Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2005-01

Diflufenzopyr
DISTINCT®

The active ingredient (a.i.) diflufenzopyr and the formulated end-use product (EP) Distinct®, containing diflufenzopyr and dicamba, for the control of specific broadleaf weeds in field corn in Eastern Canada are being proposed for full registration under Section 13 of the Pest Control Products (PCP) Regulations.

These products have been granted temporary registration, as published in Regulatory Note REG99-02. The present Proposed Regulatory Decision Document (PRDD) provides a summary of data reviewed and the rationale for the proposed regulatory decision regarding these products. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address below.

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Foreword

The PMRA has reviewed the submission for the conversion to full registration of the technical grade active ingredient (TGAI) diflufenzopyr and the formulated product Distinct®, a herbicide developed by BASF Corporation for use on field corn. Distinct®, which contains the active ingredients diflufenzopyr and dicamba, is effective against annual broadleaf weeds such as redroot pigweed, lamb's-quarters, common ragweed, wild buckwheat, lady's thumb and velvetleaf. Health Canada's PMRA had previously issued a temporary registration (Regulatory Note REG99-02) for this product with the requirement that BASF Corporation provide the following data: freezer storage stability data, field rotational crop data, a terrestrial field study and a vegetative vigour study.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18(*b*), to allow a determination of the safety, merit and value of diflufenzopyr and the EP Distinct®. The Agency has concluded that the use of diflufenzopyr and the EP Distinct® in accordance with the label directions has merit and value consistent with Section 18(*c*) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(*d*). Therefore, based on the considerations outlined above, the use of diflufenzopyr and the EP Distinct® are proposed for full registration, pursuant to Section 13 of the PCP Regulations.

Methods for analyzing diflufenzopyr in environmental media are available to research and monitoring agencies upon request to the PMRA.

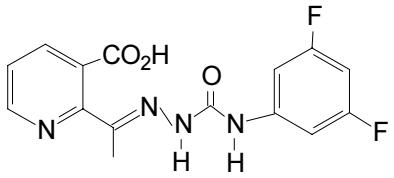
In the original review, diflufenzopyr and the EP Distinct® were jointly reviewed in Canada by the PMRA and the United States Environmental Protection Agency (USEPA). Distinct® is classed as a reduced-risk chemical pesticide, as it presents lower risks to human health than traditional chemical pesticides. The present review was conducted in Canada by the PMRA. A summary of the Agency's findings in support of this decision is found in this PRDD.

Table of Contents

1.0 The active substance, its properties and uses

1.1 Identity of active substance and impurities

TGAI identification

Active substance	diflufenzopyr
Function	herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry	2-{1-[4-(3,5-difluorophenyl)semicarbazono]ethyl} nicotinic acid
2. Chemical Abstracts Service (CAS)	2-[1-[[[(3,5-difluorophenyl)amino]carbonyl]hydrazono]-ethyl]-3-pyridinecarboxylic acid
CAS number	109293-97-2
Molecular formula	$C_{15}H_{12}F_2N_4O_3$
Molecular weight	334.28
Structural formula	
Nominal purity of active	99.1%, nominal (limits: 96.1–100%)
Identity of relevant impurities of toxicological, environmental or other significance	Impurities of toxicological concerns are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.

1.2 Physical and chemical properties

Table 1.2.1 Technical product: Diflufenzopyr acid (BAS 654 H or SAN 835 H)

Property	Result	Comment
Colour and physical state	Off-white, solid	Not applicable (N/A)
Odour	None	N/A
Melting point or range	135.5°C, decomposes before 155°C	N/A
Boiling point or range	N/A	N/A
Tap density	0.24 g/mL at 25°C	N/A
Vapour pressure at 20 and 25°C	$< 1 \times 10^{-7}$ mm Hg ($< 1.33 \times 10^{-5}$ Pa)	Relatively non-volatile under field conditions. Low potential for residues to decrease as a result of volatilization.
Henry's Law constant at 20°C	7.06×10^{-5} to 7.6×10^{-7} (Pa m^3 / mole)	Indicates a negligible potential for volatilization from water or moist soil.
Ultraviolet (UV)–visible spectrum (in water)	**λ nm** **ϵ (L/mol·cm)** 234.1 1.98×10^4 294.5 1.43×10^4 No ϵ at λ > 350 nm	Phototransformation will not be a major route of transformation.
Solubility in water at 25°C (parts per million)	**pH** **Solubility (ppm)** Reagent 63 ± 13 5.0 270 ± 27 7.0 5850 ± 98 9.0 10,546 ± 131	Highly soluble in water at neutral pH; a potential for surface runoff and leaching.
Solubility in organic solvents	**Solvent** **Solubility (mg/L)** tetrahydrofuran 30 000 hexane not detected i-PrOH 922 DMSO 248 000 $MeCl_2$ 12.1 ACN 228 acetone 3360 toluene 1.15	Soluble in polar organic solvents.

Property	Result	Comment
n-octanol–water partition coefficient (K_{ow})	**pH** **K_{ow}** 5.0 2.76 7.0 0.34 9.0 0.17	Will not bioaccumulate in biological tissue.
Dissociation constant (pK_a)	pK_a = 3.18	Predominates as an anion at acidic, neutral and basic pH; no significant effects on adsorption resulting from pH of soil in the range of values found in Canada.
Stability (temperature, metal)	The TGAI is unstable in the presence of metals and in sunlight. Recoveries after contact with iron, copper, aluminum, Fe^{+2}, Cu^{+2} and Al^{+3} ions for 28 days (d) at 25°C were 2.0, 3.1, 5.1, 21.5, 88.0 and 98.0% respectively. Photolysis $t_{1/2}$ of TGAI at pH 7 and 25°C was 54.1 d.	N/A

Table 1.2.2 End-use product: Distinct® (BAS 662H 70WG)

Property	Result
Colour	Grey
Odour	Moderate, neutral, unpleasant odour
Physical state	Solid powder
Formulation type	Wettable powder
Guarantee	Diflufenzopyr (present as sodium salt), 20% (limits: 19.4–20.6 %) Dicamba (present as sodium salt), 50% (limits: 48.5–51.5 %)
Formulants	The product does not contain any USEPA List 1 formulants or formulants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.
Container material and description	High density polyethylene jug. Future packaging may include a gable top carton container with paper polymer-laminated surface.
Bulk density	Tap density = 0.6 g/mL

Property	Result
pH of 1% dispersion in water at 25°C	8.51
Oxidizing or reducing action	Showed no reactivity with $KMnO_4$, Zn, most organic solvents and ammonium phosphate monobasic.
Storage stability	Stable for two years in glass containers at room temperature. Results before and after storage were within ± 0.2%.
Explodability	The product is not impact-explosive sensitive.

1.3 Details of uses and further information

Diflufenzopyr is a semicarbazone herbicide. Diflufenzopyr is classified as a Group 4 herbicide in which the mode of action is auxin transport inhibition. Diflufenzopyr is commercialized as a premix product with dicamba, an active ingredient that is currently registered in Canada. The commercial name for the diflufenzopy and dicamba product is Distinct®. Distinct® contains 20% diflufenzopyr and 50% dicamba, resulting in an overall guarantee of 70% a.i. Distinct® herbicide is marketed in high-density polyethylene jugs and Distinct® herbicide water dispersible granule is marketed in water-soluble bags.

Distinct® may be used for pre-emergent, spike stage (spike to one leaf), early postemergent (two to three leaf) and late postemergent (four to six leaf) application on field corn in Eastern Canada. Distinct® is not for use on sweet corn or seed corn. An application of Distinct® at the above-stated timings relative to the crop, except for pre-emergent treatment where the tankmix with dimethenamid is recommended, is effective in controlling the following broadleaf weeds: redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf is controlled by postemergent application only). Distinct® can be used for control of Canada thistle (top growth) as postemergence application (two to six leaf) on field corn.

Distinct® is to be applied at a rate of 285 g/ha (200 g a.i./ha) with ground equipment only. When applied as an early or late postemergent treatment, a non-ionic surfactant at 0.25% volume ratio (v/v) and liquid urea ammonium nitrate at 1.25% v/v must be used. Distinct® may be applied a maximum of once per year. Corn may be grazed or cut for forage or silage within 75 days of application and corn grain may be harvested within 120 days of application.

Distinct® can be tankmixed with dimethenamid at a rate of 1.125 kg a.i./ha for control of the above broadleaf weeds in addition to the following annual grass weeds: green foxtail, yellow foxtail, crabgrass (smooth and large), old witchgrass, barnyard grass and fall panicum. Distinct® can be tankmixed with Ultim 75% DF at the 2 to 6 leaf stage and with Accent 75 DF at the 4 to 8 leaf stage of field corn.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

The active ingredient and major impurities (content ≥ 0.1%) in the technical product were determined using two isocratic high performance liquid chromatography (HPLC) methods. The methods were assessed to have acceptable accuracy, precision and linearity to a suitable limit of quantitation (LOQ < 0.1%). Representative chromatograms of the standards and the samples show no interfering peaks and indicate that the methods are sufficiently specific for the determination. The identities of the active ingredient and impurities were confirmed by spectral methods.

2.2 Methods for formulation analysis

The active ingredients in Distinct® herbicide were determined using a solvent gradient HPLC method. The method was assessed to be specific, linear, precise and accurate for use as an enforcement analytical method. Representative chromatograms of the standard solution and formulation sample show no interferences around the retention times of the actives.

2.3 Methods for residue analysis

2.3.1 Methods for environmental residue analysis

In soil, analyses for the parent compound, diflufenzopyr, and its major transformation products, M1 (phthalazinone) and M5 (carbamoyl phthalazinone), were conducted using HPLC, thin layer chromatography (TLC) and radio assay. Recovery of the parent compound in soil ranged from 92% to 103%, and the LOQ for diflufenzopyr and phthalazinone residues was 10 μg/kg.

In sediment, analyses for the parent compound and transformation products were conducted using TLC, HPLC and mass spectrometry (MS). Recovery of the parent compound in sediment ranged from 90% to 100%, and the LOQ for diflufenzopyr and transformation products was 10 μg/kg.

In water, identification and quantitation of the parent compound and major transformation products were conducted using TLC, HPLC, MS and radio assay analyses. Recovery of the parent compound ranged from 97% to 103%, and the LOQ for diflufenzopyr and transformation products was 100 μg/L.

In plant matrix, analyses for the parent compound and the transformation product, M1, were conducted using gas chromatography (GC). Quantitation was performed with a GC/nitrogen-phosphorous detector (NPD) or GC/mass selective detection (MSD). The LOQ was 0.01 ppm.

Based on animal metabolism studies, residues of diflufenzopyr are unlikely to be detectable in meat, milk and eggs as a result of feeding treated corn seeds or by-product. Therefore, an analytical method for animal matrix was not required.

2.3.2 Multiresidue methods for residue analysis

Diflufenzopyr and its 8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (M1) were tested using United States Food and Drug Administration multiresidue methodology, as presented in *Pesticide Analytical Manual* Volume I: Multiresidue Methods (PAM I). None of the analytes were recovered efficiently using PAM I Multiresidue Methods.

2.3.3 Methods for residue analysis of plants and plant products

The residue of concern (ROC) for corn raw agricultural commodities (RACs) was defined from the corn metabolism study as the parent compound and its metabolites convertible to M1 and expressed as diflufenzopyr equivalents.

For corn commodities, the Sandoz Agro Method AM-0966-0995-0, a GC method, was used. According to this method, residues of diflufenzopyr are extracted with aqueous sodium bicarbonate and ammoniated acetone, and parent compound is subsequently converted to M1. Residues of diflufenzopyr and M1 are quantified collectively as M1 using a GC/NPD or a GC/MSD. The LOQ is 0.01 ppm, based on M1. Since the molecular weight of M1 is roughly half of the parent compound, the concentration of M1 determined must be doubled when expressed in diflufenzopyr equivalent (i.e., 0.02 ppm LOQ). The limit of detection (LOD) of Sandoz Agro Method AM-0966-0995-0 is 0.02 ppm, as diflufenzopyr equivalent.

The USEPA indicated that Method AM-0966-0995-0 was suitable as an enforcement method for diflufenzopyr. However, the petitioner requested a GC/MS method, BASF Method D9709, to replace AM-0966-0995-0 as the enforcement method. According to BASF Method D9709, residues of diflufenzopyr and M1 are extracted from corn using dilute aqueous sodium bicarbonate and ammoniated acetone. Following conversion of diflufenzopyr to M1, M1 is quantified using GC/MS. The reported LOQ for BASF Method D9709 is 0.05 ppm, as diflufenzopyr equivalent. The reported LOD of Method D9709 is 0.017 ppm, as diflufenzopyr equivalent. Since BASF Method D9709 utilizes a more selective detector, it is suitable as a replacement enforcement method. Furthermore, the USEPA has adopted BASF Method D9709 as an enforcement method (USEPA Index of Residue Analytical Methods).

2.3.4 Methods for residue analysis of food of animal origin

No analytical method was submitted for livestock. Based on animal metabolism studies, residues of diflufenzopyr are unlikely to be detectable in meat, milk and eggs. Therefore, an analytical method for the analysis of food of animal origin is not required.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

3.1.1 Absorption, distribution, metabolism and excretion

Male and female Wistar rats received either a single low intravenous dose (1.0 mg/kg body weight [bw]), a single low oral dose (10.0 mg/kg bw), a single high oral dose (1000 mg/kg bw) or 15 daily low oral doses (10.0 mg/kg bw) of diflufenzopyr, purity 98%, 10 or 15 rats per sex per group. Diflufenzopyr was radiolabelled as [phenyl-U-^{14}C] or [pyridinyl-4, 6-^{14}C]. Prior to dosing, 5 rats per sex in all but the repeat dose group were bile-duct cannulated and sacrificed 48 hours (h) postdosing. Of the remaining 10 rats per sex in each group (i.e., non-cannulated), 5 per sex per group were sacrificed 24 hours postdosing, and the remaining 5 per sex per group were sacrificed 72 hours postdosing.

[^{14}C]Diflufenzopyr was only partially absorbed from the gastrointestinal tract of orally dosed rats as indicated by the levels of excretion in urine and bile. In all orally dosed groups, 20–44% of the dose was excreted in the urine and 3–11% was excreted in the bile. In contrast, intravenously dosed rats excreted 61–89% of the dose in urine and 4–19% of the dose in bile. For all orally dosed groups, the level of absorption was similar between sexes. Dose level and pretreatment had little effect on the proportion of the dose excreted in urine following oral administration.

Enterohepatic circulation plays a role in the elimination of [^{14}C]diflufenzopyr in rats; 3–19% of the dose was recovered in the bile of all dose groups.

Within 72 hours of dosing, intravenously dosed rats excreted the majority of radioactivity in urine (61–89%), whereas orally dosed rats excreted most of the radioactivity in feces (49–79%), regardless of radiolabel or sex. Pretreatment did not appear to affect the pattern of excretion. Bile-cannulated rats excreted lower amounts in feces compared to non-cannulated rats; 3–19% of the dose was excreted in bile. The estimated half-lives of radiocarbon eliminated in urine and feces was 5.3–6.9 h for all single intravenous and oral dose groups, and 7.7–10.8 h for all repeat oral dose groups.

Total radioactive residues (TRRs) in tissues from rats in all dose groups were < 3% of the administered dose. Total tissue residue levels were highest in rats sacrificed at 24 h postdose; residue levels were highest in blood, blood cell and serum for the phenyl-labelled groups, and in liver and kidney for the pyridinyl-labelled groups.

Blood residue levels for all dose groups were < 1% of the administered dose at all sampling intervals through 72 h postdosing.

TLC and HPLC analyses were conducted on 0- to 72-h and 0- to 48-h urine and faeces samples, and on 0- to 48-h bile samples from each treatment regimen. The structures of the metabolites were confirmed using two-dimentional TLC, HPLC, liquid chromatography (LC)/MS, direct insertion probe (DIP)/MS, fast atom bombardment/MS, and proton nuclear magnetic resonance. For each dose group, the metabolic profile was similar between sexes, except for differences in metabolite levels. Unchanged diflufenzopyr was identified as the major component in urine, feces and bile from all dose groups using either radiolabel. Urinary metabolites identified in the ^{14}C-phenyl-labelled dose groups included 3,5-difluoroaniline (aniline) (M2) and 6-((3,5-difluorophenyl) carbamoyl)-8-methyl-pyrido (2,3-d)-5-pyridazinone (carbamoyl phthalazinone) (M5). Urinary metabolites identified in the ^{14}C-pyridinyl-labelled dose groups included M1; M5; 2-acetyl nicotinic acid (M6); 8-methylpyrido[2,3-d]pyridazine-2,5(1H, 6H)-dione (2-keto-M1) (M9); M10; and 8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (2-keto-8-hydroxymethyl-M1 or Metabolite E)(M19). Fecal metabolites identified in the phenyl label groups included methyl N-(3,5-difluorophenyl)carbamate (M8) and M5. Fecal metabolites identified in the pyridinyl label groups included M1, M5, M6, M9 and M10. Besides the parent compound, bile samples also contained minor amounts of M5 (both labels) and M1 (pyridinyl label only).

The data indicate that diflufenzopyr is excreted primarily unchanged in urine, faeces and bile. Minor amounts of hydrolysis products (M1, M5 and M6) and hydroxylation products (M9, M10 and M19) were identified in excreta. For the structure of the metabolites and the proposed metabolic pathway of diflufenzopyr, refer to Table 3.1.1.1 and Figure 3.1.1.1, respectively.

Figure 3.1.1.1 Proposed metabolic pathways for diflufenzopyr (SAN 835 H) in the rat

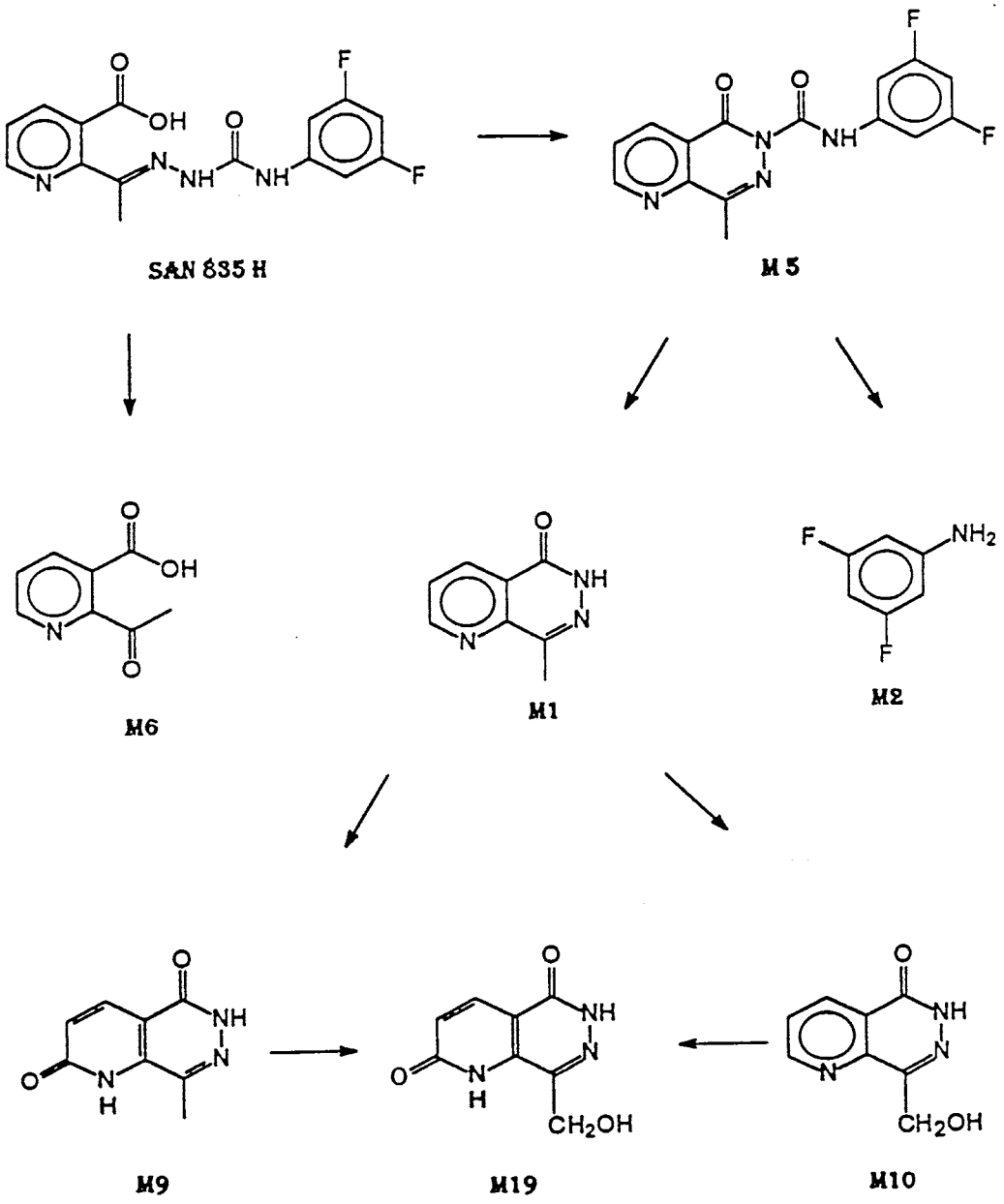


Table 3.1.1.1 TLC and HPLC characteristics of diflufenzopyr (SAN 835 H) and its model metabolites

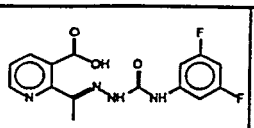
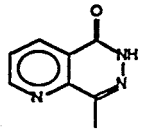
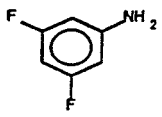
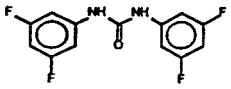
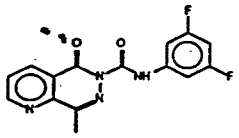
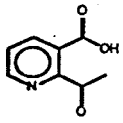
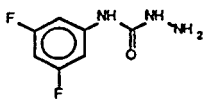
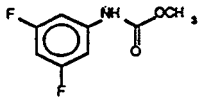
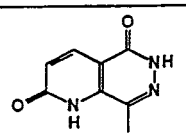
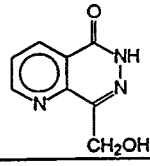
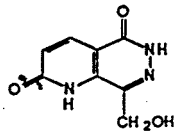
Compound designation	Structure	TLC R_f in Solvent Systems [1]						R_t (min.)
		B	L	A	I	T	N	HPLC [2]
SAN 835 H		0.45	0.43	0.31	0.55	0.57		5.2
M1 Phthalazinone		0.54	0.72	0.43	0.50	0.91		3.5
M2 3,5-difluoro-aniline		0.86	0.84	0.75				6.3
M3 Symmetric-urea		0.89	0.85	0.79				19.7
M5 Carbamoyl-Phthalazinone		0.66	0.64	0.55	0.74	0.95		8.6
M6 2-Acetyl nicotinic acid		0.37	0.16		0.42	0.54		3.5

Table 3.1.1.1 (cont'd)

Compound designation	Structure	TLC R_f in Solvent Systems [1] B	L	A	I	T	N	R_t (min.) HPLC [2]
M7 Semicarbazide		0.76	0.77	0.25				4.2
M8 Carbamate		0.87	0.84	0.78				7.4
M9 2-keto-M1		0.38	0.21		0.47	0.79	0.42	3.5
M10 8-hydroxymethyl-M1		0.35	0.57	0.25		0.71		3.2
M19 2-keto-8-hydroxymethyl-M1		0.23					0.24	

[1] TLC solvent systems:
A = ethyl acetate/toluene/acetic acid/water 90:6:2:2;
B = ethyl acetate/acetic acid/water 92:4:4;
L = ethyl acetate/methanol/ammonium hydroxide 70:25:5;
I = acetonitrile/acetic acid/water 95:2.5:2.5;
T = chloroform/methanol/acetic acid/water 68:25:5:2;
N = ethyl acetate/toluene/formic acid/water 87:3:5:5.

[2] HPLC conditions:
Phenomenex Bondclone 10 C_{18} column; mobile phase isocretic acetonitrile:water (1% acetic acid) 50:50. Flow rate; 1 ml/min.

3.1.2 Acute and dermal toxicity—technical and formulation

Diflufenzopyr, purity 96.4%, was considered to be of low acute toxicity by the oral and inhalation routes in Sprague Dawley (SD) rats (lethal dose 50% [LD_{50}] > 5.0 g/kg bw; lethal concentration 50% [LC_{50}] > 2.93 mg/L), and of low acute toxicity by the dermal route to New Zealand white (NZW) rabbits (LD_{50} > 5.0 g/kg bw). It was non-irritating when applied to the skin of NZW rabbits, and minimally irritating when instilled into the eyes of the same species. Results of skin sensitization testing using Pirbright White Dunkin Hartley (PWDH) albino guinea pigs, employing the modified Buehler method, were negative.

Based on the results of acute toxicity testing, no signal words are required to be displayed on the primary display panel.

Distinct® herbicide, containing 20% diflufenzopyr and 50% dicamba, was considered to be slightly acutely toxic by the oral route (combined LD_{50} = 1.8 g/kg bw) and of low acute toxicity by the inhalation route (LC_{50} > 5.34 mg/L) to SD rats, and of low acute dermal toxicity (LD_{50} > 5.0 g/kg bw) to NZW rabbits. It was slightly irritating when applied to the skin of NZW rabbits, and moderately irritating when instilled into the eyes of the same species. Results of skin sensitization testing using PWDH albino guinea pigs, employing the modified Buehler method, were positive.

Based on the results of acute toxicity testing, it is recommended that the words "CAUTION POISON", "CAUTION EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" be displayed on the primary panel of the label.

Technical diflufenzopyr, purity 96.4%, was moistened with distilled water and administered by dermal application to male and female NZW rabbits at dose levels of 0, 100, 300 and 1000 mg/kg bw per application, 5 rabbits per sex per group. Frequency of application was 6 hours per day, daily, for 21–24 consecutive days.

The no observed effect level (NOEL) for systemic toxicity was determined to be 1000 mg/kg bw/d, since there were no apparent signs of treatment-related systemic effects observed in male or female rabbits at any dose level tested.

A NOEL 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).

Distinct® herbicide, containing 20.0% diflufenzopyr and 51.0% dicamba, was moistened with distilled water and administered by dermal application to male and female NZW rabbits at dose levels of 0, 10, 30 and 100 mg/kg bw per application, 5 rabbits per sex per group. Frequency of application was 6 hours per day, daily, for 21–24 consecutive days.

The NOEL for systemic toxicity was determined to be 100 mg/kg bw/d, because there were no apparent signs of treatment-related systemic effects observed in male or female rabbits at any dose level tested.

A NOEL for dermal effects could not be determined since local dermal irritation was observed at all dose levels tested. Corresponding findings upon histopathological examination were noted in the 30- and 100-mg/kg bw/d groups only, and included diffuse acanthosis and diffuse/focal inflammation of the superficial dermis. In addition, diffuse hyperkeratosis was observed in the 100-mg/kg bw/d group only.

3.1.3 Genotoxicity

In a microbial reverse gene mutation study (in vitro) using the standard plate incorporation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to diflufenzopyr, purity 98.9%, vehicle dimethylsulfoxide (DMSO). Dose levels chosen were 0 (vehicle control), 667, 1000, 6667 and 10 000 μg/plate, both in the presence and absence of a metabolic activator (i.e., S9 fraction derived from Aroclor 1254-induced SD male rat livers). No appreciable cytotoxicity was seen at any of these dose levels. All strains responded in the expected manner to the appropriate positive control. There was, however, no evidence that diflufenzopyr induced a mutagenic effect in any strain at any dose level tested. Hence, under the conditions of this study, diflufenzopyr was considered non-mutagenic for point mutation.

In a repeat, gene mutation study (in vitro) using the standard plate incorporation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to diflufenzopyr, purity 97.1%, vehicle DMSO. Dose levels chosen were 0 (vehicle control), 333, 667, 1000, 3330, 6670 and 10 000 μg/plate, both in the presence and absence of metabolic activator (i.e., S9 fraction derived from Aroclor 1254-induced SD male rat livers). No cytotoxicity was observed at any of these dose levels. All strains responded in the expected manner to the positive controls. However, there was no evidence that diflufenzopyr induced a mutagenic response at any dose level tested. Hence, under the conditions of this study, diflufenzopyr was considered non-mutagenic for point mutation.

In an in vitro forward mutation assay with independent repeat, cultured L5178Y (TK+/−) mouse lymphoma cells were exposed for four hours to diflufenzopyr, purity 97.1%, dissolved in DMSO, at eight dose levels ranging from 0.05 to 3.0 mg/mL, both in the presence and absence of a metabolic activator. The confirmatory trial investigated nine doses ranging from 0.05 to 2.0 mg/mL, both in the presence and absence of metabolic activator S9 homogenate from Aroclor 1254-induced SD male rat liver.

Diflufenzopyr was insoluble at ≥ 2500 μg/mL. Cytotoxicity was seen at ≥ 2.0 mg/mL and ≥ 1.8 mg/mL, in the absence and presence of metabolic activator, respectively. Lower concentrations resulted in an adequate range of relative total growth values to allow for

an adequate assessment of mutagenic potential (i.e., 10–95% of the control values). The positive controls induced the expected mutagenic responses. There was, however, no evidence that diflufenzopyr was mutagenic at any dose under any assay condition. Under the conditions of this assay, diflufenzopyr was considered non-mutagenic.

An in vitro unscheduled deoxyribonucleic acid (DNA) synthesis assay was conducted on rat hepatocytes prepared from an adult male Fischer 344 rat, using technical diflufenzopyr, purity 97.1%. Dose levels chosen were 0 (solvent control), 5, 10, 25, 50, 100 and 250 µg/mL, both in the presence and absence of metabolic activator S9 homogenate, derived from Aroclor 1254-induced rat livers. The test material was delivered to the test system as a solution in DMSO. Under the conditions of this assay, it was concluded that diflufenzopyr did not induce unscheduled DNA synthesis.

In an in vivo mammalian cytogenetics (micronucleus) assay, groups of ICR mice (5 per sex per dose per sacrifice time) were gavaged orally with single doses (12.5 mL/kg bw) of corn oil (vehicle control), or diflufenzopyr, purity 97.1% (500, 1667 and 5000 mg/kg bw), or positive control material (cyclophosphamide, 80 mg/kg bw). In the diflufenzopyr-treated groups, 5 mice per sex per group were sacrificed 24, 48 and 72 h after dosing; all mice in the vehicle and positive control groups were sacrificed 24 h postdosing. Slides were prepared from harvested bone marrow and evaluated for the presence of micronucleated polychromatic erythrocytes (MPCEs) as well as possible cytotoxicity (ratio of polychromatic erythrocytes to total erythrocytes). No mortalities occurred during the micronucleus assay. The positive control induced the expected high yield of MPCEs in mice sacrificed at 24 h. Diflufenzopyr did not induce a clastogenic effect in either sex at any sacrifice time. Under the conditions of this assay, it was concluded that diflufenzopyr was non-clastogenic.

3.1.4 Subchronic and chronic toxicity

The subchronic and chronic toxicity of diflufenzopyr were investigated in mice, rats and dogs. Ninety-day studies were conducted, which were used to establish appropriate dose levels to be used in the long-term studies.

3.1.4.1 Subchronic and chronic toxicity in the mouse

Male and female CD-1 mice were fed test diets containing technical grade diflufenzopyr, purity 97.1%, at dietary concentrations of 0, 350, 1750, 3500 and 7000 ppm (equal to 0, 58, 287, 613 and 1225 mg/kg bw/d for males, and 0, 84, 369, 787 and 1605 mg/kg bw/d for females) for a period of 13 weeks (wk), 10 mice per sex per group. The NOEL was determined to be 7000 ppm (equal to 1225 mg/kg bw/d for males and 1605 mg/kg bw/d for females), since there were no treatment-related effects observed in male or female mice at any dose level tested. Based on the results of this study, the dose levels chosen for the mouse chronic oncogenicity feeding study were 0, 700, 3500 and 7000 ppm (limit dose).

Male and female CD-1 mice were fed test diets containing technical diflufenzopyr, purity 98.1%, at dietary concentrations of 0, 700, 3500 and 7000 ppm (equal to 0, 100, 517 and 1037 mg/kg bw/d for males, and 0, 98, 500 and 1004 mg/kg bw/d for females), 60 mice per sex per group, for a period of 78 weeks. An interim sacrifice was carried out with 10 preselected mice per sex per group after 52 weeks of treatment.

The NOEL for systemic toxicity for males was determined to be 7000 ppm (equal to 1037 mg/kg bw/d), since there were no treatment-related effects observed at any dose level tested. For females, the no observed adverse effect level (NOAEL) was determined to be 7000 ppm (1004 mg/kg bw/d). This was based on a slight, but statistically significant 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.

3.1.4.2 Subchronic and chronic toxicity in the rat

Male and female Wistar rats were fed test diets containing technical diflufenzopyr, purity 96%, at dose levels of 0, 1000, 5000, 10 000 and 20 000 ppm (equal to 0, 60.8, 352, 725 and 1513 mg/kg bw/d for males, and 0, 72.8, 431, 890 and 1750 mg/kg bw/d for females) for a period of 13 wk, 10 rats per sex per group. An additional 10 rats per sex were assigned to the 0- and 20 000-ppm groups for a four-week recovery period following treatment.

The NOEL was set at 5000 ppm (equal to 352 mg/kg bw/d for males, and 431 mg/kg bw/d 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 (20 000 ppm, males only), slight increases in cholesterol (20 000 ppm, both sexes, and 10 000 ppm, males only) and alanine aminotransferase (10 000 and 20 000 ppm, both sexes)as well as slightly lower chloride (20 000 ppm, both sexes). Histopathological findings were an increased incidence of foamy macrophages in the lungs in the 10 000- and 20 000-ppm group, both sexes, and testicular atrophy in the 20 000-ppm group. Following the four-week recovery period, the only treatment-related effects that showed partial or no evidence of recovery were foamy macrophages in the lungs and testicular atrophy.

Male and female Wistar rats were fed test diets containing technical grade diflufenzopyr, purity 97.1–99.6%, at dietary concentrations of 0, 500, 1500, 5 000 and 10 000 ppm (equal to 0, 22, 69, 236 and 518 mg/kg bw/d for males, and 0, 29, 93, 323 and 697 mg/kg bw/d for females), 72 rats per sex per group, for a period of 104 weeks. An interim sacrifice was carried out after 52 weeks on treatment, 20 preselected rats per sex per group. The NOAEL for systemic toxicity was set at 5000 ppm (equal to 236 mg/kg bw/d for males and 323 mg/kg bw/d for females) based on slightly lower final body weights in the 1500- and 5000-ppm groups. However, this was due to decreased body-weight gain

seen primarily in the second year of the study, and only attained a 10% reduction (compared to the concurrent control value), between study weeks 91 and 106. In addition, there were no other treatment-related effects noted in the 1500- and 5000-ppm groups; hence, these body weight changes were not considered to be toxicologically significant. 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.

3.1.4.3 Subchronic toxicity in the dog

Male and female beagle dogs were fed test diets containing technical diflufenzopyr, purity 98%, at dietary concentrations of 0, 1500, 10 000 and 30 000 ppm (equal to 0, 58, 403 and 1121 mg/kg bw/d for males, and 0, 59, 424 and 1172 mg/kg bw/d for females) for a period of 90 days, 4 dogs per sex per group.

The NOEL was 1500 ppm (equal to 58 mg/kg bw/d) based on erythroid hyperplasia in the bone marrow and extramedullary hematopoeisis in the liver, evident in the 10 000- and 30 000-ppm groups. The only other finding in the 10 000-ppm group, which was considered to possibly be related to treatment, was hemosiderin deposits noted in the Kupffer cells of one female dog. Additional treatment-related findings noted in the 30 000-ppm group were absence of fatty bone marrow, dry skin/non-specific skin lesions, lower body-weight gain and food consumption, regenerative anemia (i.e., reticulocytosis, anisocytosis, polychromasia, normoblasts, higher mean corpuscular volume [MCV], lower mean corpuscular hemaglobin concentration [MCHC]), hemosiderin deposits in Kupffer cells and macrophages, extramedullary hematopoeisis in the lungs, lymph nodes and kidneys, depressed myeloid/erythroid ratio in the bone marrow, higher spleen, liver and kidney weights (females only) as well as urothelial hyperplasia and cystitis.

Male and female beagle dogs were fed test diets containing technical grade diflufenzopyr, purity 98%, at dietary concentrations of 0, 750, 7500 and 15 000 ppm (equal to 0, 26, 299 and 529 mg/kg bw/d for males and 0, 28, 301 and 538 mg/kg bw/d for females) for a period of 52 wk, four dogs per sex per group.

The NOEL was determined to be 750 ppm (equal to 26 mg/kg bw/d) based on erythroid hyperplasia in the femoral and sternal bone marrow, accompanied by an increase in hemosiderin deposits in the kidneys, liver and spleen, and reddish discolouration of the diaphysis of the femur; mild to moderate reticulocytosis; and slightly lower body-weight gain and less efficient food utilization (females only) in the 7500- and 15 000-ppm groups. The only other findings considered to be treatment-related were higher MCV and lower MCHC in the 15 000-ppm group.

3.1.5 Reproductive and developmental toxicity

A two-generation reproduction study was conducted using SD rats, fed test diets containing diflufenzopyr, purity 98.1%, at concentrations of 0, 500, 2000 and 8000 ppm (equal to 0, 27.3, 113.1 and 466.2 mg/kg bw/d for males, and 0, 42.2, 175.9 and 742.0 mg/kg bw/d for females), 26 per sex per group, continuously throughout the study period. Each female in the P generation was mated to produce two litters, whereas the F_1 generation (i.e., from the F_1a litters) was mated to produce one litter only.

In the 8000-ppm group, mean body-weight gains were lower for males and females during premating (P and F generation) and for females during gestation (F_1a, F_1b and F_2a litters), and mean food consumption was increased for P and F generation males during premating, for F generation females during premating and for females during gestation with the F_1a, F_1b and F_2a litters. In the 2000-ppm group, slightly lower mean body-weight gain for P generation males during the premating period as well as marginally increased mean food consumption for P generation males and for F_1 generation females during premating only were considered to be treatment-related, but were not considered adverse. The only other parental treatment-related finding was slightly increased mean seminal vesicle weight in the 2000- and 8000-ppm groups. In the absence of any corresponding gross or histopathological findings, however, this was not considered to be an adverse effect.

The F_2 generation pups dosed at 8000 ppm had lower live birth and viability indices; moreover, the total pre-perinatal loss was significantly increased. Mean body weight was decreased in the 8000-ppm group in the F_1a generation for both sexes on day 21 of lactation, due to lower mean body-weight gains on days 4–21 of lactation. In the 8000-ppm group, F_1a and F_1b generations had a higher proportion of runts and the F_2 generation had a higher percentage of offspring with no milk in the stomach.

Based on the results obtained from this study, the NOAEL for rental toxicity was determined to be 2000 ppm, and the NOEL for reproductive toxicity was set at 2000 ppm (equal to 113.1 mg/kg bw/d for males, and 175.9 mg/kg bw/d for females).

Pregnant SD rats (Crl:CD BR) were dosed by gavage with technical grade diflufenzopyr, purity 98.1%, as a suspension in aqueous 0.5% methylcellulose, at dose levels of 0 (vehicle control), 100, 300 and 1000 mg/kg bw/d, 25 mated females per group, from day 6 to 15 of gestation, inclusive.

The NOAEL for maternal toxicity was set at 1000 mg/kg bw/d based on slightly reduced mean maternal body-weight gain and mean food consumption during the first three days of dosing, evident in the 1000-mg/kg bw/d treatment group only. This finding did not attain statistical significance and mean final body weights were comparable among all groups. Hence, this was not considered to be an adverse, toxicologically significant effect. There were no other maternal, treatment-related effects.

The NOAEL for developmental toxicity was set at 1000 mg/kg bw/d based on an increased incidence of incompletely ossified and/or unossified sternal centra at that dose level. In the absence of any other treatment-related findings or induced malformations, this minor variation was not considered to be an adverse, toxicologically significant finding. There was no evidence of any teratogenic effects related to treatment with diflufenzopyr at any dose level tested.

Pregnant NZW rabbits were dosed by gavage with technical grade diflufenzopyr, purity 98.1%, as a suspension in aqueous 0.5% methylcellulose, at dose levels of 0, 30, 100 and 300 mg/kg bw/d, 20 pregnant females per group, from day 6 to 19 of gestation, inclusive.

The NOEL for maternal toxicity was set at 100 mg/kg bw/d based on an increased incidence of mortality, abnormal feces and abortions as well as a slight but persistent mean weight loss and lower mean food consumption during the dosing period, evident in the 300-mg/kg bw/d treatment group.

The NOEL for developmental toxicity was set at 100 mg/kg bw/d based on an increased incidence of abortions in the 300-mg/kg bw/d group (a maternally toxic dose). There were no other treatment-related fetotoxic effects. There was no evidence of any teratogenic effects related to treatment with diflufenzopyr at any dose level tested.

3.1.6 Neurotoxicity (acute, delayed and subchronic)

Male and female Crl:CD BR rats were dosed once by oral gavage with diflufenzopyr, purity 96.4%, as a suspension in 1% methylcellulose, at dose levels of 0, 125, 500 and 2000 mg/kg bw, 10 rats per sex per group. Special neurological examinations included a functional observational battery (FOB) and motor activity testing (in-life), and a detailed histopathological examination of perfused central and peripheral nervous system tissues.

The NOEL was determined to be 2000 mg/kg bw since there were no treatment-related effects observed in male or female rats at any dose level tested.

Data on delayed neurotoxicity have not been generated and are not considered relevant for compounds such as diflufenzopyr.

Male and female Crl:CD BR rats were fed test diets containing technical diflufenzopyr, purity 96.4%, at levels of 0, 25, 75 and 1000 mg/kg bw/d, 10 rats per sex per group, for a period of 13 weeks. Special neurological examinations included an FOB and motor activity testing (in-life) as well as a detailed histopathological examination of perfused central and peripheral nervous system tissues.

The NOEL was determined to be 75 mg/kg bw/d based on lower body-weight gain and lower feed efficiency in the 1000-mg/kg bw/d group. There were no other treatment-related effects observed at any dose level tested.

There was no indication of neurotoxicity observed at any dose level tested.

3.1.7 Overall toxicological summary

A detailed review of the toxicity database available for the new herbicide diflufenzopyr has been completed. Data submitted were complete and well presented, and included the full battery of studies required for registration purposes. Studies were well conducted and in conformance with acceptable international testing protocols. Appendix I presents a summary table of toxicity studies for diflufenzopyr.

Results from metabolism studies demonstrated that after oral administration, a smaller percentage of the administered dose was excreted in the urine and a greater percentage in the feces, when compared to intravenous administration, indicating that diflufenzopyr was only partially absorbed following oral dosing. Within 72 hours after oral dosing, the majority of the administered dose was eliminated via the feces (i.e., 49–79%), whereas only 20–44% of the administered dose was excreted in the urine. After intravenous dosing, 61–89% of the administered dose was excreted in the urine. Sex, dose level and pretreatment had little effect on the excretion pattern. In addition, 3 to 19% of the administered dose was recovered in the bile of all dose groups, indicating that enterohepatic circulation played a role in the elimination of diflufenzopyr. The approximate half-life of diflufenzopyr was 5.3–6.9 h for all single oral and intravenous dose groups, and 7.7–10.8 h for the repeat oral dose group.

Diflufenzopyr did not accumulate in the tissues; TRRs accounted for < 3% of the administered dose for all dose groups. Residue levels were highest in blood, red blood cells and serum for the phenyl-labelled groups, and were highest in liver and kidney for the pyridinyl-labelled groups.

The major fraction of TRR extracted from urine, feces and bile was identified as unchanged diflufenzopyr. In addition, minor amounts of hydrolysis products M1, M5 and M6 as well as hydroxylation products M9, M10 and M19 were identified in excreta.

Acute single dosing revealed that technical grade diflufenzopyr was of low toxicity to laboratory animals by the oral, inhalation and dermal routes, whereas the Distinct® formulation was slightly toxic by the oral route and of low toxicity by the dermal and inhalation routes. The technical material was non-irritating to rabbit skin and did not possess potential skin sensitizing properties when tested on guinea pigs (modified Buehler method), whereas Distinct® was slightly irritating to the skin of rabbits and a potential skin sensitizer. The technical material was minimally irritating to the rabbit eye, whereas the formulation induced moderate eye irritation.

In rabbits, short-term repeated dermal (21–24 days) dosing with technical diflufenzopyr or the Distinct® formulation did not result in any treatment-related systemic effects up to and including the highest dose levels tested of 1000 mg/kg bw/d and 100 mg/kg bw/d, respectively. However, local dermal irritation was observed at all dose levels tested for both diflufenzopyr (low dose of 100 mg/kg bw/d) and Distinct® (low dose of 10 mg/kg bw/d).

In mice, short-term (13 weeks) and long-term (78 weeks) dietary exposure to technical diflufenzopyr did not result in any toxicologically significant treatment-related effects up to and including the highest dose level tested of 7000 ppm (equal to 1225 mg/kg bw/d for males and 1605 mg/kg bw/d for females in the 13-week study; and equal to 1037 mg/kg bw/d for males and 1004 mg/kg bw/d for females in the 78-week study).

Technical diflufenzopyr administered orally to dogs for either 13 weeks or 1 year resulted in erythroid hyperplasia in the bone marrow, extramedullary hematopoiesis in the liver, hemosiderin deposits in various organs and mild to moderate reticulocytosis. These effects were not observed in any other species tested. These findings indicate that the test material was directly toxic to dog erythrocytes, with a compensatory response in the bone marrow and liver (i.e., a responsive hemolytic anemia). The NOEL for these findings was 1500 ppm (58 mg/kg bw/d) after 13 weeks of treatment and 750 ppm (26 mg/kg bw/d) after 52 weeks of treatment. Lower body-weight gain was evident at dose levels $\geq$ 15 000 ppm.

In rats, body-weight gain was lower after short-term (13 weeks) and long-term (104 weeks) exposure at dose levels $\geq$ 10 000 ppm (equal to 518 mg/kg bw/d for males and 697 mg/kg bw/d for females). Slightly lower body-weight gain was also observed for females in the 5000-ppm group (equal to 323 mg/kg bw/d) after one year on treatment, but only attained a 10% reduction compared to the concurrent control group and was not considered to be toxicologically significant. After short-term exposure, an increased incidence of foamy macrophages in the lungs was noted in the 10 000- and 20 000-ppm groups, both sexes, and an increased incidence of testicular atrophy was seen in the 20 000-ppm group. However, these findings were not observed after long-term exposure at dose levels up to and including 10 000 ppm.

Lifetime studies did not demonstrate any evidence of oncogenic/carcinogenic potential of diflufenzopyr in rats and mice. In addition, all in vitro and in vivo mutagenicity assays conducted yielded negative results for genotoxic potential.

Diflufenzopyr affected reproductive performance in rats at the high dose of 8000 ppm (equal to 466.2 mg/kg bw/d), manifested as lower live birth and viability indices, increased pre-perinatal loss and an increased number of runts. In addition, mean body weights for offspring in the F_1a generation were lower on day 21 postpartum due to lower body-weight gain on days 4–21 of lactation. The only parental finding was decreased mean body weight and body-weight gain, evident in parents in the 8000-ppm group during premating (P and F generation) and in 8000 ppm females during gestation (all

litters). Hence, the systemic NOEL was set at the next lower dose of 2000 ppm (equal to 113.1 mg/kg bw/d). A slight increase in mean seminal vesicle weight was noted for parental males in the 2000- and 8000-ppm groups, but was not considered adverse since there were no corresponding gross or histopathological findings.

Diflufenzopyr was not teratogenic to rat or rabbit fetuses at dose levels up to and including 1000 mg/kg bw/d (rats) and 300 mg/kg bw/d (rabbits). Fetotoxicity was noted in rabbit fetuses at 300 mg/kg bw/d (a maternally toxic dose), manifested as an increased incidence of abortions. The only treatment-related finding for rat fetuses was an increased incidence of incompletely ossified and/or unossified sternal centra noted for rat fetuses in the 1000-mg/kg bw/d group. However, this minor variation was not considered to be an adverse, toxicologically significant finding. Maternal findings were observed in rabbits at 300 mg/kg bw/d only and included loss of body weight and decreased food intake during the dosing period, and increased mortality. The only maternal effect seen in rats was slightly lower (non-adverse) body-weight gain and lower food intake noted during the first three days of dosing in the 1000 mg/kg bw/d group.

Diflufenzopyr showed no evidence of neurotoxicity in rats by either acute or subchronic exposure up to and including the highest dose levels tested of 2000 and 1000 mg/kg bw/d, respectively.

Table 3.1.7.1 Summary of the subchronic and chronic toxicity studies with diflufenzopyr

Type of study	Species	NOEL/NOAEL (mg/kg bw/d)
Oral route, 90 d	mice	1225 in males, 1605 in females
Oral route, 90 d	rats	352 in males, 431 in females
Oral route, 90 d	dogs	58 in males, 59 in females
Dermal route, 28 d	rabbit	1000 for both sexes
Genotoxicity (in vitro and in vivo)	—	negative
Oral route, 1 yr	dogs	26 for males, 28 for females
Oral route, 78 wk	mice	1037 for males, 1004 for females
Oral route, 104 wk	rats	236 for males, 323 for females
Carcinogenicity	mice	1037 for males, 1004 for females
Carcinogenicity	rats	518 for males, 697 for females
Multigeneration	rats	Systemic and Reproductive: 113.1 for males, 175.9 for females
Teratogenicity	rats	Maternal, fetotoxic and teratogenic:
Teratogenicity	rabbits	1000 Maternal, fetotoxic: 100
Acute oral neurotoxicity	rats	Teratogenic: 300 Systemic, neurotoxic: 2000, both sexes
Neurotoxicity, 13 wk	rats	Systemic: 75, both sexes Neurotoxic: 1000, both sexes

3.2 Determination of acceptable daily intake

The lowest NOEL was 750 ppm, equal to 26 mg/kg bw/d, established in the one-year dog feeding study, based on treatment-related hemolytic anemia (responsive) at higher dose levels. This is considered an appropriate study for determination of the acceptable daily intake (ADI) since the dog was the most sensitive species and there was no evidence of treatment-related oncogenicity in rats or mice, or reproductive/developmental effects in rats and rabbits.

For the calculation of the ADI, a safety factor (SF) of 100 is proposed.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF}} = \frac{26 \text{ mg/kg bw/d}}{100} = 0.26 \text{ mg/kg bw/d of diflufenzopyr}$$

The maximum acceptable intake for a 60-kg person, calculated according to the formula, ADI × 60 kg, is 15.6 mg/d.

3.3 Acute reference dose

For the acute reference dose (ARfD), the study considered most appropriate in the submitted toxicological database is the rabbit teratology study. The dose and endpoint selected for risk assessment is 100 mg/kg bw/d, based on an increased incidence of abortions noted at 300 mg/kg bw/d, the highest dose level tested. Abortions are considered an appropriate endpoint since they could result from either maternal and/or developmental toxicity after short-term (i.e., 14 d) exposure by oral gavage.

For the calculation of the ARfD, a SF of 100 is proposed.

The ARfD proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{100 \text{ mg/kg bw/d}}{100} = 1.0 \text{ mg/kg bw/d of diflufenzopyr}$$

3.4 Toxicology endpoint selection for occupational and bystander risk assessment

The formulation is slightly acutely toxic by the oral route, and of low acute toxicity by the dermal and inhalation routes. It is a slight skin irritant and a moderate eye irritant. Results of skin sensitization studies were positive.

Given the short-term nature of the exposure for farmers (one to several days per year) and the predominantly dermal exposure route, a dermal toxicity study is considered to be the most relevant study to use in the risk assessment. A 21-d dermal rabbit study with technical grade diflufenzopyr was well conducted and did not demonstrate any systemic

toxic effects at 1000 mg/kg bw/d, the highest dose tested. A NOEL for dermal effects could not be determined since local dermal irritation was observed at all doses tested, although there were no corresponding histopathological findings. A 21-d dermal rabbit study was also conducted with the Distinct® formulation (20% diflufenzopyr and 50% dicamba). This study was well conducted and did not demonstrate any systemic toxic effects at 100 mg formulation/kg bw/d, the highest dose tested. Local dermal irritation was observed at all doses tested, with corresponding histopathological findings in the 30- and 100-mg formulation/kg bw/d dose groups. These effects included diffuse acanthosis and diffuse/focal inflammation of the superficial dermis. In addition, diffuse hyperkeratosis was observed in the 100-mg/kg bw/d group. The systemic NOEL of 1000 mg/kg bw/d determined with the diflufenzopyr technical is considered most relevant for risk assessment.

The 21-d dermal study is not considered relevant for the longer-term custom applicators, due to their longer exposure period (several weeks per year). Based on the NOELs determined in short- and long-term studies, dogs were the most sensitive species tested. The NOEL of 58 mg/kg bw/d, determined in a three-month dog feeding study, was considered the most relevant to use in the risk assessment for custom applicators. This NOEL was based on erythroid hyperplasia in the bone marrow and extramedullary hematopoeisis in the liver at higher dose levels (i.e., 403 and 1121 mg/kg bw/d). Regenerative anaemia was evident at 1121 mg/kg bw/d only. Similar findings were seen in the one-year dog feeding study, at dose levels ≥ 299 mg/kg bw/d.

In a two-generation rat reproductive study, the NOAEL for parental toxicity and the NOEL for reproductive toxicity were the same: 113 and 176 mg/kg bw/d for males and females respectively. There was no evidence of teratogenic effects in rats or rabbits at any dose level tested.

Mutagenicity testing showed negative findings. There were no signs of oncogenic potential or neurotoxicity.

3.5 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

3.5.1 Operator exposure and risk assessment

A farmer applying Distinct® by ground equipment would typically treat 90 ha/d and be exposed for one or two days per season. A custom applicator could treat up to 400 ha/d and be exposed intermittently for several weeks per growing season.

Pesticide operator exposure was estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader/ applicator and flagger passive dosimetry data with associated software that facilitates the generation of scenario specific exposure estimates. The following PHED estimates meet North American Free Trade Agreement criteria for data quality, specificity and quantity.

To estimate total dermal and inhalation exposure for groundboom application, appropriate subsets of A and B grade data were created from the mixer/loader and from the applicator PHED database files. There were no relevant data available in the mixer/loader/applicator database file. The mixer/loader file was subset for open mixing, dry flowable formulations and to exclude replicates for packaging in water soluble packets. The applicator file was subset for application by groundboom tractor or truck with open cabs. The number of replicates for inhalation and dermal data were acceptable (range 16–40). In the PHED subsets, the mean and range of pesticide mixed and applied and the sampling time were of the same order of magnitude as the estimated 5.1 kg a.i./d handled by a farmer treating 90 ha with 57 g a.i./ha in an 8-hour workday.

Protective clothing specified on the label for mixer/loaders are long-sleeved shirts, long pants, shoes and socks, chemical-resistant gloves and protective eyewear (face shield or safety glasses). Exposure was estimated for mixer/loaders wearing long pants, long-sleeved shirts and gloves and for applicators wearing long pants, long-sleeved shirts and no gloves. The PHED Version 1.1 uses actual data and does not assume clothing penetration factors.

All data were normalized for kg/a.i. handled. Exposure estimates are presented on the basis of the "best-fit" measure of central tendency (i.e., on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part [arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution]). Exposure estimates and margin of exposure calculations were based on (1) farmers mixing/loading and applying Distinct® at 57 g a.i./ha to 90 ha/d on a few days per growing season and (2) custom applicators mixing/loading and applying Distinct® at 57 g a.i./ha to 400 ha/d intermittently over several weeks. Exposure was predominantly dermal. As no percutaneous absorption data were available, the default assumption was 100% absorption.

Although the PHED does not include data from which to estimate exposure during clean-up/repair activities, PHED data provide an adequate basis for estimating occupational exposure for the proposed use.

Table 3.5.1.1 Estimated operator exposure and resulting margins of exposure

Operator exposure scenario		Daily exposure (dermal + inhalation) 70-kg operator (mg/kg bw/d)	Margin of exposure (NOEL/exposure)
Application at 57 g a.i./ha. Mixer/loaders wearing long pants, long-sleeved shirts and gloves. Applicators wearing long pants, long-sleeved shirts and no gloves.	Farmer: Mixer/loader/applicator treating 90 ha	0.015	67 000[a]
	Custom applicator: Mixer/loader treating 400 ha	0.054	1100[b]
	Custom applicator: Applicator treating 400 ha	0.011	5300[b]
	Custom applicator: Mixer/loader/applicator treating 400 ha	0.065	900[b]

[a] Based on a NOEL of 1000 mg/kg bw/d from a 21-d dermal rabbit study.

[b] Based on a NOEL of 58 mg/kg bw/d from a three-month dog feeding study and a default assumption of 100% dermal absorption.

The margins of exposure, calculated on the basis of typical Canadian use patterns, are acceptable for both farmers and custom applicators.

3.5.2 Bystanders

Given that application is by ground equipment only and the proposed agricultural use scenario, exposure and risk should be minimal.

3.5.3 Workers

Data are not available to make a quantitative estimate of re-entry exposure. However, the proposed use pattern is such that re-entry exposure should be minimal. Application is at a pre-emergence or postemergence stage (up to 60 cm crop height). Workers may re-enter treated fields to monitor crops to assess efficacy, typically 7–10 d following application, but these tasks would involve little foliar contact and, thus, minimal exposure and risk. Based on the acute toxicity profile, the restricted entry interval should be 12 hours.

4.0 Residue

4.1 Residue summary

Nature of the residue in corn

Corn metabolism studies were performed under field conditions in micro plots without soil containment. These studies showed that when corn was treated at 4× the Canadian label rate and near the proposed 4- to 6-leaf stage, the TRRs in corn silage, fodder, forage and grain were 0.15, 0.17, 0.4 and 0.008 ppm, respectively. No parent compound was detected in any of the corn matrices. Major metabolites (≥ 10% TRR and/or ≥ 0.05 ppm) identified were, in decreasing order, M1, M10 (free and as its glucoside) and M9. Minor metabolites, M19 and glucoside of M19 (M20), were also identified. The proposed metabolic pathway for diflufenzopyr in corn is shown in Figure 4.1.

TTRs (both ^{14}C-pyridine and ^{14}C-phenyl labels) in grain were < 0.01 ppm at 4× the Canadian label rate. It is, therefore, expected that the TRRs in corn grain will be even lower when diflufenzopyr is used according to the Canadian label.

Diflufenzopyr was not detected in the metabolism studies due to its rapid degradation to M1. Therefore, the ROC may be defined as the parent compound and its metabolites convertible to M1.

Accumulation in rotational crops

Field plots for the corn metabolism study were used for the submitted confined crop rotational study. Leafy vegetable (lettuce), root vegetable (carrots) and small grain cereal (barley) crops were planted in the corn metabolism plots at 30, 120, 298 and 365 d after treating the corn.

The confined crop rotational study was conducted at an application rate of 224 g a.i./ha (4× the Canadian label rate). Two rows of corn seedlings were sprayed, and it was estimated that 80% of the test solution reached the soil. For the edible fractions, results show that TRRs were ≤ 0.028 ppm for the 30 DAT samples and < 0.01 ppm for the 120 DAT samples. The results from another study, a limited field study, show that residues of diflufenzopyr and M1 were below the LOQ of BASF Method D9709 (0.05 ppm as diflufenzopyr equivalents) in radishes, lettuce and wheat that were planted 30 DAT and treated at 2.5× the Canadian label rate.

Based on the data reviewed, it is unlikely that for a plantback interval (PBI) of 30 days, any residues of the parent compound and its metabolites will exceed 0.01 ppm in the rotational crops when corn is treated with diflufenzopyr at the Canadian rate of 57 g a.i./ha.

The PMRA recommends a 30 day PBI for the formulated product.

Nature of the residue in animals

In the rat metabolism study, 20–44% of the applied dose was excreted in the urine and 49–79% of the applied dose was excreted in the faeces within 72 hours of dosing. Diflufenzopyr was excreted primarily as unchanged parent compound. Minor amounts of hydrolysis products (M1, M5 and M6) and hydroxylation products (M9, M10 and M19) were identified in excreta.

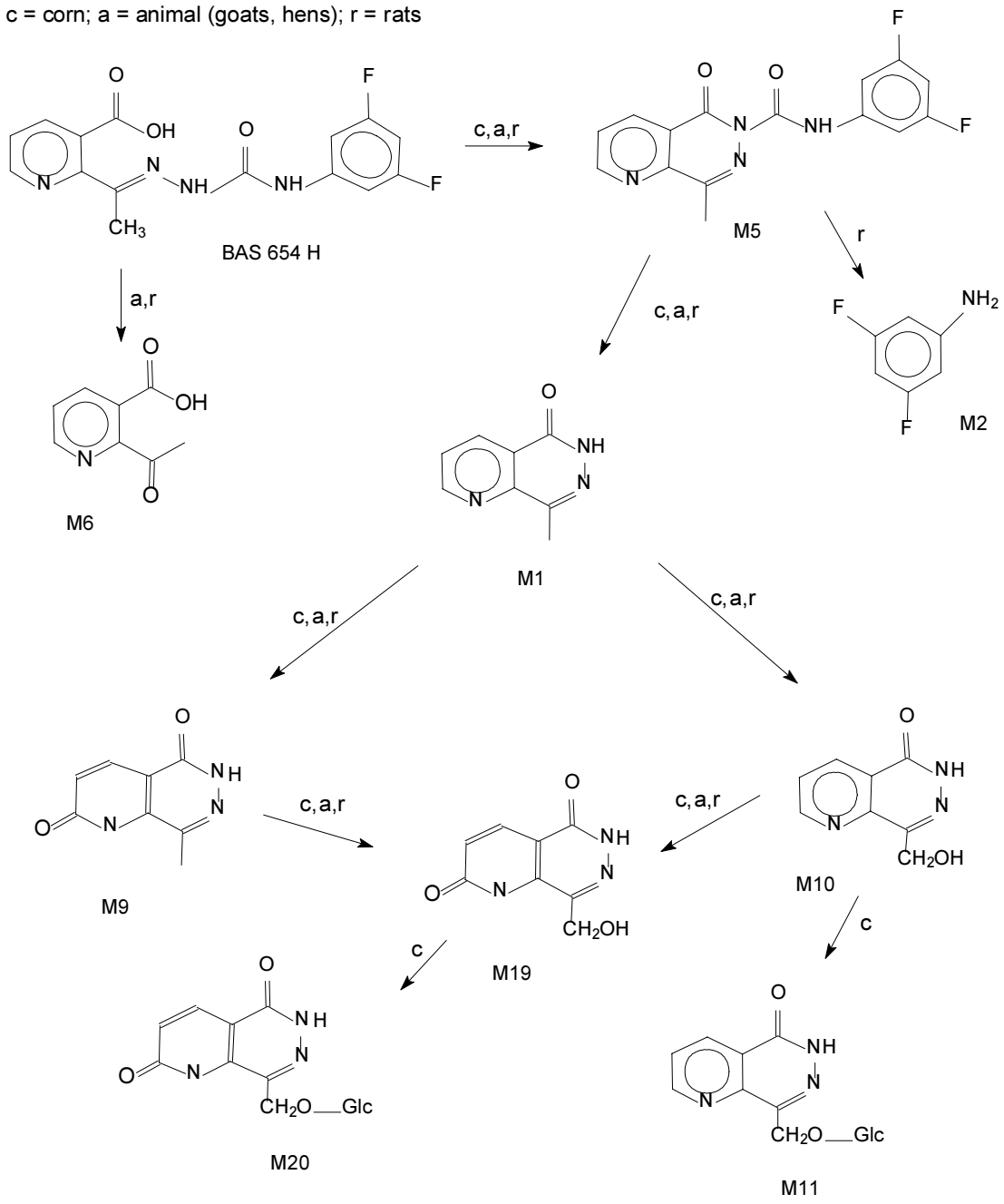
The goat metabolism study indicated that diflufenzopyr was partially metabolized and rapidly eliminated from the animals. At a feeding level of 10 ppm diflufenzopyr in the goat diet for four consecutive days, the maximum TRR, 0.113 ppm, was found in kidney at after goats were sacrificed within 24 h of the last dose. The TRRs were < 0.01 ppm in muscle and 0.09 ppm in milk samples. Approximately 90% of the applied dose was excreted in urine and faeces. In addition to the parent compound, the metabolites identified in goat urine, kidney, liver, and milk were M1, M5, M6 and M19.

In the laying hen metabolism study, at a feeding level of 10 ppm for four consecutive days, 99% of the applied dose was eliminated in the excreta when hens were sacrificed within 24 hours of the last dose. Furthermore, only 0.06–0.09% of the dose was found in the tissues and eggs. Data from excreta analysis indicate that 31.2–48.2% of the TRR was excreted as parent compound and 19.9–37.1% was excreted as M5. Minor metabolites (M1, M6, M9, M10 and M19) were also identified in the excreta. The TRRs detected in most tissues were ≤ 0.006 ppm, except for the case of ^{14}C-phenyl liver, where the TRR was detected at a maximum level of 0.022 ppm, and for the case of ^{14}C-pyridine egg white, where the TRR was detected at a maximum level of 0.015 ppm. The TRRs in muscle were < 0.005 ppm.

The metabolic profiles for diflufenzopyr in the rat, the goat and the hen are similar. Diflufenzopyr is partially metabolised to M5, which is further metabolized to M1, M9, M10, and M19. Diflufenzopyr is also metabolised to M6. These proposed pathways are shown in Figure 4.1.

The anticipated residue levels in treated corn commodities were less than the method LOQ (0.05 ppm, as diflufenzopyr equivalent). In order to compensate for the absence of data at the anticipated feeding level, extrapolation of the animal metabolism study data was undertaken to estimate residues at the 1× feeding level. On this basis, the TRRs in all edible livestock commodities are anticipated to be ≤ 0.0006 ppm (0.6 ppb). Therefore, an animal feeding study is not required, and MRLs for meat, milk and eggs are not needed.

Figure 4.1 The proposed metabolic pathway of diflufenzopyr in corn, goats, hens and rats



Methods for residue analysis of plants and plant products

Sandoz Agro Method AM-0966-0995-0 was used as a data gathering method and as an enforcement method. According to this method, residues are extracted with aqueous sodium bicarbonate and ammoniated acetone. Following conversion of diflufenzopyr to M1 by heating the residues in an ethyl acetate solution, residues of M1 are analyzed by GC/NPD or GC/MSD. The reported LOQ is 0.02 ppm and the LOD is 0.02 ppm, as parent equivalents (using NPD). The average recoveries for samples of corn grain, forage and fodder that were spiked with either diflufenzopyr or M1 at levels ranging from 0.01 to 0.1 ppm generally were within the 70–120% acceptable range (n = 126), with the following exceptions: 2 very low (10 and 12%) and 2 very high (177 and 339%) recovery values, as well as 2 samples that could not be quantified because of interference. This method was successfully validated by an independent laboratory. Radiovalidation data show variable recovery (40–95%) when samples of silage and fodder from the corn metabolism study were analyzed for diflufenzopyr. At the time that the temporary registration was granted for this product in Canada, it was indicated that more radiovalidation data would be needed if additional crops were to be registered. Since that time, no new crops have been added to the Canadian label.

BASF Method D9709 was reviewed as an enforcement method to replace Sandoz Agro Method AM-0966-0995-0. According to this replacement method, residues of diflufenzopyr are extracted from corn RACs and processed fractions using dilute aqueous sodium bicarbonate and ammoniated acetone. Diflufenzopyr is converted to M1 and analyzed using GC/MS. The LOQ is reported as 0.05 ppm and the LOD as 0.017 ppm, in parent equivalents. Individual recoveries of diflufenzopyr and M1 from corn RACs spiked at 0.05 ppm ranged from 72 to 97% (n=15) and 87 to 107% (n=15), respectively. For corn RAC spiked at 0.1 ppm, individual recoveries ranged from 69 to 94% (n=12) and 90 to 102% (n=12) for diflufenzopyr and M1, respectively. Similar recoveries were obtained for corn processed fractions (starch and refined oil) spiked in the same way.

Freezer storage stability

Plants:

All the corn samples from the supervised residue trials were analyzed within 12 months. Freezer storage stability data indicated that M1 and M10 were stable in samples of corn silage, fodder and grain spiked at 0.1 ppm and stored at -12°C (10°F) for 24 months. No data on diflufenzopyr were available. However, since the corn metabolism study showed that parent compound was not present in any of the corn RAC samples that were analyzed, the absence of freezer storage stability data for diflufenzopyr in corn RACs is not considered a deficiency for corn.

Animals:

As residues are not anticipated in the animal feedstuffs, animal feeding studies are not required. Consequently, freezer storage stability data for animal commodities are also not required.

Supervised residue trials
Seven supervised residue trials were conducted for field corn in Eastern Canada in the following zones: 2 trials in Zone 5 at 2×, 2 trials in Zone 5 at 4×, 2 trials in Zone 5B at 2× and 1 trial in Zone 5B at 1.5× the Canadian label rate. The results of these residue trials indicate that when field corn is treated with diflufenzopyr at 1.5–4× the Canadian label rate and harvested 60 d following application no residues of M1 and M10 were detected above the LOQ (0.01 ppm as M1 equivalents and 0.05 ppm, respectively) in corn forage. At harvest (preharvest interval of 120 days), residues of M1 and M10 in corn fodder and grain were also below the LOQs. Since residues of parent are converted to M1 according to the analytical method, these results also indicate that there were no detectable residues of parent. On this basis, an MRL of 0.05 ppm (diflufenzopyr plus residues convertible to M1, as diflufenzopyr equivalent) was promulgated following the joint review with the USEPA. This MRL is harmonized with American tolerances.

Processing studies
Grain was processed by both dry and wet milling into grits, refined oils, meal and starch. The corn grain and processed fractions analyzed for M1 and M10 showed that all residues were below the method LOQ. Therefore, residues are not expected to concentrate during processing, and MRLs are not recommended for corn processed fractions.

Meat/milk/poultry/eggs
The anticipated residue levels in treated corn commodities are less than the LOQ. The ROC (parent and M1) in all edible livestock commodities are anticipated to be $\leq$ 0.0006 ppm (0.6 ppb) when extrapolated from the animal metabolism studies to the anticipated 1× feeding level. Therefore, an animal feeding study is not required, and MRLs for meat, milk and eggs are not recommended.

Dietary risk assessment
The domestic use of diflufenzopyr on field corn does not pose an unacceptable chronic or acute dietary risk to any segment of the population, including infants, children, adults and seniors. For this assessment, chronic and acute dietary aggregate (food and water) exposure assessments were conducted to determine exposure and risk that would result from the use of diflufenzopyr on field corn in Eastern Canada. Because residues are below the LOQ, the dietary risk assessment assumed MRLs and that 100 % of the crop was treated. For the chronic dietary risk assessment, the risk estimate for the representative population subgroups ranged from 0.0 to 0.1% of the ADI (ADI = 0.26 mg/kg bw/d). The dietary risk estimates were below the level of concern (100 % ADI) for the general population and all of the population subgroups. The acute dietary exposure for females 13 years of age and over is 0.02 % (ARfD = 1.0 mg/kg bw/d). On this basis, there was no need to refine the dietary risk assessment.

Since the current use of diflufenzopyr is restricted to agricultural use patterns, the aggregated exposure assessment that was conducted included dietary exposure from food and water only. The acute and chronic aggregate exposures are acceptable and do not exceed the level of concern.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

Diflufenzopyr was determined to be of high solubility in water (pH 5: 270; pH 7: 5850; pH 9: 10546 mg/L). The vapour pressure of diflufenzopyr at 20 and 25°C indicates that the compound is relatively non-volatile ($< 1 \times 10^{-7}$ mm Hg). The Henry's Law constant of diflufenzopyr indicates that the compound will have a low potential to volatilize from water and moist surfaces (7×10^{-7} Pa m^3/mole). The magnitude of the *n*-octanol–water partition coefficient for diflufenzopyr indicates there is negligible potential for bioaccumulation (pH 5: 2.7; pH 7: 0.34; pH 9: 0.17). The dissociation constant, pKa, of the compound indicates it predominates as an anion at acidic and neutral and basic pH (pKa = 3.18). The UV–visible absorption spectrum of diflufenzopyr indicates that the compound has negligible potential to phototransform at environmentally relevant wavelengths of light (λ nm: 234.1 and 294.5; ϵ (l/mol-cm): 1.98×10^4 and 1.43×10^4, respectively).

5.2 Abiotic transformation

The rate of hydrolysis for diflufenzopyr was pH-dependent. The half-life values, based on first-order kinetics, were 12.9, 23.9 and 25.6 d at pH 5, pH 7 and pH 9, respectively. The major transformation products were M1 and M6 (at pH 5 only). The potential for persistence of these compounds in aqueous environments was not determined. The phototransformation half-life of diflufenzopyr on a soil surface was 14 d (total illumination). Diflufenzopyr transformed to M5 and subsequently to M1. The phototransformation half-lives of diflufenzopyr in water were 6.8, 16.8 and 13.4 d (total illumination) at pH 5, pH 7 and pH 9, respectively. Abiotic transformation, therefore, will be an important route of transformation in water.

5.3 Biotransformation

Results of biotransformation studies with diflufenzopyr in a loam soil under aerobic conditions at 23°C and 0.3 mg/kg soil application rate yielded half-lives of 8 and 10 days in the phenyl- and pyridyl- labelled material, respectively. The major transformation product M9 was formed and persisted until study termination (360 days), indicating a potential for carry-over to the next growing season. These results indicated that diflufenzopyr is not persistent, while the transformation product, M9, is persistent under aerobic soil conditions (Goring et al. 1975).

Results of biotransformation studies with diflufenzopyr under aerobic aquatic conditions at 25°C and a 0.16-µg/L application rate showed half-lives of 26 and 25 days for phenyl- and pyridyl-labelled material, respectively. Major transient transformation products M1 and M9 were detected at a maximum of 16% of the applied radioactivity. These results indicated that diflufenzopyr is slightly persistent under aerobic aquatic conditions (McEwan and Stephenson 1979).

Results of biotransformation studies with diflufenzopyr in a sandy loam soil and pond water under anaerobic conditions at 25°C and 0.01 to 5.3 mg/L application rates yielded half-lives of 20 to 26 days for the high and low doses of the pyridyl and phenyl labels, respectively. The major transformation products that were detected in the water/sediment system with pyridyl-labelled diflufenzopyr were M1 and M9. The major transformation product with the phenyl label was M2. M9 has a potential for persistence in water and in sediment. These results indicated that diflufenzopyr is slightly persistent under anaerobic aquatic conditions (McEwan and Stephenson 1979).

5.4 Mobility

The adsorption constants (K_{oc} values ranged from 18 to 156) indicated that diflufenzopyr has a moderate to very high potential for mobility. The relatively high K_{oc} value (156) for silt loam soil was attributed to the high rate of transformation that occurred in this soil. The adsorption constants for M1 (K_{oc} values ranged from 140 to 596) indicated that this transformation product has a low to high potential for mobility. The transformation product, M9, (K_{oc} values 128–1087) has a low to moderate potential for mobility.

5.5 Dissipation and accumulation under field conditions

Results of terrestrial field studies of dissipation and accumulation conducted in Canada (Strathroy, Ontario, and Cambridge, Ontario) in bare plots indicated that diflufenzopyr was not persistent in soil, with decline time (DT_{50}) values of 4 and 8.45 days, respectively. Although the aerobic soil biotransformation study indicated a potential for M9 to persist in soil, this major transformation product was not detected in either field study. Diflufenzopyr and transformation products M1 and M2 were not detected below 15 cm of the soil surface in the terrestrial dissipation studies and, thus, were not mobile under field conditions at the test sites.

5.6 Bioaccumulation

Data not required based on low K_{ow}.

5.7 Summary of fate and behaviour in the terrestrial environment

Diflufenzopyr was determined to be of high solubility in water. The vapour pressure and Henry's Law constant indicate that the compound is relatively non-volatile and has a low potential to volatilize from water and moist surfaces. The magnitude of the *n*-octanol–water partition coefficient for diflufenzopyr indicates there is negligible potential for bioaccumulation, and the dissociation constant, pKa, of the compound indicates it predominates as an anion at acidic and neutral and basic pH. The UV–visible absorption spectrum of diflufenzopyr indicates that the compound has negligible potential to phototransform at environmentally relevant wavelengths of light. The rate of phototransformation on soil is not expected to be an important route of transformation,

whereas in water it is. Hydrolysis is also expected to be an important route of transformation in the environment.

Results of biotransformation studies using a loam soil under aerobic conditions indicate that diflufenzopyr will be non persistent, and transformation product M9 will be persistent (Goring et al. 1975).

The adsorption K_{oc} values for diflufenzopyr (18 to 156 mL/g) in varying soil types (loam, sandy loam, silt loam, clay loam and sandy clay loam) indicate that diflufenzopyr has a moderate to very high potential for mobility. The adsorption constants for M1 (K_{oc} values ranged from 140 to 596) indicates that this transformation product has a low to high potential for mobility. Transformation product M9 (K_{oc} values 385–3668) has a slight to moderate potential for mobility.

Results of two terrestrial field studies of dissipation and accumulation conducted in Canada (Strathroy, Ontario, and Cambridge, Ontario) on bare plots indicate that diflufenzopyr will not be persistent in soil, with DT_{50} values of 4 and 8.45 days, respectively. Although the aerobic soil biotransformation study indicated a potential for M9 to persist in soil, this major transformation product was not detected in either field study. Diflufenzopyr and transformation products M1 and M2 were not detected below the first 15 cm of soil in the terrestrial dissipation studies and, thus, were not mobile under field conditions at the test sites.

5.8 Summary of fate and behaviour in the aquatic environment

Hydrolysis and phototransformation in water are expected to be important routes of abiotic transformation in the environment.

Results of biotransformation studies under aerobic aquatic conditions indicate that diflufenzopyr is expected to be slightly persistent under aerobic aquatic conditions (McEwan and Stephenson 1979). Major transient transformation products M1 and M9 were detected at a maximum of 16% of the applied radioactivity and are not expected to persist in the aquatic environment.

Results of biotransformation studies in a flooded sandy loam soil with pond water under anaerobic conditions indicate that diflufenzopyr is expected to be slightly persistent under anaerobic aquatic conditions (McEwan and Stephenson 1979). Of the two major transformation products that were formed, M1 was transient and M9 has potential for persistence in water and sediment under anaerobic conditions.

5.9 Expected environmental concentrations

The concentrations of diflufenzopyr in various environmental compartments were estimated based on calculations using maximum-exposure scenarios. It was assumed that, as per the label rates for Distinct®, a maximum of 57 g a.i./ha is applied once per year.

5.9.1 Soil

Assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, and bare soil application, the expected environmental concentration (EEC) of residues in soil would be 0.025 mg a.i./kg soil.

5.9.2 Aquatic systems

Direct overspray in surface water
Assuming water density of 1 mg/L, water depth of 30 cm and a scenario in which a body of water is oversprayed with the product, the EEC in water would be 0.019 mg a.i./L (equivalent to 0.095 mg EP/L).

Drinking water
Based on potential use pattern of diflufenzopyr in areas where corn is grown, residues of diflufenzopyr in potential drinking water sources in these areas were calculated using the models PRZM/EXAMS (for surface water) and LEACHM (for groundwater). The models were run using relevant, most conservative agricultural scenarios and the environmental profile of diflufenzopyr. There is no leaching of diflufenzopyr to groundwater over the 20-year simulation period (0.00056 [acute] and 0.00051 [chronic] µg/L). The acute surface water concentration is 3.66 µg/L for reservoir, and the chronic surface water concentration is 0.15 µg/L (Appendix I, Table 5).

5.9.3 Vegetation and other food sources

The applicant did not submit data on the concentrations of diflufenzopyr on crops immediately after application. Therefore, residue concentrations on vegetation were estimated using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), modified by Fletcher et al. (1994), using the maximum Canadian label rate for diflufenzopyr (57 g a.i./ha) for use in ecological risk assessment (Urban and Cook 1986) (Appendix I, Table 6). No information was available on the dissipation of diflufenzopyr on wildlife food sources; therefore, it was assumed that no dissipation occurred. A wet weight to dry weight conversion was also calculated.

5.9.4 Monitoring data

Data not required.

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The effects of diflufenzopyr on terrestrial organisms are presented in Appendix I, Table 7.

Earthworms: The 14-d LC_{50} and NOEC, based on mortality to earthworms (*Eisenia foetida*), were > 1000 and 500 mg a.i./kg soil, respectively. Diflufenzopyr is considered to be non-lethal to earthworms above a concentration of 500 mg a.i./kg soil.

Honeybees: The 48-h oral and contact LC_{50} and NOEC to honeybees (*Apis mellifera*) were > 25 µg a.i./bee and 25 µg a.i./bee, respectively, for both studies. In accordance with the classification of Atkins et al. (1981), diflufenzopyr is categorized as non-toxic to bees.

Birds: The acute oral 14-day LD_{50} and NOEL based on mortality to bobwhite quails were > 1868 and 1868 mg a.i./kg (adjusted to purity of test material), respectively. The 5-d dietary LC_{50} to bobwhite quails and mallard ducks were both > 4608 mg a.i./kg feed. The corresponding 5-d NOECs based on food consumption and body weight were 4608 and 2591 mg a.i./kg diet for the bobwhite quail and mallard duck, respectively. Thus, in accordance with USEPA classifications, diflufenzopyr is categorized as at most slightly toxic to bobwhite quails and mallard ducks. During the one-generation reproductive study with the mallard duck, diflufenzopyr caused no toxic effects to parental generation, reproductive performance parameters and hatchlings. Thus, the NOEC and LOEC were 1000 and > 1000 mg a.i./kg diet.

Mammals: Diflufenzopyr was considered to be of low acute toxicity by oral (LD_{50} > 5000 mg/kg bw), inhalation and dermal routes, and of low toxicity by the dermal and inhalation routes. In a short term dietary study (13 weeks), the NOEL based on body-weight gain were 5000 (highest dose tested) and 7000 mg a.i/kg diet, in rats and mice, respectively. Diflufenzopyr affected reproductive performance in rats at 8000 mg a.i./kg diet, manifested as lower live birth and viability indices. Mean body weights for offspring were lower in the F1 generation.

Terrestrial plants: The effect of Distinct® herbicide was studied at 0 (control), 4.4, 9.1, 17.5, 35, 70, 140, 280 and 560 g EP/ha on the vegetative vigour of 4 monocots (corn [*Zea mays*], ryegrass [Lolium perenne]), wheat [*Triticum aestivum*] and onions [*Allium cepa*]) and 6 dicots (cucumbers [*Cucumis sativus*], radishes [*Raphanus sativus*], soybeans [*Glycine max*], sugarbeets [*Beta vulgaris altissima*], sunflowers [*Heliantus annus*] and tomatoes [*Lycopersicon esculentum*]. There were no effects of Distinct® herbicide on the shoot weight, length or phytotoxicity in monocot species. In contrast, the shoot weight and length of all dicot species were inhibited (shoot length: 34–82% inhibition; shoot weight: 26–97% inhibition). The tomato was the most sensitive plant for dry shoot weight (NOEC and EC_{25}: 4.4 and 21.4 g EP/ha, respectively) and shoot length (NOEC and EC_{25}: 35 and 31.8 g EP/ha, respectively). Significant phytotoxicity was also observed in all dicot species. The most sensitive dicot species was the radish; the NOEC value (based on

phytotoxicity) was 35 g EP/ha and the EC_{25} was 14.7 g EP/ha. Statistical determination of the NOEC in this study indicated that no significant effect was observed for phytotoxicity, despite up to 30% phytotoxity in plants at 35 g EP/ha. Variation in the data set was the reason for this result. Therefore, statistically, the NOEC value was higher than the EC25; however, biological significance may occur at these rates of phytotoxicity in the environment.

6.2 Effects on aquatic organisms

The effects of diflufenzopyr on aquatic organisms are presented in Appendix I, Table 8.

Freshwater

Daphnids: The acute 48-h NOEC based on mortality and LC_{50} to *Daphnia magna* were 9.7 and 15 mg a.i./L, respectively. In accordance with the USEPA classifications (1985), diflufenzopyr would be classified as slightly toxic to daphnia on an acute basis.

Fish: The acute 96-h LC_{50} and NOEC based on mortality to rainbow trout (*Oncorhynchus mykiss*) were 106 and 80 mg a.i./L, respectively. The acute 96-h LC_{50} and NOEC based on mortality to bluegill sunfish (*Lepomis machrochirus*) were > 135 and 16 mg a.i./L, respectively. In accordance with the classification scheme of USEPA (1985), diflufenzopyr is practically non-toxic to fish on an acute basis.

Algae: The 5-d EC_{50} based on biomass and growth rate for two species of bluegreen algae, *Anabaena flos-aquae* and *Selenastrum capricortunum*, were 0.15 and 0.11 mg a.i./L, respectively. The corresponding NOECs were 0.014 and 0.0078 mg a.i./L. An additional study was conducted with the formulated EP, Distinct®, and *Anabaena flos-aquae*. The EC_{50} and NOEC for that study were > 0.26 (equivalent to 1.3 mg a.i./L) and 0.0059 mg EP/L (equivalent to 0.029 mg a.i./L), respectively.

Diatom: The 5-d EC_{50} and NOEC based on biomass to *Navicula pelliculosa* were 0.10 and 0.003 mg a.i./L, respectively.

Aquatic plants—Duckweed: The 7-d EC_{50} and NOEC based on biomass to duckweed (*Lemna minor*) were > 0.35 and 0.0039 mg a.i./L, respectively. An additional study was conducted with the formulated EP, Distinct®, and *Lemna minor*. The EC_{50} and NOEC for that study were > 0.11 (equivalent to 0.55 mg EP/L) and 0.0023 mg a.i./L, respectively.

Marine

Crustacean: The acute 96-h EC_{50} and NOEC based on inhibition of shell growth to eastern oyster (*Crassostrea virginica*) were 61 and 31 mg a.i./L, respectively. Up to 20% reduction in shell deposition was noted in the lowest test concentration, which could be biologically significant. Based on USEPA classifications (1985), diflufenzopyr is slightly toxic to eastern oyster on an acute basis.

Mysid shrimp: The acute 96-h LC_{50} and NOEC based on mortality to mysid shrimp (*Mysidopsis bahia*) were 18.9 and 4.4 mg a.i./L, respectively. Based on USEPA classifications (1985), diflufenzopyr is slightly toxic to mysid shrimp on an acute basis.

Fish: The 96-h acute LC_{50} and NOEC based on mortality to sheepshead minnow (*Cyprinodon variegatus*) were > 138 and 138 mg a.i./L, respectively. In accordance with USEPA classifications (1985), diflufenzopyr would be practically non-toxic to fish on an acute basis.

Diatom: The 5-d EC_{50} and NOEC based on biomass to diatom (*Skeletoneum costatum*) were 0.12 and 0.0064 mg a.i./L, respectively.

6.3 Effects on biological methods of sewage treatment

The PMRA does not currently require data regarding effects on biological methods of sewage treatment.

6.4 Risk characterization

Risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The PMRA currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the risk quotient method, which is the ratio of the EEC ÷ toxicity endpoint. The endpoint used for both acute and chronic toxicity is the NOEC from the appropriate laboratory study. Those cases for which a NOEC was not reported, the value was estimated as $0.1 \times LD_{50}$ or $0.1 \times LC_{50}$.

6.4.1 Environmental behaviour

For terrestrial and aquatic abiotic transformation, phototransformation in soil was not important route of transformation, whereas hydrolysis and phototransformation in water are expected to be important routes of transformation in the environment.

For biotic transformation in the terrestrial environment, diflufenzopyr was not persistent under aerobic soil conditions and transformation product M9 was persistent (Goring et al. 1975). The adsorption K_{oc} values for diflufenzopyr indicated that diflufenzopyr has a moderate to very high potential for mobility. Transformation product M1 had low to high mobility and M9 had slight to moderate mobility. Under field conditions, diflufenzopyr was not persistent and did not leach through the soil profile. The difference in mobility between the laboratory study and the field study was probably attributed to rapid transformation in the field study.

For biotic transformation in the aquatic environment, diflufenzopyr was slightly persistent under aerobic aquatic conditions (McEwan and Stephenson 1979). Major transient transformation products M1 and M9 were detected at a maximum of 16% of the applied

radioactivity, and were not expected to persist in the aquatic environment. Under anaerobic aquatic conditions, diflufenzopyr was slightly persistent (McEwan and Stephenson 1979). Of the two major transformation products that were formed, M1 was transient and M9 persisted in water.

6.4.2 Terrestrial organisms

The risk of diflufenzopyr to terrestrial organisms is presented in Appendix I, Table 10.

Earthworms: The acute NOEC and LC_{50} for earthworms were 500 and > 1000 mg a.i./kg soil, respectively, and the EEC in soil was 0.025 mg a.i./kg soil. Based on the risk quotient (0.00005), there is negligible risk to worms.

Honeybees: The acute NOEC and LC_{50} for honeybees were 25 and > 25 µg a.i./bee, respectively. According to Atkins et al. (1981), diflufenzopyr poses a negligible hazard to honey bees based on acute contact and feeding.

Wild birds: Wild birds, such as mallard ducks and bobwhite quails, could be exposed to diflufenzopyr residues as a result of spray drift or consumption of sprayed vegetation or contaminated prey. The mallard duck consists of approximately 30% arthropods and 70% grain (USEPA). The bobwhite quail diet may consist of approximately 30% small insects, 15% forage crops, and 55% grain and seeds.

Since the EECs of diflufenzopyr for bobwhite quails on small insects, forage crops and grain are 11.26, 36.94 and 1.93 mg a.i./kg dw, respectively (Appendix I, Table 6), the estimated ingestion of diflufenzopyr is calculated as follows:

$$(0.30 \times 11.26) + (0.15 \times 36.94) + (0.55 \times 1.93) = 9.98 \text{ mg a.i./kg dw}$$

Since the EECs of diflufenzopyr for mallard ducks on arthropods and grain are both 1.928 mg a.i./kg dw (Appendix I, Table 6), the estimated ingestion of diflufenzopyr is calculated as follows:

$$(0.30 \times 1.93) + (0.70 \times 1.93) = 1.93 \text{ mg a.i./kg dw}$$

Acute. The 14-d NOEC and LD_{50} for the bobwhite quail were 1868 and > 1868 mg a.i./kg bw. Assuming a mean body weight per individual (BWI) of 0.193 kg bw/ind and food consumption (FC) of 15.2 g of food, the potential daily intake (DI) of diflufenzopyr (DI = FC × EEC) was calculated as 151.70 mg a.i./ind./d. When expressed on a per individual basis, the LD_{50} (ind.) (equal to LD_{50} × BWI) was 360.5 mg a.i./ind., and the NOEL (ind.) was 360.5 mg a.i./ind. Based on the DI, it would take a bobwhite quail at least 2.4 days (LD_{50} (ind.) ÷ DI) of consumption of a contaminated diet to attain the dose equivalent to that administered in the laboratory that had no observable effect on mortality. Since it takes longer than one day to reach the NOEC for mortality, diflufenzopyr poses a negligible acute risk to bobwhite quails.

Dietary. The 8-d LC_{50} and NOEC for bobwhite quails were > 4608 and 4608 mg a.i./kg diet, respectively; the 8-d LC_{50} and NOEC for mallard ducks were > 4608 and 2591 mg a.i./kg diet, respectively. Based on the risk quotients (0.002 and 0.0007), there is negligible dietary risk to bobwhite quail and mallard ducks, respectively.

Reproductive. The one-generation reproductive LOEC and NOEC for mallard ducks were > 1000 and 1000 mg a.i./kg diet, respectively. Based on the risk quotient (0.0019), there is negligible reproductive risk to mallard ducks.

Wild mammals: Wild mammals, such as rats and mice, could be exposed to residues of diflufenzopyr as a result of the consumption of sprayed vegetation and/or contaminated prey. From Appendix I, Table 6, assuming no transformation, the EECs of diflufenzopyr in the diets of rats and mice were 28.76 and 28.58 mg a.i./kg dw, respectively.

Acute. In the assessment of the risk to rats, default values were used for food consumption (FC = 0.06 kg dw/ind/d) and body weight per individual (BWI = 0.350 kg bw/ind). Based on the daily intake (DI = FC × EEC) of 1.73 mg a.i./ind/day and the LD_{50} of 5000 mg a.i./kg bw, the LD_{50} (ind.) (LC_{50} × BWI) is 1750 mg a.i./kg bw. Since the NOEL was not reported, one tenth the LD_{50} was 500 mg a.i./kg bw, and thus the NOEL (ind.) was 175 mg a.i./kg bw. Therefore, a wild mammal would have to consume diflufenzopyr for up to 101 days to attain a dose equivalent to that administered in the laboratory resulting in no observable effect on mortality. Since it takes longer than one day to reach the NOEL for mortality, diflufenzopyr poses a negligible acute risk to small mammals.

Dietary. The short term NOELs for rats and mice were 5000 and 7000 mg a.i./kg diet, respectively. Based on the risk quotients (0.0058 and 0.0041), there is negligible dietary risk to small mammals.

Reproductive. The multigeneration reproductive NOEC for rats was 8000 mg a.i./kg diet. Based on the risk quotient (0.0036), there is negligible reproductive risk to small wild mammals.

Terrestrial plants: The most sensitive NOEC based on phytotoxicity to radish was 14.7. The EEC is equal to the maximum application rate (57 g a.i./ha or 285 g EP/ha). Based on the risk quotient (EEC ÷ EC_{25} = 19.4), there is high risk to terrestrial plants.

6.4.3 Aquatic organisms

Freshwater

Daphnids: The acute 48-h NOEC based on mortality and LC_{50} to *Daphnia magna* were 9.7 and 15 mg a.i./L, respectively; the EEC in water was 0.019 mg a.i./L. Based on the risk quotient (0.0019), there is negligible risk to daphnids.

Fish: The acute NOEC based on mortality and 96-h LC_{50} to rainbow trout (*Oncorhynchus mykiss*) were 80 and 106 mg a.i./L, respectively; the acute NOEC based on mortality and LC_{50} to bluegill sunfish (*Lepomis machrochirus*) were 16 and > 135 mg a.i./L, respectively. The EEC in water was 0.019 mg a.i./L. Based on the corresponding risk quotients (0.0002 and 0.0012), there is negligible risk to freshwater fish.

Algae (TGAI): The 5-d NOECs based on growth rate for two species of algae, *Anabaena flos-aquae* and *Selenastrum capricornutum*, were 0.014 and 0.0078 mg a.i./L, respectively, and the EEC in water was 0.019 mg a.i./L. Based on the corresponding risk quotients (1.4 and 2.4), there is moderate risk to algae.

Algae (formulation product): The 5-d NOEC based on growth rate and EC_{50} of Distinct® EP (20% diflufenzopyr + 50% dicamba) to *Anabaena flos-aquae* were 0.0059 and > 0.26 mg EP/L, respectively; the EEC in water was 0.095 mg EP/L (0.019 mg a.i./L ÷ 0.2 [% diflufenzopyr]). Based on the corresponding risk quotient (16), the EP presents a high risk to algae.

Diatom: The 5-d NOEC based on biomass and EC_{50} to *Navicula pelliculosa* were 0.003 and 0.10 mg a.i./L, respectively; the EEC in water was 0.019 mg a.i./L. Based on the risk quotient (6.3), there is moderate risk to diatoms.

Aquatic plants—duckweed (TGAI): The 7-d NOEC based on biomass and EC_{50} of the diflufenzopyr to duckweed (*Lemna minor*) were 0.0039 and > 0.35 mg a.i./L, respectively; the EEC in water was 0.019 mg a.i./L. Based on the risk quotient (4.9), the TGAI presents a moderate risk to duckweed.

Aquatic plants—duckweed (formulation product): The 7-day NOEC based on biomass and EC_{50} of Distinct® EP (20% diflufenzopyr + 50% dicamba) to duckweed (*Lemna minor*) were 0.0023 and 0.11 mg EP/L, respectively; the EEC in water was 0.095 mg EP/L (0.019 mg a.i./L ÷ 0.20 [% diflufenzopyr]). Based on the risk quotient (41.3), the EP presents a high risk to duckweed.

Marine

Crustacean: The acute 96-h NOEC based on inhibition of shell growth and EC_{50} to eastern oyster (*Crassostrea virginica*) were 31 and 61 mg a.i./L, respectively; the EEC in water was 0.019 mg a.i./L. Based on the risk quotient (0.0006), there is negligible risk to the eastern oyster.

Mysid shrimp: The acute 96-h NOEC based on mortality and LC_{50} to mysid shrimp (*Mysidopsis bahia*) were 4.4 and 18.9 mg a.i./L, respectively; the EEC in water was 0.019 mg a.i./L. Based on the risk quotient (0.004), there is negligible risk to mysid shrimp.

Fish: The 96-h acute NOEC based on mortality and LC_{50} and NOEC to sheepshead minnow (*Cyprinodon variegatus*) were 138 and > 138 mg a.i./L, respectively; the EEC in

water was 0.019 mg a.i./L. Based on the risk quotient (0.00014), there is negligible risk to marine fish.

Diatom: The 5-d EC_{50} and NOEC based on biomass to diatom (*Skeletoneum costatum*) were 0.12 and 0.0064 mg a.i./L, respectively; the EEC in water was 0.019 mg a.i./L. Based on the risk quotient (2.9), there is moderate risk to the marine diatom.

6.4.4 Incident reports / additional considerations

Not applicable

6.5 Risk mitigation

The risk of adverse effects to terrestrial plants and freshwater aquatic plants is high.

During the environmental review of diflufenzopyr and its EP, Distinct® herbicide (20% diflufenzopyr and 50% dicamba), the PMRA determined that buffer zones were required to mitigate the risk to freshwater aquatic organisms.

The following labelling is required.

> "Observe buffer zones specified under Directions for Use."
>
> "This product is toxic to terrestrial plants."
>
> "This product is toxic to aquatic plants."
>
> "To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to heavy rainfall, moderate to steep slope, bare soil and poorly draining soil (e.g., soils that are compacted, fine textured, or low in organic matter such as clay).
>
> Avoid application of this product when heavy rain is forecast.
>
> Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip (buffer zone) between the treated area and the edge of the water body."
>
> "DO NOT apply during periods of dead calm or when winds are gusty."
>
> "DO NOT apply by air."
>
> "The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats

(such as grasslands, forested areas, shelter belts, woodlots, hedgerows, pastures, rangelands, and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats."

Method of application	Crop	Buffer zone (metres) required for the protection of:		
		Freshwater habitat	Estuarine/Marine habitat	Terrestrial habitat
Field sprayer*	Corn	15	15	10

* For field sprayers, buffer zones can be reduced by 70% when using shrouds or 30% when using cones.

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended use

Diflufenzopyr is a selective, pre-emergence and postemergence herbicide that controls broadleaf weeds in field corn. This new active ingredient is efficacious at low use rates. Diflufenzopyr will be commercialized as a premix product with dicamba, an active ingredient that is currently registered in Canada. The commercial name for the diflufenzopyr + dicamba EP is Distinct®. Distinct® contains 20% diflufenzopyr and 50% dicamba, providing an overall guarantee of 70% active ingredient.

Distinct® may be used for pre-emergent, spike stage (spike–1 leaf), early postemergent (2–3 leaf) and late postemergent (4–6 leaf) application on field corn in Eastern Canada. Distinct® is not for use on sweet corn or seed corn. An application of Distinct® at the above-stated timings relative to the crop, except for pre-emergent where the tankmix with dimethenamid is recommended, is effective in controlling the following broadleaf weeds: redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with postemergent application only). Distinct® can be used for control of Canada thistle (top growth) as a postemergence application (2–6 leaf) on field corn. When applied as an early or late postemergent treatment, a non-ionic surfactant at 0.25% v/v and liquid urea ammonium nitrate at 1.25% v/v must be used.

Distinct® can be tankmixed with dimethenamid at a rate of 1.125 kg a.i./ha for control of the above broadleaf weeds as well as the following annual grass weeds: green foxtail, yellow foxtail, crabgrass, old witchgrass, barnyard grass and fall panicum.

Distinct® can be tankmixed with Ultim 75% DF at 2–6 leaf stage and with Accent 75 DF at 4–8 leaf stage of field corn.

7.1.2 Mode of action

Diflufenzopyr is an auxin transport inhibitor. Diflufenzopyr inhibits the polar transport of naturally occurring auxins (indoleacetic acid [IAA]) and synthetic auxin-like compounds, such as dicamba, in sensitive plants. Diflufenzopyr's inhibition of auxin transport causes 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® formulated product, it focuses dicamba's translocation to the meristematic sinks, where it delivers effective weed control at reduced rates. 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.

Tolerance in field corn occurs through rapid metabolism of diflufenzopyr and dicamba.

7.1.3 Crops

Field corn is the only crop on which data is presented and for which a label claim is made.

7.1.4 Effectiveness against pests

Efficacy of Distinct® applied alone and tankmixed with dimethenamid was studied in a total of 72 trials conducted over 4 growing seasons, from 1994 to 1997. A summary of the number of trials submitted in support of each weed for each time of application is presented in tables 7.1.4.1 and 7.1.4.2.

Table 7.1.4.1 Summary of the number of trials submitted for each weed claim over the various application timings, Distinct® alone

Weed	Number of trials per application timing			Total number of trials
	Spike	Early postemerge	Late postemerge	
Redroot pigweed	12	17	17	46
Lamb's-quarters	14	16	19	49
Common ragweed	7	8	10	25
Wild buckwheat	3	5	8	16
Lady's thumb	4	6	9	19
Velvetleaf	6	3	4	13

Table 7.1.4.2 Summary of the number of trials submitted for each weed claim over the various application timings, Distinct® + dimethenamid tankmix

Weed	Number of trials per application timing			Total number of trials
	Pre-emerge	Spike	Early postemerge	
Redroot pigweed	11	12	8	31
Lamb's-quarters	14	14	8	36
Common ragweed	5	7	4	16
Wild buckwheat	3	3	1	7
Lady's thumb	3	4	3	10
Velvetleaf	—	6	3	9
Green foxtail	8	8	8	24
Yellow foxtail	4	3	—	7
Crabgrass	5	5	5	15
Barnyard grass	5	6	6	17
Fall panicum	3	2	2	7
Old witchgrass	—	2	1	3

Distinct® applied alone was evaluated for annual broadleaf weed control. The Distinct® + dimethenamid tankmix was evaluated for annual grass and broadleaf weed control to ensure control of these weeds was not compromised when Distinct® is applied in a tankmix with dimethenamid. The following results were obtained.

7.1.4.1 Pre-emergent application

Distinct® 0.200 kg a.i./ha + dimethenamid 1.125 kg a.i./ha

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 11 trials conducted over 3 years at 11 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 95% (number of trials [n] = 11) at 14–41 days after application (DAA) and 90% (n = 7) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 14 trials conducted over 3 years at 12 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 93% (n = 14) at 14–41 DAA and 92% (n = 11) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in five trials conducted over three years at five locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 97% (n = 5) at 14–41 DAA and 91% (n = 2) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in three trials conducted over three years at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 89% (n = 2) at 14–41 DAA and 86% (n = 3) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in three trials conducted over one year at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 90% (n = 1) at 14–41 DAA and 88% (n = 2) at 41 or more DAA.

Green foxtail (*Setaria viridis*)
Control of green foxtail was reported in eight trials conducted over three years at seven locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 8) at 14–41 DAA and 98% (n = 6) at 41 or more DAA. The average control for an application of dimethenamid alone was 98% (n = 8) at 14–41 DAA and 99% (n = 6) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Yellow foxtail (*Setaria glauca*)
Control of yellow foxtail was reported in four trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 95% (n = 3) at 14–41 DAA and 76% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 91% (n = 3) at 14–41 DAA and 69% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Crabgrass (*Digitaria sanguinalis*)
Control of crabgrass was reported in five trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 2) at 14–41 DAA and 98% (n = 4) at 41 or more DAA. The average control for an application of dimethenamid alone was 99% (n = 2) at 14–41 DAA and 98% (n = 4) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Barnyard grass (*Echinochloa crusgalli*)
Control of barnyard grass was reported in five trials conducted over three years at five locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 4) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The average control for an application of dimethenamid alone was 96% (n = 4) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Fall panicum (*Panicum dichotomiflorum*)
Control of fall panicum was reported in three trials conducted over two years at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 91% (n = 2) at 14–41 DAA and 88% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 92% (n = 2) at 14–41 DAA and 98% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

7.1.4.2 Spike stage application

a) Distinct® at 0.200 kg a.i./ha alone

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 12 trials conducted over 3 years at 10 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 90% (n = 11) at 14–41 DAA and 83% (n = 7) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported for 14 trials conducted over 3 years at 10 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 87% (n = 12) at 14–41 DAA and 76% (n = 9) at 41 or more DAA. Due to the inconsistent control of lamb's-quarters later in the growing season when treated with Distinct® alone, the label will recommend the use of the Distinct® + dimethenamid tankmix when heavy populations of lamb's-quarters are present.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in seven trials conducted over three years at six locations across Ontario and Quebec. The average control for an application of Distinct® alone was 96% (n = 6) at 14–41 DAA and 94% (n = 3) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in three trials conducted over three years at two locations across Ontario and Quebec. The average control for an application of Distinct® alone was 88% (n = 2) at 14–41 DAA and 92% (n = 2) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in four trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of Distinct® alone was 94% (n = 4) at 14–41 DAA and 94% (n = 2) at 41 or more DAA.

b) Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 12 trials conducted over 3 years at 10 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 12) at 14–41 DAA and 97% (n = 8) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 14 trials conducted over 3 years at 10 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 14) at 14–41 DAA and 94% (n = 11) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in seven trials conducted over three years at six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 7) at 14–41 DAA and 94% (n = 4) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in three trials conducted over three years at two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 96% (n = 3) at 14–41 DAA and 95% (n = 3) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in four trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 3) at 14–41 DAA and 99% (n = 2) at 41 or more DAA.

Green foxtail (*Setaria viridis*)
Control of green foxtail was reported in eight trials conducted over three years at six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 8) at 14–41 DAA and 96% (n = 6) at 41 or more DAA. The average control for an application of dimethenamid alone was 94% (n = 7) at 14–41 DAA and 96% (n = 6) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Yellow foxtail (*Setaria glauca*)
Control of yellow foxtail was reported in three trials conducted over two years at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 3) at 14–41 DAA and 96% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 99% (n = 1) at 14–41 DAA and 95% (n = 1) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Crabgrass (*Digitaria sanguinalis*)
Control of crabgrass was reported in five trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 96% (n = 5) at 14–41 DAA and 94% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 93% (n = 5) at 14–41 DAA and 95% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Barnyard grass (*Echinochloa crusgalli*)
Control of barnyard grass was reported in six trials conducted over three years at six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 6) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The average control for an application of dimethenamid alone was 99% (n = 3) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Fall panicum (*Panicum dichotomiflorum*)
Control of fall panicum was reported in two trials conducted over two years at two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 90% (n = 1) at 14–41 DAA and 94% (n = 2) at 41

or more DAA. The average control for an application of dimethenamid alone was 76% (n = 1) at 14–41 DAA and 92% (n = 2) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Old witchgrass (*Panicum capillare*)
Control of old witchgrass was reported in two trials conducted over one year at two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 1) at 14–41 DAA and 99% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 98% (n = 1) at 14–41 DAA and 99% (n = 1) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

7.1.4.3 Early postemerge application (2- to 3-leaf stage of the corn crop)

a) Distinct® at 0.200 kg a.i./ha alone

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 17 trials conducted over two years at 12 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 96% (n = 17) at 14–41 DAA and 89% (n = 12) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 16 trials conducted over two years at 11 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 95% (n = 16) at 14–41 DAA and 91% (n = 14) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in eight trials conducted over two years at six locations across Ontario and Quebec. The average control for an application of Distinct® alone was 99% (n = 8) at 14–41 DAA and 98% (n = 3) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in five trials conducted over two years at three locations across Ontario and Quebec. The average control for an application of Distinct® alone was 98% (n = 4) at 14–41 DAA and 97% (n = 4) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in six trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 97% (n = 6) at 14–41 DAA and 99% (n = 4) at 41 or more DAA.

Velvetleaf (*Abutilon theophrasti*)
Control of velvetleaf was reported in three trials conducted over two years at two locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 85% (n = 3) at 14–41 DAA and 83% (n = 3) at 41 or more DAA.

b) Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in eight trials conducted over two years at six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 8) at 14–41 DAA and 96% (n = 5) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in eight trials conducted over two years at six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 8) at 14–41 DAA and 97% (n = 6) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in four trials conducted over one year at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 4) at 14–41 DAA and 99% (n = 3) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in one trial. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 1) at 14–41 DAA and 99% (n = 1) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in three trials conducted over one year at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 3) at 14–41 DAA and 99% (n = 1) at 41 or more DAA.

Velvetleaf (*Abutilon theophrasti*)
Control of velvetleaf was reported in three trials conducted over two years at two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 83% (n = 3) at 14–41 DAA and 81% (n = 3) at 41 or more DAA.

Green foxtail (*Setaria viridis*)
Control of green foxtail was reported in eight trials conducted over two years at five locations across Ontario and Quebec. The average control for an application of the

Distinct® + dimethenamid tankmix was 97% (n = 4) at 14–41 DAA and 94% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 88% (n = 3) at 14–41 DAA and 90% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Yellow foxtail (*Setaria glauca*)
The following rationale has been submitted in support of the claim of control yellow foxtail with the Distinct® + dimethenamid tankmix:

- the submitted data indicate consistent control of yellow foxtail with the Distinct® + dimethenamid tankmix at other stages of application; and

- the submitted data indicate dimethenamid control of annual grasses is not compromised when tankmixed with Distinct®.

Based on the above, the claim of control for yellow foxtail with the Distinct® + dimethenamid tankmix is acceptable.

Crabgrass (*Digitaria sanguonalis*)
Control of crabgrass was reported in five trials conducted over one year at three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 89% (n = 3) at 14–41 DAA and 88% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 78% (n = 3) at 14–41 DAA and 87% (n = 2) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Barnyard grass (*Echinochloa crusgalli*)
Control of barnyard grass was reported in six trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 3) at 14–41 DAA and 97% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 91% (n = 3) at 14–41 DAA and 95% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Fall panicum (*Panicum dichotomiflorum*)
Control of fall panicum was reported in two trials conducted over two years at two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 93% (n = 2) at 14–41 DAA and 89% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 84% (n = 2) at 14–41 DAA and 86% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Old witchgrass (*Panicum capillare*)
Control of old witchgrass was reported in one trial conducted in Ontario. The control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 1) at 14–41 DAA and 97% (n = 1) at 41 or more DAA. The average control for an application of dimethenamid alone was 91% (n = 1) at 14–41 DAA and 96% (n = 1) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

7.1.4.4 Late postemergent application (4- to 6-leaf stage of the corn crop)

Distinct® at 0.200 kg a.i./ha alone

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 17 trials conducted over 2 years at 11 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 94% (n = 17) at 14–41 DAA and 96% (n = 12) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 19 trials conducted over 2 years at 13 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 95% (n = 19) at 14–41 DAA and 98% (n = 15) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in 10 trials conducted over two years at nine locations across Ontario and Quebec. The average control for an application of Distinct® alone was 98% (n = 9) at 14–41 DAA and 99% (n = 6) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in eight trials conducted over two years at four locations across Ontario and Quebec. The average control for an application of Distinct® alone was 96% (n = 8) at 14–41 DAA and 98% (n = 6) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in nine trials conducted over two years at six locations across Ontario and Quebec. The average control for an application of Distinct® alone was 98% (n = 9) at 14–41 DAA and 99% (n = 6) at 41 or more DAA.

Velvetleaf (*Abutilon theophrasti*)
Control of velvetleaf was reported in four trials conducted over one year at four locations across Ontario and Quebec. The average control for an application of Distinct® alone was 87% (n = 4) at 14–41 DAA and 96% (n = 3) at 41 or more DAA.

7.2 Effects on the yield of treated plants or plant products in terms of quantity and/or quantity

7.2.1 Pre-emergent application

Distinct® + dimethenamid

A total of seven trials were taken to yield and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha + dimethenamid in the presence of weeds. In addition, these seven trials tested Distinct® at 1.5× and 2× the requested rate. The rate of dimethenamid was constant at 1.125 kg a.i./ha. The plots treated with the requested rate of Distinct® yielded 129% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 137% compared to the check. The plots treated with the 2× rate of Distinct® yielded 140% compared to the check.

7.2.2 Spike stage application (spike to 1-leaf stage of the corn crop)

a) Distinct® alone

A total of two trials were taken to yield and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha in the presence of weeds. In addition, these two trials tested Distinct® at the 1.5× and 2× rates. The plots treated with the requested rate of Distinct® yielded 106% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 108% compared to the check. The plots treated with the 2× rate of Distinct® yielded 108% compared to the check.

b) Distinct® + dimethenamid

A total of four trials were taken to yield and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha + dimethenamid in the presence of weeds. In addition, these four trials tested Distinct® at the 1.5× and 2× rates. The rate of dimethenamid was constant at 1.125 kg a.i./ha. The plots treated with the requested rate of Distinct® yielded 171% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 175% compared to the check. The plots treated with the 2× rate of Distinct® yielded 170% compared to the check.

7.2.3 Early postemergent application (2- to 3-leaf stage of the corn crop)

a) Distinct® alone

A total of 6 trials were taken to yield and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha in the presence of weeds. In addition, these 6 trials tested Distinct® at the 1.5× and 2× rates. The plots treated with the requested rate of Distinct® yielded 122% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 126% compared to the check. The plots treated with the 2× rate of Distinct® yielded 122% compared to the check.

b) Distinct® + dimethenamid

One trial was taken to yield and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha + dimethenamid in the presence of weeds. In addition, this trial tested Distinct® at the 1.5× and 2× rates. The rate of dimethenamid was constant at 1.125 kg a.i./ha. The plots treated with the requested rate of Distinct® yielded 110% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 100% compared to the check. The plots treated with the 2× rate of Distinct® yielded 99% compared to the check.

7.2.4 Late postemergent application (4- to 6-leaf stage of the corn crop)

Distinct® alone

A total of seven trials were taken to yield, and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha in the presence of weeds. In addition, these seven trials tested Distinct® at the 1.5× and 2× rates. The plots treated with the requested rate of Distinct® yielded 131% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 124% compared to the check. The plots treated with the 2× rate of Distinct® yielded 120% compared to the check.

7.3 Phytotoxicity to target plants (including different cultivars) or to target plant products

7.3.1 Pre-emergent application

Distinct® + dimethenamid

Tolerance of field corn to the Distinct® + dimethenamid tankmix was evaluated in 14 trials conducted over a 3-year period at 12 locations across Ontario and Quebec. Eight corn varieties were tested. The tankmix was tested at rates of Distinct® ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. The rate of dimethenamid was constant at 1.125 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha
Thirteen trials conducted over a three-year period reported an average of 0.4% (n = 12) visual injury at 14–41 DAA and 0.9% (n = 13) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (1.5×)
Thirteen trials conducted over a three-year period reported an average of 0.9% (n = 12) visual injury at 14–41 DAA and 1.2% (n = 13) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (2×)
Twelve trials conducted over a three-year period reported an average of 0.4% (n = 12) visual injury at 14–41 DAA and 1.1% (n = 1) at 41 or more DAA.

7.3.2 Spike stage application (spike to 1-leaf stage of the corn crop)

a) Distinct® alone

Tolerance of field corn to Distinct® alone was evaluated in 13 trials conducted over a two-year period at 11 locations across Ontario and Quebec. Eight corn varieties were tested. Distinct® alone was tested at rates ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha
Thirteen trials conducted over a two-year period reported an average of 0.3% (n = 13) visual injury at 14–41 DAA and 0% (n = 11) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha (1.5×)
Thirteen trials conducted over a two-year period reported an average of 0.8% (n = 13) visual injury at 14–41 DAA and 0.4% (n = 11) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha (2×)
Thirteen trials conducted over a two-year period reported an average of 0.7% (n = 13) visual injury at 14–41 DAA and 0.3% (n = 11) at 41 or more DAA.

b) Distinct® + dimethenamid

Tolerance of field corn to the Distinct® + dimethenamid tankmix was evaluated in 15 trials conducted over a 3-year period at 11 locations across Ontario and Quebec. Eight corn varieties were tested. The tankmix was tested at rates of Distinct® ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha
Fifteen trails conducted over a three-year period reported an average of 0.4% (n = 15) visual injury at 14–41 DAA and 0.3% (n = 13) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (1.5×)
Fifteen trails conducted over a three-year period reported an average of 1.1% (n = 15) visual injury at 14–41 DAA and 0.3% (n = 13) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (2×)
Fifteen trails conducted over a three-year period reported an average of 0.7% (n = 15) visual injury at 14–41 DAA and 0.4% (n = 13) at 41 or more DAA.

7.3.3 Early postemergent application (2- to 3-leaf stage of the corn crop)

a) Distinct® alone

Tolerance of field corn to Distinct® alone was evaluated in 22 trials conducted over a 2-year period at 13 locations across Ontario and Quebec. Ten corn varieties were tested. Distinct® alone was tested at rates ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha
Twenty-two trials conducted over a two-year period reported an average of 1.0% (n = 21) visual injury at 14–41 DAA and 0.6% (n = 14) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha (1.5×)
Twenty-two trials conducted over a two-year period reported an average of 2.2% (n = 21) visual injury at 14–41 DAA and 2.0% (n = 14) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha (2×)
Twenty-two trials conducted over a two-year period reported an average of 2.3% (n = 21) visual injury at 14–41 DAA and 0.7% (n = 14) at 41 or more DAA.

b) Distinct® + dimethenamid

Tolerance of field corn to the Distinct® + dimethenamid tankmix was evaluated in nine trials conducted over a two-year period at eight locations across Ontario and Quebec. Six corn varieties were tested. The tankmix was tested at rates of Distinct® ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha
Nine trials conducted over a two-year period reported an average of 1.4% (n = 9) visual injury at 14–41 DAA and 3.2% (n = 9) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (1.5×)
Nine trials conducted over a two-year period reported an average of 2.5% (n = 9) visual injury at 14–41 DAA and 4.6% (n = 9) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (2×)
Nine trials conducted over a two-year period reported an average of 3.4% (n = 9) visual injury at 14–41 DAA and 7.2 (n = 9) at 41 or more DAA.

7.3.4 Late postemergent application (4- to 6-leaf stage of the corn crop)

Distinct® alone

Tolerance of field corn to the Distinct® alone was evaluated in 19 trials conducted over a 2-year period at 14 locations across Ontario and Quebec. Eleven corn varieties were tested. Distinct® alone was tested at rates ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha
Nineteen trials conducted over a two-year period reported an average of 3.0% (n = 19) visual injury at 14–41 DAA and 1.5% (n = 15) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha (1.5×)
Nineteen trials conducted over a two-year period reported an average of 4.5% (n = 19) visual injury at 14–41 DAA and 1.5% (n = 15) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha (2×)
Nineteen trials conducted over a two-year period reported an average of 5.6% (n = 19) visual injury at 14–41 DAA and 2.5% (n = 15) at 41 or more DAA.

7.4 Observations on undesirable or unintended side effects

7.4.1 Impact on succeeding crops

No crop restrictions are required with the maximum Distinct® rate.

7.5 Conclusions

The data provided indicates that, when used according to label directions, Distinct® can be applied to field corn for the control of specific broadleaf weeds. Distinct® may be tankmixed with dimethenamid to provide additional annual grass control.

Distinct® provides commercially acceptable crop tolerance to field corn when applied at 285 g/ha. Distinct® will control redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with postemergent application only). Distinct® may be tankmixed with dimethenamid for control of specific annual grass weeds.

Table 7.5.1 Summary table

Crop	Field Corn
Application timing	1. Pre-emerge 2. Spike stage (spike- to 1-leaf) 3. Early postemergent (2- to 3-leaf) 4. Late postemergent (4- to 6-leaf)
Product **Rate of application** **PLUS** **Additional surfactant**	Distinct® 285 g/ha for postemerge applications • non-ionic surfactant at 0.25% v/v • liquid urea ammonium nitrate at 1.25% v/v
Weed species controlled	redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with postemergent application only)
Tankmix option	dimethenamid

8.0 Toxic Substances Management Policy

During the review of diflufenzopyr and the EP Distinct® herbicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track-1 criteria for the following reasons.

- Diflufenzopyr is not bioaccumulative. The log K_{ow} is 2.19, which is below the TSMP Track 1 cut-off criteria (log K_{ow} > 5).

- Diflufenzopyr does not meet the criteria for persistence in water and sediment. Its values for half-life in water, and sediment in whole water/ sediment system are below the TSMP Track 1 cut-off criteria for water (> 182 d), soil (> 182 d), and sediment (> 365 d).

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[1] The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics

[2] Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3758;
E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

- The toxicity is described in sections 3 and 6.

- Diflufenzopyr (technical grade) does not contain any by-products or microcontaminants that are TSMP Track-1 substances as identified in Appendix II of DIR99-03. Impurities of toxicological concern as identified in Section 2.13.4 of DIR98-04 and TSMP Track 1 substances are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- The formulated product does not contain any formulants that are known to contain TSMP Track 1 substances.

9.0 Regulatory decision

The active ingredient diflufenzopyr and the formulated product Distinct®, containing diflufenzopyr and dicamba, are proposed for registration for use on field corn in Eastern Canada, with an MRL of 0.05 ppm for corn, pursuant to Section 13 of the PCP Regulations.

List of abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
BWI	body weight per individual
CAS	Chemical Abstracts Service
d	day(s)
DAA	days after application
DIP	direct insertion probe
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DT_{50}	decline time
dw	dry weight
EC_{50}	effect concentration
EEC	expected environmental concentration
EP	end-use product
EXAMS	Exposure Analysis Modeling System
F	filial generation
FOB	functional observational battery
GC	gas chromatography
GSD	geometrical standard deviation
h	hour(s)
HPLC	high performance liquid chromatography
IAA	indoleacetic acid
kg	kilogram(s)
K_{oc}	adsorption constant
K_{ow}	octanol/water partition coefficient
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LEACHM	Leaching Estimation and Chemistry Model
LOD	limit of detection
LOQ	limit of quantitation
M1	8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (phthalazinone)
M2	3,5-difluoroaniline (aniline)
M5	6-((3,5-difluorophenyl) carbamoyl)-8-methyl-pyrido (2,3-d)-5-pyridazinone (carbamoyl phthalazinone)
M6	2-acetyl nicotinic acid
M8	methyl N-(3,5-difluorophenyl)carbamate
M9	8-methylpyrido[2,3-d]pyridazine-2,5(1H, 6H)-dione (2-keto-M1)
M10	8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (8-hydroxymethyl-M1)
M19	8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione
M20	glucoside of M19

MAS	maximum average score
MCHC	mean corpuscular hemaglobin concentration
MCV	mean corpuscular volume
mg	milligram(s)
MMAD	mass median aerodynamic diameter
mL	millilitre(s)
MPCE	micronucleated polychromatic erythrocyte
MRL	maximum residue limit
MS	mass spectrometry
MSD	mass selective detection
n	number of trials
N/A	not applicable
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen-phosphorus detector
NZW	New Zealand white
P	parental generation
PCP	pest control products
PBI	plantback interval
PDI	potential daily intake
PHED	Pesticide Handlers Exposure Database
PIS	primary irritation score
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
PRZM	Pesticide Root Zone Model
PWDH	Pirbright White Dunkin Hartley
RAC	raw agricultural commodity
ROC	residue of concern
SD	Sprague Dawley
SF	safety factor
$T_{1/2}$	half-life
TGAI	technical grade active ingredient
TLC	thin layer chromatography
TRR	total radioactive residue
USEPA	United States Environmental Protection Agency
v/v	volume ratio
wk	week(s)
yr	year

Appendix I Summary tables

Table 1 Summary table of toxicology studies for diflufenzopyr

Metabolism—technical (diflufenzopyr)

Male and female Wistar rats received either a single low intravenous dose (1.0 mg/kg bw), single low oral dose (10.0 mg/kg bw), single high oral dose (1000 mg/kg bw) or 15 daily low oral doses (10.0 mg/kg bw) of diflufenzopyr, purity > 98%, 10 or 15 rats per sex per group. Diflufenzopyr was radiolabelled as [phenyl-U- ^{14}C] or [pyridinyl-4, 6-^{14}C]. Prior to dosing, 5 rats per sex in all but the repeat dose group were bile-duct cannulated, and sacrificed 48 h postdosing. Of the remaining 10 rats per sex in each group (i.e., non-cannulated), 5 per sex per group were sacrificed 24 h postdosing, and the remaining 5 per sex per group were sacrificed 72 h postdosing.

After oral administration, a smaller percentage of the administered dose was excreted in the urine (20–44%) and more in the feces (49–79%), when compared to intravenous administration (61–89% in the urine), indicating that diflufenzopyr was only partially absorbed following oral dosing. Sex, dose level and pretreatment had little effect on the excretion pattern. In all dose groups, 3 to 19% of the administered dose was recovered in the bile, indicating that enterohepatic circulation played a role in the elimination of diflufenzopyr. The approximate half-life of diflufenzopyr was 5.3–6.9 h for all single oral and intravenous dose groups, and 7.7–10.8 h for the repeat oral dose group.

Diflufenzopyr did not accumulate in the tissues; total radioactive residues (TRRs) accounted for < 3% of the administered dose for all dose groups. Residue levels were highest in blood, red blood cells and serum for the phenyl-labelled groups, and highest in liver and kidney for the pyridinyl-labelled groups.

The major fraction of TRR extracted from urine, feces and bile was identified as unchanged diflufenzopyr. In addition, minor amounts of hydrolysis products [i.e., 8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (M1); 6-((3,5-difluorophenyl)carbamoyl)-8-methyl-pyrido(2,3-d)-5-pyridazinone (M5); and 2-acetyl nicotinic acid (M6)] and hydroxylation products [i.e., 8-methylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (M9); 8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (M10); and 8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (M19)] were identified in excreta.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Acute studies—technical (diflufenzopyr)			
Oral	Rat, SD, 5/sex, 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw	Clinical observations consisted of piloerection, pallor, hunched posture and liquid feces. Low toxicity
Dermal	Rabbit, SD, 5/sex, 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw	Slight to well-defined erythema was noted on all rabbits, recovery by day 9. Low toxicity

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Inhalation	Rat, SD, 5/sex, 2.93 mg/L	LC_{50} > 2.93 mg/L	Mass median aerodynamic diameter (MMAD) = 3.5 µm, geometrical standard deviation (GSD) = 2.2 77% <7 µm; 36% <3.5µm No clinical signs of toxicity Low toxicity
Skin irritation	Rabbit, NZW, 6 males, 0.5 g dose	primary irritation score (PIS) = 0.00	Non-irritating.
Eye irritation	Rabbit, NZW, 6 males, 0.1 mL dose (30 mg)	maximum average score (MAS) = 7.3	Minimally irritating
Skin sensitization (modified Buehler method)	Guinea pig, PWDH. Test material administered: 60% (0.5 g) for induction and 50% (0.5 g) for challenge. Positive control reference data with alpha-hexlycinnamaldehyde 85%.	Test material was minimally irritating at 60% concentration. No evidence of sensitization. Positive control was sensitizing, demonstrating responsiveness of assay.	Not a sensitizer
Acute studies—formulation (Distinct®)			
Oral	Rat, SD, 5/sex, 1260, 2000 and 3200 mg/kg bw	LD_{50} (mg/kg bw) Males: 1600 (1200–2100) Females: 2100 (1600–2800) Combined: 1800 (1500–2200)	Clinical observations consisted of piloerection, unsteadiness, delayed reflex, lethargy, pallor, hunched posture, abnormal gait, prostration, increased salivation and red/brown staining of mouth and nose. Slight toxicity Label Recommendation: "CAUTION POISON"
Dermal	Rabbit, SD, 5/sex, 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw	Slight- to well-defined erythema and edema was noted on all rabbits, recovery between days 10 and 14 for edema; erythema persisted to day 14. Desquamation, all rabbits, days 4–14. Low toxicity

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Inhalation	Rat, SD, 5/sex, 2.93 mg/L	LC_{50} > 5.34 mg/L	MMAD = 3.5 µm, GSD = 2.3. Wet fur on snout and facial brown staining, days 0 and 1. Low toxicity
Skin irritation	Rabbit, NZW, 6 males, 0.5 g dose	PIS = 1.5	Slightly irritating
Eye irritation	Rabbit, NZW, 6 males, 0.1 mL dose (30 mg)	MAS = 19.7	Mildly irritating Label recommendation: "CAUTION EYE IRRITANT"
Skin sensitization (modified Buehler method)	Guinea pig, PWDH. Test material administered: 40% (0.5 g) for induction; 20% (0.5 g) for challenge. Positive control reference data with alpha-hexylcinnamaldehyde 85%.	Test material was minimally irritating at 40% concentration. Positive skin reaction in 95% of the test animals after challenge. Positive control was sensitizing, demonstrating responsiveness of assay.	Skin sensitizer Label recommendation: "POTENTIAL SKIN SENSITIZER"
Short term—technical (diflufenzopyr)			
21- to 24-d dermal	Rabbits, NZW, 5/sex/group, 0, 100, 300 and 1000 mg/kg bw/d	NOEL = 1000 mg/kg bw/d	No systemic treatment-related effects at any dose level tested. Local dermal irritation was observed at all dose levels tested.
90-d dietary	Mouse, CD-1, 10/sex/group, 0, 350, 1750, 3500 and 7000 ppm (equal to 0, 58, 287, 613 and 1225 mg/kg bw/d for males and 0, 84, 369, 787 and 1605 mg/kg bw/d for females)	NOEL = 7000 ppm (1225 mg/kg bw/d for males, and 1605 mg/kg bw/d for females)	No treatment-related effects at any dose level tested.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
90-d dietary	Rat, Wistar, 10/sex/group, 0, 1000, 5000, 10 000 and 20 000 ppm (equal to 0, 60.8, 352, 725 and 1513 mg/kg bw/d for males and 0, 72.8, 431, 890 and 1750 mg/kg bw/d for females). An additional 10/sex were assigned to the 0- and 20 000-ppm groups for a 4-wk recovery period.	NOEL = 5000 ppm (352 mg/kg bw/d for males, and 431 mg/kg bw/d for females)	10 000 and 20 000 ppm: Lower body-weight gain and decreased food efficiency; increased incidence of foamy macrophages in the lungs. 20 000 ppm: Increased incidence of testicular atrophy. After the 4-wk recovery period, foamy macrophages in the lungs and testicular atrophy were still evident at 20 000 ppm.
90-d dietary	Dog, beagle, 4/sex/group, 0, 1500, 10 000 and 30 000 ppm (equal to 0, 58, 403 and 1121 mg/kg bw/d for males and 0, 59, 424 and 1172 mg/kg bw/d for females)	NOEL = 1500 ppm (58 mg/kg bw/d)	10 000 and 30 000 ppm: Erythroid hyperplasia in the bone marrow; extramedullary hematopoiesis in the liver; hemosiderin deposits in Kupffer cells. 30 000 ppm: Lower body-weight gain and food consumption; regenerative anemia; extramedullary hematopoiesis in the lungs, lymph nodes and kidneys; absence of fatty bone marrow; urothelial hyperplasia and cystitis.
52-wk dietary	Dog, beagle, 4/sex/group, 0, 750, 7500 and 15 000 ppm (equal to 0, 26, 299 and 529 mg/kg bw/d for males and 0, 28, 301 and 538 mg/kg bw/d for females)	NOEL = 750 ppm (26 mg/kg bw/d)	7500 and 15 000 ppm: Erythroid hyperplasia in the bone marrow; hemosiderin deposits in the kidneys, liver and spleen; reticulocytosis; lower body-weight gain and decreased food utilization (females only).
Short term—formulation (Distinct®)			
21- to 24-d dermal	Rabbits, NZW, 5/sex/group, 0, 10, 30 and 100 mg/kg bw/d	NOEL = 100 mg/kg bw/d	No systemic treatment-related effects at any dose level tested. Local dermal irritation was observed at all dose levels tested.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Chronic toxicity/oncogenicity—technical (diflufenzopyr)			
78-wk dietary	Mouse, CD-1, 60/sex/group, 0, 700, 3500 and 7000 ppm (equal to 0, 100, 517 and 1037 mg/kg bw/d for males and 0, 98, 500 and 1004 mg/kg bw/d for females)	Chronic effects: Males, NOEL = 7000 ppm (1037 mg/kg bw/d) Females, NOAEL = 7000 ppm (1004 mg/kg bw/d) Oncogenicity: NOEL = 7000 ppm (1037 mg/kg bw/d for males and 1004 mg/kg bw/d for females)	Males: No treatment-related findings at any dose level tested. Females, at 7000 ppm: Slightly lower body-weight gain during the second year of the study. No treatment-related oncogenic effects at any dose level tested.
104-wk dietary	Rat, Wistar, 72/sex/group, 0, 500, 1500, 5000 and 10 000 ppm (equal to 0, 22, 69, 236 and 518 mg/kg bw/d for males and 0, 29, 93, 323 and 697 mg/kg bw/d for females)	Chronic effects: NOAEL = 5000 ppm (236 mg/kg bw/d for males, and 323 mg/kg bw/d for females) Oncogenicity: NOEL = 10 000 ppm (518 mg/kg bw/d for males and 697 mg/kg bw/d for females)	1500 and 5000 ppm: Slightly lower body-weight gain during the second year of the study (only attaining a maximum 10% reduction; non-adverse). 10 000 ppm: Lower body-weight gain throughout the study period. No treatment-related oncogenic effects at any dose level.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Reproduction/developmental toxicity—technical (diflufenzopyr)			
Two-generation dietary, two litters in the P generation, one litter in the F_1 generation	Rat, SD, 26/sex/group, 0, 500, 2000 and 8000 ppm (equal to 0, 27.3, 113.1 and 466.2 mg/kg bw/d for males and 0, 42.2, 175.9 and 742.0 mg/kg bw/d for females)	Systemic effects: NOAEL = 2000 ppm (113.1 mg/kg bw/d for males and 175.9 mg/kg bw/d for females) Reproductive effects: NOEL = 2000 ppm (113.1 mg/kg bw/d for males, and 175.9 mg/kg bw/d for females)	2000 ppm: Slightly lower body-weight gain, P males during premating only. 8000 ppm: Lower body-weight gain and increased food consumption, P and F generation during premating, both sexes, and F and P generation females during gestation. 2000 and 8000 ppm: Slightly higher seminal vesicle weight, non-adverse in the absence of any related gross or histopathological findings. 8000 ppm: Lower body-weight gain (F_1a); lower live birth and viability indices, and increased pre-perinatal loss (F_2 generation); increased number of runts (F_1a and F_1b).
Teratogenicity, oral gavage	Rat, SD, 25/group, 0, 100, 300 and 1000 mg/kg bw/d	Maternal NOAEL = 1000 mg/kg bw/d Developmental NOAEL = 1000 mg/kg bw/d	1000 mg/kg bw/d: Slightly lower body-weight gain during the first three days of dosing only (not statistically significant). 1000 mg/kg bw/d: Increased incidence of incompletely ossified and/or unossified sternal centra. No teratogenic effects noted at any dose level tested.
Teratogenicity, oral gavage	Rabbit, NZW, 20/group, 0, 30, 100 and 300 mg/kg bw/d	Maternal NOEL = 100 mg/kg bw/d Developmental NOEL = 100 mg/kg bw/d	300 mg/kg bw/d: Mortality; abortions; weight loss and lower food consumption during the dosing period; abnormal feces. 300 mg/kg bw/d: Increased incidence of abortions. No teratogenic effects noted at any dose level tested.

Study	Species/strain or cell type	Doses employed	Significant effects/comments
Mutagenicity—technical (diflufenzopyr)			
Salmonella / Ames Test	*S. typhimurium* - TA 98, TA 100, TA 1535, TA 1537 and TA 1538	0, 333, 667, 1000, 3330, 6670 and 10 000 µg/plate, ± S9	Negative
Forward cell mutation assay, in vitro	Cultured L5178Y (TK+/-) mouse lymphoma cells	0.05, 0.1, 0.5, 0.8, 1.0, 1.2, 1.4, 1.5, 1.6, 1.8, 2.0 and 3.0 mg/mL, ± S9	Negative
Cytogenetic assay, in vitro	Cultured human lymphocytes	100, 250, 500, 750 and 1000 µg/mL	Negative
Unscheduled DNA synthesis assay, in vitro	Rat hepatocytes	0, 5.0, 10.0, 25.0, 50.0, 100 and 250 µg/mL, ± S9	Negative
Mammalian cytogenetics (micronucleus) assay, in vivo	Mouse, ICR	0, 500, 1667 and 5000 mg/kg bw, with sacrifice at 24, 48 and 72 h after dosing	Negative
Neurotoxicity—technical (diflufenzopyr)			
Acute oral gavage	Rat, Crl:CD BR, 10/sex/group, 0, 125, 500 and 2000 mg/kg bw	NOEL = 2000 mg/kg bw	No treatment-related effects were noted at any dose level tested.
13-wk feeding study	Rat, Crl:CD BR, 10/sex/group, 0, 25, 75 and 1000 mg/kg bw/d	NOEL = 75 mg/kg bw/d	1000 mg/kg bw/d: Lower body-weight gain and lower feed efficiency. No treatment-related neurotoxic effects were noted at any dose level tested.
Recommendation for ADI: 0.26 mg/kg bw/d, based on the lowest NOEL of 26 mg/kg bw/d in the chronic rat study and a 100-fold safety factor. Recommendation for ARfD: 1.00 mg/kg bw/d, based on the NOEL of 100 mg/kg bw/day in the rabbit teratology study and a 100-fold safety factor.			

Table 2 Integrated food residue chemistry summary

Direction for use					
Crop	**Formulation type**	**Rate (g a.i./ha)**	**Application/ season**	**Maximum rate (g a.i./ha)**	**Preharvest interval (days)**
Field corn (Eastern Canada only)	Wet dispersible granule / dry powder	57	1	57	120

Physicochemical properties	
Water solubility at (25°C) (mg/L)	**pH** / **Solubility (mg/L)** 5.0 / 270 ± 27 7.0 / 5850 ± 98 9.0 / 10,546 ± 131
Solvent solubility at (mg/L)	**Solvent** / **Solubility (mg/L)** tetrahydrofuran / 30 000 hexane / nd i-PrOH / 922 DMSO / 248 000 MeCl2 / 12.1 ACN / 228 acetone / 3360 toluene / 1.15
n-Octanol–water partition coefficient (Log K_{ow})	**pH** / **K_{ow}** 5.0 / 2.76 7.0 / 0.34 9.0 / 0.17
Dissociation constant (pKa) at 25°C	3.18
Vapour pressure at 20 and 25°C	$< 1 \times 10^{-7}$ mm Hg ($< 1.33 \times 10^{-5}$ Pa)
Relative density at 25°C (g/mL)	0.24
Melting point (°C)	135.5
UV/Visible absorption spectrum	**λ nm** / **ϵ (L/mol-cm)** 234.1 / 1.98×10^4 294.5 / 1.43×10^4

Analytical methodology			
Parameters	**Plant matrices**		
Method ID	D9709	AM-0966-0955-0	D9702
Type	Replacement enforcement method	Previous enforcement method	Data gathering method

Analytes	Diflufenzopyr and metabolites convertible to M1	Diflufenzopyr and metabolites convertible to M1	M10
Instrumentation	GC/MS	GC-NPD, GC/MSD	LC/MS/MS
LOQ	0.05 ppm as diflufenzopyr equivalents, 0.025 ppm as M1 equivalents	0.02 ppm as diflufenzopyr equivalents	0.05 ppm as M10
LOD	0.017 ppm as diflufenzopyr equivalents	0.02 ppm as diflufenzopyr equivalents	Not reported
Standard	Internal standardisation using M1		Internal standardisation using M10
ILV	Method D9709 was successfully validated by an independent laboratory	Method AM-0966-0397-1 (identical to AM-0966-0955-0) was successfully validated by an independent laboratory	Method D9702 was successfully validated by an independent laboratory
Extraction, conversion and clean-up	Extraction using aqueous $NaHCO_3$ (0.5 %) and ammoniated acetone. Conversion of diflufenzopyr to M1 by refluxing residue in EtOAC/MeOH for 2 hours. Clean-up on a mini column containing Oasis HLB™ .	Extraction using aqueous $NaHCO_3$ (0.5 %) and ammoniated acetone. For conversion of diflufenzopyr to M1, several extraction steps are involved before heating at 95°C for 3 hours. Clean-up is by a silica SPE column.	Simultaneous extraction and hydrolysis using 1 N H_2SO_4 at 95°C for 1 hour.
Multiresidue method	None submitted. The USEPA does not list one on their Pesticide Analytical Method website.		

Nature of the residue in corn		
Radiolabel	Pyridine-^{14}C	Phenyl-^{14}C
Test Site	Outdoor pots, Madera, California	
Treatment	Postemergent treatment of corn seedlings 14 days after emergence (3- to 4-leaf stage).	
Rate	0.224 and 0.896 kg a.i./ha	0.224 and 0.896 kg a.i./ha
PHI	98 d for silage; 145-146 d for fodder and grain; 28 d for non-RAC corn forage and corn forage thinnings	
Norent was detected in both the pyridine- and phenyl-labelled metabolism studies. In the pyridine-labelled study, major metabolites (≥ 10 % TRR and/or ≥ 0.05 ppm) in decreasing order were M1, M10 (free and as its glucoside) and M9. In phenyl-labelled corn RAC, no major or minor metabolites were identified, but M19 was identified as a minor metabolite in the pyridine-labelled study.		

Matrix	Major metabolites (> 10 % TRR)	Minor metabolites (< 10 % TRR)
	Pyridine-^{14}C	Pyridine-^{14}C
Silage	M1, M10*, M9	M19
Fodder	M1, M10*, M9	M19
*Free and as its glucoside.		

Confined rotational crop study—lettuce, barley, carrot and soybean		
Radiolabels	Pyridine-^{14}C	Phenyl-^{14}C
Test Site	Outdoor pots, Madera, California	
Treatment	Postemergent treatment of corn seedlings 14 days after emergence (3- to 4-leaf stage).	
Rate	0.224 kg a.i./ha	0.224 kg a.i./ha
PBI	30, 120, 298, and 365 DAT	
No metabolites were identified in rotated crops. The highest total radioactive residues (TRRs) in the tested rotational crops were found in barley straw at the 0.06 ppm level. The TRR in human consumable RACs (lettuce, barley grain and carrots) were ≤ 0.028 ppm at the 30 d PBI and < 0.01 ppm at the 120 d PBI.		

Limited field crop rotation study—radish, lettuce, and wheat	
Test site(s)	Georgia and California
Rate (g a.i./ha)	1) 28 2) 112 (total rate of 2.5× the Canadian label rate)
Treatment	1) When corn was 3–6 inches 2) When corn was 24 inches
PBI	30 and 60 DAT
Residues of parent and M1 were < 0.05 ppm (LOQ Method D9709, as parent equivalents) in all samples from the 30 d PBI. Samples for 60 d PHI were not analyzed. Based on data reviewed, it is unlikely that residues will exceed 0.01 ppm in rotational crops planted at a PBI of 30 d. The PMRA recommends a 30 d PBI for the formulated product.	

Nature of the residue in lactating goat		
Radiolabel	**Dose level**	**Sacrifice**
Pyridine-C^{14}	Equivalent to 10 ppm in the diet.	Within 24 h after the 4th daily dose.
Phenyl-C^{14}	Equivalent to 10 ppm in the diet.	Within 24 h after the 4th daily dose.
The goat metabolism study indicated that diflufenzopyr was partially metabolized, and rapidly eliminated from the animals. Approximately 90% of the administered dose was excreted in urine and faeces. In addition to parent, the metabolites identified in goat urine, kidney, liver, and milk were M5, M1, M6 and M19.		

Matrix	Major metabolites (> 10 % TRR)		Minor metabolites (< 10 % TRR)	
	Phenyl-^{14}C	Pyridine-^{14}C	Phenyl-^{14}C	Pyridine-^{14}C
Milk	Parent, M5	Parent, M1, M19	—	M5, M6
Kidney	Parent, M5	Parent	—	M5, M1, M6
Liver	M5	Parent, M5	Parent	M1
The concentration of metabolites M5, M1, M6 and M19 represent various combinations of free, acid and base released quantities.				

Nature of the residue in laying hen (leghorn species)		
Radiolabel	**Dose level**	**Sacrifice**
Pyridine-C^{14}	Equivalent to 10 ppm in the diet.	Within 24 h after the 4th daily dose.
Phenyl-C^{14}	Equivalent to 10 ppm in the diet.	Within 24 h after the 4th daily dose.
At sacrifice, 99% of the dose was eliminated in the excreta with only 0.06–0.09% of the dose recovered in the tissues and eggs. The metabolic profile for hen is similar to that in goat and rat: diflufenzopyr was partially metabolized to M5, which is further metabolised to M1, M9, M10 and M19. Diflufenzopyr is also metabolised to M6.		

Matrix	Major metabolites (> 10 % TRR)		Minor metabolites (< 10 % TRR)	
	Phenyl-^{14}C	Pyridine-^{14}C	Phenyl-^{14}C	Pyridine-^{14}C
Excreta	Parent, M5	Parent, M5	—	M1, M6, M10, M9, M19
Liver	—	—	—	—
Egg white	—	M1	—	—
* free and acid released				

Supervised residue trials—corn				
Seven field trials were conducted in the following zones: 2 trials in Zone 5 at 2×, 2 trials in Zone 5 at 4×, 2 trials in Zone 5B at 2×, and 1 trial in Zone 5B at 1.5× the Canadian label rate.				
Commodity	**Rate (g a.i.*/ha)**	**PHI (days)**	**Residues (ppm)**	
			M1	**M10**
Field corn, Pioneer 3861	400 (Zone 5)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
	400 (Zone 5)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
	800 (Zone 5)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
	800 (Zone 5)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
Commodity	**Rate (g a.i.*/ha)**	**PHI (days)**	**Residues (ppm)**	
			M1	**M10**
Field Corn, Variety NK2879	400 (Zone 5B)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
	400 (Zone 5B)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
	300 (Zone 5B)	60	Forage < 0.01	Forage < 0.05
		120	Forage < 0.01	Forage < 0.05
		120	Fodder < 0.01	Fodder < 0.05
		120	Grain < 0.01	Grain < 0.05
* The active ingredient (a.i.) in this case refers to both diflufenzopyr and dicamba.				
Residue decline				
Not required since residues in field trials conducted at 1.5–4× the Canadian label rate were below the method LOQ.				

Maximum residue limits	
Corn	0.05 ppm, for diflufenzopyr and M1 expressed as parent equivalents (harmonized with the United States)

Processing studies

The processing study was conducted with corn treated at 0.224 kg a.i./ha, 0.672 kg a.i./ha, and 1.12 kg a.i./ha. Only 1.12 kg a.i./ha corn grain was processed by dry and wet milling. No concentration of residues was seen in any fraction.

Fraction	Mean residue levels of parent and metabolites convertible to M1, expressed as parent equivalents (ppm)	Calculated concentration factor
Corn grain	< 0.02	—
Grits	< 0.02	N/A
Refined oil (dry)	< 0.02	N/A
Meal	< 0.02	N/A
Refined oil (wet)	< 0.02	N/A
Starch	< 0.02	N/A

Livestock feeding

Livestock feeding studies were not required since the anticipated residues in corn commodities treated according to the label are unlikely to exceed LOQ (0.05 ppm, as parent equivalents).

Storage stability

Stability of M1 and M10 was demonstrated for 24 months in corn forage, grain and fodder under storage conditions of -10ºC .

Table 3 Overview of metabolism studies and risk assessment

Plant studies			
ROC for enforcement and risk assessment **Primary crop (corn)** **Rotational crops**			 Diflufenzopyr and metabolites convertible to M1 Diflufenzopyr and metabolites convertible to M1
Metabolic profile in corn (Figure 4.1)			The urea bond is cleaved to yield metabolites containing a new bicyclic ring system (M1, M10, M9). No diflufenzopyr was detected in any of the corn matrices.
Animal studies			
ROC for enforcement and risk assessment			No ROC required for animal commodities since residues of diflufenzopyr are not expected.
Metabolic profile in animals (Figure 4.1)			Metabolism of diflufenzopyr in ruminants, poultry and the rat is similar to that which occurs in corn. Diflufenzopyr is partially metabolized to M5, which is further metabolized to M1, M9, M10, and M19
Fat-soluble residue			Yes, but does not concentrate in any fatty tissue or corn oil.
MRL— level dietary risk from food and water			
Chronic non-cancer dietary risk **ADI = 0.26 mg/kg bw/day** **EEC = 0.15 µg a.i./L** Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates that would result from the use of diflufenzopyr on field corn in Canada and uses on sweet and popping corn that are registered in the United States. The assessment used the maximum residues limits and assumed 100% crop treated.	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (MRLs)	**Food + EEC**
	All infants < 1 yr old	0	0
	Children 1 to 2 yrs	0.1	0.1
	Children 3 to 5 yrs	0.1	0.1
	Children 6 to 12 yrs	0.1	0.1
	Youth 13 to 19 yrs	0	0
	Adults 20 to 49 yrs	0	0
	Adults 50+ yrs	0	0
	Females 13 to 49 yrs	0	0
	Total Population	0	0

Acute dietary exposure analysis, Deterministic, 95th percentile EEC = 3.66 µg a.i./L ARfD = 1.0 mg/kg bw (females 13+)	POPULATION	ESTIMATED RISK (% of ARD)	
		Food	Food + EEC
	Females 13+	0.02	0.02

Table 4 Fate and behaviour of diflufenzopyr in the aquatic and terrestrial environment

Fate process	Endpoint	Interpretation[a]
AQUATIC		
Hydrolysis	$T_{1/2}$: 12.9 d at pH 5 $T_{1/2}$: 23.9 d at pH 7 $T_{1/2}$: 25.6 d at pH 9	An important route of transformation in the environment.
Phototransformation in water	$T_{1/2}$: 6.8 d at pH 5 $T_{1/2}$: 16.8 d at pH 7 $T_{1/2}$: 13.4 d at pH 9	An important route of transformation under acidic environmental conditions.
Aerobic sediment/ water	$T_{1/2}$: 26 d, phenyl label $T_{1/2}$: 25 d, pyridyl label	Slightly persistent in aerobic water-sediment systems.
Anaerobic sediment/ water	$T_{1/2}$: 20 d, phenyl label $T_{1/2}$: 26 d, pyridyl label	Slightly persistent in anaerobic water sediment systems.
TERRESTRIAL		
Hydrolysis	$T_{1/2}$: 12.9 d at pH 5 $T_{1/2}$: 23.9 d at pH 7 $T_{1/2}$: 25.6 d at pH 9	An important route of transformation.
Phototransformation on soil	$T_{1/2}$: 14 d	Not an important route of transformation.
Aerobic soil biotransformation	$T_{1/2}$: 8 d $T_{1/2}$: 10 d	Non persistent.
Adsorption/ desorption	Adsorption K_{oc} (diflufenzopyr): 18–156 mL/g Adsorption K_{oc} (M1): 140–596 mL/g Adsorption K_{oc} (M9): 385–3668 mL/g	Moderate to very high mobility. Low to high mobility. Slight to moderate mobility.
Field dissipation of Distinct® herbicide on bare plots	**Ontario, Canada** DT_{50}: 4 d DT_{50}: 8.45 d	Non-persistent. Did not leach below the top 15 cm of soil.

[a] Classification of persistence in soil according to Goring et al. (1975); classification of persistence in water according to McEwan and Stephenson (1979); classification of adsorption/ desorption and mobility according to McCall et al. (1981).

Table 5 Diflufenzopyr drinking water EECs

Crop and rate of application	Groundwater (µg a.i./L)		Surface water	
			Reservoir (µg a.i./L)	
	Acute[1]	Chronic[2]	Acute[3]	Chronic[4]
Corn	0.00056	0.00051	3.66	0.15

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peaks
4 90th percentile of yearly averages

Table 6 Maximum EECs of diflufenzopyr on vegetation and other food sources immediately following application at a rate of 57 g a.i./ha[a]

Environmental compartment	Concentration fresh weight (mg a.i./kg)[a]	Fresh weight / dry weight ratios	Concentration dry weight (mg a.i./kg)
short range grass	12.19	3.3	40.25
leaves and leafy crops	6.38	11	70.22
long grass	5.59	4.4	24.58
forage crops	6.84	5.4	36.94
small insects	2.96	3.8	11.26
pods with seeds	0.61	3.9	2.38
large insects	0.51	3.8	1.93
grain and seeds	0.51	3.8	1.93
fruit	0.76	7.6	5.8

a Maximum application rate
b Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)

Table 7 Summary of effects of diflufenzopyr on terrestrial organisms

Organism	Exposure	Endpoint value	Degree of toxicity[a]
Earthworm (*Eisenia foetida*)	14-day chronic	LC_{50}: > 1000 mg a.i./kg soil NOEC (mortality): 500 mg a.i./kg soil	Non-lethal > 500 mg a.i./kg substrate
Bee	48-hour chronic contact	LC_{50}: > 25 µg a.i./bee NOEC (mortality): 25 µg a.i./bee	Non-toxic (Atkins et al. 1981)
	48-hour chronic oral	LC_{50}: > 25 µg a.i./bee NOEC (mortality): 25 µg a.i./bee	Non-toxic (Atkins et al. 1981)
Bobwhite quail (*Colinus virginianus*)	14-day chronic oral	LD_{50}: > 1868 mg a.i./kg bw NOEL (mortality): 1868 mg a.i./kg bw	At most slightly toxic
	5-day dietary	LC_{50}: > 4608 mg a.i./kg diet NOEC (food consumption + body weight): 4608 mg a.i./kg diet	Practically non-toxic
Mallard duck (*Anas platyrhynchos*)	5-day dietary	LC_{50}: > 4608 mg a.i./kg diet NOEC (FC + bw): 2591 mg a.i./kg diet	At most slightly toxic
	22-week reproduction	NOEC (reproductive parameters, hatchling + parental): 1000 mg a.i./kg diet NOEC (reproductive parameters, hatchling + parental): 1000 mg a.i./kg diet	—
Mammals			
Rats	Chronic oral	LD_{50}: > 5000 mg a.i./kg bw	Low toxicity
	13-week dietary	NOEL: 5000 mg a.i./kg diet	—
	Reproduction	$NOEL_{reproduction}$: 8000 mg a.i./kg diet	—
Mouse	13-week dietary	NOEL: 7000 mg a.i./kg diet	—

Organism	Exposure	Endpoint value	Degree of toxicity[a]
Vascular plants			
Vascular plants	Phytotoxicity (radish)	EC_{25}: 14.7 g EP/ha NOEC: 35 g EP/ha	
	Dry plant weight (tomato)	EC_{25}: 21.4 g EP/ha NOEC: 4.4 g EP/ha	
	Shoot length (tomato)	EC_{25}: 31.8 g EP/ha NOEC: 35 g EP/ha	

[a] Based on the USEPA's classification scheme (1985) unless otherwise stated. Where no degree of toxicity is presented, no toxicity classification is available based on study type.

Table 8 Summary of toxicity of diflufenzopyr to aquatic organisms

Group	Organism	Exposure	Test substance	Endpoint	Degree of toxicity[a]
Freshwater					
Invertebrates	*Daphnia magna*	48 h	diflufenzopyr	NOEC (mortality): 9.7 mg a.i./L LC_{50}: 15 mg a.i./L	Slightly toxic
Fish	Rainbow trout (*Oncorhynchus mykiss*)	96 h	diflufenzopyr	NOEC (mortality): 80 mg a.i./L LC_{50}: 106 mg a.i./L	Practically non-toxic
	Bluegill sunfish (*Lepomis machrochirus*)	96 h	diflufenzopyr	NOEC (mortality): 16 mg a.i./L LC_{50}: >135 mg a.i./L	Practically non-toxic
Algae	Bluegreen (*Anabaena flos-aquae*)	5 d	diflufenzopyr	NOEC (biomass): 0.014 mg a.i./L EC_{50}: 0.15 mg a.i./L	—
			Distinct® EP	NOEC (biomass): 0.0059 mg EP/L EC_{50}: > 0.26 mg EP/L	—
	Bluegreen (*Selenastrum capricortunum*)	5 d	diflufenzopyr	NOEC (biomass): 0.0078 mg a.i./L EC_{50}: 0.11 mg a.i./L	—
Diatom	*Naviculla pelliculosa*	5 d	diflufenzopyr	NOEC (biomass): 0.003 mg a.i./L EC_{50}: 0.10 mg a.i./L	—
Aquatic plants	*Lemna minor*	7 d	diflufenzopyr	NOEC (biomass): 0.0039 mg a.i./L EC_{50}: > 0.35 mg a.i./L	—
			Distinct® EP	NOEC (biomass): 0.0023 mg EP/L EC_{50}: 0.11 mg EP/L	—
Marine					
Invertebrates	Eastern oyster (*Crassostrea virginica*)	96 h	diflufenzopyr	NOEC (shell growth): 31 mg a.i./L EC_{50}: 61 mg a.i./L	Slightly toxic
	Mysid shrimp (*Mysidopsis bahia*)	96 h	diflufenzopyr	NOEC (mortality): 4.4 mg a.i./L LC_{50}: 18.9 mg a.i./L	Slightly toxic
Fish	Sheepshead minnow (*Cyprinodon variegatus*)	96 h	diflufenzopyr	NOEC (mortality): 138 mg a.i./L LC_{50}: > 138 mg a.i./L	Practically non-toxic
Diatom	*Skeletoneum costatum*	5 d	diflufenzopyr	NOEC (mortality): 0.0064 mg a.i./L EC_{50}: 0.12 mg a.i./L	—

[a] Based on the USEPA's classification scheme (1985) unless otherwise stated. Where no degree of toxicity is presented, no toxicity classification is available based on study type.

Table 9 Maximum EEC in diets of birds and mammals

Organism	Matrix	Diflufenzopyr (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	9.98
Mallard duck	30% large insects 70% grain	1.93
Rat	70% short grass 20% grain/seeds 10% large insects	28.76
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	28.58

Table 10 Risk to terrestrial organisms

Organism	Exposure	Endpoint value	EEC (mg/kg)	Risk quotient[a]	Degree of risk
Earthworm (*Eisenia foetida*)	chronic	LC_{50}: > 1000 mg a.i./kg soil NOEC (mortality): 500 mg a.i./kg soil	0.025	0	Negligible
Bee	chronic	LC_{50}: > 25 µg a.i./bee NOEC (mortality): 25 µg a.i./bee	N/A	N/A	Negligible hazard (Atkins et al. 1981)
	chronic	LD_{50}: > 25 µg a.i./bee NOEC (mortality): 25 µg a.i./bee	N/A	N/A	Negligible hazard (Atkins et al. 1981)
Bobwhite quail (*Colinus virginianus*)	chronic	LD_{50}: > 1868 mg a.i./kg bw NOEL (mortality): 1868 mg a.i./kg bw	9.98	2.4 days	Negligible based on DI[b]
	dietary	LC_{50}: > 4608 mg a.i./kg diet NOEC (FC + bw): 4608 mg a.i./kg diet	9.98	0.002	Negligible

Organism	Exposure	Endpoint value	EEC (mg/kg)	Risk quotient[a]	Degree of risk
Mallard duck (*Anas platyrhynchos*)	dietary	LC_{50}: > 4608 mg a.i./kg diet NOEC (FC + bw): 2591 mg a.i./kg diet	1.93	0.001	Negligible
	reproduction	NOEC (reproductive parameters, hatchling + parental): 1000 mg a.i./kg diet NOEC (reproductive parameters, hatchling + parental): 1000 mg a.i./kg diet	1.93	0.0019	Negligible
Mammals					
Rat	chronic	LD_{50}: > 5000 mg a.i./kg bw	28.76	101 days	Negligible based on DI[b]
	dietary	NOEL: 5000 mg a.i./kg diet	28.76	0.0058	Negligible
	reproduction	$NOEL_{reproduction}$: 8000 mg a.i./kg diet	28.76	0.0036	Negligible
Mouse	dietary	NOEL: 7000 mg a.i./kg diet	28.58	0.0041	Negligible based on DI[b]
Vascular plants					
Vascular plants	phytotoxicity	EC_{25}: 14.7 g EP/ha	285[c]	19.4	High

[a] RQ = EEC ÷ NOEC, expect for terrestrial plants where RQ = EEC ÷ EC_{25}

[b] DI (daily intake). The risk criteria is < 1 day.

[c] Figures calculated in mg EP/L.

Table 11 Risk to aquatic organisms

Organism	Exposure	Endpoint	EEC (mg/L)	Risk quotient[a]	Degree of risk
Freshwater					
Daphnia magna	48 h	NOEC (mortality): 9.7 mg a.i./L LC_{50}: 15 mg a.i./L	0.019	0.0019	Negligible
Rainbow trout (*Oncorhynchus mykiss*)	96 h	NOEC (mortality): 80 mg a.i./L LC_{50}: 106 mg a.i./L	0.019	0.0002	Negligible
Bluegill sunfish (*Lepomis machrochirus*)	96 h	NOEC (mortality): 16 mg a.i./L LC_{50}: > 135 mg a.i./L	0.019	0.0012	Negligible
Bluegreen algae (*Anabaena flos-aquae*)	5 d	NOEC (biomass): 0.014 mg a.i./L EC_{50}: 0.15 mg a.i./L	0.019	1.4	Moderate
		NOEC (biomass): 0.0059 mg EP/L EC_{50}: > 0.26 mg EP/L	0.095[b]	16	High
Bluegreen algae (*Selenastrum capricortunum*)	5 d	NOEC (biomass): 0.0078 mg a.i./L EC_{50}: 0.11 mg a.i./L	0.019	2.4	Moderate
Diatom (*Naviculla pelliculosa*)	5 d	NOEC (biomass): 0.003 mg a.i./L EC_{50}: 0.10 mg a.i./L	0.019	6.3	Moderate

Organism	Exposure	Endpoint	EEC (mg/L)	Risk quotient[a]	Degree of risk
Duckweed (*Lemna minor*)	7 d	NOEC (biomass): 0.0039 mg a.i./L EC_{50}: > 0.35 mg a.i./L	0.019	4.9	Moderate
		NOEC (biomass): 0.0023 mg EP/L EC_{50}: > 0.11 mg EP/L	0.095[b]	41.3	High
Marine					
Eastern oyster (*Crassostrea virginica*)	96 h	NOEC (shell growth): 31 mg a.i./L EC_{50}: 61 mg a.i./L	0.019	0.0006	Negligible
Mysid shrimp (*Mysidopsis bahia*)	96 h	NOEC (mortality): 4.4 mg a.i./L LC_{50}: 18.9 mg a.i./L	0.019	0.004	Negligible
Sheepshead minnow (*Cyprinodon variegatus*)	96 h	NOEC (mortality): 138 mg a.i./L LC_{50}: > 138 mg a.i./L	0.019	0.00014	Negligible
Diatom (*Skeletoneum costatum*)	5 d	NOEC (mortality): 0.0064 mg a.i./L EC_{50}: 0.12 mg a.i./L	0.019	2.9	Moderate

[a] RQ = EEC ÷ NOEC

[b] Figures calculated in mg EP/L.

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