Proposed Registration Decision PRD2011-05

Diflufenzopyr-sodium

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Overview

Proposed Registration Decision for Diflufenzopyr-sodium

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Sodium Diflufenzopyr Technical Herbicide and the end use product Overdrive Herbicide, containing the technical grade active ingredients diflufenzopyr-sodium and dicamba, to control broadleaf weeds in pasture, rangeland and non-cropland situations such as railroad, utility, pipeline and highway rights-of-way, railroad crossings, roadside, petroleum tank farms, non-agriculture fencerows and airports.

Diflufenzopyr-sodium is currently registered for use in Canada for weed control in terrestrial food and feed crops. The detailed review for this use can be found in Proposed Regulatory Decision Document (PRDD) 2005-01: *Diflufenzopyr Distinct* as well as Regulatory Decision Document (RDD)2005-04: *Diflufenzopyr Distinct*.

Dicamba is currently registered for use in the non-cropland, pasture and rangeland sites proposed for Overdrive Herbicide. Therefore, this document will present the health and environmental assessments for diflufenzopyr-sodium and Overdrive Herbicide as well as the value assessment for the end use product Overdrive Herbicide.

Both PRDD2005-01: *Diflufenzopyr Distinct* and RDD 2005-04: *Diflufenzopyr Distinct* refer to the acid form of diflufenzopyr. The PMRA subsequently determined the more accurate name for the active ingredient is diflufenzopyr-sodium.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Sodium Diflufenzopyr Technical Herbicide and the end use product Overdrive Herbicide for use in pasture, rangeland and non-cropland situations for broadleaf weed control.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed a nd the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management Portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on diflufenzopyr-sodium the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on diflufenzopyr-sodium which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

What Are Diflufenzopyr-sodium and Overdrive Herbicide?

Diflufenzopyr-sodium is an active ingredient in the end-use product Overdrive Herbicide. Overdrive Herbicide contains the active ingredients dicamba at 50% and diflufenzopyr-sodium at 20%. Overdrive is a post-emergence herbicide, i.e. a herbicide applied after weeds and crops have emerged from the ground, which is applied using ground application equipment to pasture, rangeland and non-cropland situations such as railroad, utility, pipeline and highway rights-of-way, railroad crossings, roadside, petroleum tank farms, non-agriculture fencerows and airports, for the control of broadleaf weeds. Diflufenzopyr-sodium inhibits the transport of naturally occurring auxin and synthetic auxin-like compounds, like dicamba, in sensitive plants. When diflufenzopyr-sodium is applied with dicamba, it focuses translocation of dicamba to the growing points of the plant and providing weed control at lower rates of dicamba than when dicamba is applied alone.

Health Considerations

Can Approved Uses of Diflufenzopyr-sodium Affect Human Health?

Diflufenzopyr-sodium is unlikely to affect your health when used according to label directions.

Potential exposure to diflufenzopyr-sodium may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when diflufenzopyr-sodium products are used according to label directions.

In laboratory animals technical diflufenzopyr-sodium was of low acute toxicity via oral, dermal and inhalation routes of exposure. It was not irritating when applied to the skin, but was minimally irritating to the eye. It did not produce an allergic skin reaction. The end use product Overdrive herbicide, containing diflufenzopyr-sodium and dicamba, was slightly acutely toxic via the oral route and of low toxicity via the dermal and inhalation routes of exposure. It was minimally irritating to the skin, mildly irritating to the eye and caused an allergic skin reaction. Consequently, the hazard signal words CAUTION-POISON, CAUTION– EYE IRRITANT and POTENTIAL SKIN SENSITIZER are required on the label.

Diflufenzopyr-sodium did not cause cancer in animals and did not damage genetic material. There was also no indication that diflufenzopyr-sodium caused damage to the nervous system or birth defects. Health effects in animals given repeated doses of diflufenzopyr-sodium over longer periods of time included lower body weight and effects indicative of mild compensatory anaemia.

When diflufenzopyr-sodium was given to pregnant animals, effects of a serious nature on the developing foetus (embryo/fetal loss) were observed at doses that were toxic to the mother.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most diflufenzopyr-sodium relative to body weight, are expected to be exposed to less than 1.0% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from diflufenzopyr-sodium is not of concern for all population sub-groups.

Animal studies revealed no acute health effects. Consequently, a single dose of diflufenzopyr-sodium is not likely to cause acute health effects in the general population (including infants and children).

The Food and Drugs Act (FDA) prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the Pest Control Products Act (PCPA). Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States using diflufenzopyr-sodium on pasture and rangeland grasses were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Risks in Residential and Other Non-Occupational Environments

Entry by the public into treated commercial areas is considered acceptable.

Potential for bystander exposure is considered minimal due to the restricted nature of many of the non-cropland areas, and is expected to be significantly less than exposures estimated for operators and workers.

Occupational Risks From Handling Overdrive Herbicide

Occupational risks are not of concern when Overdrive Herbicide is used according to the proposed label directions, which include protective measures.

Workers who mix, load or apply Overdrive Herbicide as well as workers re-entering treated areas can come in direct contact with dicamba and diflufenzopyr-sodium residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Overdrive Herbicide must wear chemical-resistant gloves, long-sleeved shirt, long pants, socks and shoes as well as protective eyewear during mixing and loading. The label also requires that workers do not enter treated areas for 12 hours after application in pasture and rangeland. For all other applications, workers must wait until sprays have dried before re-entering treated areas. Taking into consideration these label statements, the number of applications and the expected exposure period for handlers and workers, the risk to workers handling Overdrive Herbicide is not of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Diflufenzopyr-sodium Is Introduced Into the Environment?

Diflufenzopyr-sodium poses a potential risk to aquatic organisms and terrestrial plants, therefore, risk-reduction measures must be observed.

Diflufenzopyr-sodium is non-persistent in soil. Therefore, accumulation in soil and carryover are not expected to be significant. Diflufenzopyr-sodium can enter aquatic systems by spray drift or runoff. It is slightly persistent in the aquatic environment. Based on its low volatility, diflufenzopyr-sodium residues are not expected in the air. There is low potential for bioaccumulation of diflufenzopyr-sodium.

Diflufenzopyr-sodium is expected to pose a risk to aquatic organisms and terrestrial vascular plants. As such, mitigative measures must be taken to minimise adverse effects on plant populations and aquatic organisms. Diflufenzopyr-sodium presents negligible risk to wild birds and mammals, bees and other arthropods.

To minimize potential exposure, spray buffer zones are required. The width of these buffer zones are specified on the product label.

Value Considerations

What Is the Value of Overdrive Herbicide?

Overdrive Herbicide contains the active ingredients dicamba at 50% and diflufenzopyr-sodium at 20% a.e. Overdrive Herbicide is a post-emergence herbicide which is applied using ground application equipment to pasture, rangeland and non-cropland situations to control common ragweed, lady's thumb, lamb's-quarters, redroot pigweed, tall waterhemp, velvetleaf, wild buckwheat, biennial wormwood, Canada thistle (top growth control), sweet clover (top growth control), vetch (top growth control), dandelion (top growth suppression) and leafy spurge (top growth suppression).

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Overdrive Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Overdrive Herbicide on the skin, anyone mixing, loading and applying Overdrive Herbicide must wear a long-sleeved shirt, long pants, shoes and socks, chemical-resistant gloves as well as protective eyewear during mixing and loading. The label also requires a restricted entry interval (REI) of 12 hours for workers re-entering treated pasture and rangeland. For all other applications, workers must wait until sprays have dried before re-entering treated areas. In addition, standard label statements to protect against drift during application were added to the label.

Next Steps

Before making a final registration decision on Sodium Diflufenzopyr Technical Herbicide and Overdrive Herbicide, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on diflufenzopyr-sodium and Overdrive Herbicide (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

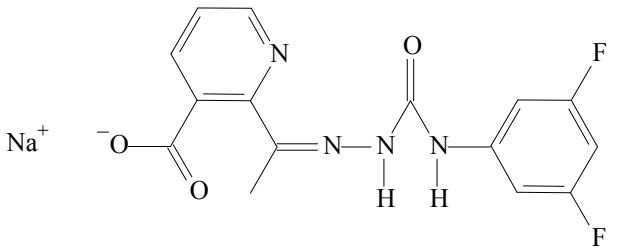
Science Evaluation

Diflufenzopyr-sodium

1.0 The Active Ingredient, Its Properties and Uses

Please refer to the PRDD2005-01: *Diflufenzopyr Distinct* for the complete chemistry evaluation of Sodium Diflufenzopyr Technical Herbicide. Below is presented the chemistry evaluation of the end use product Overdrive Herbicide.

1.1 Identity of the Active Ingredient

Active substance	Diflufenzopyr-sodium
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	sodium 2-{(*EZ*)-1-[4-(3,5-difluorophenyl)semicarbazono] ethyl}nicotinate
2. Chemical Abstracts Service (CAS)	2-[1-[[[(3,5-difluorophenyl)amino]carbonyl]hydrazono]ethyl]-3-pyridinecarboxylic acid, monosodium salt
CAS number	109293-98-3
Molecular formula	$C_{15}H_{11}N_4O_3F_2Na$
Molecular weight	356.26
Structural formula	
Purity of the active ingredient	86.3%

1.2 Physical and Chemical Properties of the End-Use Product

End-Use Product— Overdrive Herbicide

Property	Result
Physical state	Solid
Formulation type	WG (wettable granules)
Guarantee	Diflufenzopyr (present as sodium salt) - 20% Dicamba (present as sodium salt) - 50%
Container material and description	High density polyethylene (HDPE) containers with induction sealed caps.
Density	0.61 g/mL
pH of 1% dispersion in water	8.51 at 25°C
Storage stability	Stable for 40 months in the commercial HDPE containers under warehouse conditions.
Corrosion characteristics	No adverse effect on the commercial HDPE containers was detected following 40 months of storage under warehouse conditions.

1.3 Directions for Use

1.3.1 Overdrive Herbicide

Overdrive Herbicide is a selective herbicide for use as a post-emergence treatment on pasture, rangeland and non-cropland situations for the control of specific broadleaf weeds. The product is applied once per growing season, when weeds are actively growing, as a broadcast treatment with ground application equipment only. Overdrive Herbicide is applied at a rate of 199.5 g a.e./ha (142.5 g a.e./ha dicamba and 57 g a.e./ha diflufenzopyr-sodium) and must be applied with a non-ionic surfactant at a rate of 0.25% (v/v) and liquid urea ammonium nitrate (UAN 28%) at a rate of 1.25% (v/v). (Table 1.3.1.1)

Table 1.3.1.1 Weed Control Claims for Overdrive Herbicide*

Herbicide Rate	Weeds Controlled
199.5 g a.e./ha or 285 g product/ha (142.5 g a.e./ha dicamba + 57 g a.e./ha diflufenzopyr-sodium)	Common ragweed, lady's thumb, lamb's-quarters, redroot pigweed, tall waterhemp, velvetleaf, wild buckwheat, biennial wormwood, Canada thistle (top growth control), sweet clover (top growth control), vetch (top growth control), dandelion (top growth suppression), leafy spurge (top growth suppression)

*Overdrive Herbicide must be applied with a non-ionic surfactant at a rate of 0.25% (v/v) and liquid urea ammonium nitrate (UAN 28%) at a rate of 1.25% (v/v).

1.4 Mode of Action

Diflufenzopyr-sodium is classified as a Group 4 Herbicide (refer to Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*, for details). The primary mode of action of diflufenzopyr-sodium is inhibition of polar transport of naturally occurring auxin (indoleacetic acid or IAA) and synthetic auxin-like compounds such as dicamba, in sensitive plants. Inhibition of transportation of auxin and auxin-like compounds causes an abnormal accumulation of IAA and synthetic auxin compounds in the newest tissue of roots and shoots, causing a disruption of the auxin balance needed for plant growth. When diflufenzopyr-sodium is applied with dicamba, it focuses translocation of dicamba to the growing points of the plant providing weed control at lower rates of dicamba than when dicamba is applied alone.

2.0 Methods of Analysis

2.1 Method for Formulation Analysis

The method provided for the analysis of the active ingredients in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.2 Methods for Residue Analysis

Refer to PRDD2005-01: *Diflufenzopyr Distinct* for a detailed assessment of the methods of analysis for diflufenzopyr-sodium in crop commodities.

Method D0102 (LC/MS/MS) was developed and proposed for data generation and enforcement purposes in livestock commodities. This method fulfills the requirements with regards to specificity, accuracy and precision at the method limit of quantitation. Acceptable recoveries were obtained in livestock matrices. Although Method D0102 has not been radiovalidated, the extraction schemes were similar to those used in the livestock metabolism studies (PRDD2005-01: *Diflufenzopyr Distinct*).

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Refer to PRDD2005-01: *Diflufenzopyr Distinct* for detailed assessment of the toxicology of technical diflufenzopyr-sodium.

The toxicology database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to diflufenzopyr-sodium.

Following oral dosing in the rat, diflufenzopyr-sodium was only partially absorbed (about 50%) and was not extensively metabolized. It was rapidly eliminated (half life 3.3-6.9 hours), primarily via the feces (20-44% in urine, 51-79% in feces and 3-11% in bile). Dose level and pretreatment had little effect on the proportion of the dose excreted. It was excreted primarily unchanged in excreta. Minor amounts of hydrolysis and hydroxylation products were identified. There were no sex differences in absorption or metabolism. For each dose group the metabolic profile was similar between sexes except for differences in metabolite level. Bioaccumulation was minimal (<3%) with residue levels highest in blood, blood cells and serum.

Technical diflufenzopyr-sodium was of low toxicity via oral and inhalation routes of exposure in the rat and dermal route in rabbits. It was not irritating when applied to the skin of the rabbit but was minimally irritating to the rabbit eye. It is not a skin sensitizer.

The end use product, Overdrive herbicide, was slightly acutely toxic via the oral route in rats and of low toxicity via the dermal route in rabbits and inhalation routes in rats. It was minimally irritating to the skin and mildly irritating to the eye of the rabbit. It was a potential skin sensitizer in the guinea pig.

No evidence of toxicity was observed in rabbits following a 21-day dermal exposure up to 1000 mg/kg bw/day.

In short term dietary toxicity studies, there were no treatment related effects at any dose in mice; however, a decrease in body weight gain, increase in alanine amino transferase, increased cholesterol and an increased incidence of foamy macrophages in the lungs were noted in rats. In the 90-day dog study, treatment related erythroid hyperplasia in the bone marrow, extramedullary hematopoiesis in the liver and hemosiderin deposits in the Kupffer cells was noted.

In the one year dog study, treatment related effects included decreases in body weight gain and increased erythroid hyperplasia in the femoral and sternal bone marrow of both sexes. Food efficiency was decreased in females only. There were hemosiderin deposits in the kidney, liver and spleen, reddish discoloration of the diaphysis of the femur and mild to moderate reticulocytosis in both sexes, clearly categorizing the dog as the most sensitive of the species tested.

In the long-term dietary study, no treatment related effects were noted up to the limit dose in mice. In the rat there were decreases in body weight and body weight gain seen primarily in the second year of a long term study. There was no evidence of carcinogenicity in either species.

No evidence of genotoxic potential of diflufenzopyr-sodium was observed when tested in a battery of in-vitro and in vivo genotoxicity assays, assessing gene mutation and clastogenicity.

In the rat developmental toxicity study there was no evidence of maternal or developmental toxicity at any dose, however, in the reproductive toxicity study, effects noted consisted of an increase in total post implantation loss, and a decrease in live-birth index at doses with parental toxicity (decrease in mean body weight and body weight gain despite increased mean food consumption). Offspring toxicity included a decrease in body weight and body weight gain pre-weaning and an increase in the proportion of runts as well as offspring with no milk in the stomach. In the rabbit developmental toxicity study, effects included abortions and maternal death, which occurred at the same dose late in gestation.

There was no evidence of neurotoxicity in either the acute or short term neurotoxicity studies.

Results of the toxicology studies conducted on laboratory animals with diflufenzopyr-sodium and its associated end-use product, are summarized in Tables 2 and 3 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 4 of Appendix I.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for active diflufenzopyr-sodium. As of January 2011, there was one incident report submitted for products containing diflufenzopyr-sodium. The incident occurred in the United States. Symptoms were deemed inconsistent with diflufenzopyr-sodium . The PMRA concluded that the information from the incident report did not impact the risk assessment. Detailed information for the incidents can be found on the PMRA Public Registry.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the Pest Control Products Act requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for diflufenzopyr-sodium. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the rat developmental and reproductive toxicity studies. In the two generation rat toxicity study parental females experienced increased post implantation loss and a corresponding decrease in live birth index in addition to decreased body weight and body weight gain. Offspring effects included decreased live birth and viability indices, body weight and body weight gains pre-weaning, and an increased proportion of runts as well as offspring with no milk in the stomach. In the rabbit developmental toxicity study, effects included abortions and maternal death which occurred at the same dose, late in gestation.

Overall, effects on the young are well characterized and there is a low level of concern for sensitivity of the young. The abortions in rabbits and the post implantation loss in rats were considered serious endpoints although the concern for these findings was tempered by the presence of maternal toxicity. Therefore, the PCPA factor was reduced to 3-fold when using the rabbit developmental toxicity study to establish the point of departure for scenarios assessing risk to women of child bearing age. For all other scenarios, the endpoint selected was considered protective of prenatal and postnatal concerns, therefore the PCPA factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

An ARfD was not established as no relevant endpoint was identified. Although serious effects, namely increased abortions and mortality, were observed in the rabbit developmental toxicity study, the effects occurred late in the study and were not considered appropriate for acute exposure scenarios.

3.3 Acceptable Daily Intake (ADI)

To estimate dietary risk from repeat exposure, the 1-year dog study with a NOAEL of 26 mg/kg bw/day was selected for risk assessment. At the Lowest Observed Adverse Effect Level (LOAEL) of 299 mg/kg bw/day, effects indicative of mild compensatory anemia and decreased food efficiency were observed. This study provides the lowest No Observed Adverse Effects Level (NOAEL) in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{26 mg/kg bw/day}}{100} = 0.26 \text{ mg/kg bw/day of diflufenzopyr-sodium}$$

The ADI provides a margin of 385 to the NOAEL for abortions observed in the rabbit developmental toxicity study.

Cancer Assessment
There was no evidence of carcinogenicity and therefore, a cancer risk assessment was not necessary.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

For short- and intermediate-term dermal and inhalation occupational exposures, the NOAEL of 100 mg/kg bw/d from the rabbit developmental toxicity study was selected for risk assessment. At a dose of 300 mg/kg bw/day abortions and maternal death were observed. Worker populations could include pregnant women and, therefore, these endpoints were considered appropriate for the occupational risk assessment. The short term dermal study did not address the relevant endpoint of concern (i.e. abortion) thus necessitating the use of an oral study for risk assessment. A short term inhalation study was not available. The target margin of exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, as well as a factor of 3-fold for the reasons outlined in the PCPA hazard characterization section. The selection of this study and MOE was considered to be protective of all populations, including the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

There were no dermal absorption data submitted for diflufenzopyr-sodium. Therefore, the dermal absorption is considered to be 100%.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to Overdrive Herbicide during mixing, loading and application. As chemical specific data for assessing human exposures were not submitted, dermal and inhalation exposure estimates for workers were estimated using the Pesticide Handlers Exposure Database (PHED), version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data which facilitates the generation of scenario-specific exposure estimates. Data with the highest confidence were used when available. Exposure estimates are outlined in Table 1. As the use of dicamba fits within the registered use pattern for this active on non-cropland sites, pasture and rangeland, worker exposure and risk assessments for dicamba were not required.

Table 1 PHED Unit Exposure Estimates for Mixer/Loader and Applicators While Handling Overdrive Herbicide (µg/kg a.i. handled)

Scenario	Exposure (in µg/kg a.i. handled)		
	Dermal Exposure	Inhalation Exposure	Total Exposure
Dry flowable, open mixing and loading; single layer + gloves, and groundboom application; single layer, no gloves[1]	196.75	1.98	198.73
Dry flowable, open mixing and loading; single layer + gloves, and right-of-way sprayer application; single layer + gloves	1036.31	6.02	1042.33
Dry flowable, open mixing and loading + liquid mixing/loading, high-pressure handwand application; single layer + gloves[2]	5749.26	151.00	5900.26
Dry flowable, open mixing and loading + liquid mixing/loading, low-pressure handwand application; single layer + gloves[2]	1107.14	45.20	1152.34
Dry flowable, open mixing and loading + liquid mixing/loading, backpack application; single layer + gloves[2]	5609.62	62.10	5671.72

[1]Higher confidence data used

[2]PHED open mixing/loading values for dry flowables are higher than those for liquid formulations. In order to be conservative, open mixing and loading exposure for dry flowables (163.77 µg/kg a.i. handled) was added to the M/L/A exposure for handheld application equipment

Exposure estimates for diflufenzopyr-sodium were derived for mixer/loaders and applicators applying Overdrive Herbicide to non-cropland sites, pasture and rangeland using groundboom, right-of-way sprayer, low- and high-pressure handwands and backpack sprayer equipment. Handlers are assumed to have potential short- to intermediate-term dermal and inhalation exposure to Overdrive Herbicide. Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and a default dermal absorption (DA) of 100%. Dermal exposure estimates are based on mixers, loaders and applicators of Overdrive Herbicide wearing a long-sleeved shirt, long pants and chemical-resistant gloves. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product

handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight (bw). Exposure estimates were compared to the No Observed Adverse Effects Level (NOAEL) of 100 mg/kg bw/day to obtain the margin of exposure (MOE); the target MOE is 300. The area treated per day (ATPD) values were taken from default PMRA values, coupled with the minimum volume of solution required to treat one hectare (220 L) if necessary. The risk assessment results for diflufenzopyr-sodium are summarized in Table 2. All uses exceed the target MOE and are considered acceptable based on the label directions and PPE.

Table 2 Mixer/Loader/Applicator Risk Assessment for Diflufenzopyr-sodium

Scenario	Total Exposure (µg/kg a.i./day)	ATPD (ha)	Daily Dose[1] (mg/kg bw/day)	Dermal and Inhalation NOAEL (mg/kg bw/day)	Combined MOE[2]
Custom, groundboom	198.73	360	0.0583	100	1,700
Right-of-way sprayer	1042.33	18	0.0153	100	6,500
High-pressure handwand	5900.26	17.05[3]	0.0819	100	1,200
Low-pressure handwand	1152.34	0.68[4]	0.0006	100	156,300
Backpack	5671.72	0.68[4]	0.0031	100	31,800

[1]Daily dose = [Dermal + inhalation exposure (µg/kg a.i. handled) x ATPD (ha) x Application rate (0.057 kg a.i./ha)]/ (70 kg bw x 1000 µg/mg)
[2] MOE = NOAEL (mg/kg bw/day)/Daily dose (mg/kg bw/day); target MOE = 300
[3]Based on a default value of 3750 L/day handled, and a minimum spray volume of 220 L/ha
[4]Based on a default value of 150 L/day handled, and a minimum spray volume of 220 L/ha

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Overdrive Herbicide to perform cultural activities such as irrigation and scouting. Given the nature of activities performed, the duration of exposure is considered short- to intermediate-term and the primary route of exposure for workers that enter treated crops would be dermal, through contact with residues on leaves.

The dermal exposure to diflufenzopyr-sodium of workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients and the dermal absorption factor for diflufenzopyr-sodium. Activity transfer coefficients are based on reviewed Agricultural Re-Entry Task Force studies, of which BASF is a member, and United States Environmental Protection Agency (U.S. EPA) Policy 3.1 data. Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue (DFR) value of 20% of the application rate on the day of application and a default daily dissipation rate of 10% were used in the exposure assessment. Exposure was normalized by using 70 kg adult body weight and a default dermal absorption (DA) of 100% was used.

Exposure estimates were compared to the NOAEL of 100 mg/kg bw/day to obtain the MOE; the target MOE is 300. Calculated MOEs are presented in Table 3.

Table 3 Postapplication Risk Assessment of Re-entry Activities for Non-Cropland Sites, Pasture and Rangeland

Activity	Application Rate (µg/cm²)	Number of Apps.	Day	Day 0 DFR After Last App. (µg/cm²)[1]	Transfer Coefficient (cm²/hr)[2]	Exposure (mg/kg bw/day)[3]	MOE[4]
Scouting, irrigation (tall)	0.57	1	0	0.11	1500	0.020	5,100
Scouting, irrigation (short)	0.57	1	0	0.11	100	0.001	76,800

[1]Day 0 DFR after last application based on default DFR (20%) and default daily dissipation (10%)
[2]Transfer coefficients based on U.S. EPA Policy 3.1 for crops like barley, wheat and forage crops, at minimum (short) and full (tall) foliage
[3]Exposure = (Day 0 DFR × TC × 8 hrs/day × 100% DA)/(70 kg body weight x 1000µg/mg)
[4]MOE = NOAEL (100 mg/kg bw/day)/Exposure (mg/kg bw/day) ; target MOE = 300

3.4.3 Residential Exposure and Risk Assessment

There are no domestic class products. Therefore, a residential handler assessment was not required.

3.4.3.1 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to non-cropland sites where public access is often restricted, and only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

As the use of dicamba fits within the registered use pattern for this active on non-cropland sites, pasture and rangeland, exposure to residues of dicamba in food and drinking water should not change.

Refer to PRDD2005-01: *Diflufenzopyr* Distinct for a detailed assessment of the residue chemistry of diflufenzopyr-sodium.

In support of the current application supervised crop field trials, a data gathering/ enforcement method for livestock, freezer storage stability data for livestock commodities and a livestock feeding study were submitted.

Supervised residue trials conducted throughout the United States using an end-use product containing diflufenzopyr-sodium in or on grasses are sufficient to support the proposed uses.

Goat and hen metabolism studies were previously reviewed (PRDD2005-01: *Diflufenzopyr* Distinct). Based on the residue profile of diflufenzopyr-sodium in livestock, the residue definition for enforcement is diflufenzopyr-sodium and the metabolites convertible to M1 (pyrido[2,3-d]pyridazin-5(6H)-one, 8-methyl-), expressed as diflufenzopyr-sodium. For risk assessment, the residue definition is diflufenzopyr-sodium and the metabolites convertible to M1 in all commodities, except milk; and is diflufenzopyr-sodium, the metabolites convertible to M1, and free and acid released M19 (8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H, 6H)-dione) in milk, expressed as diflufenzopyr-sodium. Based on the results of the dairy cattle feeding study and the estimated dietary burdens, maximum residue limits are proposed for meat, fat, meat byproducts and milk. A freezer storage stability study was conducted concurrently during the dairy cattle feeding study that demonstrated that residues of diflufenzopyr-sodium and the metabolites convertible to M1 were stable in liver, fat and muscle for 41-42 days under frozen conditions.

3.5.2 Dietary Risk Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994-1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The refined chronic dietary exposure from all supported diflufenzopyr-sodium food uses (alone) for the total population, including infants and children, and all representative population subgroups is <1.0% of the acceptable daily intake (ADI). Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to diflufenzopyr-sodium from food and water is 0.30% (0.000673 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 1.0% (0.002479 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for diflufenzopyr-sodium consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.4.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Meat byproducts of cattle, goats, hogs, horses and sheep	0.5
Fat and meat of cattle, goats, hogs, horses and sheep	0.2
Milk	0.05

For additional information on Maximum Residue Limits (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The livestock analytical methodology, freezer storage stability (livestock commodities), field trial data, livestock feeding study and the chronic dietary risk estimates are summarized in Tables 1, 6 and 7 in Appendix I.

4.0 Impact on the Environment

A complete evaluation is available in PRDD2005-01: *Diflufenzopyr* Distinct for the registration of diflufenzopyr-sodium technical and Distinct for the control of specific broadleaf weeds in field corn.

The application rates of diflufenzopyr-sodium and dicamba when Overdrive Herbicide is used on non-cropland sites, pasture and rangeland are the same or less than the currently registered rates for these active ingredients when used on terrestrial food and feed crop. Therefore, no increase in environmental risk is expected from the use of Overdrive Herbicide. Appropriate mitigation measures are on the label.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Overdrive Herbicide

In support of proposed pest claims, data were submitted from 13 operational trials conducted in 2008 at several locations in three provinces (Ontario, Saskatchewan and Alberta) and four replicated small plot trials conducted in 2001 in Ontario. Herbicide treatments were applied using small plot application equipment.

The efficacy of Overdrive Herbicide applied as a stand-alone herbicide treatment for control of certain weed species was visually assessed as percent control and compared to an untreated weedy check. Observations were made 19-36 days after treatment.

Data relevant to Overdrive Herbicide were provided to extrapolate efficacy claims from Distinct Herbicide (which is another formulation which contains the diflufenzopyr-sodium and dicamba). Rationales were also provided to extrapolate efficacy claims from Banvel II Herbicide, a product containing dicamba, but registered for control claims with higher rates of dicamba than that which is applied with Overdrive Herbicide.

5.1.2 Acceptable Efficacy Claims for Overdrive Herbicide

The submitted efficacy data support the weed control claims that are summarized in Table 5.1.2.1. Overdrive Herbicide must be applied with a non-ionic surfactant and 28% UAN.

Table 5.1.2.1 Weed Control claims for Overdrive Herbicide*

Herbicide Rate	Weeds Controlled
199.5 g a.e./ha or 285 g product/ha (142.5 g a.e./ha dicamba + 57 g a.e./ha diflufenzopyr-sodium)	Common ragweed, lady's thumb, lamb's-quarters, redroot pigweed, tall waterhemp, velvetleaf, wild buckwheat, biennial wormwood, Canada thistle (top growth control), sweet clover (top growth control), vetch (top growth control), dandelion (top growth suppression), leafy spurge (top growth suppression)

*Overdrive Herbicide must be applied with a non-ionic surfactant at a rate of 0.25% (v/v) and liquid urea ammonium nitrate (UAN 28%) at a rate of 1.25% (v/v).

5.2 Phytotoxicity to Host Plants

A rationale was provided to demonstrate grass tolerance to Overdrive Herbicide, based on the existing registered use pattern of dicamba. Banvel II, containing 480 g a.e./L dicamba, is registered for use in pasture, rangeland and non-cropland sites at a rate of 1008 g a.e./ha, seven times greater than the labelled use rate of dicamba for Overdrive. In addition, data were submitted to demonstrate tolerance of grass species with Distinct Herbicide, containing diflufenzopyr-sodium and dicamba in the same concentration as Overdrive Herbicide. The data submitted were relevant to demonstrating tolerance of grass species to an application of Overdrive Herbicide.

Based on the information provided, it is not anticipated that the use of Overdrive Herbicide would cause persistent injury to desirable grass vegetation in pasture, rangeland and non-crop land sites.

5.2.1.1 Supported Use pattern for Overdrive Herbicide

Treatment	Rate	Use site
Overdrive Herbicide*	199.5 g a.e./ha (142.5 g a.e./ha dicamba + 57 g a.e./ha diflufenzopyr-sodium)	pasture rangeland non-cropland

*Overdrive Herbicide must be applied with a non-ionic surfactant at a rate of 0.25% (v/v) and liquid urea ammonium nitrate (UAN 28%) at a rate of 1.25% (v/v).

5.3 Economics

An economic assessment was not conducted for this registration.

5.4 Sustainability

Dicamba has been registered for selective broadleaf weed control in pasture and rangeland grasses and crop free land. Overdrive will provide another option for weed control in these use patterns with reduced rates of dicamba.

5.4.1 Survey of Alternatives

Registered herbicides with a comparable use pattern in pasture and rangeland grasses and non-cropland sites include the following and are grouped by resistance management classification.

Group 4 herbicides by active ingredient

- dicamba containing products such as Banvel VM Herbicide, (480 g a.e./L) Reg. No. 29249
- clopyralid containing products such as Lontrel 360 Herbicide, (360 g/L) Reg. No. 23545
- aminopyralid containing products such as Milestone Herbicide, (240 g/L) Reg. No. 28517

- 2,4-D containing products such as 2,4-D ester 700 Herbicide, (658 g a.e./L) Reg. No. 23563
- MCPA containing products such as MCPA ester 500 Herbicide, (500 g/L) Reg. No. 22199
- picloram containing products such as Tordon 22K Herbicide (240 g/L) Reg. No. 9005

Group 2 herbicides by active ingredient

- metsulfuron-methyl containing products such as Escort Herbicide 60% DF Reg. No. 23005
- tribenuron-methyl containing products such as Express SG Herbicide Reg. No. 28262 (50%)

Group 9 herbicides by active ingredient

- glyphosate containing products such as Roundup Original Liquid Herbicide (356 g a.e./L) Reg. No. 13644

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Dicamba based products are recognized as important tools for vegetation management in pasture and rangeland grasses, and non-cropland sites. Overdrive Herbicide offers an additional tool for vegetation management at reduced rates of dicamba.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of naturally selecting the biotypes, a group of plants within a species which has biological traits that are not common to the population as a whole, with less susceptibility to the herbicides using that mode of action. Therefore, Overdrive Herbicide should be used in rotation with herbicides having different modes of action.

The Overdrive Herbicide label includes the resistance management statements, as per Regulatory Directive DIR99-06, Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

Refer to PRDD2005-01: *Diflufenzopyr Distinct* for a detailed discussion of the toxic substances management policy considerations.

6.2 Formulants and Contaminants of Health or Environmental Concern

Refer to PRDD2005-01: *Diflufenzopyr Distinct* for a detailed discussion of formulants and contaminants of health or environmental concern.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted is adequate to define the majority of toxic effects that may result from exposure to diflufenzopyr-sodium. There was no evidence of carcinogenicity in rats or mice after long-term dosing. Diflufenzopyr-sodium is neither neurotoxic nor genotoxic. In short-term and chronic studies on laboratory animals the primary target was the hematopoietic system in the dogs. A serious effect on the developing foetus (embryo/fetal loss) was observed in the presence of maternal toxicity.

The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders, applicators and workers entering treated fields are not expected to be exposed to levels of diflufenzopyr-sodium that will result in unacceptable risk when Overdrive Herbicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers. Risk to workers re-entering treated areas is not of concern provided that specified restricted entry intervals are observed.

The residue definition in corn and grasses for enforcement and risk assessment is diflufenzopyr-sodium and the metabolites convertible to M1, expressed as diflufenzopyr-sodium. In livestock, the residue definition for enforcement is diflufenzopyr-sodium and its metabolites convertible to M1, expressed as diflufenzopyr-sodium. For risk assessment, the residue definition is diflufenzopyr-sodium and its metabolites convertible to M1 in all commodities, except milk; and is diflufenzopyr-sodium, its metabolites convertible to M1, and free and acid released M19 in milk, expressed as diflufenzopyr-sodium. The use of diflufenzopyr-sodium on pasture and rangeland grasses and on non-cropland sites does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health. The PMRA recommends that the following maximum residue limits be specified for diflufenzopyr-sodium:

Commodity	Recommended MRL (ppm)
Meat byproducts of cattle, goats, hogs, horses and sheep*	0.5
Fat and meat of cattle, goats, hogs, horses and sheep*	0.2
Milk**	0.05

* Residues of diflufenzopyr-sodium and the metabolites convertible to M1

** Residues of diflufenzopyr-sodium, the metabolites convertible to M1, and free and acid released M19

7.2 Environmental Risk

Diflufenzopyr-sodium is non-persistent in soil and slightly persistent in aquatic systems. Diflufenzopyr-sodium can enter aquatic systems by spray drift or runoff. However, accumulation in soil and water, and carryover, are not expected to be significant. Diflufenzopyr-sodium presents negligible risk to wild birds and mammals, bees and other arthropods. Diflufenzopyr-sodium is expected to pose a risk to aquatic organisms and terrestrial vascular plants. As such, mitigative measures must be taken to minimise adverse effects on plant populations and aquatic populations. To reduce the effects of diflufenzopyr-sodium in the environment, mitigation in the form of precautionary label statements and spray buffer zones are required.

7.3 Value

The value data submitted to register Overdrive Herbicide are adequate to describe its efficacy for use as a post emergence application in pasture, rangeland and in non-cropland sites to control certain broadleaf weeds. Overdrive herbicide provides an alternative product for control of common ragweed, lady's thumb, lamb's-quarters, redroot pigweed, tall waterhemp, velvetleaf, wild buckwheat, biennial wormwood, Canada thistle (top growth control), sweet clover (top growth control), vetch (top growth control) leafy spurge (top growth suppression) and dandelion (top growth suppression) in grass pastures, rangeland grasses and non-cropland sites.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Sodium Diflufenzopyr Technical Herbicide and Overdrive Herbicide, containing the technical grade active ingredients diflufenzopyr-sodium and dicamba, to control broadleaf weeds in pasture, rangeland and non-cropland sites such as railroad, utility, pipeline and highway rights-of-way, railroad crossings, roadside, petroleum tank farms, non-agriculture fencerows and airports.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
a.e.	acid equivalent
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
ATPD	area treated per day
bw	body weight
CAF	composite assessment factor
cm	centimetres
DA	dermal absorption
DAT	days after treatment
g	gram
ha	hectare(s)
kg	kilogram
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
mg	milligram
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit
NAFTA	North American Free Trade Agreement
N/A	not applicable
NOAEL	no observed adverse effect level
PBI	plantback interval
PCPA	Pest Control Products Act
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
USEPA	United States Environmental Protection Agency
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Livestock	D0102	Diflufenzopyr-sodium and the metabolites M1 and M5*	LC-MS/MS	For each analyte: 0.05 ppm in liver, fat, kidney and muscle; and 0.01 in milk	PMRA # 1815880

*Residues of M5 are converted to and analyzed as M1.

Table 2 Toxicity Profile of End-use Product Containing Diflufenzopyr-sodium

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley CD rats PMRA # 1176003	LD_{50} (males) = 1.6 g/kg bw (95% C.I =1.2-2 g/kg bw) Slight acute toxicity
Acute dermal toxicity New Zealand White rabbits PMRA #1176004	LD_{50} > 5000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley albino rats PMRA #1176005	LC_{50} > 5.34 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA #1176008	MAS = 0.17/8 Minimally-irritating
Eye irritation NZW rabbits PMRA #1176006	Eyes were normal at day 7. MAS = 11.1/110, MIS 1 hour =17.3/110 Mildly irritating
Dermal sensitization (Modified Beuhler test) Hartley guinea pigs PMRA #1184182	Potential Skin Sensitizer

Table 3 Toxicity Profile of Technical Sodium Diflufenzopyr
(Effects are known or assumed to occur in both sexes unless otherwise noted; organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Metabolism Single and repeated dosing	**Absorption** Partially absorbed from gastrointestinal tract of orally dosed rats of both sexes **Distribution** Bioaccumulation was minimal (<3%, residue levels highest in blood, blood cells and serum within 24 hours) **Excretion** In all orally dosed groups 20-44% of dose was excreted in urine, and 3-11% in bile. Dose level and pretreatment had little effect on the proportion of the dose excreted in urine following oral administration. In contrast intravenously dosed rats excreted 61-89% of the dose in urine and 4-19% in bile. **Metabolism** Diflufenzopyr-sodium is excreted primarily unchanged in urine, feces and bile. Minor amounts of hydrolysis products (M1, M5 and M6) and hydroxylation products (M9,M10 and M19) were identified.
Acute oral toxicity Sprague-Dawley CD rats PMRA #1175855	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Dermal Toxicity NZW rabbits PMRA # 1175856 _____ Acute inhalation toxicity (nose-only) Sprague-Dawley albino rats PMRA #11758557	LD_{50} > 5000 mg/kg bw Low toxicity. _____ _____ LC_{50} > 2.93 mg/L Low toxicity.
Eye Irritation NZW rabbits PMRA # 1175858	MAS = 0.11/110 Minimally Irritating

Study Type/Animal/PMRA #	Study Results
Dermal irritation NZW rabbits PMRA # 1175859	MAS = 0.0/80 Non-irritating
Skin Sensitization (Beuhler method) Hartley guinea pigs PMRA # 1175860	Not a dermal sensitizer
21 day dermal toxicity study N Z W Rabbit PMRA # 1175893	NOAEL (systemic) = 1000 mg/kg bw/day LOAEL (dermal) = 100 mg/kg bw/day. No treatment related systemic effects at any dose level Local dermal irritation was observed at all dose levels tested No corresponding histopathological findings
90-day dietary toxicity CD-1 Mice PMRA # 1184177	NOAEL = 1225/1605 mg/kg bw/day(♂/♀) LOAEL Not established. No treatment related effects at any dose
90 day dietary Wistar rats PMRA# 1175861	NOAEL = 352/431 mg/kg bw/day (♂/♀) LOAEL = 725/890 mg/kg bw/day(♂/♀) based on decreased body weight gain, food consumption and food efficiency, increased cholesterol, alanine aminotransferase and incidence of foamy macrophages in the lungs
90-day dietary Beagle dogs PMRA # 1175892	NOAEL = (58/59 mg/kg bw/day) (♂/♀) LOAEL = (403/424- mg/kg bw/day) (♂/♀) based on erythroid hyperplasia in the bone marrow and extramedullary haematopoiesis in the liver. Hemosiderin deposits in the Kupffer cells of one female dog at 424 mg/kg bw/day
12-month/52 weeks dietary Beagle dogs PMRA # 1175862	NOAEL = 26/28 mg/kg bw/day (♂/♀) LOAEL = 299/301 mg/kg bw/day(♂/♀) based on erythroid hyperplasia in the femoral and sternal bone marrow, increased hemosiderin deposits in the kidneys, liver and spleen, reddish discoloration of the diaphysis of the femur, mild to moderate reticulocytosis, and slightly decreased body weight gain. Decreased food efficiency (♀)
78-week dietary CD-1 Mice PMRA # 1175881	NOAEL = 1037/1004 mg/kg bw/day(♂/♀) LOAEL Not established. No treatment related effects at any dose

Study Type/Animal/PMRA #	Study Results
2-year dietary(104 weeks) Wistar rats PMRA # 1175883	NOAEL = 69/93 mg/kg bw/day(♂/♀) LOAEL = 236/323 mg/kg bw/day (♂/♀) based on decreased final body weight, (due to decreased body weight gain noted primarily in the second year of the study, (weeks 91 to 106.)
Two-generation Sprague-Dawley rats PMRA # 1175889	**Parental toxicity** NOAEL = 113/175.9 mg/kg bw/day (♂/♀) LOAEL = 466.2/742.0 mg/kg bw/day (♂/♀) based on decreased mean body weight and body weight gain for both generations. Increased mean food consumption for parental and offspring generation during pre-mating Decreased mean body weight and body weight gain during gestation for both generations **Reproductive Toxicity** NOAEL = 113/175.9 mg/kg bw/day(♂/♀) LOAEL = 466.2/742.0 mg/kg bw/day (♂/♀)based on decreased live birth index and increased total preperinatal (post implantation) loss **Offspring Toxicity** NOAEL = 113/175.9 mg/kg bw/day(♂/♀) LOAEL = 466.2/742.0.mg/kg bw/day(♂/♀) based on F2 generation, ↓ live birth and viability indices Increased total pre perinatal (post implantation) loss, decreased mean body weight (F1a generation) for both sexes on Day 21 of lactation, due to decreased mean body weight gain on Days 4-21 of lactation F1a and F1b generations had a higher proportion of runts and the F2 generation had a higher percentage of offspring with no milk in the stomach
Developmental toxicity Sprague-Dawley Rats (Crl,CD BR) PMRA # 1175863	**Maternal toxicity** NOAEL = 1000 mg/kg bw/day LOAEL: not established **Developmental toxicity** NOAEL = 1000 mg/kg bw/day LOAEL not established. There was no evidence of a developmental effect.
Developmental toxicity New Zealand White Hra (NZW, SPF) Rabbits PMRA# 1175864	**Maternal toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day based on increased incidence of mortality abnormal feces, abortions (25%) and a slight but persistent mean weight loss and decreased food consumption during the dosing period **Developmental toxcity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day based on increased incidence of abortions.

Study Type/Animal/PMRA #	Study Results
Gene mutations in bacteria *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; and TA1538 PMRA# 1175866	**Negative**
Unscheduled DNA synthesis *in vitro* Primary rat hepatocytes (adult male Fischer 344 rats) *PMRA#* 1175870	**Negative**
Mouse lymphoma assay in vitro Cultured L5178Y (TK +/-) mouse lymphoma cells PMRA# 1175868/69	**Negative**
Micronucleus assay (*in vivo*) Male and female CD-1 (ICR) mice PMRA# 1175871	**Negative**
Acute Neurotoxicity Crl:CD BR rats PMRA# 1175888	NOAEL = 2000 mg/kg bw LOAEL: not established No treatment- related effects at any dose
Subchronic Neurtoxicity (13 week dietary) Crl:CD BR rats PMRA# 1175691	NOAEL = 75 mg/kg bw/day. LOAEL = 1000 mg/kg bw/day based on body weight gain and decreased food efficiency. No indication of neurotoxicity at any dose level tested.

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Diflufenzopyr-sodium

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
ARfD No appropriate endpoint was identified			
Repeated dietary	1-year dog	NOAEL = 26 mg/kg bw/day based on Mild compensatory anaemia and decreased food efficiency at the LOAEL of 299 mg/kg bw/day.	100
	ADI = 0.26 mg/kg bw/day		
Short-term dermal[2] and inhalation[3]	Rabbit developmental toxicity	NOAEL of 100 mg/kg bw/day based on increased abortions and mortality at the LOAEL of 300 mg/kg bw /day	300
Intermediate –term dermal[2] and inhalation[3]			

[1]CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessment. MOE refers to a target MOE for occupational and residential assessments.
[2]Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) was used in a route to route extrapolation.
[3]Since an oral NOAEL was selected an inhalation absorption factor of 100% (default value) was used in route to route extrapolation.

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Diflufenzopyr-sodium

Dermal and inhalation (short- to intermediate-term)	100 mg/kg bw/day from a rabbit developmental toxicity study
Target MOE	300
Dermal Absorption	100% (default)

Table 6 Residue Summary

FREEZER STORAGE SABILITY- LIVSTOCK MATRICES | **PMRA # 1815879**

A freezer storage stability study was conducted concurrently during the dairy cattle feeding study. The residue data indicate that residues of diflufenzopyr-sodium and the metabolites were stable in liver, fat and muscle for 41-42 days under frozen conditions.

CROP FIELD TRIALS ON PASTURE AND RANGELAND GRASSES | **PMRA # 1815876**

During the 1999 growing season a sufficient number of trials were conducted in representative NAFTA growing regions to evaluate the magnitude of diflufenzopyr-sodium residues in/on pasture and rangeland grasses.

During all trials, each treated plot received one spray application of diflufenzopyr-sodium (BAS 662 01 H; co-formulation of diflufenzopyr-sodium and dicamba) at 0.078-0.083 kg a.e./ha. Samples of forage were harvested immediately after application but not before the plants were dry (0 days after treatment; DAT). Plants cut 7 to 8 DAT were allowed to dry in the field for 1-4 days before the hay was collected. At one site, samples of forage and hay were collected at 0, 3, 7, 10 and 15 DAT in order to evaluate residue decline.

Forage and hay samples were analyzed for total residues convertible to M1 (including diflufenzopyr-sodium) using method D9709 (GC-MSD). The limit of quantitation of diflufenzopyr-sodium residues in/on grass forage and hay was reported as 0.05 ppm.

The residue decline data show that residues declined gradually in/on grass forage with increasing pre-harvest intervals. In hay, residues declined gradually by 10-DAT but increased slightly by 15-DAT.

Commodity	Total Applic. Rate (kg a.e./ha)	PBI (days)	Total Residues Convertible to M1 (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Grass, Forage	0.078-0.083	0	26	0.07	10.12	9.35	2.59	3.11	2.68
Grass, Hay		7-8	26	0.37	3.27	3.16	1.15	1.34	0.785

LIVESTOCK FEEDING – Dairy cattle | **PMRA # 1815879**

A feeding study was conducted with lactating dairy cows to determine the magnitude of diflufenzopyr-sodium residues in milk and tissues following oral administration of diflufenzopyr-sodium at target dose levels of 8 ppm, 24 ppm and 80 ppm in the feed (dry weight basis) daily for 29 consecutive days.

Whole milk samples were collected in the afternoon and the following morning throughout the study on days -1, 1, 3, 5, 7, 10, 14, 17, 21, 24, 28, 31, 34 and 36, and the PM and AM milk samples were pooled for each animal. Day 24 whole milk samples from the two highest dose groups were separated into skim milk and cream. Animals were sacrificed within approximately 3.5 hours following the final dose (day 29), with the exception of two animals from the high dose group that were terminated on days 32 and 37 as part of a depuration study.

At sacrifice, samples of liver, kidney, fat and muscle were collected.

Milk and tissue samples were analyzed by method D0102 (LC-MS/MS), which determines residues of diflufenzopyr-sodium, and the metabolites M1, and M5 (converted to and analyzed as M1).The LOQ (limit of quantitation) was reported as 0.05 ppm in tissues (liver, fat, kidney and muscle) and 0.01 ppm in milk, for all three analytes. Residues of diflufenzopyr-sodium and M1 were expressed as the analyte *per se*.

In all whole milk samples, residues of diflufenzopyr-sodium and M1 were each non-quantifiable at the 8 ppm dose level. At the 24 ppm dose level, the maximum residue of diflufenzopyr-sodium was 0.022 ppm (day 10), while residues of M1 were non-quantifiable in all samples. At the 80 ppm dose level, the maximum residue of diflufenzopyr-sodium was 0.077 ppm (day 3) and the maximum residue of M1 was 0.040 ppm (day 21).

Results of the depuration study indicate that residues of diflufenzopyr-sodium and the metabolite M1 declined to non-quantifiable levels in all tissues within 8 days of withdrawal from treated feed.

Matrix	Target Feeding Level (ppm/d)	n	Min	Max	Median	Mean	Standard Deviation
Diflufenzopyr-sodium							
Whole Milk (day 28)	8	3	<0.01	<0.01	<0.01	<0.01	0
	24	3	0.011	0.017	0.014	0.014	0.003
	80	5	0.022	0.063	0.045	0.043	0.015
Skim Milk (day 24)	24	3	0.01	0.039	0.013	0.021	0.016
	80	3	0.032	0.059	0.043	0.045	0.014
Cream (day-24)	24	3	<0.01	<0.01	<0.01	<0.01	0
	80	3	0.022	0.047	0.036	0.035	0.013
Fat (day 29)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	<0.05	<0.05	<0.05	<0.05	0
	80	3	<0.05	<0.05	<0.05	<0.05	0
Liver (day 29)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	0.094	0.239	0.138	0.157	0.074
	80	3	0.217	0.768	0.482	0.489	0.276
Kidney (day 29)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	0.166	0.234	0.176	0.192	0.037
	80	3	0.548	0.868	0.756	0.724	0.162
Muscle (day 29)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	<0.05	<0.05	<0.05	<0.05	0
	80	3	<0.05	<0.05	<0.05	<0.05	0
M1 (including M5)							
Whole Milk (day 28)	8	3	<0.01	<0.01	<0.01	<0.01	0
	24	3	<0.01	<0.01	<0.01	<0.01	0
	80	5	0.014	0.031	0.017	0.020	0.007
Skim Milk (day 28)	24	3	<0.01	<0.01	<0.01	<0.01	0
	80	3	<0.01	0.013	0.011	0.011	0.002
Cream (day 28)	24	3	<0.01	<0.01	<0.01	<0.01	0
	80	3	0.010	0.014	0.014	0.013	0.002
Fat (day 28)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	<0.05	<0.05	<0.05	<0.05	0
	80	3	<0.05	<0.05	<0.05	<0.05	0
Liver (day 28)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	<0.05	<0.05	<0.05	<0.05	0
	80	3	<0.05	0.052	0.050	0.051	0.001
Kidney (day 28)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	<0.05	<0.05	<0.05	<0.05	0
	80	3	<0.05	<0.05	<0.05	<0.05	0
Muscle (day 28)	8	3	<0.05	<0.05	<0.05	<0.05	0
	24	3	<0.05	<0.05	<0.05	<0.05	0
	80	3	<0.05	<0.05	<0.05	<0.05	0

When estimating the dietary burden, all M1 residues were expressed as diflufenzopyr-sodium equivalents using the molecular weight conversion factor of 2.074 [(334.28 g/mole diflufenzopyr-sodium) ÷ (161.16 g/mole M1)]. Based on the anticipated residues in corn and grasses, the dietary burden was determined to be 0.05 ppm in swine, 1.20 ppm in beef cattle and 37.83 ppm in dairy cattle. Anticipated residues at the dietary burden were determined by linear regression in liver, kidney and milk. Anticipated residues in the remaining matrices were estimated either at the method LOQ (fat and muscle), or extrapolated linearly from the residues seen at the highest feeding level (cream and skim milk). For cattle, the anticipated residues were calculated using the MTDB for dairy cattle as a conservative estimate.

Commodity	Feeding level (ppm)	Maximum Total Residues, Expressed as Diflufenzopyr-sodium Equivalents (ppm)	MTDB (ppm)		Anticipated Residue (ppm)	
			Beef/Dairy	Hog	Cattle	Hog
Whole Milk (day 28)	8	<0.031	1.20/37.83	0.05	0.051	Not applicable
	24	<0.038				
	80	0.107				
Skim Milk (day 24)	24	<0.034			0.032	Not applicable
	80	0.086				
Cream (day 24)	24	<0.031			0.029	Not applicable
	80	0.076				
Fat	8	<0.154			0.154	0.154
	24	<0.154				
	80	<0.154				
Kidney	8	<0.154			0.431	0.076
	24	<0.338				
	80	<0.972				
Liver	8	<0.154			0.384	0.177
	24	<0.343				
	80	0.876				
Muscle	8	<0.154			0.154	0.154
	24	<0.154				
	80	<0.154				
LIVESTOCK FEEDING – Laying hens						
There are no poultry feed commodities associated with the proposed uses on grasses. It was previously determined that finite residues of diflufenzopyr-sodium are not anticipated in the meat, meat by-products and eggs of poultry fed treated corn commodities (PRDD2005-01: *Diflufenzopyr Distinct*).						

Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (corn)** **Rotational crops (radish, lettuce and wheat)**	diflufenzopyr-sodium and its metabolites convertible to M1, expressed as diflufenzopyr-sodium
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	diflufenzopyr-sodium and its metabolites convertible to M1, expressed as diflufenzopyr-sodium
METABOLIC PROFILE IN DIVERSE CROPS	Not applicable

ANIMAL STUDIES			
ANIMALS		**Ruminant and Poultry**	
RESIDUE DEFINITION FOR ENFORCEMENT		diflufenzopyr-sodium and its metabolites convertible to M1, expressed as diflufenzopyr-sodium.	
RESIDUE DEFINITION FOR RISK ASSESSMENT		diflufenzopyr-sodium and its metabolites convertible to M1 in all commodities except milk; and diflufenzopyr-sodium, its metabolites convertible to M1, and free and acid released M19 in milk, expressed as diflufenzopyr-sodium.	
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)		Similar in rat, goat and hen.	
FAT SOLUBLE RESIDUE		Yes, but does not concentrate in any fatty tissue or corn oil.	
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Refined chronic non-cancer dietary risk **ADI = 0.26 mg/kg bw** **Estimated chronic drinking water concentration = 0.15μg a.i./L**	**All infants < 1 year**	0.3	0.3
	Children 1–2 years	1.0	1.0
	Children 3 to 5 years	0.7	0.7
	Children 6–12 years	0.5	0.5
	Youth 13–19 years	0.2	0.2
	Adults 20–49 years	0.2	0.2
	Adults 50+ years	0.2	0.2
	Total population	0.3	0.3

Table 8 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Applicant proposed label claims	Accepted label claims	Unsupported label claims
Application rate: 200 g a.e./ha (142 g a.e./ha dicamba + 57 g a.e./ha diflufenzopyr-sodium)	-accepted as proposed	
Adjuvant: non-ionic surfactant at a rate of 0.25% (v/v) and liquid urea ammonium nitrate (UAN 28%) at a rate of 1.25% (v/v).	-accepted as proposed	

Applicant proposed label claims	Accepted label claims	Unsupported label claims
Pest claims: Canada fleabane cleavers common ragweed corn spurry cow cockle false ragweed giant ragweed green smartweed hare's ear mustard Indian mustard lady's thumb lamb's-quarters redroot pigweed Russian pigweed tall waterhemp tartary buckwheat tumble mustard velvetleaf wild buckwheat wild mustard wormseed mustard biennial wormwood Canada thistle (top growth control) clover (top growth control) dandelion (top growth control) field bindweed leafy spurge perennial sow thistle (top growth control) vetch (top growth control)	Common ragweed Lady's thumb Lamb's-quarters Redroot pigweed Tall waterhemp Velvetleaf Wild buckwheat biennial wormwood Canada thistle (top growth control) sweet clover (top growth control) dandelion (top growth suppression) leafy spurge (top growth suppression) vetch (top growth control)	Canada fleabane cleavers corn spurry cow cockle false ragweed giant ragweed green smartweed hare's ear mustard Indian mustard Russian pigweed tartary buckwheat tumble mustard wild mustard wormseed mustard dandelion (top growth control) field bindweed leafy spurge perennial sow thistle (top growth control)
Crop claims: Pasture, rangeland and non-cropland sites	-accepted as proposed	
Method of application: Ground application only	-accepted as proposed	
Number of applications per year: one	-accepted as proposed	
Misc.: -national registration	-accepted as proposed	

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

The proposed MRLs in Canada for livestock commodities differ from the corresponding tolerances established in the United States (40 CFR Part 180). Currently, there are no CODEX MRLs (Codex MRLs) searchable by pesticide or commodity) established for diflufenzopyr-sodium in/on any commodity.

Table 1 Differences Between Canadian MRLs and Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)*	Codex** (ppm)
Meat byproducts of cattle, goats, hogs, horses and sheep	0.5	0.50 (meat byproducts, except kidney); 4.0 (kidney)	None
Fat of cattle, goats, hogs, horses and sheep	0.2	0.30	None
Meat of cattle, goats, hogs, horses and sheep	0.2	0.60	None
Milk	0.05	3.0	None

*The residue definition for tolerance expression in all livestock commodities in the U.S. is the combined residues of diflufenzopyr-sodium, its metabolites convertible to the metabolite M1, and the metabolite M19 (free and acid released). Note that the tolerances listed herein were established as time-limited tolerances (revocation date 7/31/2005).

**Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

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