dosage preparation and analysis *Each* pregnant female received by oral gavage a single daily dose of vehicle (0.6% carboxymethyl cellulose) or Dowco 433 suspended in the vehicle on days six through 19 of gestation. Dosage suspensions were prepared daily. The volume administered daily was based on the animal's body weight on the day administered.

Results - Homogeneity Analysis: Not provided

Stability Analysis: Not provided

Concentration Analysis: Not provided.

These data were to be provided by the Sponsor, and are not part of the study report.

6. Dosage administration: All doses were administered once daily by gavage, on gestation days six through 19 in a volume of 5 ml/kg of body weight/day. Dosing was based on the body weight on the day of treatment.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked for mortality or clinical signs daily. Body weights were recorded daily; food consumption data collection was not specified. Dams were sacrificed on day 29 of gestation. Each animal was examined macroscopically for evidence of disease or adverse reaction to treatment, and specimens of tissues considered abnormal were retained in an appropriate fixative. The reproductive tract, including ovaries, was dissected out and the following recorded: number of corpora lutea/ovary; number of implantation sites (Salewski staining was used in apparently non-pregnant animals to discover evidence of implantation sites); number of resorption sites, classified as early or late; number and distribution of live and dead fetuses.

2. Fetal Evaluations - The fetuses were examined in the following manner:
External Examination included fetal weights, placental weights, external abnormalities of each fetus and placenta.
Internal examination: all fetuses were killed by subcutaneous injection of pentobarbitone sodium. The neck, thoracic and abdominal cavities of all fetuses from each litter were dissected, the contents examined and sex recorded. Following examination, the fetuses were eviscerated prior to fixation in industrial methylated spirit.
Skeletal Examination Eviscerated fetuses were processed using a modification of the Dawson Alizarin staining technique, and skeletons were examined.

D. DATA ANALYSIS

1. Statistical analyses: The following procedures were utilized in examination of the numerical data: multiple t-test or t-test used for body weights, body weight change, fetal weight, placental weight and litter size; Mann-Whitney U-test for corpora lutea count, implantation count and resorption count; Chi-square test, Fischer's Exact Probability test or Mann-Whitney U-test for pre-implantation loss and post-implantation loss.

2. Historical control data: Historical control data were not provided to allow comparison

with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: The following observations were reported: The 400 mg/kg/day group exhibited significant toxicity such as increased respiratory rate, ataxia and muscular weakness to the degree that animals were terminated on gd 9 and a lower dose level (250 mg/kg/day) was initiated. Lower dose levels showed no toxicity greater than controls.

2. Body Weight - Body weight data are summarized in Table 2 and as follows: Body weight gains among the control group and the treatment groups (25 mg/kg/day or LDT; 100 mg/kg/day or MDT; 250 mg/kg/day or HDT) were similar.

TABLE 2. Maternal Body Weight Gain (g)[a]

Interval	Dose in mg/kg/day (# of Dams)			
	Control (N)	LDT (N)	MDT (N)	HDT (N)
Pretreatment: Days 0 - 6	0.10 (25)	0.09 (24)	0.12 (24)	0.18 (24)
Treatment: Days 6 - 18	0.20 (25)	0.19 (24)	0.17 (24)	0.12 (24)
Posttreatment: Days 18 - 28	0.15 (25)	0.08 (24)	0.19 (24)	0.12 (24)

a Data extracted from report no. 84/0CC006/025, Table 2.

3. Food Consumption - Food consumption data were not presented or reported on.

4. Gross Pathology - Gross pathology data are summarized as follows: At necropsy on gd 29, no macroscopic changes in maternal condition were observed that could be attributed to treatment with Dowco 433. Kidney weights were measured and showed no treatment-related effects.

5. Cesarean Section Data - Data are as follows: *[Describe findings]*; as summarized in Table 3. ***[Some form of this table is MANDATORY; data should be presented as both fetal and litter incidences]***

TABLE 3 Cesarean Section Observations[a]

Observation	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
# Animals Assigned (Mated)	29	29	29	29
# Animals Pregnant Pregnancy Rate (%)	26	25	25	25
# Nonpregnant				
Maternal Wastage # Died # Died Pregnant # Died Nonpregnant # Aborted # Premature Delivery	3 1	1 1	1	1
Total # Corpora Lutea Corpora Lutea/Dam	11.5 ± 3.5	11.2 ± 2.4	10.7 ± 2.4	12.4 ± 2.7
Total # Implantations Implantations/Dam	Not reported 9.4 ± 2.0	Not reported 9.1 ± 2.9	Not reported 9.0 ± 2.3	not reported 9.6 ± 3.0
Total # Litters	26	25	25	25
Total # Live Fetuses Live Fetuses/Dam	218 8.4	203 8.1	195 7.8	190 7.6
Total # Dead Fetuses Dead Fetuses/Dam	Not reported	not reported	not reported	not reported
Total # Resorptions Early Late Resorptions/Dam Early Late Litters with Total Resorptions	Not reported 1.0 ± 1.0 0.2 ± 0.5 0.8 ± 0.9 0	Not reported 1.0 ± 1.0 0.3 ± 0.5 0.7 ± 0.8 0	Not reported 1.2 ± 1.1 0.2 ± 0.4 1.0 ± 1.0 1	not reported 2.0 ± 1.4 1.4 ± 1.2 0.6 ± 0.8 1
Mean Fetal Weight (g) Males Females	Not reported	Not reported	Not reported	not reported
Sex Ratio (% Male)	46	53	51	50
Preimplantation Loss (%)	18.4	18.7	16.0	22.9
Postimplantation Loss (%)	11.1	11.0	13.8	20.9

a Data extracted from report no. 84/0CC006/025, table 4.)

B. DEVELOPMENTAL TOXICITY

1. External Examination - No external findings were reported.

2. Visceral Examination - The data presented show an increase in "gall bladder variants" at the high dose level, compared with controls (table 4b) Independent analysis by HED shows this finding to be statistically significant. No other apparent treatment-related effects were reported.

3. Skeletal Examination - No skeletal findings of toxicological importance were observed (see Table 4c).

TABLE 4a. External Examinations[a]

Observations+	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
#Fetuses(litters) examined	205 (25)	194 (24)	194 (24)	189 (24)
#Fetuses(litters) affected				
Findings: None repported				

a Data extracted from report no. 84/0CC006/025)
b Fetal (litter) incidence

TABLE 4b. Visceral Examinations[a]

Observations	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
#Fetuses(litters) examined	205 (25)	194 (24)	194 (24)	189 (24)
#Fetuses(litters) affected				
gall bladder variants	26.2 (20)[b]	23.2 (10)	22.2 (18)	43.4 (21)

a Data extracted from report no. 84/0CC006/025, table 5.)
b Fetal (litter) incidence

TABLE 4c. Skeletal Examinations[a]

Observations+	Dose (mg/kg/day)			
	0	LDT	MDT	HDT

#Fetuses(litters) examined	205 (25)	194 (24)	194 (24)	189 (24)
#Fetuses(litters) affected				
Number with heads of long bones unossified	37.8 (22)[b]	47.9 (18)	50.5 (23)	51.3 (21)

\+ Some observations may be grouped together
a Data extracted from report no. 84/0CC006/025, table 6.)
b Fetal (litter) incidence

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The investigators have concluded that within the parameters of the study, there was no "adverse effect upon the progress and outcome of pregnancy. Fetal morphogenisis and growth were similarly unaffected by treatment." As such, the maternal and developmental NOEL would be 250 mg/kg/day, the highest dose level used in this study.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: No maternal effects were observed at the highest dose level used (250 mg/kg/day).
2. DEVELOPMENTAL TOXICITY:
   a. Deaths/Resorptions: An increase in post-implantation loss was observed at the high dose level (20.9%) vs. controls (11.1%). These values are derived from all the animals, including those with total litter loss. (The author's comparisons exclude animals with total litter loss, resulting in a lower incidence (18.2%) of post-implantation loss.)
   The original HED DER states that this difference is statistically significant, as "determined independently". Therefore, while details concerning the degreee of significance, etc. are missing, there is no reason at this time for HED to challenge its own analysis. The historical mean for this endpoint, derived from 71 studies, is 10%, with the range being 1.0 - 20.5%). Thus, the value for the current study is about twice the historical mean, and is just outside the historical range, supporting the conclusion that the effect is real.
   b. Altered Growth: No significantly altered patterns of growth were observed. Upon further examination, the gall bladder anomalies observed in fetuses were not of toxicological significance.
   c. Developmental Variations: None observed
   d. Malformations: No malformations were observed.

C. STUDY DEFICIENCIES

1. Test substance stability data were not provided, nor homogeneity of test suspensions.
2. Food consumption data were not provided.

Normally, these deficiencies would lead to a supplementary classification, but since this test substance data is readily available from other studies submitted, and since credible endpoints were identified with LOELs and NOELs, the HAZID committee concluded that an **Acceptable** classification is appropriate.