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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 20-DEC-2001

SUBJECT: **PP#0E6185. DIFLUFENZOPYR ON SWEET CORN, POP CORN, AND PASTURE AND RANGELAND GRASS. Health Effects Division (HED) Human Health Risk Assessment. PC Code: 005107. DP Barcode: D271603. Case#: 293208. Submission#: S590359.**

TO: Robert Forrest/Shaja Brothers, PM Team 05
Registration Division (RD) (7505C)

FROM: Jennifer R. Tyler, Chemist
William Dykstra, Ph.D., Toxicologist
Mark Dow, Ph.D., Biologist
Registration Action Branch 1 (RAB1)/HED (7509C)

THRU: G. Jeffrey Herndon, Branch Senior Scientist
RAB1/HED (7509C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of diflufenzopyr [2-(1-[([3,5-difluorophenylamino] carbonyl)hydrazono]ethyl)-3-pyridinecarboxylic acid] in/on sweet corn, popcorn, and pasture and rangeland grass.

A summary of the findings and an assessment of human health risk resulting from the proposed use of diflufenzopyr is provided in this document. The risk assessment, the residue chemistry data review, and the dietary exposure/risk assessment were provided by Jennifer R. Tyler (RAB1), the hazard characterization by William Dykstra (RAB1), the occupational/residential exposure assessment by Mark Dow (RAB1), and the drinking water assessment by Karen McCormick of the Environmental Fate and Effects Division (EFED).

NOTE: HED recently completed a Section 3 risk assessment for the use of diflufenzopyr on field corn (Memo, W. Dykstra et al., 11/17/98; D238413). This document contains only those aspects of the risk assessment which are affected by the addition of these new uses of diflufenzopyr on sweet corn, pop corn, and grass.

Recommendation for Tolerances and Registration

Provided revised Sections B and F, confirmation of the basis for the 12- hour restricted entry interval (REI), and an **adequate analytical enforcement method for livestock commodities** (including independent laboratory validation (ILV) and radiovalidation) are submitted, the available toxicological and residue chemistry databases support a ***conditional registration*** and the following:

permanent tolerances for residues of diflufenzopyr and its metabolites convertible to M1, expressed as diflufenzopyr, in/on:

corn, sweet, forage	0.05 ppm
corn, sweet, fresh	0.05 ppm
corn, sweet, stover	0.05 ppm
corn, pop, grain	0.05 ppm
corn, pop, stover	0.05 ppm
grass, forage	22 ppm
grass, hay	7.0 ppm

time-limited tolerances for residues of diflufenzopyr and its metabolites convertible to M1, and free and acid-released M19, expressed as diflufenzopyr, in:

meat*	0.60 ppm
kidney*	4.0 ppm
meat by-products (except kidney)*	0.50 ppm
fat*	0.30 ppm
milk	3.0 ppm

* of cattle, goat, hog, horse, and sheep

The registration should be conditional upon submission of an adequate livestock feeding study.

NOTE TO RD: The appropriate tolerance expressions to be included in 40 CFR §180.549(a) are 1) for corn and grass: "diflufenzopyr, 2-(1-[([3,5-difluorophenylamino] carbonyl)hydrazono]ethyl)-3-pyridinecarboxylic acid, and its metabolites convertible to 8-methylpyrido[2,3-d]pyridazin-5(6H)-one, expressed as diflufenzopyr, in/on..." and 2) for livestock commodities: "diflufenzopyr, 2-(1-[([3,5-difluorophenylamino] carbonyl)hydrazono]ethyl)-3-pyridinecarboxylic acid, its metabolites convertible to 8-methylpyrido[2,3-d]pyridazin-5(6H)-one, and free and acid-released 8-hydroxymethylpyrido[2,3-d] pyridazine-2,5(1H,6H)-dione, expressed as diflufenzopyr, in/on..."

Table of Contents

1.0. EXECUTIVE SUMMARY

Diflufenzopyr is a postemergence herbicide which acts by inhibiting the polar transport of naturally occurring auxin (indoleacetic acid, or IAA) and synthetic auxin-like compounds (e.g., dicamba). This results in an abnormal accumulation of IAA and synthetic auxin agonists in meristematic shoot and root regions, disrupting the auxin balance needed for plant growth.

The Interregional Research Project No. 4 (IR-4), on behalf of the Agricultural Experiment Stations of Minnesota, North Dakota, and Wisconsin, has submitted an application for tolerances for residues of the herbicide diflufenzopyr [2-(1-[([3,5-difluorophenylamino] carbonyl)hydrazono]ethyl)-3-pyridinecarboxylic acid] in/on pastures, pop corn, and sweet corn. Section F of the current petition proposes the establishment of the following permanent tolerances for residues of diflufenzopyr and its metabolites convertible to M1 (8-methylpyrido[2,3-d]pyridazin-5(6H)-one):

Corn, sweet, forage	0.05 ppm
Corn, sweet, fresh	0.05 ppm
Corn, sweet, stover	0.05 ppm
Corn, pop, stover	0.05 ppm

Crop Group 17, Grass forage, fodder, and hay:

Forage	3.0 ppm
Hay	1.5 ppm

Concurrently, the petitioner has submitted a request for Section 3 registration of Distinct® Herbicide (EPA Reg. No. 7969-150), a multiple active ingredient water-dispersible granule (WDG) formulation containing 21.4% diflufenzopyr and 55% dicamba, for use on the aforementioned raw agricultural commodities (RACs) for the control of various weeds. HED recently completed a Section 3 risk assessment for the use of dicamba on sweet corn (Memo, G. Kramer et al., 12/14/01; D271606).

Permanent tolerances are currently established for the combined residues of diflufenzopyr and its metabolites convertible to M1 in/on field corn forage, grain, and stover at 0.05 ppm [40 CFR §180.549(a)]. There are currently no registered or proposed residential uses of diflufenzopyr.

Hazard Assessment and *Dose Response Assessment*

Diflufenzopyr is of low acute toxicity (Toxicity Category III or IV for all routes of exposure). The technical is not a dermal sensitizer, but the formulation, Distinct®, is a dermal sensitizer. Acute and subchronic neurotoxicity studies did not display any evidence of neurotoxic effects and the no-observed-adverse-effect-levels (NOAELs) were 2000 mg/kg and 1000 mg/kg/day for each study, respectively, which were the limit doses. Developmental NOAELs and lowest-observed-adverse-effect-level (LOAEL) for both rats and rabbits occurred at either the same dose

levels or were above the NOAELs and LOAELs for maternal toxicity. The NOAEL for pup effects in the 2-generation rat reproduction study occurred at dose levels above the NOAEL for parental findings. Based on these data, the HED Hazard Identification Assessment Review Committee (HIARC) determined that there was no evidence of increased sensitivity for infants and children.

Diflufenzopyr was not tumorigenic at the limit dose (7000 ppm) in CD-1 mice fed for 18 months or in Wistar rats fed up to 10,000 ppm for 2 years. The HIARC determined that diflufenzopyr was **"not likely"** to be a human carcinogen. The 13-week and 52-week dog feeding studies demonstrated that dogs were the most sensitive species tested. The NOAELs for compensated hemolytic anemia were 58 and 26 mg/kg/day, respectively for the 13-week and 52-week feeding studies in dogs. The LOAELs were 403 and 299 mg/kg/day for the two dog studies, respectively. The acute reference dose (RfD) was set at 1.0 mg/kg/day for females 13-50 years old based on the developmental NOAEL of 100 mg/kg/day in rabbits and utilizing a 100-fold uncertainty factor (10x for interspecies extrapolation and 10x for intraspecies variation). The chronic RfD was established at 0.26 mg/kg/day based on the NOAEL of 26 mg/kg/day from the 52-week dog study. and utilizing a 100-fold uncertainty factor (10x for interspecies extrapolation and 10x for intraspecies variation). The HIARC determined that there were no endpoints of concern for dermal exposures and did not require a risk assessment. Inhalation exposure (short- and intermediate-, but not long-term) should be converted to oral equivalents and compared to the NOAEL of 58 mg/kg/day from the 13-week dog feeding study.

Food Quality Protection Act (FQPA) Decision

The FQPA Safety Factor Committee (SFC) determined that the 10x safety factor (SF) to account for enhanced sensitivity of infants and children (as required by FQPA) should be reduced to 1x (Memo, B. Tarplee 10/5/98; HED Doc. No.012904). The acute and chronic population adjusted doses (aPAD and cPAD, respectively) are modifications of the acute and chronic RfDs to include the FQPA SF. The acute or chronic PAD is equal to the acute or chronic RfD divided by the FQPA SF. Consequently, the acute RfD and aPAD values are equivalent (1.0 mg/kg/day), and the chronic RfD and cPAD values are equivalent (0.26 mg/kg/day). The rationale for removal of the FQPA SF was based on the following: 1) the toxicology database is complete; 2) there is no indication of increased susceptibility of rats and rabbits fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity data; 3) unrefined (Tier 1) dietary exposure estimates are protective since they will exaggerate dietary exposure estimates; 4) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and 5) there are currently no registered residential uses for diflufenzopyr.

Occupational Exposure Estimates

The level of concern for occupational exposures to diflufenzopyr is for margins of exposure (MOEs) less than 100. Based on use patterns, the potential for short- and intermediate-term

dermal and inhalation exposure to occupational handlers exist. Based on the seasonal use pattern, long-term exposures resulting from the proposed uses are not expected. Since the HIARC did not identify dermal toxicological endpoints of concern, only short- and intermediate-term inhalation exposures and risks were assessed for pesticide handlers. No chemical specific data were available with which to assess pesticide handler exposure; therefore, data were used from studies contained in the Pesticide Handlers Exposure Database (PHED) Surrogate Table (v1.1., 1998). The short- and intermediate-term inhalation MOEs for pesticide handlers are greater than $2.6x10^5$. These estimates indicate that the risks from worker exposure from the proposed uses of diflufenzopyr do not exceed the HED's level of concern. Since no dermal toxicological endpoint was established for diflufenzopyr, it was not necessary to estimate worker post-application exposure. The interim Worker Protection Standard (WPS) REI is 24 hours based on toxicity **category II** for primary eye and skin irritation for **dicamba**. **HED suggests confirmation of the basis for a 12-hour REI for this product.**

Dietary Exposure Estimates

Tier 1 acute and chronic dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model (DEEM™, ver 7.73), which utilizes consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). Cancer dietary exposure analysis was not conducted since diflufenzopyr was classified as "not likely" to be a human carcinogen.

The acute dietary exposure assessment was performed for females 13-50 years old using tolerance level residues (livestock) and total residues of concern (plants; parent and metabolites). No appropriate dietary endpoint for the general U.S. population (including infants and children) was chosen by the HIARC. The chronic dietary exposure analysis was performed for the general U.S. population and all population subgroups using tolerance level residues (livestock) and total residues of concern (plants; parent and metabolites). For plant commodities, the residues of concern for tolerance purposes differ from the residues of concern for risk assessment purposes. Therefore, the total residues of concern (parent and metabolites) used in dietary exposure assessment were determined from the submitted residue field trial studies (Memo, J. Tyler; 12/05/01; D279534). For ruminant commodities, recommended tolerance levels were used. Default DEEM™ concentration factors and 100% crop treated information was used for all commodities in both the acute and chronic analyses. For acute and chronic dietary risk estimates, HED's level of concern is >100% aPAD and cPAD, respectively. The results of the acute analysis indicate that the estimated acute dietary risks associated with the registered and proposed uses of diflufenzopyr do not exceed HED's level of concern for females 13-50 years old (4% of the aPAD). The results of the analysis indicate that the estimated chronic dietary risks associated with the registered and proposed uses of diflufenzopyr do not exceed HED's level of concern for the general U.S. population (9% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-6 years old at 32% of the cPAD.

Drinking Water

Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of diflufenzopyr levels in surface and ground water were made using Tier 1 models. Tier 1 models represent the most conservative estimates of potential residues in drinking water. The estimated environmental concentration (EEC) for groundwater [using SCI-GROW (Screening Concentration in Ground Water) model] is 0.006 ppb. The EECs for surface water [using Generic Estimated Environmental Concentration (GENEEC) model] were 3.80 and 1.95 for the peak (acute) and chronic (56-day average), respectively. HED interim policy allows the 56-day GENEEC value to be divided by an adjustment factor of 3 to obtain a value for chronic risk assessment calculations. Therefore, a surface water value of **0.65 ppb** was used for chronic risk assessment. Drinking water levels of comparison (DWLOCs) for acute and chronic dietary risk from drinking water were calculated. All the EEC values are less than the lowest DWLOC value of 1800 (specifically for the "children 1-6 years old" subpopulations) determined for the acute and chronic scenarios, and, therefore, do not exceed HED's level of concern.

Exposure Scenarios and Risk Conclusions

For the proposed uses on sweet corn, pop corn and grass, human health risk assessments were conducted for the following scenarios: acute and chronic dietary exposures (food only), aggregate acute and chronic exposures (food and water), and short- and intermediate-term occupational exposures. Other scenarios were not evaluated for diflufenzopyr because there are no registered or proposed residential uses, diflufenzopyr is not carcinogenic, and long-term occupational exposures are not expected. **All exposure estimates associated with the proposed uses of diflufenzopyr do not exceed HED's level of concern for the general U.S. population or any population subgroups.**

Recommendation for Tolerances and Registration

Provided revised Sections B and F, confirmation of the basis for the 12- hour REI, and an **adequate analytical enforcement method for livestock commodities** (including ILV and radiovalidation) are submitted, the available toxicological and residue chemistry databases support a ***conditional registration*** and the following:

permanent tolerances for residues of diflufenzopyr and its metabolites convertible to M1, expressed as diflufenzopyr, in/on:

corn, sweet, forage	0.05 ppm
corn, sweet, fresh	0.05 ppm
corn, sweet, stover	0.05 ppm
corn, pop, grain	0.05 ppm
corn, pop, stover	0.05 ppm
grass, forage	22 ppm
grass, hay	7.0 ppm

time-limited tolerances for residues of diflufenzopyr and its metabolites convertible to M1, and free and acid-released M19, expressed as diflufenzopyr, in:

meat*	0.60 ppm
kidney*	4.0 ppm
meat by-products (except kidney)*	0.50 ppm
fat*	0.30 ppm
milk	3.0 ppm

* of cattle, goat, hog, horse, and sheep

The registration should be conditional upon submission of an adequate livestock feeding study.

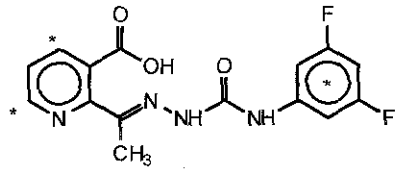
NOTE TO RD: The appropriate tolerance expressions to be included in 40 CFR §180.549(a) are 1) for corn and grass: "diflufenzopyr, 2-(1-[([3,5-difluorophenylamino] carbonyl)hydrazono]ethyl)-3-pyridinecarboxylic acid, and its metabolites convertible to 8-methylpyrido[2,3-d]pyridazin-5(6H)-one, expressed as diflufenzopyr, in/on..." and 2) for livestock commodities: "diflufenzopyr, 2-(1-[([3,5-difluorophenylamino] carbonyl)hydrazono]ethyl)-3-pyridinecarboxylic acid, its metabolites convertible to 8-methylpyrido[2,3-d]pyridazin-5(6H)-one, and free and acid-released 8-hydroxymethylpyrido[2,3-d] pyridazine-2,5(1H,6H)-dione, expressed as diflufenzopyr, in/on..."

2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

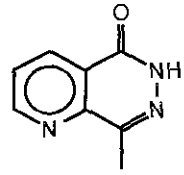
2.1. Identification of Active Ingredient

Chemical Name:	2-(1-[([3,5-Difluorophenylamino]carbonyl)-hydrazono]ethyl)-3-pyridinecarboxylic acid
Common Name:	Diflufenzopyr
Chemical Class:	Semicarbazones
Chemical Type:	Herbicide
Trade Name:	Distinct®
Mode of Action:	Inhibition of the polar transport of naturally occurring auxin (indoleacetic acid, or IAA) and synthetic auxin-like compounds (e.g., dicamba).
PC Code Numbers:	005107 and 005108
CAS Registry No.:	109293-97-2
Empirical Formula:	$C_{15}H_{12}F_2N_4O_3$
Molecular Weight:	334.3

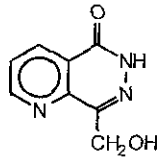
2.2. Structural Formulae



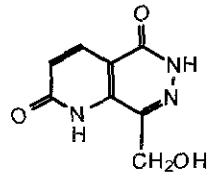
diflufenzopyr



M1



M10



M19

2.3. Physical and Chemical Properties

Product chemistry data for the diflufenzopyr technical product were reviewed (Memos, S. Mathur, 2/4/97, A. Smith, 1/14/98, H. Podall, 4/2/98, Registration Division). These reviews concluded that the available product chemistry data were adequate to fulfill the requirements for technical diflufenzopyr.

Appearance:	Off-white, odorless powder-solid at 26 °C
Vapor Pressure:	$<1 \times 10^{-7}$ mm Hg at 20°C & 25°C
Water Solubility:	pH 5: 63 ± 13 ppm; pH 7: 5850 ± 98 ppm; pH 9: 10546 ± 131 ppm
Partition Coefficient (Octanol/Water):	pH 5: $K_{OW} = 2.76$; pH 7: $K_{OW} = 0.34$; pH 9: $K_{OW} = 0.19$
Melting Point Range:	135.5 °C/155 °C (dec)
Relative Density:	0.24 g/mL at 25°C

Diflufenzopyr is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

3.0. HAZARD CHARACTERIZATION

A complete hazard characterization is presented in the Section 3 risk assessment for the use of diflufenzopyr on field corn (Memo, W. Dykstra et al., 11/17/98; D238413). For purposes of clarity, the hazard characterization and response assessment are summarized below.

3.1. Hazard Characterization and Dose Response Assessment

On September 24, 1998, the HED HIARC evaluated the toxicology database of diflufenzopyr, established a RfD, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to diflufenzopyr as required by FQPA (Memo, W. Dykstra 10/6/98; HED Doc. No. 012894).

Diflufenzopyr is of low acute toxicity (Toxicity Category III or IV for all routes of exposure). The technical is not a dermal sensitizer, but the formulation, Distinct®, is a dermal sensitizer. Acute and subchronic neurotoxicity studies did not display any evidence of neurotoxic effects and the NOAELs were 2000 mg/kg and 1000 mg/kg/day for each study, respectively, which were the limit doses. Developmental NOAELs and LOAELs for rats and rabbits occurred at either the same dose levels or were above the NOAELs and LOAELs for maternal toxicity. The NOAEL for pup effects in the 2-generation rats reproduction study occurred at dose levels above the NOAEL for parental findings. Based on these data, the HED Hazard Identification Assessment Review Committee (HIARC) determined that there was no evidence of increased sensitivity for infants and children.

Diflufenzopyr was not carcinogenic in mice following dietary administration at the limit dose (7000 ppm) to CD-1 mice for 18 months or to Wistar rats at the limit dose (20,000 ppm) for 2-years. Dogs were the most sensitive species tested. The NOAEL for compensated hemolytic anemia was 26 mg/kg/day and the LOAEL was 299 mg/kg/day in the diet in the 52-week dog study. The metabolites isolated from rat urine in the rat metabolism study were comparable to those found in corn. Most of the radiolabeled diflufenzopyr remained unchanged. Tissue levels of radioactivity in the rat were below 3% of the total radioactivity.

FQPA Considerations

The FQPA SFC determined that the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be reduced to 1x (Memo, B. Tarplee 10/5/98; HED Doc. No.012904). The rationale for removal of the FQPA SF was based on the following: 1) the toxicology database is complete; 2) there is no indication of increased susceptibility of rats and rabbits fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity data; 3) unrefined (Tier 1) dietary exposure estimates are protective since they will exaggerate dietary exposure estimates; 4) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and 5) there are currently no registered residential uses for diflufenzopyr.

Cancer

In accordance with the *1996 Proposed Guidelines for Carcinogenicity Risk Assessments*, diflufenzopyr was classified as **"not likely"** to be a human carcinogen. This classification is based on the lack of evidence of carcinogenicity in mice and rats when tested at doses that were judged to be adequate to assess carcinogenicity.

Table 1 summarizes the toxicological doses and endpoints for diflufenzopyr for use in human risk assessment. HED has revised the definitions used in its human health risk assessments to describe occupational and residential exposure durations (Memo, M. Stasikowski, June 4, 2001, "Changes in the Definition of Exposure Durations for Occupational/Residential Risk Assessments Performed in the Health Effects Division"). The new exposure durations are as follows: 1) short-term, defined as lasting from 1 day to 1 month; 2) intermediate-term, defined as lasting from 1 to 6 months; 3) long-term, defined as lasting longer than 6 months. The RAB1 toxicologists determined that the toxicity endpoint (subchronic feeding study in the dog) originally selected for the short- (1-7 days) and intermediate-term (7 days-3 months) inhalation endpoints is also applicable for the new short- and intermediate exposure duration definitions.

Table 1. Summary of Toxicological Endpoints for Use in Human Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary Females 13-50 years old	NOAEL = 100 mg/kg/day UF = 100 **Acute RfD = 1.0** mg/kg/day	FQPA SF = **1x** **aPAD** = acute RfD / FQPA SF = **1.0** mg/kg/day	Rabbit Developmental Study. LOAEL = 300 mg/kg/day based on extra ribs and other skeletal variations in the rabbit developmental study. These effects can occur from a single dose and females 13-50 are the population subgroup of concern. The developmental findings occurred at a level of severe maternal toxicity.
Acute Dietary general population	NOAEL = None UF = None Acute RfD = None	An appropriate endpoint attributable to a single exposure for this population subgroup was not identified in the oral toxicity studies including the maternal effects in rat and rabbit developmental studies.	
Chronic Dietary all populations	NOAEL= 26 mg/kg/day UF =100 Chronic RfD = 0.26 mg/kg/day	FQPA SF = **1x** **cPAD** = chronic RfD / FQPA SF = **0.26** mg/kg/day	52-week Dog Feeding Study. LOAEL = 299 mg/kg/day based on compensated hemolytic anemia in both sexes of dogs
Short-Term Dermal (1 to 7 days) (Occupational)	oral study NOAEL= None	No dermal or systemic toxicity was seen at 1000 mg/kg/day in the 21-day dermal toxicity study in rabbits. Therefore, this risk assessment is not required.	
Intermediate-Term Dermal (1 week to several months) (Occupational)	oral study NOAEL= None	No dermal or systemic toxicity was seen at 1000 mg/kg/day in the 21-day dermal toxicity study in rabbits. Therefore, this risk assessment is not required.	

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Long-Term Dermal (several months to lifetime) (Occupational)	oral study NOAEL= None	The use pattern does not indicate a concern for potential dermal exposure. Therefore, this risk assessment is not required.	
Short-Term Inhalation (1 to 7 days) (Occupational)	oral study NOAEL = 58 mg/kg/day (inhalation absorption factor = 100%)	LOC for MOE = 100 (Occupational)	Subchronic feeding- dog. LOAEL = 403 mg/kg/day based on the occurrence of erythroid hyperplasia in the bone marrow, extramedullary hemopoiesis in the liver, and hemosiderin deposits in Kupffer cells.
Intermediate-Term Inhalation (1 week to several months) (Occupational)	oral study NOAEL =58 mg/kg/day (inhalation absorption factor = 100%)	LOC for MOE = 100 (Occupational)	Subchronic feeding- dog. LOAEL = 403 mg/kg/day based on the occurrence of erythroid hyperplasia in the bone marrow, extramedullary hemopoiesis in the liver, and hemosiderin deposits in Kupffer cells.
Long-Term Inhalation (several months to lifetime) (Occupational)	inhalation (or oral) study NOAEL= None (inhalation absorption factor = 100%)	The use pattern does not indicate a concern for potential exposure via this route. Therefore, this risk assessment is not required.	
Cancer (oral, dermal, inhalation)	None	Q* = None	In accordance with the *1996 Proposed Guidelines for Carcinogenicity Risk Assessments*, diflufenzopyr was classified as **"Not Likely"** to be a human carcinogen. This classification is based on the lack of evidence of carcinogenicity in mice and rats when tested at doses that were judged to be adequate to assess carcinogenicity.

1. UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, cPAD = chronic population adjusted dose, RfD = reference dose, MOE = margin of exposure, LOC = level of concern.

3.2. Endocrine Disruption

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

effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

4.0. EXPOSURE ASSESSMENT

4.1. Summary of Registered and Proposed Uses

The petitioner provided a proposed label for Distinct® Herbicide (EPA Reg. No. 7969-150), a selective herbicide containing diflufenzopyr and dicamba as active ingredients. This product contains 20% diflufenzopyr or 0.20 lb. ae/ lb. product. Distinct® is proposed for use on pop corn, sweet corn and pastures for the control of various weeds. Surfactants (0.25% v/v) should be added to the postemergence finished spray. The application volume is 3-50 gal/acre by ground equipment. Rotational crops can be planted 120 days after the last application of Distinct®. However, in the event of crop failure, corn can be planted 7 or more days after application. Table 2 lists a summary of the proposed use patterns.

Table 2. Summary of Proposed Use Patterns for Diflufenzopyr on Pasture and Rangeland Grasses, Pop corn and Sweet Corn.

Commodity	Max. Appl. Rate (lb. diflufenzopyr/A)		Max. No. of Appl.	RTI[1] (days)	PHI[2] (days)	Comments/Restrictions
	Per Application	Per Season				
Pasture and Rangeland Grass	0.1	0.1	2	14	0	Areas treated with Distinct® can be grazed or harvested for feed immediately after application.
Pop corn	0.1	0.125	2	14	72 - stover	Do not apply without first verifying the selectivity of Distinct® on specific hybrid.
Sweet Corn	0.05	0.075	2	14	32 - forage and fresh 72 - stover	Do not apply without first verifying the selectivity of Distinct® on specific hybrid. Do not use on sweet corn grown for seed.

1. RTI = Retreatment Interval
2. PHI = Preharvest Interval

NOTE TO RD: There is a discrepancy between the submitted Section B and Supplemental Label concerning the proposed maximum single and seasonal application rates on pop corn and grass. The Section F reads "Pasture and popcorn have a maximum single application rate of 8 ounces

per acre with a maximum seasonal use of 10 ounces per acre." The Supplemental Label reads 1) for pasture and rangeland "Do not exceed 8 ounces of Distinct® per acre per calendar year" and 2) for pop corn "Apply 4 to 6 ounces of Distinct® per acre....." and no maximum seasonal application rate is specified. Per personal communication with BASF, the appropriate maximum single and seasonal application rates for pop corn are 8 oz. Distinct®/A (0.1 lb. diflufenzopyr/A) and 10 oz. Distinct®/A (0.125 lb. diflufenzopyr/A), respectively; and the appropriate maximum seasonal application rate on grass is 8 oz. Distinct®/A (0.1 lb. diflufenzopyr/A) (personal communication between J. Tyler and M. Graben; 11/2/01). These proposed application rates are reflected in this document.

The proposed use directions for sweet corn, pop corn, and pasture and rangeland grasses are adequate and are supported by the submitted residue data. In the absence of adequate rotational crop data, **the label should be revised to include a 30-day label restriction prohibiting rotation to any non-labeled crop.**

4.2. Dietary Exposure/Risk Pathway

4.2.1. Residue Profile

Background

IR-4, has submitted an application for tolerances for residues of the herbicide diflufenzopyr in/on pastures, pop corn, and sweet corn. Section F of the current petition proposes the establishment of the following permanent tolerances for residues of diflufenzopyr and its metabolites convertible to M1:

Corn, sweet, forage	0.05 ppm
Corn, sweet, fresh	0.05 ppm
Corn, sweet, stover	0.05 ppm
Corn, pop, stover	0.05 ppm

Crop Group 17, Grass forage, fodder, and hay:

Forage	3.0 ppm
Hay	1.5 ppm

Permanent tolerances are currently established for the combined residues of diflufenzopyr and its metabolites convertible to M1 in/on field corn forage, grain, and stover at 0.05 ppm [40 CFR §180.549(a)]. The residue chemistry data submitted in support of PP#0E6185 were reviewed in the HED memorandum dated 12/5/01 (Memo, J. Tyler; D279534).

Nature of the Residue

Plants: The nature of the residue in field corn is understood. An acceptable metabolism study using [^{14}C]-diflufenzopyr labeled separately in the pyridine and phenyl rings has been performed

in field corn. The urea bond is cleaved to yield metabolites containing a new bicyclic ring system. No diflufenzopyr was detected in any of the corn matrices; metabolites comprising >10% of the total radioactive residues (TRR) include M1 (8-methylpyrido[2,3-d]pyridazin-5(6H)-one), M10 (8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazone) and its glucose conjugate, and M9 (8-methylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione in forage and fodder, and 6-14% TRR lignin was found in fodder. Corn grain contained 3-4 discrete unknowns, all at <10% TRR or <0.05 ppm each.

The HED Metabolism Assessment Review Committee (MARC) met on 9/28/98 to discuss the toxicological significance of metabolites of diflufenzopyr. The Committee concluded that diflufenzopyr and metabolites convertible to metabolite M1 need to be included in the tolerance expression. Furthermore, for dietary exposure assessment, metabolite M10 should be included in addition to diflufenzopyr and metabolites convertible to M1 (Decision memo, L. Cheng, 10/29/98; No DP Barcode).

Livestock: The nature of the residue in ruminants and poultry is understood. The HED MARC met on 9/28/98 to discuss the metabolism of diflufenzopyr in livestock.

Ruminants: An acceptable metabolism study using [^{14}C]-diflufenzopyr labeled separately in the pyridine and phenyl ring has been performed in goats. Based on the metabolites identified, the metabolism of diflufenzopyr in ruminants is similar to that in corn. Major metabolites include M1, M5 (6-((3,5-difluorophenylcarbamoyl-8-methyl-pyrido[2,3-d]-5-pyridazinone) and M19 (8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione). A substantial amount (8-50%) of diflufenzopyr was also found in milk, kidney, and liver. The Committee concluded if any livestock feeding studies are conducted in the future, analyses should be done for parent, metabolites convertible to M1, and free and acid-released M19 (Decision memo, L. Cheng, 10/29/98; No DP Barcode).

HED notes that the new use of diflufenzopyr on pasture and rangeland grasses significantly increases the calculated ruminant theoretical dietary burden (TDB) to 53 ppm (See section entitled Magnitude of Residue in Meat, Milk, Poultry, Eggs). Using the new diet, the submitted ruminant metabolism studies were performed at 0.19x the TDB. It is possible that more metabolites could be identified if the metabolism studies are performed at a higher dose. However, as liver was the only ruminant commodity that had a high amount of minor unidentified bands and liver is not a major human consumption item, **HED concludes that additional ruminant metabolism data are not necessary *at this time.*** If new uses are submitted which will significantly increase the ruminant TDB, then additional ruminant metabolism data performed at a higher dose may be required.

Poultry: An acceptable metabolism study using [^{14}C]-diflufenzopyr labeled in the pyridine or phenyl ring has been performed in hens. Based on the metabolism results, diflufenzopyr was not detected in poultry, and M1 was the only significant metabolite identified, and in egg white only. The Committee commented that since the dose administered in the poultry metabolism studies

had been at such an exaggerated level (250x), transfer of secondary residues to poultry would not be expected (Decision memo, L. Cheng, 10/29/98, No DP Barcode).

Residue Analytical Methods

Plants: An adequate enforcement method (Method D9709) is available for enforcement of the proposed tolerances. The reported method limits of detection and quantitation (LOD and LOQ) are 0.02 ppm and 0.05 ppm, respectively. HED has conducted a successful petition method validation (PMV) of Method D9709 (Memo, J. Tyler, 10/31/01; D278522). The method will be forwarded to the Food and Drug Administration (FDA) for inclusion in Pesticide Analytical Method Volume (PAM) Vol. II.

For the measurement of the metabolite M10, Method D9702 (Draft Method for Determination of 8-Hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazone Residues in Corn RAC, and Corn Process Fractions by LC/MS, S. Abdel-Baky and S. A. Baumann, 8/11/97) was used in the submitted sweet corn residue field trial study. The report states a LOQ of 0.05 ppm and an LOD of 0.02 ppm.

Livestock: No analytical method has been submitted for livestock. **Based on the calculated TDB and the results of the ruminant metabolism study, tolerances for residues of diflufenzopyr and a ruminant feeding study are required. An adequate analytical enforcement method (including ILV and radiovalidation data) should be submitted.**

Multiresidue Method (MRM)

The results of multiresidue testing of diflufenzopyr and its metabolites M1 and M10 have been forwarded to the FDA for inclusion in PAM Vol. I (Memo, J. Tyler; 10/11/01; D278336). Neither diflufenzopyr nor M1 was detected through Protocol C, however, M10 was detected through Protocol C.

Storage Stability Data

The results of a freezer storage stability study were submitted in support of the use of diflufenzopyr on field corn (PP#7F4848) and reviewed by HED (Memo, J. Tyler, 10/11/01; D254989). The previously submitted storage stability data indicate that residues of diflufenzopyr (M1 and M10 residues) are relatively stable under frozen storage conditions in/on fortified samples of field corn forage, grain and fodder for up to 24 months. The submitted storage stability data are adequate to support the storage conditions and intervals of the samples from the sweet corn, and pasture and rangeland grasses field trial studies (24 months and 8 months, respectively).

Magnitude of Residues in Plants

Sweet Corn: The submitted field trials are adequate to support the proposed tolerances for residues of diflufenzopyr in/on sweet corn forage, ears, and fodder. A total of 9 field residue trials were conducted in Regions 1 (1 trial), 2 (1 trial), 3 (1 trial), 5 (3 trials), 6 (1 trial), 10 (1 trial) and 12 (1 trial). The locations of the field trials do not match that required for sweet corn: 12 trials conducted in Regions 1 (2 trials), 2 (1 trial), 3 (1 trial), 5 (5 trials), 10 (1 trial), 11 (1 trial) and 12 (1 trial). However, the petitioner previously submitted the results of 24 field corn residue trials conducted in 1995 and 1996 (Memo, L. Cheng, 11/2/98; D239675). In that study, the field corn samples were treated with 2 applications of Distinct® at 0.1 lb. diflufenzopyr/A for a total of 0.2 lb. diflufenzopyr/A (2.7x proposed maximum sweet corn application rate). The results showed that residues of diflufenzopyr and metabolites convertible to M1 resulting from proposed use would not exceed 0.05 ppm. HED can generally translate field corn forage and stover data to sweet corn. Therefore, additional sweet corn residue trials will not be required. Based on the available data, the following tolerances for residues of the herbicide diflufenzopyr and its metabolites convertible to M1, expressed as diflufenzopyr, are appropriate: "corn, sweet, forage" at 0.05 ppm; "corn, sweet, fresh" at 0.05 ppm; and "corn, sweet, stover" at 0.05 ppm. For dietary exposure analysis, a residue value of 0.10 ppm should be used to estimate combined residues of diflufenzopyr, M1 and M10 in sweet corn.

Pop Corn: No pop corn field trial data were submitted in support of this petition. HED can generally translate field corn grain/stover data to pop corn grain/stover provided the use patterns are the same and there is adequate field corn data. As mentioned previously, adequate field corn residue data have been submitted by the petitioner. In addition, the proposed use pattern for pop corn is the same as the use pattern for field corn: maximum of 2 applications/season; maximum single application of 0.1 lb. diflufenzopyr/A with a maximum seasonal application rate of 0.125 lb. diflufenzopyr/A; 72-day preharvest interval (PHI) for grain and stover. Therefore, pop corn field trial data will not be required. Based on the available data, the following tolerances for residues of the herbicide diflufenzopyr and its metabolites convertible to M1, expressed as diflufenzopyr, are appropriate: "corn, pop, grain" at 0.05 ppm and "corn, pop, stover" at 0.05 ppm. **A revised Section F should be submitted.** For dietary exposure analysis, a residue value of 0.06 ppm should be used to estimate combined residues of diflufenzopyr, M1 and M10 in pop corn.

Pasture and Rangeland Grasses: The submitted field residue trials are adequate and indicate that residues of diflufenzopyr will not exceed 22 ppm in forage and 7.0 ppm in hay when treated with a single application of 0.1 lbs. diflufenzopyr/A (1x). Therefore, based on the available field trial data, the following tolerances for residues of diflufenzopyr and its metabolites convertible to M1 are appropriate: "grass, forage" at 22 ppm and "grass, hay" at 7.0 ppm. **A revised Section F should be submitted.**

Magnitude of Residues in Processed Commodities

As there are no processed commodities associated with sweet corn, pop corn or pasture and rangeland grasses, processing studies not are required to support the subject petition.

Magnitude of Residues in Meat, Milk, Poultry and Eggs (MMPE)

No livestock feeding studies have been submitted in support of this petition. There are livestock feed items associated with the registered and proposed uses of diflufenzopyr.

Ruminants: Based on the calculated TDB (see Table 3) and the results of the ruminant metabolism study, **tolerances for residues of diflufenzopyr in ruminant commodities and a ruminant feeding study are required.** The study should be performed at 1x, 3x, and 10x the calculated TDB of 53 ppm. In order to account for possible dietary exposure to diflufenzopyr residues in ruminant commodities, appropriate tolerances were calculated by extrapolating the results of the ruminant metabolism study (0.19x TDB) to 10x the TDB. A level of 10x was chosen rather than 1x to account for differences in the species and durations of dosing in ruminant feeding (cow) and metabolism (goat) studies. If those residues are extrapolated down to a 10x feeding level (the highest feeding level that would be required in a feeding study), expected residues would be 0.52 ppm in muscle (using TRR), 3.2 ppm in kidney, 0.44 ppm in liver, 2.6 ppm in milk, and 0.26 ppm in fat. **Provided an adequate analytical enforcement method (including ILV and radiovalidation) is submitted**, the following time-limited tolerances for residues of diflufenzopyr and its metabolites convertible to M1, and free and acid-released M19, expressed as diflufenzopyr, in ruminant commodities (cattle, goats, hogs, horses and sheep) are appropriate: meat at 0.60 ppm, kidney at 4.0 ppm, meat by-products (except kidney) at 0.50 ppm, fat at 0.30 ppm, and milk at 3.0 ppm. **A revised Section F should be submitted.**

Poultry: The petitioner previously submitted the results of a radiolabelled poultry metabolism study. Based on the current tolerance of 0.05 ppm on field corn grain that comprises 80% of the diet, the calculated TDB would be 0.04 ppm (see Table 3). Therefore, the 10 ppm dose in the poultry metabolism study would be equivalent to 250x the TDB. HED previously concluded that based on the exaggerated dose administered in the poultry metabolism study (250x), transfer of secondary residues of diflufenzopyr to poultry and eggs are not expected (Memo, L. Cheng, 11/2/98; D239675). Therefore, tolerances for poultry commodities are not needed.

Table 3. Estimation (based on U.S. feeding practices as reflected in Table 1 of OPPTS 860.1000) of the TDB[1] of diflufenzopyr to livestock.

Feed Commodity	Proposed Tolerance, ppm[3]	% Dry Matter	% of Diet	Burden, ppm [2]
Beef and Dairy Cattle				
Grass (pasture & rangeland), forage	22	25	60	53
Field corn, grain	0.05	88	40	0.023
		TOTAL		53
Poultry[4]				
Field corn, grain	0.05		80	0.04
		TOTAL		0.04

1. TDB = Theoretical Dietary Burden.
2. Burden = [tolerance / % dry matter (if cattle)] x % of diet).
3. Recommended tolerance levels were used all for all commodities.
4. Poultry feed items are not corrected for % dry matter.

Confined Accumulation in Rotational Crops

The results of a confined accumulation in rotational crop study were submitted in support of the use of diflufenzopyr on field corn (PP#7F4848). In a memo dated 11/2/98, HED concluded that the "confined" rotational crop study is not acceptable since diflufenzopyr was not applied directly to the soil before planting the rotated crops (Memo, L. Cheng; D239675). Furthermore, the TRR's in the rotational crops were fractionated among several organic solvents without identification of the metabolites. HED recommended that a new confined rotational crop study be submitted along with a revised Section B be submitted to impose a 1-year label restriction prohibiting rotation to any crop other than field corn. However, in a memo dated 11/23/98, RD requested that the registrant be given the option to submit either a new confined rotational crop study or limited field rotational crop study to fulfill the rotational crop data gap (Memo, J. Miller, no DP Barcode). The registrant would need to submit trials for 3 representative crops (2 sites for each crop): a small grain crop, a root crop, and a leafy vegetable crop. In a memo dated 1/13/99, HED concurred with RD's request (Memo, O. Odiott, no DP Barcode).

Field Accumulation in Rotational Crops

In response to the rotational crop data gap, BASF submitted the results of a limited field trial. The results of this study were reviewed by HED (Memo, J. Tyler, 10/11/01; D254989). The results of the limited field rotational crop study are acceptable. Residues of diflufenzopyr were less than the method's LOQ of 0.05 ppm in/on all treated representative rotational crops (radish roots and tops, lettuce, and winter wheat grain, forage, and hay) from the 30-day PBI. Therefore, no tolerances on rotational crops are needed. However, as residues were found at a 30-day PBI in the previously submitted confined rotational crop study, a PBI is required. **The petitioner should submit a revised Section B to include a 30-day PBI restriction.**

International Harmonization of Tolerances

There are currently no established Codex, Mexican maximum residue limits (MRLs) for residues of diflufenzopyr in/on plant or livestock commodities. A Canadian MRL of 0.05 ppm for residues of diflufenzopyr, expressed as the parent and metabolites convertible to M1, has been established for corn. No compatibility issues exist with regard to the existing and proposed U.S. tolerances.

4.2.2. Dietary Exposure Analyses

Diflufenzopyr acute and chronic dietary exposure assessments were conducted using the DEEM™ software Version 7.73, which incorporates consumption data from USDA's CSFII, 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and, therefore, represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM™ software. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

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

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups from the general U.S. population which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations

having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years old). Therefore, the population subgroups listed in Table 4 include those subgroups having sufficient numbers of survey respondents in the CSFII food consumption survey.

4.2.2.1. Acute Dietary Exposure Analysis

The Tier 1 acute dietary exposure assessment was performed for females 13-50 years old using tolerance level residues (livestock) and total residues of concern (plants; parent and metabolites) (Memo, J. Tyler; 12/12/01; D278338). For plant commodities, the residues of concern for tolerance purposes differ from the residues of concern for risk assessment purposes. Therefore, the total residues of concern (parent and metabolites) used in dietary exposure assessment were determined from the submitted residue field trial studies (Memo, J. Tyler; 12/05/01; D279534). For ruminant commodities, recommended tolerance levels were used. Default DEEM™ concentration factors and 100% crop treated information was used for all commodities. No appropriate dietary endpoint for the general U.S. population (including infants and children) was chosen by the HIARC.

Acute dietary exposure estimate for females 13-50 years old is presented in Table 4. For acute dietary risk estimates, HED's level of concern is >100% aPAD. The results of the analysis indicate that the estimated acute dietary risks associated with the registered and proposed uses of diflufenzopyr do not exceed HED's level of concern for females 13-50 years old.

4.2.2.2. Chronic Dietary Exposure Analysis

The chronic dietary exposure analysis was performed the general U.S. population and all population subgroups using tolerance level residues (livestock) and total residues of concern (plants; parent and metabolites). For plant commodities, the residues of concern for tolerance purposes differ from the residues of concern for risk assessment purposes. Therefore, the total residues of concern (parent and metabolites) used in dietary exposure assessment were determined from the submitted residue field trial studies (Memo, J. Tyler; 12/05/01; D279534) For ruminant commodities, recommended tolerance levels were used. Default DEEM™ concentration factors and 100% crop treated information was used for all commodities.

Chronic dietary exposure estimates for the general U.S. population and all population subgroups are presented in Table 4. For chronic dietary risk estimates, HED's level of concern is >100% cPAD. The results of the analysis indicate that the estimated chronic dietary risks associated with the registered and proposed uses of diflufenzopyr do not exceed HED's level of concern for the general U.S. population and all population subgroups.

Table 4. Summary of Dietary Exposure and Risk for Diflufenzopyr.

Population Subgroup	Acute Dietary [1]		Chronic Dietary [2]	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	NA	NA	0.022356	9
All Infants (< 1 year old)			0.036425	14
Children 1-6 years old			0.082228	32
Children 7-12 years old			0.042522	16
Females 13-50 years old	0.038926	4	0.012571	5
Males 13-19 years old	NA	NA	0.024247	9
Males 20+ years old			0.011552	4
Seniors 55+ years old			0.011438	4

1. Acute dietary endpoint applies to females 13-50 years old only. No appropriate acute dietary endpoint was chosen by the HIARC for the general U.S. population (including infants and children).
2. Chronic dietary endpoint applies to general U.S. population and all population subgroups.

4.2.2.3. Cancer Dietary Exposure Analysis

In accordance with the *1996 Proposed Guidelines for Carcinogenicity Risk Assessments*, diflufenzopyr was classified as **"Not Likely"** to be a human carcinogen. This classification is based on the lack of evidence of carcinogenicity in mice and rats when tested at doses that were judged to be adequate to assess carcinogenicity. Therefore, a cancer dietary exposure assessment was not performed.

4.3. Water Exposure/Risk Pathway

Environmental Fate Assessment

Based on information in an EFED memo, diflufenzopyr is not very stable and mobile (Memo, K. McCormick and B. Grimm, 10/6/98; D239666). Based upon proposed uses, fate characteristics, and model predictions, EFED does not expect diflufenzopyr to reach drinking water resources in significant quantities.

Ground Water EECs

The groundwater EECs were estimated with SCI-GROW II. Table 5 lists the ground water EECs.

Note: From SCI-GROW, EFED provides one concentration value to be used for ground water assessments. The value from SCI-GROW is considered an upper bound concentration estimate.

Because residues of pesticides in ground water do not fluctuate as widely as in surface water, the upper bound estimate is considered adequate for screening-level purposes.

Table 5. Diflufenzopyr (Parent) Ground Water EECs.

Crop	Application Rate: 0.12 lb ai/A corn
	modeling (ppb)
corn: acute (peak)	0.006
corn: chronic	0.006

Surface Water EECs Environmental Fate Assessment

The surface water EECs were estimated with GENEEC. GENEEC is based on a regression approach which relates the concentrations found in ground water from Prospective Ground Water studies to aerobic soil metabolism rate and soil-water partitioning properties of the chemical. Table 6 lists the surface water EECs.

Table 6. Surface Water EECs Reflecting the Application Rates: 0.12 lb ai/A in corn.

Crop	Diflufenzopyr (ppb)
corn: acute (peak)	3.80
corn: chronic (56-day average)	1.95

HED interim policy allows the 56-day GENEEC value to be divided by an adjustment factor of 3 to obtain a value for chronic risk assessment calculations. Therefore, a surface water value of **0.65 ppb** will be used for chronic risk assessment.

4.4. Residential Exposure/Risk Pathway

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

4.4.1. Other (Spray Drift, Farm Worker Kids, etc.)

This assessment for diflufenzopyr reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its

guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

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

5.0. AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

For the proposed uses on sweet corn, pop corn and grass, aggregate exposure risk assessments were performed for the following scenarios: acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short- and intermediate-term and cancer aggregate risk assessments were not performed because there are no registered or proposed residential non-food uses, and diflufenzopyr is not carcinogenic, respectively.

Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate the acute DWLOCs, the acute dietary exposure estimates from food (from DEEM™) were subtracted from the aPAD value to obtain the allowable acute exposure to diflufenzopyr in drinking water. To calculate the chronic DWLOCs, the chronic dietary exposure estimates from food (from DEEM™) were subtracted from the cPAD value to obtain the allowable average exposure to diflufenzopyr in drinking water. DWLOCs were then calculated using the standard

body weights and drinking water consumption figures: 70 kg/2L (adult male and U.S. population), 60 kg/2L (adult female), and 10 kg/1L (infant & children).

DWLOCs are compared to EECs for a pesticide in surface water and ground water. If the DWLOCs are greater than the EECs, HED concludes with reasonable certainty that estimates of aggregate risks are below HED's level of concern.

5.1. Acute Aggregate Risk Assessment

The Tier 1 (conservative, deterministic assessment tolerance level residues (livestock) and total residues of concern (plants; parent and metabolites) and 100% CT information) acute dietary exposure estimates for females 13-50 years old accounted for 4% of the aPAD. The EECs generated by EFED are less than HED's calculated chronic DWLOCs for acute exposure to diflufenzopyr in drinking water. Therefore, the acute aggregate risk associated with the proposed use of diflufenzopyr does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 7 summarizes the chronic aggregate exposure estimates to diflufenzopyr residues.

Table 7. Acute Aggregate Exposures to Diflufenzopyr Residues.

Population Subgroup[1]	aPAD, mg/kg/day	Acute Food Exposure, mg/kg/day	Maximum Acute Water Exposure [2], mg/kg/day	Ground Water EEC [3], ppb	Surface Water EEC [3], ppb	Acute DWLOC [4], (μg/L)
Females (13-50 years old)	1.0	0.038926	0.961074	0.006	3.80	29000

1. Acute dietary endpoint applies to females 13-50 years old. No appropriate acute dietary endpoint was chosen by the HIARC for the general U.S. population (including infants and children).
2. Maximum acute water exposure (mg/kg/day) = aPAD (mg/kg/day) - acute food exposure from DEEM™ (mg/kg/day).
3. Ground and surface water EECs resulting from the maximum proposed application rate (0.12 lbs ai/A/season).
4. Because there are no residential uses, the acute DWLOCs were calculated as follows:

$$DWLOC\ (\mu g/L) = \frac{maximum\ water\ exposure\ (mg/kg/day)\ x\ body\ weight\ (kg)}{consumption\ (L/day)\ x\ 0.001\ mg/\mu g}$$

5.2. Chronic Aggregate Risk Assessment

The Tier 1 (conservative, deterministic assessment using tolerance level residues (livestock) and total residues of concern (plants; parent and metabolites) and 100% CT information) chronic dietary exposure estimates for the general U.S. population and all population subgroups accounted for <32% of the cPAD. The most highly exposed population subgroup was Children 1-6 years old at 32% of the cPAD. The EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to diflufenzopyr in drinking water. Therefore, the chronic aggregate risk associated with the proposed use of diflufenzopyr does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 8 summarizes the chronic aggregate exposure estimates to diflufenzopyr residues.

Table 8. Chronic Aggregate Exposures to Diflufenzopyr Residues.

Population Subgroup [1]	cPAD, mg/kg/day	Chronic Food Exposure, mg/kg/day	Maximum Chronic Water Exposure[2], mg/kg/day	Ground Water EEC [3], ppb	Surface Water EEC [3], ppb	Chronic DWLOC [4], (μg/L)
U.S. Population	0.26	0.022356	0.237644	0.006	0.65	8300
All infants (< 1 year old)	0.26	0.036425	0.223575	0.006	0.65	2200
Children (1-6 years old)	0.26	0.082228	0.177772	0.006	0.65	1800
Children (7-12 years old)	0.26	0.042522	0.217478	0.006	0.65	2200
Females (13-50 years old)	0.26	0.012571	0.247429	0.006	0.65	7400
Males (13-19 years old)	0.26	0.024247	0.235753	0.006	0.65	8300
Males (20+ years old)	0.26	0.011552	0.248448	0.006	0.65	8300
Seniors (55+ years old)	0.26	0.011438	0.248562	0.006	0.65	8700

1. Chronic dietary endpoint applies to general U.S. population and all population subgroups.
2. Maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM™ (mg/kg/day).
3. Ground and surface water EEC resulting from the maximum proposed application rate (0.12 lbs ai/A/season).
4. Because there are no residential uses, the chronic DWLOCs were calculated as follows:

$$DWLOC\ (\mu g/L) = \frac{maximum\ water\ exposure\ (mg/kg/day)\ x\ body\ weight\ (kg)}{consumption\ (L/day)\ x\ 0.001\ mg/\mu g}$$

6.0. CUMULATIVE RISK

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

EPA does not have, at this time, available data to determine whether diflufenzopyr 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 diflufenzopyr has a common mechanism of toxicity with other substances.

On this basis, the petitioner 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 diflufenzopyr shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for diflufenzopyr need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with diflufenzopyr, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf
In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized in 2002.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0. OCCUPATIONAL EXPOSURE

An occupational exposure assessment for diflufenzopyr was prepared in an HED memo dated 11/13/01 (Memo, M. Dow; D276174).

The BASF Corporation, Agricultural Products, has submitted requests for registration of Distinct® herbicide for controlling annual and perennial broad leaf weed species in pop corn, sweet corn, and pasture or rangeland. This memorandum presents HED's estimate of pesticide handler exposures and risks that might result from the proposed new uses.

Distinct® is a wettable granule herbicide that is comprised of 0.20 lb acid equivalent diflufenzopyr per pound of product and 0.50 lb acid equivalent dicamba per pound of product. The proposed new uses comprise an amendment to the EPA Registered Product No. 7969-150 which is registered for use on field corn and non-crop areas.

For pop corn and sweet corn, applications should be made by early post-emergence of weed species. For pasture or rangeland grass, applications for some weed species may be made in early Fall, prior to the first killing frost. Table 9 contains a summary of the proposed new use patterns.

Table 9. Use Pattern Summary of Proposed New Uses of Distinct® Herbicide on Pop Corn, Sweet Corn, and Pasture or Rangeland.

Formulation	Wettable Granule; diflufenzopyr 0.20 lb acid equivalent/ lb product
Use Site	Pop Corn, Sweet Corn, Pasture, Rangeland
Application Method	ground
Maximum Application Rate* **lbs. diflufenzopyr/A**	Sweet corn - 0.05 lb. diflufenzopyr/A Pop corn - 0.10 lb. diflufenzopyr/A Pasture/Range - 0.10 lb. diflufenzopyr/A **seasonal max** - 0.1 lb. diflufenzopyr/A for pasture/range; 0.125 lb. diflufenzopyr/A for pop corn; 0.075 lb. diflufenzopyr/A for sweet corn
Frequency/Timing	two application/season; 14 day interval
PHI	Sweet corn = 72 days dry grain and stover; 32 days for ears and stover. Pop corn = 72 days for grain or stover; 32 days for forage. Pasture/Range = NO PHI
REI	label lists 12 hours needs clarification see section labeled "Restricted Entry Interval"
Manufacturer	BASF Corporation

* Sweet corn max rate = 4 oz product/A = 0.25 lb product/A * 0.2 lb a.e./lb product diflufenzopyr = 0.05 lb a.e./A and Pop corn max rate = 8 oz product/A = 0.5 lb product/A * 0.2 lb a.e./lb product diflufenzopyr = 0.10 lb a.e./A
Pasture/Range max rate = 8 oz product/A = 0.5 lb product/A * 0.2 lb a.e./lb product diflufenzopyr = 0.10 lb a.e./A

7.1. Occupational Handler

According to the Reference Files System (REFS v. 2.3, 12 July 01), diflufenzopyr is registered for use on field corn. This assessment addresses the registration of diflufenzopyr on sweet corn, pop corn, and pasture/rangeland. **NOTE** that the registered product (EPA Reg. No. 7969-150) nor the proposed label amendment language (Supplemental label wjm 5-9-00 NVA 2000-04-078-0056) **do not** include directions for use in aerial application and precludes use in any irrigation system. The estimates of pesticide handler exposure are therefore limited here to a mixer/loader using open pour, dry flowable material and an applicator using open cab, ground boom equipment. No chemical specific data were available with which to assess pesticide handler exposure therefore data were used from studies contained in the PHED Surrogate Table (v1.1., 1998).

Estimates of exposure and risk were conducted for a mixer/loader and an applicator. See Table 10 for a summary of those findings.

Table 10. Estimated Exposures and Risk to Pesticide Handlers Applying Distinct® Herbicide to Sweet Corn, Pop Corn and Pasture/Rangeland.

Inhalation Unit Exposure[1] mg a.i./lb handled	Application Rate[2] lb a.i. handled/A	Units Treated[3]	Avg. Daily Dose[4] mg a.i./kg bw/day	NOAEL[5] mg a.i./kg bw/day	MOE[6]
Mixer/Loader - Dry Flowable - Open Pour					
0.00077 HC	0.10	200 A/day	$2.2X10^{-4}$	58	260,000
Applicator - Ground Boom - Open Cab					
0.00074 HC	0.10	200 A/day	$2.1X10^{-4}$	58	280,000

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; Inhalat. = Inhalation. HC = high confidence data;
2. Application Rate from proposed amendments to EPA Reg No. 7969-150. The highest rate of application is to pasture/range; 8 oz **product**/A = 0.5 lb **product**/A ∴ 0.5 lb product/A * 0.20 lb a.e. diflufenzopyr/lb product = 0.10 lb a.e./A
3. Acres Treated are derived from Sci.Adv.Coun Pol. No. 9.
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated ÷ 70 kg body weight. Inhalation exposure assumes 100% inhalation absorption.
5. NOAEL = No Adverse Effect Level (mg a.i./kg bw/day). For diflufenzopyr, the short and intermediate term inhalation endpoint is 58 mg a.i./kg bw/day.
6. Margin of Exposure (MOE) = NOAEL ÷ ADD

All MOEs for pesticide handlers are ≥100; therefore, the estimated risks do not exceed HED's level of concern.

7.2. Occupational Postapplication

Since no dermal toxicological endpoint was established for diflufenzopyr, it is not necessary to estimate worker post-application exposure.

REI

The copy of the label (EPA Reg. No. 7969-150, "Accepted with COMMENTS In EPA Letter Dated OCT 25, 1999") given to HED lists and an REI of 12 hours (page 3). **Dicamba** is listed as Toxicity Category II for Primary Eye Irritation and Primary Skin Irritation (see APPENDIX I). The interim WPS REI for compounds exhibiting Toxicity Category II effects for primary eye and skin irritation is 24 hours (40 CFR Part 156 § 156.208 (c) (1) and (2). **HED suggests confirmation of the basis for a 12-hour REI for this product.**

7.3. Incidents

The Incident Data System lists 12 incidents for diflufenzopyr from a report on 11 June 1999.

8.0. DATA NEEDS/LABEL REQUIREMENTS

8.1. Chemistry

- ☐ Revised Section B.
- ☐ Revised Section F.
- ☐ Livestock analytical enforcement method (including ILV and radiovalidation) which measures all residues of concern.
- ☐ Ruminant feeding study.

8.2. Toxicology

- None.

8.3. Occupational Exposure

- Confirmation of the 12-hour REI.

cc: J. Tyler; M. Dow; W. Dykstra; J. Miller (RD; 7505C)
RDI: G. Herndon (12/20/01), RAB1 Branch (12/19/01); Team 1 (12/13/01), G. Kramer (12/13/01)
J. Tyler: 806W: CM#2: (703)305-5564: 7509C: RAB1

13544

035324

Chemical:	**3-Pyridinecarboxylic acid, 2-{1-{{{(3,5-**
PC Code:	**005107**
HED File Code	**14000 Risk Reviews**
Memo Date:	**12/20/2001**
File ID:	**DPD271603**
Accession Number:	**412-02-0281**

HED Records Reference Center
04/30/2002