



Pesticide
Fact Sheet

Name of Chemical: Diflufenzopyr
Reason for Issuance: Conditional Registration
Date Issued: January 28, 1999

1. DESCRIPTION OF CHEMICAL

Generic Name: 2-(1-[(3,5-difluorophenylamino)carbonyl]-hydrazono)ethyl)-3-pyridinecarboxylic acid

Common Name: Diflufenzopyr

Trade Name: Distinct™ Herbicide

EPA Shaughnessy Code: 005107

Chemical Abstracts
Service (CAS) Number: 109293-97-2

Year of Initial
Registration: 1999

Pesticide Type: Herbicide

Chemical Family: Semicarbazone

U.S. Producer: BASF Corporation

2. USE PATTERNS AND FORMULATIONS

Application Sites: Diflufenzopyr is registered for use on field corn.

Types of Formulations: 99% technical product (acid); 93% manufacturing use product (sodium salt); wettable granular end use product containing 21.4% sodium diflufenzopyr and 55% sodium dicamba

Types and Methods of Application: Ground application using standard commercial sprayers

Application Rates: Use rates on field corn range from 4 to 8 ounces of formulated product (0.05 to 0.10 pounds active ingredient, diflufenzopyr) per acre per application. The maximum number of applications per season is two with a total of no more than 10 ounces product (0.12 pounds active ingredient) per acre.

Carrier: Water

3. SCIENCE FINDINGS

Summary Science Statements

Diflufenzopyr is the first active ingredient from a chemical class called semicarbazones. The review of product chemistry, environmental fate, toxicology, ecological effects and residue chemistry data have been completed. Based on available data, diflufenzopyr has been determined to be of low toxicity to humans, birds, aquatic organisms, mammals, and bees. Acute toxicology studies place technical-grade diflufenzopyr in Toxicity Category III. It is neither teratogenic nor carcinogenic. Additionally, the data indicate no significant risk to non-target organisms, and diflufenzopyr is not expected to pose a risk of groundwater contamination.

Chemical Characteristics

PROPERTY	TECHNICAL	END-USE
Physical State	powder, solid	rod-like, granular solid
Color	off-white	tan
Odor	no odor	N/A
Melting Point	135.5°C ; decomp. @155°C	N/A
Density	0.24 g/mL @ 25°C	0.63 g/mL @ 25°C
Solubility (Water)	63 ppm @ pH 5; 5850 ppm @ pH7;10,546 ppm @ pH9	N/A

PROPERTY	TECHNICAL	END-USE
Vapor Pressure	1.0×10^{-7} kPa @ 20°C and 25°C	N/A
Octanol/Water Partition Coefficient	average $K_{ow} = 1.09$ (pH dependent)	N/A
pH	3.90	8.51

Toxicology Characteristics

Acute Toxicity (Diflufenzopyr Technical)

- Acute Oral Toxicity in Rats - $LD_{50} > 5000$ mg/kg in males and females; Toxicity Category IV
- Acute Dermal Toxicity in Rabbits - $LD_{50} > 5000$ mg/kg in males and females; Toxicity Category IV
- Acute Inhalation Toxicity in Rats - $LC_{50} > 2.93$ mg/L in males and females; Toxicity Category IV
- Primary Eye Irritation in Rabbits - Mild irritation resolved within 48 hours in 4/6 rabbits; 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 (Diflufenzopyr Manufacturing Use Product)

- Acute Oral Toxicity in Rats - $LD_{50} = 4800$ mg/kg in males and 3300 mg/kg in females; Toxicity Category III
- Acute Dermal Toxicity in Rabbits - $LD_{50} > 5000$ mg/kg in males and females; Toxicity Category IV
- Acute Inhalation Toxicity in Rats - $LC_{50} > 5.21$ mg/L in males and females; Toxicity Category IV
- Primary Eye Irritation in Rabbits - Slight to mild irritation resolved within 48 hours in all eyes; Toxicity Category III

- Primary Dermal Irritation in Rabbits - Very slight irritation resolved within 24 hours in all rabbits; Toxicity Category IV
- Primary Dermal Sensitization in Guinea-Pigs - Did not exhibit any sensitization potential.

Acute Toxicity (Distinct Herbicide)

- Acute Oral Toxicity in Rats - LD₅₀ = 1600 mg/kg in males and 2100 mg/kg in females; Toxicity Category III
- Acute Dermal Toxicity in Rabbits - LD₅₀ > 5000 mg/kg in males and females; Toxicity Category IV
- Acute Inhalation Toxicity in Rats - LC₅₀ > 5.34 mg/L for males and females; Toxicity Category IV
- Primary Eye Irritation in Rabbits - Mild to moderate irritation (resolved within 7 days in all eyes); Toxicity Category III
- Primary Dermal Irritation in Rabbits - Very slightly irritating (resolved within 48 hours in 5/6 rabbits and within 72 hours in all rabbits); Toxicity Category IV
- Primary Dermal Sensitization in Guinea-Pigs - Strongly positive as a skin sensitizer.

Subchronic Toxicity

- In a subchronic study in rats, Wistar rats were fed test diets containing technical diflufenopyr at dose levels of 0, 1000, 5000, 10,000 and 20,000 ppm for a period of 13 weeks. The NOAEL was set at 5000 ppm (equal to 352 mg/kg bw/day for males, and 431 mg/kg bw/day for females) based on lower mean body weight gain and decreased food efficiency in the 10,000 and 20,000 ppm groups, both sexes. Additional findings were decreased food intake; slight increases in cholesterol and alanine aminotransferase (ALAT); and slightly lower chloride. Histopathological findings were an increased incidence of foamy macrophages in the lungs in the 10,000 and 20,000 ppm groups and testicular atrophy in the 20,000 ppm group. Following the 4-week recovery period, the only treatment-related effects which showed partial or no evidence of recovery were foamy macrophages in the lungs and testicular atrophy.
- In a subchronic study in mice, CD-1 mice were dosed with diflufenopyr at 0, 350, 1750, 3500 and 7000 ppm in the diet for 13 weeks. The NOEL was determined to be the highest dose tested of 7000 ppm (1225 mg/kg/day in males and 1605 mg/kg/day in females) as no clear toxic effects were observed.

- In a subchronic study in dogs, diflufenzopyr was administered to beagle dogs in the diet at dose levels of 0, 1500, 10,000, or 30,000 ppm for 13 weeks. The LOAEL for this study is 10,000 ppm (403 mg/kg/day in males and 424 mg/kg/day in females), based on the occurrence of erythroid hyperplasia in the bone marrow, extramedullary hemopoiesis in the liver, and hemosiderin deposits in Kupffer cells. The NOAEL is 1500 ppm (58 mg/kg/day in males and 59 mg/kg/day in females)
- In a subchronic dermal toxicity study, technical diflufenzopyr was administered by dermal application to male and female New Zealand White rabbits at dose levels of 0, 100, 300 and 1000 mg/kg bw per application. Duration of application was 6 hours a day, daily for 21 to 24 consecutive days. The NOAEL for systemic toxicity was determined to be 1000 mg/kg bw/day, since there were no apparent signs of treatment-related systemic effects observed in male or female rabbits at any dose level tested. A NOAEL for dermal effects could not be determined since local dermal irritation was observed at all dose levels tested (there were no corresponding findings upon histopathological examination).

Chronic Toxicity/Carcinogenicity

- In a chronic toxicity study in dogs, diflufenzopyr was administered to beagle dogs in the diet at dose levels of 0, 750, 7500, or 15,000 ppm for 52 weeks. The LOAEL for this study is 7500 ppm (299 mg/kg/day for males and 301 mg/kg/day for females), based on erythroid hyperplasia in the bone marrow in bone sections, reticulocytosis, and increased hemosiderin deposits in the liver, kidneys, and spleen. The NOAEL is 750 ppm (26 mg/kg/day for males and 28 mg/kg/day for females).
- In a mouse carcinogenicity study, male and female CD-1 mice were fed test diets containing technical diflufenzopyr at dietary concentrations of 0, 700, 3500 and 7000 ppm for a period of 78 weeks. The NOAEL for systemic toxicity was determined to be 7000 ppm (equal to 1037 mg/kg bw/day for males and 1004 mg/kg bw/day for females). There were no treatment-related effects observed at any dose level tested in male rats. There was a slight, but statistically significantly lower mean overall body weight gain for females in the 7000 ppm group, due primarily to decreased gain/increased weight loss during the second year of the study. In the absence of any other treatment-related findings, this was not considered to be an adverse, toxicologically significant finding. There was no evidence of oncogenic potential of diflufenzopyr for male or female mice at any dose level tested.
- In a combined chronic toxicity/carcinogenicity study, male and female Wistar rats were fed test diets containing technical diflufenzopyr at dietary concentrations of 0, 500, 1500, 5000 and 10,000 ppm for a period of 104 weeks. The NOAEL for systemic toxicity was set at 5000 ppm (equal to 236 mg/kg bw/day for males and 323 mg/kg bw/day for females). Treatment-related effects in the 10,000 ppm group were significantly lower body weight and body weight gains throughout the study period and decreased food efficiency. There was no evidence of oncogenic potential of diflufenzopyr at any dose level tested.

Developmental Toxicity

- In a developmental toxicity study, technical diflufenzopyr was administered by gavage to female Sprague Dawley rats at dose levels of 0, 100, 300, or 1000 mg/kg/day from days 6 through 15 of gestation. The maternal NOAEL is 300 mg/kg/day and the maternal LOAEL is 1000 mg/kg/day based on decreases in food consumption and weight gain. Developmental effects, characterized as significantly lower fetal body weights in males (↓5%) and skeletal variations, exhibited as incompletely ossified and unossified sternal centra and reduced fetal ossification sites for caudal vertebrae, were observed at 1000 mg/kg/day. The developmental LOAEL is 1000 mg/kg/day, based on decreased fetal body weights and skeletal variations. The developmental NOAEL is 300 mg/kg/day.

- In a developmental toxicity study, technical diflufenzopyr was administered by gavage to female New Zealand White rabbits at dose levels of 0, 30, 100, or 300 mg/kg/day from days 6 through 19 of gestation. The maternal LOAEL is 100 mg/kg/day, based on minimal reductions in body weight gain with no reduction in food consumption and clinical signs of toxicity (abnormal feces). The maternal NOAEL is 30 mg/kg/day. Developmental effects, characterized as significant increases in the incidence of supernumerary thoracic rib pair ossification sites occurred at the 300 mg/kg/day dose. No treatment-related developmental effects were noted at the low and mid doses. The developmental LOAEL is 300 mg/kg/day based on increased skeletal variations (supernumerary rib ossification sites). The developmental NOAEL is 100 mg/kg/day.

Reproductive Toxicity

- In a 2-generation reproduction study, technical diflufenzopyr was administered continuously in the diet to Wistar at dose levels of 0, 500, 2000 or 8000 ppm in the diet. The systemic LOAEL is 2000 ppm (113.1-175.9 mg/kg/day) based on reduced body weight gain, increased food consumption, and increased seminal vesicle weights. The systemic NOAEL is 500 ppm (27.3-42.2 mg/kg/day). The reproductive LOAEL is 8000 ppm (466.2-742.0 mg/kg/day) based on lower live birth and viability indices, total pre-perinatal loss, reduced body weights and body weight gain during lactation, a higher proportion of runts, and a higher percentage of offspring with no milk in the stomach. The reproductive NOAEL is 2000 ppm (113.1-175.9 mg/kg/day).

Mutagenicity

- Four acceptable mutagenicity studies were available for review: a microbial (Salmonella typhimurium) mutagenicity assay; an in vitro mammalian (mouse lymphoma) cell gene mutation assay; an in vivo mouse bone marrow micronucleus assay; and an unscheduled DNA synthesis assay. Diflufenzopyr was negative for mutagenic potential in all assays.

Neurotoxicity

● In an acute neurotoxicity study, diflufenzopyr was administered by gavage to Crl:CD BR rats at dose levels of 0, 125, 500 or 2000 mg/kg. Diflufenzopyr had no definite impact on neurotoxic responses, although a few abnormalities were observed in the functional battery on the day of dosing. A decrease in immediate righting responses that was observed in several males in all treatment groups was not concentration-dependent. Nasal staining was observed in more rats in the 2000 mg/kg treatment groups (6 males; 3 females), but was not considered a definite or significant response to treatment. Lower mean brain weights in all female treatment groups lacked associated macroscopic and microscopic histopathological changes, and were only 4-5% lower than the control brain weight. Mean locomotor activities for the 2000 mg/kg female treatment groups were decreased on Days 7 and 14 after dosing, but the pattern of activity for the individual animals was similar to the individual controls over time. There were no definite treatment-related differences in body weights or food consumption in any of the treatment groups. There was no evidence of treatment-related neuropathology in the 2000 mg/kg treatment group. A LOAEL was not established. The NOAEL for acute neurotoxicity is 2000 mg/kg (the limit dose).

● In a subchronic neurotoxicity study, diflufenzopyr was administered in the diet to Crl:CD BR rats at dose levels of 0, 25, 75 or 1000 mg/kg/day for 13 weeks. No treatment-related neurotoxicological effects were observed at any treatment level. A LOAEL for neurotoxicological effects was not established; the NOAEL was 1000 mg/kg/day for both sexes. Treatment-related toxic effects were observed at the 1000 mg/kg/day treatment level. The toxicological LOAEL for this study is 1000 mg/kg/day, based on decreased body weight gains for both sexes. The toxicological NOAEL is 75 mg/kg/day.

Metabolism

● In a rat metabolism study, [phenyl-U-¹⁴C] or [pyridinyl-4,6-¹⁴C]diflufenzopyr was administered to Wistar rats as a single intravenous dose at 1 mg/kg/day, a single oral dose (gavage) at 10 or 1000 mg/kg or a single dose at 10 mg/kg following a 14-day pretreatment with unlabeled diflufenzopyr at 10 mg/kg. Following oral administration, diflufenzopyr was partially absorbed and rapidly eliminated. By oral administration, 20 to 44 % of the dose was eliminated in urine and 49 to 79 % in feces. By contrast, intravenously dosed rats excreted 61-89% of the dose in urine. Biliary elimination accounted for 3 to 19 % of the dose in all dose groups. Elimination half-life in urine and feces was 5.2-6.9 hours for all single dose groups and 7.7-10.8 hours for all repeat oral dose groups. Total radioactive residues in tissues from rats in all dose groups were <3% of the administered dose. Blood residue levels for all dose groups were <1% of the administered dose at all sampling intervals through 72 hours post-dose. Diflufenzopyr was eliminated in urine, feces and bile primarily as unchanged parent compound. Hydrolytic and hydroxylation products were also found in excreta but in low percentages of the dose.

Metabolism of diflufenzopyr was also conducted in laying hens and lactating goats. The data showed diflufenzopyr was rapidly eliminated from the animals. With a feeding level of 10 ppm

equivalent in the diet, residue levels in edible tissues, milk and eggs were less than 0.12 ppm equivalent. The metabolite profile in rat was similar in hen and goat. The major plant corn metabolites M1, M9, and M10 were also found in rat, goat and hen.

Human Exposures and Risks

The chronic Reference Dose (RfD) has been established at 0.26 mg/kg/day, based on the NOAEL of 0.26 mg/kg/day from the one-year dog feeding study and an uncertainty factor of 100. The acute RfD has been established at 1.0 mg/kg/day, based on the NOAEL from the rabbit developmental toxicity study and an uncertainty factory of 100. The population subgroup of concern for acute effects is females, 13 years of age and older.

Dietary exposure was calculated by using a Theoretical Maximum Residue Concentration (TMRC) approach, which assumed 100% of field corn commodities contain residues of diflufenzopyr at the tolerance level of 0.05 ppm. Dietary (food and drinking water) exposures and risks are summarized below for relevant subgroups:

Population Subgroup	Food		Drinking Water	
	Exposure (mg/kg/day)	% RfD	Estimated Concentration (ppb)	Drinking Water Level of Comparison (DWLOC) (ppb)
I. Acute Exposure and Risk:				
Females, 13 + years	0.000128	0.01	≤3.8	29,970
II. Chronic Exposure and Risk:				
Overall U.S. Population	0.000063	<0.1	≤1.95	9,100
Infants and Children	≤0.000200	0.1	≤1.95	2,600

Environmental Characteristics

STUDY TYPE	HALF LIFE/OTHER
Hydrolysis (Half Life)	13 days (pH 5) 24 days (pH 7) 26 days (pH 9)
Photolysis in Water (Half Life)	7 days (pH 5) 17 days (pH 7) 13 days (pH 9)
Photolysis on Soil (Half Life)	14 days
Aerobic Soil Metabolism (Half Life)	8-10 days
Aerobic Aquatic Metabolism (Half Life)	25-26 days
Anaerobic Aquatic Metabolism (Half Life)	20 days
Mobility- Leaching (Parent)	Mobile - very mobile ($K_{OC} = 18$ to 156 mL/g)
Mobility- Leaching (Metabolites)	Mobile - very mobile (K_{OC} for M1 = 199 to 557 mL/g; K_{OC} for M9 = 128 to 1087 mL/g)
Terrestrial Field Dissipation* (Half Life)	4 days

* Based on Canadian study; additional Field Dissipation data required.

Potential to Contaminate Drinking Water

Based upon proposed uses, fate characteristics, and model predictions, EPA does not expect diflufenzopyr to reach drinking water resources in significant quantities.

Ecological Characteristics

Terrestrial

Diflufenzopyr is practically non-toxic on an acute basis to avian species ($LD_{50} > 2250$ mg ae/kg; $LC_{50} > 5620$ ppm ai), of low acute toxicity to small mammals ($LD_{50} = 4000$ mg/kg) and practically non-toxic to honey bees ($LD_{50} > 25$ µg ae/bee) .

Aquatic - Freshwater

Diflufenzopyr is slightly toxic to practically non-toxic to freshwater organisms ($LC_{50} = 15$ to > 135 ppm ae) .

Aquatic - Estuarine/Marine

Diflufenzopyr is slightly toxic to practically non-toxic to estuarine/marine organisms (LC_{50} or $EC_{50} = 18.9$ to > 138 ppm ae).

Plants

Diflufenzopyr is highly toxic to terrestrial plants. Seedling emergence studies identified the turnip as the most sensitive dicot species ($EC_{25} = 0.0008$ pounds acid equivalent/acre) and ryegrass as the most sensitive monocot (Shoot Length $EC_{25} = 0.0055$ lbs. ae/A).

Mechanism of Pesticidal Action

Diflufenzopyr is an auxin transport inhibitor. Diflufenzopyr inhibits the polar transport of naturally occurring auxin (indoleacetic acid, or IAA) and synthetic auxin-like compounds, such as dicamba, in sensitive plants. Diflufenzopyr's inhibition of auxin transport causes an abnormal accumulation of IAA and synthetic auxin agonists in meristematic shoot and root regions, disrupting the delicate auxin balance needed for plant growth. When diflufenzopyr is applied with dicamba, as in the Distinct Herbicide formulated product, it focuses dicamba's translocation to the meristematic sinks, where it delivers effective weed control at reduced dicamba rates and across a wider range of weed species. Sensitive broadleaf weeds exhibit rapid and severe plant hormonal effects (e.g., epinasty) after application of Distinct; symptoms are visible within hours, and plant death usually occurs within a few days. Symptomology, in sensitive annual grasses, is characterized by a "herbistatic" stunting effect on growth. Tolerance in corn occurs through rapid metabolism of diflufenzopyr and dicamba.

4. SUMMARY OF REGULATORY POSITION AND RATIONALE

Available data provide adequate information to support the conditional registrations of Diflufenzopyr Technical, Sodium Diflufenzopyr Technical, and Distinct Herbicide for use on field corn.

Use, Formulation, Manufacturing Process or Geographic Restrictions

Restrictions for Use on Corn:

- Do not apply more than a total of 10 ounces of Distinct Herbicide (0.125 pounds diflufenzopyr and 0.313 pounds dicamba) per acre, per season.
- Do not apply if corn is more than 24" tall.
- Do not apply within 32 days of forage harvest. Do not apply within 72 days of corn grain and stover harvest.

- Allow a minimum of 15 days between sequential applications of Distinct.
- Do not plant any crops within 120 days after the last application of Distinct. In the event of crop failure, corn can be replanted 7 or more days after application.
- Do not use penetrants such as petroleum-based oils or methylated seed oils with Distinct as crop injury may result.
- Do not apply to corn showing injury (leaf phytotoxicity or plant stunting) produced by any other prior herbicide applications, because this injury may be enhanced or prolonged.
- Do not apply through any type of irrigation system.
- Do not treat irrigation ditches or water used for crop irrigation or domestic uses.
- This product cannot be used to formulate or reformulate any other pesticide product.

5. **SUMMARY OF DATA GAPS**

Residue Chemistry Data:

- Rotational crop data
- Storage stability data

Environmental Fate Data:

- Terrestrial field dissipation data (end use product)
- Aerobic soil metabolism (metabolites)

Ecological Effects Data:

- Tier 2 vegetative vigor
- Acute freshwater invertebrate toxicity (end-use product)
- Chronic aquatic invertebrate toxicity (end-use product)
- Acute freshwater invertebrate toxicity (end-use product)
- Avian reproduction test (end-use product)
- Fish early life-stage test (end-use product)

6. **CONTACT PERSON AT EPA**

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