United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: Fluroxypyr
Reason for Issuance: Conditional Registration
Date Issued: September 30, 1998

Description of Chemical

Generic Name:	1-methylheptyl ((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)acetate
Common Name:	Fluroxypyr
Trade Name:	Starane EC Herbicide
EPA Shaughnessy Code:	128959
Chemical Abstracts Service (CAS) Number:	69377-81-7
Year of Initial Registration:	1998
Pesticide Type:	Herbicide
Chemical Family:	Pyridinoxy acid
U.S. Producer:	Dow AgroSciences LLC

Use Patterns and Formulations

Application Sites:	Fluroxypyr is registered for use on wheat, barley, oats, fallow cropland, and on-farm non-cropland.
Types of Formulations:	98% technical product 26.2% emulsifiable concentrate end-use product
Types and Methods of Application:	Aerial and ground application using standard commercial sprayers
Application Rates:	Application rates 2/3 to 1 1/3 pints of formulated product (0.125 to 0.25 pounds active ingredient acid equivalent) per acre. One application is allowed per season.
Carrier:	Water

Science Findings

Summary Science Statements

Based upon a battery of acute toxicity studies, Starane EC Herbicide is classified as Toxicity Category II. Fluroxypyr is classified as a "not likely" human carcinogen. It does not demonstrate developmental or reproductive toxicity. The data available at this time indicate that fluroxypyr is highly phytotoxic. Available data indicate that fluroxypyr acid is mobile to very mobile in the submitted laboratory studies. However, dissipation by hydrolysis and microbial degradation reduced persistence and limited downward transport (i.e., leaching) in the submitted field studies.

Chemical Characteristics

PROPERTY	TECHNICAL	END-USE
Physical State	Solid	Liquid
Color	Gray olive	Tan
Odor	Musty, slightly chlorine	Kerosene
Melting Point	57.5°C	N/A
Density	1.3 g/mL @ 21°C	0.989 g/mL @ 20°C
Solubility (Water)	136 μg/L @ pH 7	N/A
Vapor Pressure	2.0 x 10^{-5} kPa @ 25°C	N/A
Octanol/Water Partition Coefficient	Log_{10} K_{ow} = 5.04 @ pH 7	N/A
pH	6.81	3.94

Toxicology Characteristics

Acute Toxicity (Starane F Technical)

- Acute Oral Toxicity in Rats - LD_{50} > 5000 mg/kg in males and females; Toxicity Category IV
- Acute Dermal Toxicity in Rats - LD_{50} > 2000 mg/kg in males and females; Toxicity Category III
- Acute Inhalation Toxicity in Rats - LC_{50} > 2 mg/L in males and females; Toxicity Category IV
- Primary Eye Irritation in Rabbits - Mild irritation (slight conjunctival irritation) resolved within 24 hours in 2 rabbits and within 48 hours in 1 rabbit; Toxicity Category III
- Primary Dermal Irritation in Rabbits - Non-irritating; Toxicity Category IV
- Primary Dermal Sensitization in Guinea-Pigs - Did not exhibit any sensitization potential.

Acute Toxicity (Starane EC Herbicide)

- Acute Oral Toxicity in Rats - LD_{50} = 3738 mg/kg in males and 3162 mg/kg in females; Toxicity Category III

- Acute Dermal Toxicity in Rats - LD_{50} > 2000 mg/kg in males and females; Toxicity Category III

- Acute Inhalation Toxicity in Rats - LC_{50} > 6.2 mg/L for males and females; Toxicity Category IV

- Primary Eye Irritation in Rabbits - Irritation based on findings of corneal opacity (resolved within 7 days in 5 rabbits and by 14 days in 1 rabbit) and slight to marked redness, chemosis, and ocular discharge of the conjunctivae (resolved by 21 days); Toxicity Category II

- Primary Dermal Irritation in Rabbits - Slight irritation resolved by 48 hours; Toxicity Category IV

- Primary Dermal Sensitization in Guinea-Pigs - Did not exhibit any sensitization potential.

Subchronic Toxicity

- In a 90-day feeding study in rats, 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 LOAEL is 750 mg/kg/day based on kidney effects and death. In females the NOEL is 750 mg/kg/day, with the LOAEL at 1000 mg/kg/day based on kidney effects and death.

- In a 90-day feeding study in mice, no significant effects were observed at any dose level. The NOAELs 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 LOAEL could not be established.

- In a range finding feeding study in dogs, dogs at 500 mg/kg/day exhibited ataxia and hind limb weakness as well as decreases in body weight and food consumption. 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 LOAEL was 150 mg/kg/day based on histopathological lesions in the kidneys, decreased testes weights, and increased adrenal weights in both sexes.

- In a 21-day dermal study in rabbits, no dermal or systemic toxicity was observed at any dose

level. The NOEL for males and females is therefore 1000 mg/kg/day. A LOAEL could not be established.

Chronic Toxicity/Carcinogenicity

- In the combined chronic toxicity/carcinogenicity study in rats, there was no apparent treatment-related increase in any tumor type in either sex at the doses tested [with the exception of an increased incidence of parafollicular cell adenomas (single only) in males at 500 mg/kg/day]. The LOAEL 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).

- In the carcinogenicity study in mice, there were no adverse effects on survival or clinical signs in either sex. There was no apparent treatment-related increase in the incidence of any tumor type in either sex. The LOAEL 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.

- In a one-year chronic feeding study in dogs, 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 LOAEL could not be established.

Developmental Toxicity

- In a developmental toxicity study in rats, 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 LOAEL is 250 mg/kg/day based on clinical signs. The developmental NOEL is 250 mg/kg/day, the LOAEL is 500 mg/kg/day based on reduced ossification.

- In a developmental toxicity study in rats, fluroxypyr administration resulted in 8 deaths at the

high-dose level, and decreased body-weight gain 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. There were no treatment-related effects on gross pathologic alterations or absolute and relative liver and kidney weights at any dose level. The maternal NOEL is 300 mg/kg/day, the LOAEL 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 LOAEL is 600 mg/kg/day, based on an increase in two ossification variations (incompletely ossified cervical vertebral transverse processes and pubes).

- In a developmental toxicity study in rabbits, fluroxypyr administration resulted in maternal toxicity at the high-dose level, as evidenced by an increased incidence of abortions. 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. The maternal/developmental LOAEL is 1000 mg/kg/day, based on an increased incidence of abortions. The maternal NOEL is 500 mg/kg/day.

- In a prenatal developmental toxicity study in rabbits, a large number of maternal deaths in the 400 mg/kg/day group resulted in a dose level of 250 mg/kg/day being 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 LOAEL was 400 mg/kg/day based on maternal deaths. For developmental toxicity, the NOEL was 100 mg/kg/day and the LOAEL was 250 mg/kg/day, based on increased postimplantation loss.

Reproductive Toxicity

- In a 2-generation reproduction study in rats, treatment-related deaths due to renal failure occurred in both sexes at the high dose in both generations. The effects observed 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). The NOEL for maternal/paternal toxicity is 500/100 mg/kg/day, and the LOAEL is 1000/500 mg/kg/day, based on death in females and increased kidney weight with corresponding gross and microscopic findings 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 LOAEL is 1000 mg/kg/day, based on decreased pup body weight/body-weight gain and slightly lower survival.

Mutagenicity

- 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. 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*.

Metabolism

- 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%) showed the principal route of excretion being expired $^{14}CO_2$, which contained ≈61% and 63% of the radioactivity for the fluroxypyr methylheptyl ester 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 methylheptyl ester and methylheptanol groups, respectively. Each was extensively absorbed and rapidly eliminated. Approximately 52% and 54% of the administered fluroxypyr methylheptyl ester 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 and rapidly expired as $^{14}CO_2$ and eliminated in the urine with a half-life of 6 hours. Half-lives for the elimination phase were ≈18.2 and 17.4 hours for fluroxypyr methylheptyl ester and Methylheptanol, respectively. Data indicate that the fluroxypyr methylheptyl ester bond is readily hydrolyzed and that the methylheptyl ester portion of fluroxypyr is bioequivalent to Methylheptanol.

Exposures and Risks

The Reference Dose (RfD) has been established at 0.5 mg/kg/day. Dietary exposure was calaculated by using a Theoretical Maximum Residue Concentration (TMRC) and by assuming 100% field corn crops treated. Exposures and risks, including margins of exposure (MOE), % of RfD occupied, and drinking water levels of concern (DWLOC), are for relevant subgroups are reported below:

ACUTE RISK			
SUB-POPULATION	ACCEPTABLE MOE	ESTIMATED MOE	DWLOC (ppb)
Females (13+ years)	100	50,000	9,940
CHRONIC RISK			
SUB-POPULATION	% RfD OCCUPIED		DWLOC (ppb)
U.S. Population	0.41 %		17,400
Females (13+ years)	0.37 %		14,900
Children (1-6 years)	1.1 %		4,950

Environmental Characteristics

STUDY TYPE	HALF LIFE/OTHER
Hydrolysis	Stable at pH 5; Stable (extrapolated at 454 days) at pH 7; 3.2 days at pH 9
Photolysis in Water	Stable (extrapolated at 197 to 429 days) at pH 5
Photolysis on Soil	Stable (extrapolated at 119 days)
Aerobic Soil Metabolism	23 days
Aerobic Aquatic Metabolism	14 days
Anaerobic Aquatic Metabolism	8 days
Mobility-Unaged Leaching	Mobile to very mobile
Mobility-Aged Leaching	Generally not found below 6 inches of soil depth
Terrestrial Field Dissipation	36.3 days

Mechanism of Pesticidal Action

Fluroxypyr induces auxin-type responses in susceptible annual and perennial broadleaf weeds (auxin being a type of plant growth hormone). Once absorbed into the plant, it accumulates in growing tissues to higher concentrations than the native auxin does, and degrades more slowly. Plant growth is disrupted by the deregulation of cellular growth process following binding of fluroxypyr to plant cell auxin receptor sites. Fluroxypyr also interferes with the plant's ability to metabolize nitrogen and produce enzymes. When a plant's strict growth regulation is disrupted in this fashion, plant growth becomes disorganized, disrupting key metabolic process and results in plant death.

Potential to Contaminate Groundwater

Available data indicate that fluroxypyr acid is mobile to very mobile in the submitted laboratory studies. However, dissipation by hydrolysis and microbial degradation reduced persistence and limited downward transport (i.e., leaching) in the submitted field studies.

Ecological Characteristics

Terrestrial

Fluroxypyr is practically non-toxic to the mallard duck and the bobwhite quail on an acute basis (LD_{50} > 2000 mg/kg) and practically non-toxic to the mallard duck and the bobwhite quail on a sub-acute basis (5-day LC_{50} > 5000 ppm). It is slightly toxic to small mammals (LD_{50} = 880 mg/kg) and practically non-toxic to honey bees (LD_{50} > 25 μg/bee).

Aquatic - Freshwater

Fluroxypyr is slightly toxic to the bluegill sunfish (96-hour LC_{50} > 14.3 mg/L) and slightly toxic to practically non-toxic to the rainbow trout (96-hour LC_{50} ranges from 13.4 mg/L to > 100 mg/L). It is also practically non-toxic to *Daphnia magna* (48-hour EC_{50} > 100 mg/L).

Aquatic - Estuarine/Marine

Fluroxypyr is slightly toxic to the silverside (96-hour LC_{50} = 40 mg/L). Fluroxypyr acid is highly toxic to the eastern oyster (96-hour LC_{50}/EC_{50} = 0.068 mg/L); fluroxypyr 1-methylheptyl ester is slightly toxic to the eastern oyster (96-hour LC_{50}/EC_{50} = 51 mg/L). It is practically non-toxic to the grass shrimp (96-hour LC_{50}/EC_{50} > 120 mg/L).

Plants

Fluroxypyr is highly toxic terrestrial plants. Seedling emergence studies identified the most sensitive species to fluroxypyr methylheptyl ester being the cucumber (EC_{25} = 0.075 pounds active ingredient/acre). Since fluroxypyr methylheptyl ester may degrade to fluroxypyr acid before reaching non-target plants, seedling emergence studies were performed on fluroxypyr acid and identified cotton as the most sensitive species (EC_{25} = 0.025 pounds active ingredient/acre). Vegetative vigor studies with fluroxypyr methlyheptyl ester also identified cotton as the most sensitive species (EC_{25} = 0.0012 pounds active ingredient/acre).

Summary of Regulatory Position and Rationale

Available data provide adequate information to support the conditional registrations of Starane F Technical and Starane EC Herbicide for use on wheat, barley, and oats.

Use, Formulation, Manufacturing Process or Geographic Restrictions

Environmental Hazards

Drift or runoff from treated areas may be hazardous to aquatic organisms and non-target plants. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwaters.

Physical or Chemical Hazards

Do not use or store near heat or open flame.

Drift Reduction

Spray drift, even very small quantities of the spray which may not be visible, may severely injure susceptible crops whether dormant or actively growing. Use low pressure equipment capable of producing sprays of uniform droplet size with a minimum of fine spray droplets. Under adverse weather conditions, fine spray droplets that do not settle rapidly onto target vegetation may be carried a considerable distance from the treatment area. A drift control or spray thickening agent may be used with this product to improve spray deposition and minimize the potential for spray drift.

To minimize spray drift with ground applications, apply in a total spray volume of 8 or more gallons per acre using spray equipment designed to produce large droplet, low pressure sprays. Spot treatments should be applied only with a calibrated boom to prevent over-application. Operate equipment at spray pressures no greater than is necessary to produce

a uniformly overlapping pattern between spray nozzles. Do not apply with hollow cone-type

insecticide nozzles or other nozzles that produce a fine droplet spray.

To minimize spray drift with aerial applications, apply in a total spray volume of 3 or more gallons per acre. Drift potential is lowest between wind speeds of 2 to 10 miles per hour. However, many factors, including droplet size and equipment type, determine drift potential at any given speed. Application should be avoided below 2 miles per hour due to variable wind direction and high potential for temperature inversion. Spray drift from aerial application can be minimized by applying a coarse spray at spray boom pressure no greater than 30 psi; by using straight stream nozzles directed straight back; and by using a spray boom no longer than 3/4 the rotor or wing span of the aircraft. Spray pattern and droplet size distribution can be evaluated by applying sprays containing a water soluble dye marker or appropriate drift control agents over a paper tape (adding machine tape). Mechanical flagging devices may also be used.

Do not apply under conditions of a low level air temperature inversion.

Use Directions - General Precautions

Do not apply this product directly to, or otherwise permit it to come in direct contact with, susceptible crops or desirable plants including, but not limited to, alfalfa, canola, cotton, lettuce, edible beans, lentils, mustard, peas, potatoes, radishes, soybeans, sugar beets, sunflowers, tomatoes, or tobacco.

Avoid applications where proximity of susceptible crops or other desirable plants is likely to result in exposure to spray or spray drift.

Do not contaminate irrigation ditches or water used for domestic purposes.

Do not apply more than 1 1/3 pints of product per acre per growing season.

If replanting is required, only wheat, barley or oats may be planted in treated fields within 120 days following application.

Do not apply this product through any type of irrigation system.

Use Directions - Wheat, Barley, Oats

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 growing season.

Do not apply closer than 14 days before cutting of hay or 40 days before harvesting of grain and straw.

Summary of Data Gaps

Residue Chemistry Data:
- Processed food/feed study for wheat germ

Environmental Fate Data:
- Soil mobility data
- Terrestrial field dissipation data
- Bioaccumulation in fish

Ecological Effects Data:
- Acute toxicity to aquatic plants (*Navicula pelliculosa*)
- Seedling emergence data (3 monocot species and 5 dicot species)

Contact Person at EPA

Joanne I. Miller
Product Manager 23
Herbicide Branch
Registration Division (7505C)
Office of Pesticide Programs
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Office Location and Telephone Number

Room 237, Crystal Mall Building #2

1921 Jefferson Davis Highway
Arlington, VA 22202
(703) 305-7830

DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.