Proposed Registration Decision PRD2023-07

Diflufenican, SC500, SC600, and SC617

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Overview

Proposed registration decision for Diflufenican, SC500, SC600, and SC617

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Diflufenican Technical and SC500 containing the technical grade active ingredient diflufenican, for pre-plant and pre-emergent weed control in corn and soybean; SC600, containing the technical grade active ingredients diflufenican and metribuzin for pre-plant and pre-emergent weed control in soybean; and SC617 containing the technical grade active ingredients diflufenican and isoxaflutole for pre-plant and pre-emergent weed control in field corn.

Metribuzin is currently registered as a herbicide on crops, including soybean, and shelterbelt plants. For details, see Proposed Acceptability for Continuing Registration PACR2005-07, *Re-evaluation of Metribuzin*, and Re-evaluation Registration Decision RRD2006-15, *Metribuzin*.

Isoxaflutole is currently registered as a broad-spectrum herbicide for use in field corn and isoxaflutole-tolerant soybeans. For details, see Proposed Re-evaluation Decision PRVD2021-02, *Isoxaflutole and Its Associated End-use Products*, and Re-evaluation Decision Document RVD2022-04, *Isoxaflutole and Its Associated End-use Products*.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

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 diflufenican, SC500, SC600, and SC617.

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.

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

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 (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides portion of the Canada.ca website

Before making a final registration decision on diflufenican, SC500, SC600, and SC617, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on diflufenican, SC500, SC600, and SC617, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada'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.

What is diflufenican?

Diflufenican is a herbicide that inhibits synthesis of phytoene desaturase, which causes degradation of chlorophyll and destruction of chloroplast membranes responsible in carotenoid production. Sensitive plants develop symptoms of stunting, discolouration, and necrosis, leading to plant death.

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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*.

Health considerations

Can approved uses of diflufenican affect human health?

SC500, SC600, and SC617, containing diflufenican, are unlikely to affect your health when used according to label directions.

Potential exposure to diflufenican may occur through the diet (food and drinking water), when handling and applying the end-use product(s), or when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. 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 level at which no effects are observed. The health effects noted in animals occur at dose levels more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient diflufenican was of low acute toxicity by the oral, dermal and inhalation routes. Diflufenican was minimally irritating to the eyes and non-irritating to the skin and did not cause an allergic skin reaction.

The end-use product, SC500, containing diflufenican, was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes and skin and did not cause an allergic skin reaction.

The end-use product, SC617, containing diflufenican and isoxaflutole, was of low acute toxicity via the oral and inhalation routes of exposure and considered of low acute dermal toxicity. It was mildly irritating to the eyes and minimally irritating to the skin. It did not cause an allergic skin reaction.

The end-use product, SC600, containing diflufenican and metribuzin, was of slight acute toxicity via the oral route and low acute toxicity via the inhalation route of exposure and considered of slight acute dermal toxicity. It was minimally irritating to the eyes and skin and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of diflufenican to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on body weight. There was no evidence of tumourigenicity, nor was there evidence of increased

sensitivity of the young compared to adult animals. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Residues in food and drinking water

Dietary risks from food and drinking water are not of health concern.

Studies in laboratory animals showed no acute health effects of diflufenican. Consequently, a single dose of diflufenican is not likely to cause acute health effects in the general population (including infants and children).

Aggregate chronic dietary (food plus drinking water) intake estimates for diflufenican indicated that the general population and all population subgroups are exposed to less than 6% of the acceptable daily intake, and therefore are not of health concern.

Metabolite BCS-BT38895 is a unique soybean seed metabolite for which separate dietary exposure assessments were conducted. Acute dietary (soybean seed commodities alone) intake estimates indicated that the general population and all population subgroups are exposed to less than 1% of the acute reference dose, and therefore are not of health concern. Chronic non-cancer dietary (food alone) intake estimates indicated that the general population and all population subgroups are exposed to less than 1% of the acceptable daily intake, and therefore are not of health concern. The lifetime cancer risk for exposure to the metabolite BCS-BT38895 from the use of diflufenican on soybeans is not of health concern to the general population (including infants and children).

The *Food and Drugs Act* 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 *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Given that dietary risks from the consumption of foods are shown to be acceptable when diflufenican is used according to the proposed label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2023-XX, *Diflufenican*).

MRLs for diflufenican determined from the acceptable residue trials conducted throughout the United States, including growing regions representative of Canada, on soybeans, field corn and seed corn can be found in the Science evaluation of this document.

Some diflufenican products are also formulated with the active ingredients metribuzin or isoxaflutole. These co-active ingredients are already registered for these uses in Canada, and residues in treated commodities will be covered under the existing MRLs for each active ingredient.

Occupational risks from handling SC500, SC617 and SC600

Occupational risks are not of health concern when SC500, SC600, and SC617 are used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying SC500, SC600, and SC617, and workers entering recently treated fields can be exposed to diflufenican residues through direct skin contact or through inhalation. Therefore, the labels of SC500, SC600 and SC617 specify that anyone mixing, loading and applying these products must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. In addition, the label of SC617 specifies that protective eyewear (goggles or face shield) must be worn during mixing, loading, clean-up and repair activities. The labels of SC500, SC600 and SC617 also require that workers do not enter or be allowed into treated fields during the restricted-entry interval (REI) of 12 hours. Taking into consideration the label statements, the single application permitted per season and the duration of exposure for handlers and postapplication workers, the risks to these individuals from exposure to SC500, SC600, and SC617 are not of health concern when the end-use products are used according to the proposed label directions.

Health risks to bystanders

Bystander risks are not of health concern when SC500, SC600, and SC617 are used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the labels. Therefore, health risks to bystanders are not of concern when the end-use products are used according to the proposed label directions.

Environmental considerations

What happens when diflufenican is introduced into the environment?

Diflufenican can enter the environment when it is applied as a pre-plant surface or pre-emergence spray to corn or soybean for the control of redroot pigweed, green pigweed, tall waterhemp and palmer amaranth. Diflufenican is slightly persistent to persistent under most terrestrial and aquatic conditions. Diflufenican can be broken down by microbes in soil but is not broken down by water or sunlight. Diflufenican binds to soil, thus, it is expected to have limited mobility to groundwater. In surface water, diflufenican will move into sediments where it can persist. Diflufenican is not likely to accumulate in tissues of organisms. It is not expected to travel long distances from where it was applied.

Diflufenican presents a negligible risk to earthworms, beneficial arthropods, bees, birds and mammals. Diflufenican may, however, present a risk to non-target terrestrial plants adjacent to treated fields, which could also affect wildlife habitat. In waterbodies, diflufenican may pose a risk to aquatic organisms, such as invertebrates, fish, plants, and amphibians. Spray buffer zones and precautionary label statements, are thus required to minimize the exposure to non-target

terrestrial plants and aquatic habitats. When diflufenican is used in accordance with label directions, and when the required risk reduction measures are applied, the risks to the environment are considered to be acceptable.

Value considerations

What is the value of SC500 Herbicide, SC600 Herbicide, and SC617 Herbicide?

SC500 Herbicide provides early-season and season-long residual control of *Amaranthus* species, which are problematic and highly resistant to many herbicide modes of action in corn (field and seed) and soybean. SC600 Herbicide and SC617 Herbicide, co-formulations of diflufenican with other registered herbicides, control a broader spectrum of weeds with soil residual activity and also aim to manage existing and the future evolution of herbicide resistant weeds in corn (field and seed) and soybean.

SC500 Herbicide is formulated with diflufenican for pre-plant surface and pre-emergent application to corn (field and seed) and soybean. It provides early-season control of redroot pigweed, green pigweed, tall waterhemp, and palmer amaranth, including biotypes resistant to many herbicide modes of action, at 120–180 mL/ha and season-long control of these weeds at 180–360 mL/ha.

SC600 Herbicide is a co-formulation of diflufenican with metribuzin for pre-plant surface and pre-emergent application to soybean. It provides early-season or season-long control of weeds controlled by SC500 Herbicide and weeds controlled by registered metribuzin-based herbicides, applied at similar active ingredient rates.

SC617 Herbicide is a co-formulation of diflufenican with isoxaflutole for pre-plant surface and pre-emergent application to corn (field and seed) in Eastern Canada and British Columbia. It provides early-season or season-long control of weeds controlled by SC500 Herbicide and weeds controlled by registered isoxaflutole-based herbicides, applied at similar active ingredient rates.

Registrations of these herbicides provide users with options for pre-plant or pre-emergent residual control of broadleaf weeds, including *Amaranthus* species that are problematic and highly resistant to many herbicide modes of action, in corn (field and seed) and/or soybean. The application of these herbicides reduces early-season weed competition to the emerging crop allowing the crop to benefit from additional moisture, nutrients, and light that would otherwise be captured by the weeds. Weed management at this time is critical as the crop does not compete well with weeds until crop canopy closure. As all three end-use products have soil residual activity, the reduction in weed competition with the crop is extended.

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 labels of Diflufenican Technical, SC500, SC600 and SC617 to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential exposure of workers to diflufenican through direct skin contact or inhalation of sprays, workers mixing, loading, and applying SC500, SC617 or SC600 and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label of SC617 also requires workers to wear protective eyewear (goggles or face shield) during mixing, loading, clean-up and repair activities. In addition, the labels of SC500, SC617 or SC600 require that workers do not enter or be allowed entry into treated fields during the REI of 12 hours. Furthermore, a standard label statement to protect against drift during application is on the labels.

Environment

The following risk reduction measures are required to be added to the label:

- Environmental precautionary statements for non-target terrestrial plants and aquatic organisms;
- Spray buffer zones to protect aquatic and non-target terrestrial habitats;
- Standard runoff statements

Next steps

Before making a final registration decision on diflufenican, SC500, SC600, and SC617, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada 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). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

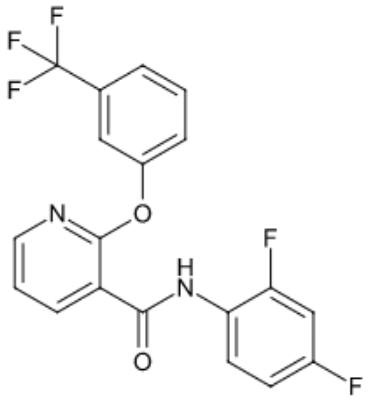
When the Health Canada makes its registration decision, it will publish a Registration Decision on diflufenican, SC500, SC600, and SC617 (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Science evaluation

Diflufenican

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Diflufenican
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2',4'-difluoro-2-[3-(trifluoromethyl)phenoxy]pyridine-3-carboxanilide
2. Chemical Abstracts Service (CAS)	*N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide
CAS number	83164-33-4
Molecular formula	$C_{19}H_{11}F_5N_2O_2$
Molecular weight	394.298
Structural formula	
Purity of the active ingredient	99%

1.2 Physical and chemical properties of the active ingredient and end-use product

Technical product—Diflufenican Technical

Property	Result
Colour and physical state	Beige solid
Odour	Weak
Melting point	Pure active: 159.5°C
Boiling point	N/A
Density	1.585 g/cm^3
Vapour pressure	Temp (°C) v.p. (Pa) 25 4.25×10^{-6} 35 8.19×10^{-6} 50 3.52×10^{-5}
Ultraviolet (UV)-visible spectrum	Not expected to absorb at $\lambda > 300$ nm
Solubility in water at 20°C	0.05 mg/L
Solubility in organic solvents at 20°C	Solvent Solubility (g/L) n-heptane 0.75 toluene 35.7 dichloromethane 114.0 acetone 72.2 methanol 4.7 ethyl acetate 65.3 acetonitrile 17.6 n-octanol 1.9
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 4.2
Dissociation constant (pK_a)	Does not dissociate in environmental pH range
Stability (temperature, metal)	Stable to elevated temperatures (54°C) and to metals and metal ions.

End-use product—SC500

Property	SC500
Colour	Light cream
Odour	Unpleasant
Physical state	Liquid
Formulation type	Suspension
Label concentration	diflufenican 500 g/L

Property	SC500
Container material and description	HDPE
Density	1.170–1.210 g/mL
pH of 1% dispersion in water	6.5–8.5
Oxidizing or reducing action	Not oxidizing or reducing
Storage stability	Stable for 14 days at 54°C
Corrosion characteristics	Not corrosive to HDPE packaging
Explodability	Not explosive

End-use products—SC617 and SC600

Property	SC617	SC600
Colour	Beige	Light brown
Odour	Odourless	Weak musty
Physical state	Liquid	Liquid
Formulation type	Suspension	Suspension
Label concentration	diflufenican … 257 g/L isoxaflutole … 180 g/L	diflufenican … 200 g/L metribuzin … 400 g/L
Container material and description	HDPE	HDPE
Density	1.24–1.28 g/mL	1.16–1.20 g/mL
pH of 1% dispersion in water	4.0–6.0	4.5–5.5
Oxidizing or reducing action	Not oxidizing or reducing	Not oxidizing or reducing
Storage stability	Stable for 14 days at 54°C	Stable for 14 days at 54°C
Corrosion characteristics	Not corrosive to HDPE packaging	Not corrosive to HDPE packaging
Explodability	Not explosive	Not explosive

1.3 Directions for use

1.3.1 SC500 Herbicide

The application of SC500 Herbicide provides early-season control of redroot pigweed, green pigweed, tall waterhemp, and palmer amaranth at 120–180 mL/ha and season-long control of these weeds at 180–360 mL/ha, based on the weed spectrum. SC500 Herbicide only controls non-emerged weeds and emerged weeds up to 5 cm in height. Efficacy of SC500 Herbicide is maximized when adequate rainfall is received within 14 days after application.

SC500 Herbicide may be applied alone or in combination with listed tank mixes as a broadcast spray up to 14 days before planting or after planting but prior to crop emergence in field and seed corn and soybean in all tillage systems. The maximum annual application rate is 300 mL/ha for corn and 360 mL/ha for soybean.

SC500 Herbicide can only be applied using ground equipment in a minimum of 100 L/ha of spray volume. Sprayable fluid nitrogen fertilizer may replace all or part of the water as a carrier.

1.3.2 SC600 Herbicide

The application of SC600 Herbicide provides early-season or season-long control of weeds controlled by SC500 Herbicide and a cited end-use product containing metribuzin applied at similar active ingredient rates. SC600 Herbicide controls non-emerged weeds and emerged weeds up to 4 cm in height.

SC600 Herbicide is recommended for application at 375–900 mL/ha, based on the efficacy claims (early-season versus season-long) and weed spectrum and pressure, or in combination with listed tank mixes as a broadcast spray up to 14 days before planting or within three days after planting but prior to emergence of soybean in all tillage systems. Use higher rates within the labelled rate range for more consistent weed control. Efficacy of SC600 Herbicide is maximized when adequate rainfall is received within 14 days after application.

SC600 Herbicide can only be applied using ground equipment in 100–300 L/ha of spray volume.

1.3.3 SC617 Herbicide

The application of SC617 Herbicide provides early-season or season-long control of weeds controlled by SC500 Herbicide and a cited end-use product containing isoxaflutole applied at similar active ingredient rates in Eastern Canada and British Columbia. SC617 Herbicide controls non-emerged weeds and emerged weeds up to 5 cm in height.

SC617 Herbicide is recommended for application alone at 292–585 mL/ha, based on efficacy claims and weed spectrum and pressure, or in combination with listed tank mixes as a broadcast spray up to 14 days before planting or within three days after planning but prior to emergence of field and seed corn in all tillage systems. Use the higher rates within the labelled rate range for more consistent and longer residual control. Efficacy of SC617 Herbicide is maximized when adequate rainfall is received within 14 days after application. Use of SC617 Herbicide on seed corn must be approved by the contracting seed corn company and comply with the directions given by the contractor.

SC617 Herbicide can only be applied using ground equipment in a minimum of 150 L/ha of spray volume. Sprayable fluid nitrogen fertilizer may replace all or part of the water as a carrier.

1.4 Mode of action

Diflufenican is an inhibitor of phytoene desaturase belonging to the anilide chemical family. It causes degradation of chlorophyll and destruction of chloroplast membranes responsible in carotenoid production. Selectivity in crops is due to rapid metabolism of the herbicide, whereas sensitive plants develop symptoms of stunting, discolouration, and necrosis, leading to plant death.

Diflufenican is classified as a Group 12 herbicide by the Weed Science Society of America and mainly controls *Amaranthus* weed species that have developed resistance to many other herbicide modes of action.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable.

2.2 Method for formulation analysis

The methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for residue analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method DC-003-P18-02 in plant matrices and Method DC-005-A19-02 in animal matrices) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated for plant enforcement Method DC-003-P18-02 using radiolabelled soybean forage, hay and seed analyzed with the enforcement method. Extraction solvents used in livestock enforcement Method DC-005-A19-02 were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled animal tissues was not required for the livestock enforcement method. Methods for residue analysis in plant and animal matrices are summarized in Appendix I, Tables 1A and 1B.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Diflufenican is a new phytoene desaturase inhibitor (PDS Inhibitor) herbicide. It is currently registered in Europe, Latin America, and Asian Pacific countries for selective weed control in cereal grains.

A detailed review of the toxicology database for diflufenican was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes and includes studies, high-throughput screening and in silico read-across assessments, performed on diflufenican and select metabolites of diflufenican. These studies were carried out in accordance with Good Laboratory Practices. The human health risk assessment also considered any relevant information found in the published literature. The scientific quality of the data is acceptable, and the database is considered adequate to characterize the potential health hazards associated with diflufenican.

In a series of metabolism and toxicokinetic studies, diflufenican was administered to Wistar and Sprague-Dawley rats as either unlabelled test substance or test substance radiolabelled on the pyridine, difluorophenyl or trifluoromethylphenyl rings. Diflufenican was rapidly absorbed, especially at low doses. Although some estimates of systemic exposure were slightly lower in females than males, as evidenced by lower maximum plasma concentrations, shorter elimination half-lives and lower area under the curve values in females, not all of the differences were observed in whole blood. Therefore, these differences between the sexes were not considered biologically significant. Diflufenican was widely distributed with highest tissue concentrations in the fat, ovaries, uterus, liver, and intestine and intestinal contents. Recovery of radioactivity was high at 168 hrs and the majority of the administered dose (AD) was excreted in the feces. Biliary excretion represented 45% of the total excretion in males, but up to 80% of the total excretion in females. Urinary excretion was less than 10% of the excreted radioactivity. Over 75% of the recovered dose was excreted within the first 72 hrs. The most common fraction in the faeces was unchanged diflufenican, which was also found at low concentrations in the urine, but was not found in the bile. The metabolite RPA 312546 was found in all three matrices, as was diflufenican hydroxide. There were three identified metabolites that only occurred in the feces, two that only occurred in the urine and one that only occurred in the bile. The metabolite only found in bile represented 10–12% of the AD. Evidence from studies with radiolabels on the difluorophenyl or trifluoromethylphenyl rings indicates that the diflufenican molecule is not cleaved during the metabolic pathway.

Diflufenican was of low acute oral, dermal and inhalation toxicity in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. It was not a dermal sensitizer in guinea pigs in a Maximization Test.

The end-use product, SC500, containing diflufenican, was of low acute oral, dermal and inhalation toxicity in rats. It was minimally irritating to the eyes and skin of rabbits and was not a dermal sensitizer in a Local Lymph Node Assay (LLNA) in mice.

The end-use product, SC617, containing diflufenican and isoxaflutole, was of low acute oral and inhalation toxicity in rats and considered of low acute dermal toxicity. It was mildly irritating to the eyes and minimally irritating to the skin of rabbits. It was not a dermal sensitizer in a LLNA in mice.

The end-use product, SC600, containing diflufenican and metribuzin, was of slight acute toxicity via the oral route and of low acute inhalation toxicity in rats and considered of slight acute dermal toxicity. It was minimally irritating to the eyes and skin of rabbits and was not a dermal sensitizer in a LLNA in mice.

Repeat-dose dietary toxicity studies with diflufenican were available in mice and rats, and diflufenican was administered via gavage or capsule in repeat-dose oral toxicity studies in dogs. Body weight and body weight gain were the most commonly affected endpoints in the short- and long-term, and reproductive toxicity studies. Short-term studies were conducted in many strains of rats and body weight results were inconsistent across strains and within each strain in different studies of the same duration. A weight of evidence approach was used to determine the overall point of departure for body weight and body weight gain effects following short-term exposure across the various studies. There were no other treatment-related, adverse changes below the limit dose in the short-term rat studies. In the 2-year toxicity study in the rat body weight and body weight gain effects were observed in the first 13 weeks and food consumption was decreased at the mid-dose level. Body weight effects in adults and offspring in the reproductive toxicity study, including effects on birth weights, were present at similar dose levels as those eliciting body weight effects in the long-term rat study. Body weight gain was decreased in maternal animals in the rat and rabbit developmental toxicity studies. In the 90-day dietary mouse toxicity study, body weight and body weight gain were decreased starting at the lowest dose tested in males and at the highest dose tested in females; decreased food efficiency was also observed in both sexes at the highest dose tested. In the 2-year combined chronic toxicity and oncogenicity study in mice, treatment-related, adverse changes were limited to decreased body weight and body weight gain at the mid-dose level and above. In short-term toxicity studies in dogs, the first signs of toxicity were an increase in vomiting in the 90-day study, along with decreased body weight and body weight gain at the high-dose level.

Effects on the liver were observed in the 90-day mouse and 1-year dog oral toxicity studies. In the mouse, changes in the liver occurred in males at a dose level close to the limit dose and consisted of periacinar hepatocytic hypertrophy and focal necrosis with inflammatory infiltrate. In the dog at the mid-dose level and above, liver weight was increased in males and females, cholesterol was increased in males, and alkaline phosphatase (AP) values were increased in females. Cholesterol was also increased in female dogs at the high-dose level.

Changes to the hematopoietic system consisted of effects on the spleen in males at the high-dose level in the 2-year combined chronic toxicity and oncogenicity study in the rat and decreased thymus weights at the mid-dose level and above in parental females in the reproductive toxicity study. A waiver rationale was submitted for the immunotoxicity study and based on a lack of consistent findings in the spleen or thymus and lack of effects on immune system function in the rest of the database, the waiver was considered acceptable.

A two-generation dietary reproductive toxicity study was performed in Sprague Dawley rats and was conducted according to the test guideline in place at the time, which lacked evaluation of certain parameters that are included in the current test guideline. A weight of evidence document was submitted to justify the acceptance of the reproductive toxicity and developmental toxicity studies performed to their contemporary guidelines and was supplemented with a high-throughput screening evaluation to assess the endocrine toxicity potential of diflufenican. The changes observed in the reproductive toxicity study included the body weight effects observed in both adults and offspring noted above at the mid-dose level, as well as increased mortality in adult females as a result of dystocia, decreased birth weight in pups, and decreased offspring viability at the high dose level. As the dystocia and effects on pup viability and birth weights occurred at or above the limit dose, there is no evidence of effects on endocrine tissues in the rest of the database and given a lack of indication of endocrine effects in the published literature for diflufenican, the study was considered sufficient for risk assessment purposes. Although there were serious effects noted above the limit dose, effects were noted at the same doses in offspring and parental animals.

There was no evidence of increased sensitivity of the young when compared to adult animals in the gavage developmental toxicity studies in the rat or rabbit. Two developmental toxicity studies were performed in different strains of rats. In Sprague Dawley rats, effects were limited to decreased body weight gain in the dams. There were no maternal or developmental effects observed up to the highest dose tested in Wistar rats. In rabbits given doses above the limit dose, maternal animals exhibited pale feces and red discoloured urine, along with decreased body weight gain and decreased food consumption; however, there were no effects observed in the fetuses.

A waiver for the short-term dermal toxicity study was submitted and considered acceptable based on the low acute oral and dermal toxicity of diflufenican and available dermal absorption studies. A waiver for a study to assess the neurotoxic potential of diflufenican was also submitted and considered acceptable based on the lack of evidence of neurotoxicity observed in the toxicology database.

Genotoxicity studies conducted with diflufenican were negative and there was no evidence of tumourigenicity in the mouse or rat long-term studies.

Toxicity studies were submitted on the metabolites and transformation products BCS-BT38895 (a malonic acid conjugated aniline soybean seed metabolite), M&B 38,181 (rat metabolite), and 2,4-difluoroaniline (environmental transformation product). Additionally, in silico read-across reports were submitted for 2,4-difluoroaniline and BCS-BT38895 as well as for diflufenican. The

in silico modelling for diflufenican was performed for comparison to that of the metabolites and predicted a positive chromosomal aberration alert and plausible alerts for methaemoglobinaemia for anilines or precursors and equivocal alerts for nephrotoxicity for halogenated benzenes. However, these effects were not observed in the database.

The soybean seed metabolite, BCS-BT38895, was of low acute oral toxicity in rats. The bacterial reverse mutation assays, in vitro mammalian cell mutation test, and in vitro micronucleus test were negative. In a 14-day oral toxicity study in rats, there was no NOAEL established. At the lowest dose tested, there were slight increases in methaemoglobin; more pronounced increases in methaemoglobin and effects on the spleen were observed at the high-dose level. In a 28-day oral toxicity study in rats, no NOAEL was established. Methaemoglobin was slightly increased at the lowest dose tested along with changes to the spleen and increased reticulocytes. Increased spleen weight and hematology changes indicative of regenerative anaemia were observed at higher dose levels. In silico predictions for BCS-BT38895 flagged a positive alert for methaemoglobinaemia, a positive bacterial mutation alert for aromatic amines and a chromosomal aberration alert, plausible alerts for hepatotoxicity and an equivocal alert for nephrotoxicity for halogenated benzenes. Of these, the equivocal alert for nephrotoxicity for halogenated benzenes was also seen in the read-across studies on diflufenican and were considered of lesser concern due to the lack of nephrotoxicity in the main database.

Based on the in vivo study and in silico reports, BCS-BT38895 was considered to cause methaemoglobinaemia. BCS-BT38895 was not tested for carcinogenicity; however, it may have carcinogenic properties because it is a structural analog of p-chloroaniline, which was found to be carcinogenic in male rats (PMRA No. 1819485). The carcinogenic potential of all chloroanilines is assumed to be the same as that of p-chloroaniline unless there is sufficient evidence that the chloroaniline in question is either not carcinogenic or is of a different potency than p-chloroaniline. A read-across review confirmed that p-chloroaniline was the appropriate surrogate. It was determined that there could potentially be dietary exposure to BSC-BT38895 through the consumption of soybean seeds from treated plants (see section 3.6.3 for more details). As the endpoint of methaemoglobinaemia occurred at lower doses than those at which the most sensitive effects for diflufenican were observed and carcinogenicity could not be ruled out, separate reference values for the metabolite were established and the cancer potency of p-chloroaniline was used as a surrogate for BCS-BT38895 (see Section 3.3).

Reports in the published literature indicate that infants are more susceptible to methaemoglobinaemia than adults due to a normal transient deficiency in methaemoglobinaemia reductase in neonatal erythrocytes.[5] Given that there were no specific studies that assessed methaemoglobinaemia in the young following exposure to BCS-BT38895 and the lack of a NOAEL in either of the two repeat-dose studies, an additional threefold uncertainty factor was applied to the human health reference values (HHRVs) selected.

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[5] Methaemoglobinaemia in the Newborn Infant - ScienceDirect [accessed Dec 07, 2022]

A separate 3-fold factor for the use of a LOAEL was not considered necessary due to the very small magnitude of the change at the lowest doses tested.

M&B 38,181, a metabolite identified in rats, was of low acute oral and slight acute dermal toxicity in rats. It was negative in a bacterial reverse mutation assay, negative in a mammalian micronucleus test and weakly positive in a chromosome aberration test.

2,4-Difluoroaniline, an environmental transformation product, did not induce mutations in a supplemental bacterial reverse mutation assay. The in silico predictions for this environmental transformation product were positive for bacterial mutation for aromatic amines, chromosomal aberration, bacterial and salmonella mutation, and flagged plausible alerts for hepatotoxicity and methaemoglobinaemia and equivocal alerts for bone marrow toxicity, carcinogenicity, nephrotoxicity, skin sensitization and splenotoxicity for anilines or precursors. However, as noted in Section 4.1.1, 2,4-difluoroaniline is not likely to leach into the groundwater as it is volatile, non-persistent, and expected to dissipate very rapidly under field conditions and, thus, would not be a residue of concern.

The identification of select metabolites and transformation products is presented in Appendix I, Table 2. The toxicology reference values (TRVs) for use in the human health risk assessment are summarized in Appendix I, Tables 3 and 4. Results of the toxicology studies conducted on laboratory animals with diflufenican and relevant metabolites, and with its associated end-use products, are summarized in Appendix I, Tables 5 and 6, respectively.

3.1.2 *Pest Control Products Act* 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.[6]

With respect to the completeness of the toxicity database as it pertains to the toxicity of diflufenican to infants and children, the database contains the full complement of required studies including oral gavage developmental toxicity studies in rats and rabbits and a dietary 2-generation reproductive toxicity study in rats.

With respect to concerns regarding potential prenatal and postnatal toxicity, no evidence of increased sensitivity of the young was observed in the dietary 2-generation reproductive toxicity study in rats. Both parents and offspring demonstrated effects on body weight at the same dose levels which was the LOAEL. Decreased pup viability was observed at the high-dose level. Although a serious effect, this dose represented a limit dose which also resulted in significant

[6] SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

toxicity in the maternal animals, namely deaths due to dystocia. Furthermore, the established toxicology reference values provide sufficient margins to this effect. No developmental effects were observed in the rat or rabbit developmental toxicity studies.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young as effects in the young are well-characterized and, as noted above, sufficient margins exist between the serious effect observed in the reproductive toxicity study and the established toxicology reference values. On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) for diflufenican was reduced to 1-fold.

For the soybean seed metabolite, BCS-BT38895, there were no specific studies that would identify potential sensitivity of the young. The available dietary toxicity studies for BCS-BT38895 indicate methaemoglobinaemia as the critical endpoint. Published literature indicates that infants are more susceptible to methaemoglobinaemia than adults due to a normal transient deficiency in methaemoglobinaemia reductase in neonatal erythrocytes.[7] As stated above, concerns relating to this were addressed by the application of an additional 3-fold database uncertainty factor. The requirement to retain a PCPA factor of 10-fold is therefore subsumed by the use of this uncertainty factor. On the basis of this information, the PCPA factor for BCS-BT38895 was reduced to 1-fold.

3.2 Toxicology reference values

Separate toxicology reference values were derived for Diflufenican and the BCS-BT38895 metabolite.

3.2.1 Route and duration of exposure

For mixers, loaders and applicators, occupational exposure to SC500, SC617 and SC600 is characterized as short-term in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure, which is predominantly by the dermal route, is expected to be low due to the preemergence timing of application resulting in negligible foliar residues.

3.2.2 Occupational toxicology reference values

For the short- and intermediate-term dermal and inhalation occupational risk assessments, the NOAEL of 23 mg/kg bw/day from the 2-year chronic toxicity and oncogenicity study in rats was selected, based on decreased body weight and body weight gains observed during the first 13 weeks of the study. As repeat-dose dermal and inhalation toxicity studies were not available, the use of a study conducted via the oral route was considered appropriate.

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7 Methaemoglobinaemia in the Newborn Infant - ScienceDirect [accessed Dec 07, 2022]

The target margin of exposure (MOE) for these scenarios is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed female workers.

3.2.3 Acute reference dose

Establishment of an acute reference dose (ARfD) is not required, as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.

3.2.4 Acceptable daily intake

To estimate risk following repeated dietary exposure, the NOAEL of 23 mg/kg bw/day from the 2-year dietary chronic toxicity and oncogenicity study in the rat was selected. At the LOAEL of 120 mg/kg bw/day, reductions in body weight, body weight gain and food consumption were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The acceptable daily dose (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{23 \text{ mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day of diflufenican}$$

The ADI provides a margin of 5200 to the dose level at which effects on pup viability and maternal dystocia were observed in the reproductive toxicity study.

3.2.5 Cancer assessment

There was no evidence of tumourigenicity and therefore, a cancer risk assessment is not necessary.

3.2.6 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). For diflufenican, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected. The most relevant toxicology endpoints and assessment factors for acute and chronic oral aggregate exposure are the same as those selected for the ADI (see Section 3.2.4).

3.3 Metabolite of toxicological concern – BCS-BT38895

3.3.1 Acute reference dose

To estimate acute dietary risk, the LOAEL of 16 mg/kg bw/day from the 14-day oral toxicity study in the rat was selected. At the LOAEL there was a slight increase in blood methaemoglobin in males and females. There was no NOAEL established for the study. The effect on methaemoglobin was considered to potentially result from a single exposure and was therefore relevant to an acute risk assessment. Since there is concern that the critical endpoint in adults may not be adequate for assessment of the young, a 3-fold database uncertainty factor was applied for risk assessment purposes. Consequently, the PCPA factor was reduced to 1-fold as discussed in the *Pest Control Products Act* hazard considerations section. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were also applied, resulting in a composite assessment factor (CAF) of 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{16 \text{ mg/kg bw/day}}{300} = 0.05 \text{ mg/kg bw of BCS-BT38895}$$

3.3.2 Acceptable daily intake

To estimate risk following repeated dietary exposure, the LOAEL of 4 mg/kg bw/day from the 28-day oral toxicity study in the rat was selected. At the LOAEL there was an increase in blood methaemoglobin in males and females. There was no NOAEL established for the study. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. Since there is concern that the critical endpoint in adults may not be adequate for assessment of the young, a 3-fold database uncertainty factor was applied for risk assessment purposes. Consequently, the PCPA factor was reduced to 1-fold as discussed in the *Pest Control Products Act* hazard considerations section. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were also applied, resulting in a composite assessment factor (CAF) of 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{4 \text{ mg/kg bw/day}}{300} = 0.01 \text{ mg/kg bw/day of BCS-BT38895}$$

3.3.3 Cancer assessment

Due to a lack of long-term studies on the soybean seed metabolite, in silico predictions were performed. The most appropriate surrogate compound was p-chloroaniline which has an established q_1* of 6.38×10^{-2} mg/kg bw/day^{-1} based on an increased incidence of hemangiosarcomas (spleen) in rats (PMRA No. 1819485).

3.4 Dermal absorption

An in vivo dermal absorption study in rats and in vitro dermal absorption studies in rat and human skin were reviewed. Based on the data presented in the rat in vivo study, a dermal absorption value of 44% (from the mid-dose group sacrificed at 120 hours) was selected for the risk assessment of diflufenican and this is considered not to underestimate exposure as all tape strips were included (Appendix I, Table 7). The amounts recovered in all skin strips decreased with increasing sacrifice time from 8 hours to 120 hours in the mid- and low-dose groups. Therefore, these amounts are considered bioavailable over time and were included in the calculation of the potentially absorbable dose.

The in vitro results were not used to select a dermal absorption value as there were uncertainties and limitations identified in the studies, with the main one being the use of a Geiger counter to determine remaining skin residues following extensive skin washes. This is not representative of a worker taking a shower at the end of the day. With this procedure, the potential amount of test material absorbed may be underestimated, therefore, the highest dermal absorption value observed in the rat in vivo study was chosen.

3.5 Occupational and residential exposure assessment

3.5.1 Acute hazards of end-use products and mitigation measures

3.5.1.1 SC500

The acute hazard assessment indicated that SC500 has low acute oral, dermal and inhalation toxicity. SC500 is minimally irritating to the eyes and skin and is not a dermal sensitizer.

Based on these low acute hazards, no hazard signal word is required on the label and no additional PPE is triggered for workers during mixing, loading, application, clean-up and repair. The PPE on the proposed label is considered acceptable to protect against the acute hazard of SC500.

3.5.1.2 SC617

The acute hazard assessment indicated that SC617 has low acute oral, dermal and inhalation toxicity. SC617 is mildly irritating to the eyes and minimally irritating to the skin and is not a dermal sensitizer. Based on these acute hazards, the signal words “Caution Eye irritant” are required on the label, however, no additional PPE is triggered for workers during mixing, loading, application, clean-up and repair. The PPE on the proposed label is considered acceptable to protect against the acute hazard of SC617.

3.5.1.3 SC600

The acute hazard assessment indicated that SC600 causes slight acute oral toxicity. SC600 has low acute dermal and inhalation toxicity. SC600 is minimally irritating to the eyes and skin and is not a dermal sensitizer. Based on these acute hazards, the hazard signal words “Caution –

Poison" are required on the label, and no additional PPE is triggered for workers during mixing, loading, application, clean-up, and repair. The PPE on the proposed label is considered acceptable to protect against the acute hazard of SC600.

3.5.2 Occupational exposure and risk assessment

3.5.2.1 Mixer/loader/applicator exposure and risk assessment

Individuals have potential for exposure to diflufenican during mixing, loading, application, clean-up and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database for workers mixing and loading a liquid with an open-transfer system and applying SC500, SC617 or SC600 field corn, seed corn or soybeans using groundboom sprayer equipment. The unit exposure values in the risk assessment are based on handlers wearing a single layer of clothing and chemical-resistant gloves during mixing, loading and applying (no gloves within a closed-cab tractor) (Appendix I, Table 8).

Dermal exposure was estimated by coupling the unit exposure values adjusted for the dermal absorption value of 44% with the amount of product handled per day, which was derived from the maximum application rate of diflufenican on field or seed corn and soybeans, and the standard area treated per day values with groundboom sprayer for farmers and custom applicators. 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 80 kg adult body weight.

The estimated dermal and inhalation exposure values were combined since the dermal and inhalation reference values are based on the same study, and the same toxicological adverse effects are observed. Total daily exposure estimates were compared to the selected toxicology reference value to obtain the margin of exposure (MOE); the target MOE is 100. All calculated MOEs were above the target MOE of 100 for all chemical handler scenarios for field or seed corn and soybeans and are therefore not of health concern (Appendix I, Table 9).

Considering both the acute toxicity of the end-use products and the results of risk assessment for diflufenican, the PPE on the proposed SC500, SC617 and SC600 labels is adequate to protect workers while mixing, loading and applying the end-use products when used according to the proposed label directions.

3.5.2.2 Postapplication exposure and risk assessment

There is a restriction on the SC500, SC617 and SC600 labels: "Do not apply to emerged crop." Therefore, as crops are not emerged at the time of the preseed or preemergence application, negligible foliar residues are expected following a single application in fields of corn (field and seed) and soybeans.

As a result, the postapplication exposure potential for workers entering treated fields to conduct agronomic activities is low and a quantitative postapplication dermal exposure risk assessment is not required. Dermal risk is not of health concern for postapplication workers when the end-use products are used according to the proposed label directions.

Inhalation exposure is not expected as diflufenican is considered non-volatile with a vapour pressure of 4.25×10^{-9} kPa at 25°C, which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios [1×10^{-4} kPa at 20–30°C]. As such, a quantitative inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as diflufenican is considered to be non-volatile and the restricted-entry interval of 12 hours will allow residues to dry, suspended particles to settle and vapours to dissipate.

3.5.3 Residential exposure and risk assessment

3.5.3.1 Handler exposure and risk assessment

SC500, SC617 and SC600 are not domestic class products and are not permitted for use in residential settings; therefore, a residential handler exposure assessment is not required.

3.5.3.2 Postapplication exposure and risk assessment

SC500, SC617 and SC600 are not domestic class products and are not permitted for use in residential settings; therefore, a residential postapplication exposure assessment is not required.

3.5.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible as application is limited to agricultural crops 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.

A standard label statement to protect against drift during application is on the labels. Therefore, bystander exposure and risk are not of health concern since the potential for drift is expected to be minimal.

3.6 Dietary exposure and risk assessment

3.6.1 Exposure from residues in food of plant and animal origin

The residue definition for enforcement in cereal grains, pulses/oilseeds, rotational crops and edible livestock commodities is diflufenican. The residue definition for risk assessment in primary and rotational crops and in edible animal commodities is diflufenican. The data gathering and enforcement analytical methods are valid for the quantitation of diflufenican residues in crop and livestock matrices. Residues of diflufenican are stable in representative matrices from the five commodity categories (high water, high oil, high protein, high starch and

high acid content) for up to 24 months when stored frozen at -18°C. Therefore, diflufenican residues are considered stable in all raw agricultural commodities and processed commodities for up to 24 months. Residues of diflufenican did not concentrate in processed field corn and soybean commodities. Quantifiable residues are not expected to occur in edible livestock commodities with the current use pattern. Crop field trials conducted throughout the United States including regions representative of Canada using end-use products containing diflufenican at proposed rates in or on soybeans and field corn are sufficient to support the proposed maximum residue limits. Field rotational crop studies were conducted in/on mustard greens (a leafy commodity), turnips, carrots, potatoes and sugar beets (root and tuber vegetables), and wheat (a cereal grain). The data are adequate to demonstrate that a 30-day plantback interval is appropriate for non-labelled crops.

For soybean seed, the residue definition for risk assessment purposes also includes the metabolite BCS-BT38895, for which separate risk assessments were conducted. A validated analytical method is available for the quantitation of BCS-BT38895 for data gathering purposes in soybean seed. Residues of BCS-BT38895 are stable in frozen storage in soybean seed for up to 18 months and concentrate (1.3-fold) in soybean flour only. Quantifiable residues of BCS-BT38895 are not expected to occur in edible livestock commodities with the current use pattern. Crop field trials conducted throughout the United States including growing regions representative of Canada using end-use products containing diflufenican at proposed rates in or on soybeans are sufficient to demonstrate anticipated levels of the BCS-BT38895 metabolite in soybean seed for consideration in dietary exposure assessments.

3.6.2 Exposure from residues in drinking water

Estimated environmental concentrations (EECs) in potential drinking water sources are calculated for both groundwater and surface water.

For drinking water, diflufenican was modelled as a combined residue with its transformation products diflufenican-acid (DFF-acid) and diflufenican-amide (DFF-amide) (Table 3.6.2-1).

Estimated environmental concentrations in water for the combined residues were calculated for use in human health risk assessments using the Pesticide Water Calculator (PWC; version 2.0).

For surface water, PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. EECs are calculated by modelling a single standard scenario for 50 years, where a total land area of 173 ha drains into a 5.3 ha reservoir with a depth of 2.7 m.

Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1m of a water table. EECs in groundwater were calculated for several scenarios representing different regions of Canada; only the highest EECs from across these scenarios are reported. All scenarios were run for 50 years.

Drinking water modelling follows a tiered approach consisting of progressive levels of refinement. Level 1 EECs are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application timing, and geographic scenario.

Level 2 EECs are based on a narrower range application timing, methods, and geographic scenarios. Level 2 EECs are not considered conservative values that cover all regions of Canada and are only calculated when the dietary risk assessment requires further refinement.

Modelling was performed at Level 1 and EECs, expressed as parent equivalent, are reported in Table 3.6.2-2, below.]

Table 3.6.2-1 Major fate inputs for the modelling

Fate parameter	Drinking water[1]	Ecological water[2]	Details
K_{oc} (L/kg)	6.1	5429.7	**Drinking water:** The 20th percentile (P20) of 4 values for DFF-acid (the lowest K_{oc} among all compounds of concern). **Ecological:** The P20 of 6 K_{oc} values for diflufenican.
Water column metabolism half-life[3] (day) at 20°C	680.76	394.7	80th percentile of 6 aerobic water/sediment systems.
Benthic metabolism half-life[4] (day) at 20°C	805.6	475.7	80th percentile of 3 values.
Aqueous Photolysis half-life (day) at 40°N	201	201.4	Single study
Hydrolysis (day)	Stable	Stable	Single study
Soil half-life[5] (day) at 20°C	221	171	90% upper confidence bound on the mean from 9 soils.

- [1] Diflufenican and two transformation products (DFF-acid and DFF-amide)
- [2] Diflufenican alone
- [3] Aerobic aquatic whole system
- [4] Anaerobic aquatic whole system/soil
- [5] Aerobic soil metabolism

Table 3.6.2-2 Level 1 Estimated environmental concentrations of combined residue of diflufenican and its two transformation products (DFF-acid and DFF-amide) in potential sources of drinking water

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)		
	Peak[1]	Average[2]	Daily[3]	Yearly[4]	Overall[5]
1 application at 180 g a.i./ha annually	159.0	149.1	14.4	2.22	0.88

[1] Peak of daily concentrations.
[2] Average of post-breakthrough concentrations.
[3] 90th percentile of the highest 1-day average concentration from each year.
[4] 90th percentile of yearly average concentrations.
[5] Average of all yearly average concentrations.

3.6.3 Dietary risk assessment

A chronic dietary risk assessment for diflufenican and, acute, chronic (non-cancer) and cancer dietary risk assessments for metabolite BCS-BT38895 were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 4.02, 05-10-c), which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the year 2005-2010.

3.6.3.1 Acute dietary exposure results and characterization

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

For BCS-BT38895, a unique metabolite in soybean seed only, the following assumptions were applied in the intermediate level of refinement of the acute analysis: 100% soybean crop treated, the highest average field trial (HAFT) residue from the soybean field trials, and default and experimental (where available) processing factors. The acute dietary exposure from soybean alone is estimated to be less than 1% (3×10^{-5} mg/kg bw/day) of the ARfD for the general population (95th percentile, deterministic).

3.6.3.2 Chronic dietary exposure results and characterization

The following criteria were applied to the basic chronic analysis for diflufenican: 100% crop treated, default and experimental processing factors (where available), and proposed MRLs for field corn, dry soybeans and all animal commodities. The basic (i.e., most conservative) chronic dietary exposure (food alone) from all supported diflufenican food commodities for the total population, including infants and children, and all representative population subgroups is less than 1% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable.

The PMRA estimates that chronic dietary exposure to diflufenican from food and drinking water is 1.6% (3×10^{-3} mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 5.7% (1×10^{-2} mg/kg bw/day) of the ADI.

For metabolite BCS-BT38895, the following criteria were applied to the intermediate level of refinement of the chronic non-cancer analysis: 100% crop treated, the supervised trial median residue (STMdR) value from the soybean field trials and default and experimental processing factors (where available) for soybean processed commodities. The chronic non-cancer dietary exposure (food alone) from the consumption of soybeans for the total population, including infants and children, and all representative population subgroups is less than 1% of the ADI.

The intermediate level of refinement of the chronic cancer risk assessment was conducted for metabolite BCS-BT38895 with the same criteria used for the chronic non-cancer assessment. The lifetime cancer risk from exposure to BCS-BT38895 from the consumption of soybean seed and derived processed commodities was estimated to be 4×10^{-7} for the general population (including infants and children), which is not of health concern.

3.7 Aggregate exposure and risk assessment

For diflufenican, the aggregate exposure assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected.

3.8 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of mammalian toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for diflufenican. Diflufenican is a phytoene desaturase (PDS) inhibitor (pesticidal mode of action), and only one other PDS inhibitor is registered for use in Canada, picolinafen. Diflufenican and picolinafen do not have similar mammalian toxicity profiles, and as a result, no common mechanism of toxicity was identified. Other PDS inhibitor pesticides not registered for use in Canada include norflurazon, fluridone, and flurtamone, none of which share a common mechanism of mammalian toxicity with diflufenican. Overall, for the current evaluation, the PMRA did not identify information indicating that diflufenican shares a common mechanism of mammalian toxicity with other pest control products. Therefore, no cumulative health risk assessment is required at this time.

3.9 Maximum residue limits

Dietary risks from the consumption of food commodities listed in Table 3.9.1 were shown to be acceptable when diflufenican is used according to the supported label directions. Therefore, foods containing residues at these levels are safe to eat, and the PMRA recommends that the following MRLs be specified for residues of diflufenican.

Table 3.9.1 Recommended maximum residue limits

MRL (ppm)	Food Commodity
0.01	Dry soybeans; eggs; fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep; field corn; milk

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

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1B, 10 and 11.

3.10 Health incident reports

Diflufenican is a new active ingredient pending registration for use in Canada and as of 23 June 2022, no human or domestic animal incidents have been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

4.1.1 Terrestrial environment

A summary of the environmental fate properties of diflufenican and its transformation products are found in Appendix I; Tables 12 and 13.

In the terrestrial environment, abiotic transformation processes are not expected to contribute significantly to the dissipation of diflufenican in soil, as this compound was stable to hydrolysis and photolysis, under acidic and neutral conditions.

Biotransformation was an important route of dissipation for diflufenican in the terrestrial environment. Diflufenican was slightly persistent to persistent in both laboratory and field studies. In aerobic soils, diflufenican transformed to the major products DFF-amide, DFF-acid and CO_2; while in anaerobic soil conditions, 2,4-difluoroaniline (2,4-DFA) was predominantly formed. Additional studies with transformation products DFF-amide, DFF-acid and 2,4-DFA showed that they were non-persistent to moderately persistent under aerobic soil conditions.

The weight of evidence suggests that diflufenican is not expected to leach based on the criteria of Cohen et al. (1981) and the groundwater ubiquity score of Gustafson (1989); diflufenican is immobile in soil, slightly persistent to persistent, and it was not detected below 30 cm in the terrestrial field dissipation studies. Transformation products DDF-acid and DDF-amide have the potential to leach based on the criteria of Cohen et al. (1981) and the groundwater ubiquity score of Gustafson (1989). Laboratory studies indicated that transformation products, DDF-acid and

DDF-amide, were mobile and slightly persistent in soil; however, in terrestrial field studies these transformation products were not detected below 15 cm, suggesting that they would not reach groundwater. Transformation product 2,4-DFA is not likely to leach as it is volatile, non-persistent and, thus, expected to dissipate very rapidly under field conditions.

Diflufenican is not expected to carry over to the next growing season.

4.1.2 Aquatic environment

In the aquatic environment, abiotic transformation is not expected to contribute significantly to the dissipation of diflufenican as it is stable to hydrolysis and photolysis under basic and neutral or acid conditions.

Biotransformation was a major route of dissipation for diflufenican in the water system and large amounts of diflufenican were shown to partition into sediment prior to transformation. Diflufenican dissipated rapidly from the water phase and was persistent in the sediment phases in clay and sand. Transformation products DFF-acid and CO_2 were major products identified in aquatic systems.

4.1.3 Air transformation

Diflufenican has low solubility in water, low vapour pressure, and a low Henry's Law Constant, suggesting diflufenican is not likely to volatilize from moist soil or water surfaces under field conditions. All these physico-chemical properties, combined with a high absorptive capacity to organic matter in soil and water, indicate diflufenican would have a low potential for transport in the atmosphere. Transformation products DFF-acid and DFF-amide are also not expected to be found in air based on their low vapour pressure. While 2,4-DFA is highly volatile, it is expected to dissipate / transform very rapidly in soil and was not detected in field dissipation studies.

4.1.4 Bioaccumulation

The potential for bioaccumulation of diflufenican in fish is low. Diflufenican is, therefore, not expected to bioaccumulate.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates,

vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level). A summary of the terrestrial and aquatic endpoints and the effects metrics used in the risk assessment are presented Appendix I, Tables 14, 15 and 16, respectively.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible, and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to terrestrial organisms

Terrestrial organisms, such as earthworms, honeybees, beneficial arthropods, birds, small mammals, and terrestrial non-target vascular plants can be exposed to diflufenican through direct contact with spray, spray drift, run-off, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment of diflufenican, its transformation products, and the associated end-use product and co-formulations was undertaken based on available toxicity data for earthworms, honeybees and other beneficial arthropods, birds, small wild mammals, and terrestrial plants. A summary of the toxicity of diflufenican to terrestrial organisms is provided in Appendix I, Table 14. The most sensitive endpoints used in the risk assessment are provided in Appendix I, Table 16. Results of the accompanying risk assessment are presented in Appendix I, Tables 17, 18, 19, and 20.

Earthworms and soil-dwelling arthropods

Earthworms and soil-dwelling arthropods may be exposed to diflufenican through contact with residues in soil. Soil EECs were calculated based on a direct overspray, considering the maximum seasonal application rate of 180 g a.i./ha. Effects metrics were compared to the screening level soil EEC of 0.08 mg a.i./kg. The resulting RQs did not exceed the LOC for diflufenican technical and the end-use product SC500, indicating that risks to earthworms and soil-dwelling arthropods are acceptable when diflufenican is used according to the label.

Foliar-dwelling beneficial arthropods

The main route of exposure of diflufenican to foliar-dwelling beneficial arthropods is via contact to surface residues as a result of a spray application. For direct overspray to plant surfaces in the field, the maximum seasonal application rate of 180 g a.i./ha was used as the screening level foliar EEC. Effects metrics were compared to the foliar EEC. The RQs did not exceed the LOC for the end-use product, SC500, indicating that risks to foliar-dwelling arthropods are acceptable when diflufenican is used according to the label.

Bees

Foraging bees could be exposed directly to diflufenican via spray droplets during application, to residues on the surface of leaves (acute contact exposure), and through the ingestion of contaminated pollen and nectar (oral exposure). In addition, brood may be exposed to diflufenican as foraging bees bring contaminated pollen and nectar back to the hive. For the screening level risk assessment, it was assumed that diflufenican is systemic and expected to move through plants to the pollen and nectar. The estimated contact and oral exposure for bees is compared to the toxicity endpoints (expressed in µg a.i./bee) derived from laboratory studies. As such, a conversion of the application rate from kg a.i./ha to µg a.i./bee is required for both contact and oral studies.

The LOC was not exceeded for all bee studies with either diflufenican or the end-use product, SC500, except for chronic oral exposure to adult bees, where the LOC was marginally exceeded for the end-use product, SC500 (RQ = 1.1). The chronic oral exposure to adult bees is conservative because the calculation is based on the estimated residues directly in/on the plant and thus overestimates the residues in diet as the residues in the diet would be lower than those directly in/on the plant. Thus, risks to pollinators are acceptable when diflufenican is used according to the label and no mitigation measures are required.

Terrestrial vertebrates

Birds and mammals could be exposed directly to diflufenican via spray droplets during application or to residues on the surface of leaves (acute contact exposure). Foraging birds and small mammals could also be exposed to diflufenican through the ingestion of a contaminated diet (oral exposure). To assess the risk to birds and mammals, the estimated concentration of diflufenican on various food items was used to determine the amount of pesticide in the diet (the estimated daily exposure (EDE).

The LOC was not exceeded for all feeding guilds of mammals. The LOC was exceeded for insectivorous small and medium sized birds, on a chronic basis (RQs >1.7).

The risk to birds was further characterized considering feeding guilds, maximum and mean residue levels, and on-field and off-field exposures (Appendix I, Table 19). When considering the maximum residue values, the feeding preference and food items contaminated from spray drift on the treated field, the maximum risk quotients were for insectivorous small and medium

sized birds (RQ >1.7 and >1.3, respectively, for reproductive effects). When considering mean on-field residues of diflufenican in food items, risk quotients exceeded the level of concern for small and medium sized insectivorous small and medium sized birds (RQ >1.2 and >0.9, respectively). No risk is expected for all birds exposed to off-field drift residues estimated by assuming a 6% spray drift factor for ground application.

Overall conclusion about potential risks to birds

The overall potential risk to birds is low given that the risk assessment is conservative (assumes 100% diet is comprised of insects or plants from the treated field) and the RQs are low.

It should be noted that three avian reproduction studies were available for review; the most sensitive no observed effect dietary doses (NOEDDs) were <8.6 and 162 mg a.i./kg bw/day (Mallard duck) and 9.42 mg a.i./kg bw/day (Bobwhite quail). The lowest NOEDD used in risk assessment was unbounded (<8.6 mg a.i./kg bw/day), resulting in some uncertainty. However, it is the opinion of the PMRA that when all three NOEDDs are considered, they offer sufficient weight of evidence that risks to birds are expected to be low. Therefore, the risks are considered acceptable and no mitigation measures are required.

Non-target terrestrial plants

Non-target plants may be exposed to diflufenican through direct overspray and spray drift of SC500 and co-formulations SC600 and SC617. The EECs were equal to the maximum seasonal application rate of the diflufenican component (180 g a.i./ha) in all co-formulations, except for SC617 (150 g a.i./ha). Based on EECs and the most sensitive ER_{25} for seedling emergence and for vegetative vigour, the calculated risk quotients exceeded the LOC at the screening level (RQs: 3.5 to 555.5), indicating a potential risk to non-target terrestrial plants. The risk was thus further characterized.

Further risk characterization

Spray drift

Further characterization of exposure was conducted considering off-field EECs using a 6% spray drift factor for ground application of SC500 and co-formulations SC600 and SC617 (Appendix I, Table 19). The level of concern for non-target terrestrial vascular plants was still exceeded for ground application (RQs: 1.7 to 33.3). The use of diflufenican is expected to pose a risk to non-target terrestrial plants. The risk will be mitigated by terrestrial spray buffer zones and precautionary label statements.

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, amphibians, and aquatic plants can be exposed to diflufenican via spray drift or through runoff entering aquatic habitats. The aquatic risk assessment was conducted following a tiered approach, with a conservative screening assessment

followed by refinements for spray drift and runoff if concerns were identified at the screening level. A summary of the effects on aquatic organisms considered in the selection of toxicity endpoints is provided in Appendix I, Table 15. The most sensitive aquatic endpoints used in the risk assessment are provided in Appendix I, Table 16. Results of the accompanying risk assessment are presented in Appendix I, Tables 21–23.

Aquatic invertebrates

Freshwater

In the screening level risk assessment, the LOC was exceeded for both acute (RQ < 1.1) and chronic (RQ = 1.0) diflufenican exposure to the water flea, *Daphnia magna*. Risks to *Daphnia* were further characterized (see section Further risk characterization below). Acute and chronic exposures to SC500 and the transformation products DFF-acid, DFF-amide and 2,4-DFA did not exceed the LOC.

The concentration of diflufenican in sediment did not pose a chronic risk to the sediment-dwelling amphipod, *Hyalella Azteca*, nor did diflufenican and the transformation product DFF-acid pose a risk to the sediment-dwelling midge, *Chironomus dilutus*.

Marine

The risk quotients for marine invertebrates resulting from acute and chronic exposures to diflufenican exceeded the LOC in two cases; diflufenican poses an acute risk to eastern oysters, *Crassostrea virginica* (RQ < 1.1), and is expected to pose a chronic risk to saltwater mysids, *Americamysis bahia* (RQ = 3.8), but not to the sediment dwelling amphipod, *Leptocheirus plumulosus*, based on sediment concentration. Risks to marine invertebrates were further characterized (see Section Further risk characterization below).

Fish

Freshwater

The risk quotients for rainbow trout, *Oncorhynchus mykiss* and fathead minnow, *Pimephales promelas*, resulting from acute exposure to diflufenican (RQ < 6.9), and fathead minnow resulting from chronic exposure to diflufenican (RQ = 7.4) exceeded the LOC. There were no effects of acute exposure to the transformation products on freshwater fish. Risks to freshwater fish were further characterized (see Section Further risk characterization below).

Marine

The risk quotients for the marine fish sheepshead minnow, *Cyprinodon variegatus*, resulting from acute and chronic exposures to diflufenican, exceeded the LOC (RQs of 6.4 and 4.9, respectively). Risks to marine fish were further characterized (see Section Further risk characterization below).

Amphibians

The risk quotients for African clawed frog, *Xenopus laevis,* resulting from acute exposure to diflufenican exceeded the LOC (RQ = 17.0). When fathead minnows were used as surrogates for amphibians, the LOC was exceeded with RQs of 39.3 for chronic exposure to diflufenican. Risks to amphibians were further characterized (see Section Further risk characterization below).

Algae and vascular plants

Freshwater

The LOC was exceeded for green algae, *Pseudokirchneriella subcapitata*, exposed to diflufenican (RQ < 204.5) and for green alga, *Desmodesmus subspicatus*, exposed to SC500 (RQ = 25). The LOC was not exceeded for freshwater algae and vascular plants exposed to the transformation products DFF-acid, DFF-amide and 2,4-DFA. The LOC was exceeded for duckweed, *Lemna gibba*, exposed to diflufenican (RQ = 1.1). Risks to freshwater plants were further characterized (see Section Further risk characterization below).

Marine

The LOC was exceeded for the marine diatom, *Skeletonema costatum* exposed to diflufenican (RQ = 12.2). Risks to marine plants were further characterized (see Section Further risk characterization below).

Further risk characterization

Spray drift

Non-target aquatic organisms can also be exposed to diflufenican via spray drift. The refinement parameters for freshwater organisms and amphibians were the same as for the terrestrial spray drift refinement. For marine organisms, spray buffer zones are determined based on acute endpoints and the maximum single application rate only to reflect the lower potential of chronic exposure due to higher water renewal rates in tidal/estuarine areas.

The further risk characterization resulted in RQs of 0.1 to <12.3 (Appendix I, Table 22). Only acute and chronic exposure of diflufenican to amphibians (RQs of < 1 and 2.4, respectively), and acute exposures of diflufenican to green algae, *P. subcapitata* and *D. subspicatus* (RQs: <12.4 and 1.5, respectively) resulted in an exceedance of the LOC. The LOC for all other aquatic organisms was not exceeded (Appendix I, Table 22). The risk will be mitigated by aquatic spray buffer zones and precautionary label statements.

Runoff

The screening level risk quotients for amphibian, fish, aquatic invertebrates, algae and aquatic vascular plants exposed to diflufenican exceeded the level of concern. The EEC used for the screening level assumes a direct application to a water body. In order to better characterize the

risk, the risk from exposure to runoff into a body of water directly adjacent to the application field was determined using the runoff 90th percentile of the EECs predicted by PRZM-EXAMS for an appropriate time-frame.

The risk quotients for exposure to diflufenican through runoff are provided in Appendix I, Table 23. The risk quotients presented were calculated using toxicity endpoints and EECs representing the 90th percentile of 24-hour and 96-hour concentrations (acute assessment) and 21-day concentration (chronic assessment). Although diflufenican poses potential risk to algae through runoff (RQ <17.3), studies have shown diflufenican to have algistatic effects (inhibition of growth) rather than algicidal effects (killing of algal cells). Algae are expected to regenerate following runoff exposure. Standard precautionary runoff statements are required on all diflufenican product labels.

4.2.3 Environmental incident reports

As of 23 June 2022, no environmental incidents involving diflufenican have been submitted to the PMRA.

5.0 Value

Diflufenican, the active ingredient of SC500 Herbicide, is a herbicide with soil residual activity. It provides early-season or season-long control of *Amaranthus* weed species in corn (field and seed) and soybean when it is applied as a broadcast spray up to 14 days before planting or within three days after planting but prior to emergence of the crop in all tillage systems.

There are many herbicides registered for the control of *Amaranthus* species in corn and soybean. However, *Amaranthus* species have been identified to be highly resistant to many herbicide modes of action, including Groups 2, 3, 5, 9, 14, 15, and/or 27, in North America. Diflufenican provides control of *Amaranthus* species, including biotypes resistant to many other herbicide modes of action.

SC600 Herbicide and SC617 Herbicide, which are co-formulations of diflufenican with the registered active ingredients metribuzin or isoxaflutole, provide additional control of the weeds controlled by these active ingredients in corn (field and seed) or soybean. These products contain two active ingredients from different modes of action that may help users to manage herbicide resistant weeds, especially *Amaranthus* species, and to delay the evolution of future herbicide resistant weeds in corn and soybean fields.

Pre-plant and pre-emergent applications of diflufenican and its co-formulations fit well into Integrated Pest Management (IPM) programs, which may include the use of cultural practices, crop rotation, biological control agents, pest scouting and pest forecasting systems aimed at preventing economic pest damage. It also does not preclude the use of sequential applications of other herbicides with different modes of action for post-emergent weed control.

The applications of these herbicides reduce early-season weed competition to the emerging crop allowing the crop to benefit from additional moisture, nutrients, and light that would otherwise be captured by weeds. Weed management at this time is critical as the crop does not compete well with weeds until crop canopy closure. As all three end-use products have soil residual activity, the reduction in weed competition with the crop is extended.

5.1 Support for efficacy claims

Efficacy information submitted for review included scientific rationales, registrations of the cited end-use products containing metribuzin or isoxaflutole, and data from 52 field research trials, which were conducted in field corn, soybean, and non-cropland in Canada and the United States in the common corn and soybean growing regions between 2017 and 2020.

5.1.1 SC500 Herbicide

In the 23 trials in which efficacy of SC500 Herbicide was evaluated, it was demonstrated that a pre-plant surface or pre-emergent application of SC500 Herbicide at 120–360 mL/ha provided acceptable early-season or seasonal-long control of green pigweed, redroot pigweed, tall waterhemp, and palmer amaranth, including weed biotypes resistance to Group 2, 3, 4, 5, 9, 14, 15, and 27 herbicides.

The following tank mixtures are supported for labelling:

Pre-emergence to field corn: Aatrex Liquid 480, XtendiMax with VaporGrip Technology, and XtendiMax 2 with VaporGrip Technology.
Pre-plant surface and pre-emergence to field corn and seed corn: Converge Flexx and Roundup WeatherMax with Transorb 2 Technology.
Pre-plant surface and pre-emergence to field corn: Roundup Transorb HC, R/T 540 Liquid, Co-op Vector 540 Liquid, Roundup Xtend with VaporGrip Technology, and Roundup Xtend 2 with VaporGrip Technology.
Pre-plant surface and pre-emergence to soybean: Sencor 75 DF, Sencor 480 F, Roundup WeatherMax with Transorb 2 Technology, and Roundup Transorb HC.
Pre-plant surface and pre-emergence to Roundup Ready 2 Xtend soybean: Roundup Xtend with VaporGrip Technology, Roundup Xtend 2 with VaporGrip Technology, XtendiMax with VaporGrip Technology, and XtendiMax 2 with VaporGrip Technology.

5.1.2 SC600 Herbicide

In the 17 field trials in which efficacy of SC600 Herbicide was evaluated, it was demonstrated that a pre-plant surface or pre-emergent application of SC600 Herbicide at 375–900 mL/ha provided acceptable early-season or season-long control of the weeds controlled by SC500 Herbicide and the weeds listed on the cited metribuzin end-use product label at the similar active ingredient rates. In addition, value information also supported the claims for early-season control of barnyard grass, large crabgrass, smooth crabgrass, green foxtail, giant foxtail, yellow foxtail, fall panicum, and witchgrass with SC600 Herbicide at 900 mL/ha.

The following tank mixtures are supported:

Pre-plant surface and pre-emergence to soybean: Roundup WeatherMax with Transorb 2 Technology and Roundup Transorb HC.
Pre-plant surface and pre-emergence to Roundup Ready 2 Xtend soybean: Roundup Xtend with VaporGrip Technology, Roundup Xtend 2 with VaporGrip Technology, XtendiMax with VaporGrip Technology, and XtendiMax 2 with VaporGrip Technology.

5.1.3 SC617 Herbicide

In the 12 field trials in which efficacy of SC617 Herbicide was evaluated, it was demonstrated that a pre-plant surface or pre-emergent application of SC617 Herbicide at 292–585 mL/ha provided acceptable early-season or season-long control of the weeds controlled by SC500 Herbicide and the cited end-use product containing isoxaflutole at the similar active ingredient rates.

The following tank mixtures are supported:

Pre-plant surface and pre-emergence to field and seed corn: Roundup WeatherMax with Transorb 2 Technology.
Pre-plant surface and pre-emergence to field corn: Roundup Transorb HC, R/T 540 Liquid, Co-op Vector 540 Liquid, Roundup Xtend with VaporGrip Technology, and Roundup Xtend 2 with VaporGrip Technology.
Pre-emergence to field corn: Aatrex Liquid 480, XtendiMax with VaporGrip Technology, and XtendiMax 2 with VaporGrip Technology.

5.2 Support for host crop claims

Crop tolerance information submitted for review consisted of scientific rationales, registrations of the cited end-use products containing metribuzin or isoxaflutole, and data from 46 combined efficacy and crop tolerance trials and 30 dedicated crop tolerance trials, conducted in Canada and the United States between 2017 and 2020.

5.2.1 Field and seed corn

In 19 combined efficacy and crop tolerance trials and 16 dedicated crop tolerance trials, it was demonstrated that 25 field corn hybrids exhibited adequate margins of tolerance to both SC500 Herbicide and SC617 Herbicide when they were applied as per their label instructions. Yield data from 11 trials corroborated the crop injury observations. The scientific rationales justifying extrapolation of observed field grain corn tolerance to field silage corn was reviewed and considered acceptable.

Seed corn as a host crop is also supported based on the crop tolerance observed in field corn, and herbicide screening systems that are in place for seed corn production in Canada.

5.2.2 Soybean

In 22 combined efficacy and crop tolerance trials and 14 dedicated crop tolerance trials, it was demonstrated that 29 soybean varieties exhibited adequate margins of tolerance to SC500 Herbicide and SC600 Herbicide when they were applied as per their label instructions. Yield data from 29 trials corroborated the crop injury observations.

5.3 Support for rotational crop claims

Rotational crop tolerance information submitted included registrations of the cited end-use products containing metribuzin or isoxaflutole, use history information from Australia, Argentina, and several European countries, scientific rationales, and data from 23 field trials, which were conducted in Manitoba, Alberta, and Ontario between 2018 and 2020.

Based on the weight of evidence, the following rotational crops are supported for labelling:

Field corn and soybean can be planted as rescue crops if initial planting of the host crop fails in fields treated with SC500 Herbicide at 300 and 360 mL/ha, respectively.
Field corn and winter wheat as rotational crops can be safely planted 30 days and four months, respectively, after the application of SC500 Herbicide at 360 mL/ha.
Other listed small grain cereals, grasses, pulse crops, potato, and tomato as rotational crops can be safely planted anytime in the year following the application of SC500 Herbicide at 360 mL/ha. Canola and sugar beet as rotational crops can be safely planted anytime in the year following the application of SC500 Herbicide at 240 mL/ha.

Rotational crops supported for SC600 Herbicide and SC617 Herbicide are based on the most restrictive rotational crop restrictions supported for SC500 Herbicide and registered on the cited end-use products containing metribuzin or isoxaflutole.

6.0 Pest control product policy considerations

6.1 Assessment of the active ingredient under the toxic substances management policy

The *Toxic Substances Management Policy* (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, diflufenican and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[8] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Diflufenican does not meet all Track 1 criteria, and is not considered a Track 1 substance.
- Diflufenican does not form any transformation products that meet all Track 1 criteria.

Please refer to Appendix I, Table 24 for further information on the TSMP assessment.

6.1.1 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[9] The list is used as described in the PMRA Science Policy Note SPN2020-01[10] and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy*,[11] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999,* (substances designated under the Montreal Protocol).

The PMRA has reached the conclusion that:

- Diflufenican Technical, the end-use product SC500 and co-formulations SC600 and SC617 do not contain any formulants or contaminants that require environmental risk management.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Diflufenican Technical and SC500 containing the technical grade active ingredient diflufenican, for pre-plant and pre-emergent weed control in corn and

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8 DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

9 SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

10 PMRA's Science Policy Note SPN2020-01, Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act

11 DIR2006-02, Formulants Policy and Implementation Guidance Document

soybean; SC600, containing the technical grade active ingredients diflufenican and metribuzin for pre-plant and pre-emergent weed control in soybean; and SC617 containing the technical grade active ingredients diflufenican and Isoxaflutole for pre-plant and pre-emergent weed control in field corn.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
ºC	degrees Celsius
µg	micrograms
µm	micrometre
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
AHETF	Agricultural Handlers Exposure Task Force
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
atm	atmosphere
ATPD	area treated per day
AUC	area under the growth curve
BAF	bioaccumulation factor
BAX	active code for metribuzin
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
Bq	becquerel
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CL	clay loam
cm	centimetre
cm^2	square centimetre
cm^3	cubic centimetre
C_{max}	maximal concentration
CO_2	carbon dioxide
CR	chemical-resistant
D	day(s)
DALA	days after last application
DAN	active code for diflufenican
DEEM–FCID	Dietary Exposure Evaluation Model
DFA	difluoroaniline
DFF	diflufenican
DFF_{-acid}	diflufenican acid
DFF_{-amide}	diflufenican amide

DFOP	double first-order in parallel
DIR	directive
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
E_bC_{50}	effective concentration on 50% of the population (algae biomass)
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ELS	early life stage
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
E_rC_{50}	effective concentration on 50% of the population (algae growth rate)
EU	European Union
EXAMS	Exposure Analysis Modeling System
F1	first filial generation
FC	food consumption
FDA	*Food and Drugs Act*
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
GD	gestation day
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HDPE	high-density polyethylene
HHRV	human health reference value
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
IC_{50}	inhibitory concentration 50%
ILV	independent laboratory validation
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
IXF	active code for isoxaflutole
kg	kilogram
K_d	soil-water partition coefficient
$K_{F(ads)}$	Freundlich adsorption coefficient
$K_{F(des)}$	Freundlich desorption coefficient
$K_{F,OC(ads)}$	Freundlich adsorption coefficient normalized to organic carbon
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
kPa	kilopascal
L	litre

LAFT	lowest average field trial
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LDD_{50}	lethal daily dose 50%
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LS	loamy sand
mg	milligram
mL	millilitre
mm	millimetre
M	Molar
M/L/A	mixer/loader/applicator
M&B	initials for diflufenical products
MAS	maximum average score
MEA	method efficiency adjustment
MOE	margin of exposure
MRL	maximum residue limit
MRM	multiresidue method
MS	mass spectrometry
NA	not applicable
NAFTA	North American Free Trade Agreement
ND	not detected
NHANES/WWEIA	National Health and Nutrition Examination Survey/What We Eat in America
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEDD	no observed effect dietary dose
OC	organic carbon content
OM	organic matter content
P	parental generation
Pa	pascal
PBI	plantback interval
PCPA	*Pest Control Products Act*
PES	post extraction solids
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRZM	Pesticide Root Zone Model

PWC	Pesticide Water Calculator
q_1*	cancer potency factor
QSAR	quantitative structure-activity relationship
REI	restricted-entry interval
RQ	risk quotient
S9	mammalian metabolic activation system
SC	suspension concentrate
SDEV	standard deviation
SFO	single first order
SiL	silt loam
SL	sandy loam
SLS	silt loam from Aventis CropScience
SLV	sandy loam from Aventis CropScience
SMILES	simplified molecular-input line-entry system
SPN	science policy note
SSi	sandy silt
STMdR	supervised trial median residue
$t_{1/2}$	half-life
TFMP-NA	company code for 2-(3-trifluoromethyl-phenoxy)-nicotinic acid
T_{max}	time of maximal concentration
T_R	representative half-life
TRR	total radioactive residue
TRV	toxicity reference value
TSMP	Toxic Substances Management Policy
TWA	time-weighted average
UF	uncertainty factor
UK	United Kingdom
UR	unextracted residue
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
w	week
wt	weight
w/w	weight by weight
v.p.	vapour pressure
v/v	volume per volume dilution

Appendix I Tables and figures

Table 1A Residue analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	-	diflufenican	HPLC-MS-MS	1.5 ng/g	PMRA No. 3201068, 3201069, 3201070
		AE 0542291			
		AE B107137			
Sediment	-	diflufenican	HPLC-MS-MS	1.5 ng/g	PMRA No. 3201068, 3201069, 3201070
		AE 0542291			
		AE B107137			
Water	-	diflufenican	HPLC-MS-MS	0.05 ng/mL	PMRA No. 3201071, 3201072, 3201073
		AE 0542291			
		AE B107137			

Table 1B Residue analysis in plant and animal matrices

Analytical methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
Livestock commodities					
Enforcement Method	Poultry breast, bovine liver and milk	Diflufenican	Method DC-005-A19-02/ LC-MS/MS	0.01 ppm in all matrices	PMRA No. 3201074/3200136
Data-Gathering Method					
ILV of Enforcement Method	DC-005-A19-01: Poultry breast DC-005-A19-02: Bovine liver and milk	Diflufenican	Methods DC-005-A19-01 and DC-005-A19-02/ LC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200141, 3201080

Analytical methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
	Bovine liver, bovine milk and chicken muscle	Diflufenican	Method-No. DC-005-A19-02/ LC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200140, 3200141
Radiovalidation	None submitted. However, the extraction procedure with enforcement Method DC-005-A19-02 is comparable to the extraction procedures used in the livestock metabolism studies. Therefore, radiovalidation of the enforcement method is not required.				
Plant commodities					
Enforcement Method	Corn (forage, grain and stover) Soybean (forage, hay, and seed)	Diflufenican	Method DC-003-P18-02/ HPLC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200137
Data Gathering Methods	Corn (forage, grain and stover) Soybean (forage, hay, and seed)	Diflufenican BCS-BT38895 (soybean seed metabolite)	Method DC-003-P18-02/ HPLC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200137

Analytical methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
	Mustard Greens (leaves) Turnips (roots and tops) Wheat (forage, grain, hay and straw)	Diflufenican	Method DC-003-P18-01/HPLC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200135
	Potato (tubers) Sugar Beets (roots and tops)	Diflufenican	Method 01143/HPLC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200134
ILV of Enforcement Method	Soybean (forage, hay, and seed)	Diflufenican	Method DC-003-P18-02/HPLC-MS/MS	0.01 ppm in all matrices	PMRA No. 3200139
Radiovalidation	Soybean (forage, hay, and seed)	Diflufenican	N/A	N/A	PMRA No. 3200138

Table 2 Identification of select metabolites of Diflufenican

Code	Chemical Name	Source
BCS-BT38895	3-(2,4-difluoroanilino)-3-oxopropanoic acid	Soybean seed metabolite
BCS-BS35087 (M&B 40,401)	2,4-difluoroaniline	Environmental metabolite
M&B 38,181	2-3' -trifluoromethylphenoxy-nicotinic acid	Rat metabolite

Table 3 Toxicology reference values for use in health risk assessment for Diflufenican

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Establishment of an acute reference dose is not required, as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.		
Repeated (chronic) dietary	Combined chronic toxicity/oncogenicity dietary study in rats	NOAEL = 23 mg/kg bw/day ↓ bw, bwg	100
ADI = 0.2 mg/kg bw/day			
Short- and intermediate-term dermal[2]	Combined chronic toxicity/oncogenicity dietary study in rats	NOAEL = 23 mg/kg bw/day ↓ bw, bwg during first 13 weeks of the study	100
Short- and intermediate-term inhalation[3]	Combined chronic toxicity/oncogenicity dietary study in rats	NOAEL = 23 mg/kg bw/day ↓ bw, bwg during first 13 weeks of the study	100
Cancer	No evidence of tumourigenicity, therefore a cancer risk assessment is not required.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE (margin of exposure) refers to a target MOE for occupational assessments.

[2] Since an oral NOAEL was selected, a dermal absorption factor of 44% 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 4 Toxicology reference values for use in health risk assessment for BCS-BT38895 (soybean seed metabolite)

Exposure scenario	Study	Point of departure and endpoint	CAF[1]
Acute dietary general population	14-day dietary toxicity study in rats	LOAEL = 16 mg/kg bw/day ↑ MetHb	300
ARfD = 0.05 mg/kg bw			
Repeated (chronic) dietary	28-day dietary toxicity study in rats	LOAEL = 4 mg/kg bw/day ↑ MetHb	300

Exposure scenario	Study	Point of departure and endpoint	CAF[1]
ADI = 0.01 mg/kg bw/day			
Cancer	q1* based on p-chloroaniline of 6.38×10^{-2} mg/kg bw/day^{-1} for male rat hemangiosarcomas (spleen).		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments.

Table 5 Toxicity profile of Technical Diflufenican

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study type/ Animal/PMRA No.	Study results
Toxicokinetic Studies	
Tissue distribution PMRA No. 3201030 Repeat oral low dose PMRA No. 3201031 ADME PMRA No. 3201032 Metabolite characterization PMRA No. 3201033 Bile cannulation PMRA No. 3201034 Modified repeat dose PMRA No. 3201035 ADME and Kinetics Study	In a series of metabolism studies performed between 1984 and 2001, diflufenican (-96.6 - > 99%) unlabelled or radiolabelled was administered to Wistar and Sprague-Dawley rats. Early studies (1984–1994) were performed with diflufenican labelled on the pyridine ring. Studies from 2001 were performed with diflufenican radiolabelled on either the difluorophenyl or trifluoromethylphenyl rings. **Absorption:** Diflufenican was rapidly but incompletely absorbed, especially at low doses, with T_{max} between 5 and 11 hours depending on matrix and label position at 5 mg/kg bw/d. The T_{max} at 250 mg/kg bw/d ranged between 6 and 19 hours. Absorption was between 46 and 58% at low doses and 16 and 18% at high doses. Dose normalized C_{max} values ranged from 0.079–0.130 mg/mL in females to 0.141–0.180 mg/mL in males at the low dose. At the high dose, C_{max} values were 1.35 mg/mL and 1.482 mg/mL in the plasma and whole blood, respectively in males; however, they were 0.77 mg/mL and 1.532 mg/mL in plasma and whole blood, respectively, in females. Half lives of elimination varied the most widely, ranging from 14 hours to 62 hours. There was no consistency within matrices or dose groups between the studies; however, half lives in females were generally shorter with the exception of the low-dose assay in whole blood performed in 2001. The AUC was generally lower in females than males; however, there were no large differences between the sexes.

Study type/ Animal/PMRA No.	Study results
PMRA No. 3201036	**Distribution:** Diflufenican was widely distributed. The amounts found in the tissues following 168 hrs were less than 0.5% of the recovered dose; however, the percentage increased following repeat dosing. It is lipophilic and the highest tissue concentrations were in the fat, ovaries, uterus, liver, and intestine and contents. **Excretion:** Recovery was high at 168 hrs and the majority of the administered dose (AD) was excreted in the faeces. Biliary excretion represented 45% of the total excretion in males, but up to 80% of the total excretion in females. Urinary excretion was less than 10%. Over 75% of the recovered dose was excreted within the first 72 hrs. **Metabolism:** The most common fraction in the faeces was unchanged diflufenican, which was also found at low concentrations in the urine, but was not found in the bile. RPA 312546 was found in all three matrices, as was diflufenican+OH. There were three identified metabolites that only occurred in the faeces, two that only occurred in the urine and one that only occurred in the bile. The biliary metabolite was 10–12% of the AD. Evidence from studies with labels on the difluorophenyl or trifluoromethylphenyl rings indicates that diflufenican is not cleaved during the metabolic pathway.
Acute Toxicity Studies	
Acute oral toxicity Sprague-Dawley rats PMRA No. 3200965 (3200966 analysis)	LD_{50} > 5000 mg/kg bw (♂/♀) Low acute toxicity
Acute oral and dermal toxicity and eye and skin irritancy Sprague-Dawley rats New Zealand rabbits PMRA No. 3209968	Rat: LD_{50} > 5000 mg/kg bw - (♂/♀) Low acute toxicity. LD_{50} > 2000 mg/kg bw - (♂/♀) Low acute toxicity. New Zealand Rabbit: MAS = 0.2/110 MIS = 3.7/110 at 1h Minimally irritating based on non-zero scores at 24 hrs MAS = 0/8

Study type/ Animal/PMRA No.	Study results
	MIS = 0/8 Not irritating
Acute dermal toxicity Sprague-Dawley rats PMRA No. 3200971 (3200972 analysis)	LD_{50} > 2000 mg/kg bw - (♂/♀) Low acute toxicity
Acute inhalation toxicity Sprague-Dawley rats PMRA No. 3200973	LC_{50} > 2.26 mg/L Low acute toxicity MMAD 4.25 µm
Dermal Sensitization – Magnusson-Kligman Maximization Test Guinea pig PMRA No. 3200974	Negative
Short-term toxicity studies	
90-day oral toxicity study (diet) B6C3F1 mice PMRA No. 3200976	NOAEL = Not established (♂); 104 mg/kg bw/day (♀) LOAEL = 79 mg/kg bw/day ♂; 1024 mg/kg bw/day ♀ Effects at LOAEL (♂):↓ bw/bwg (♂) Effects at LOAEL (♀): ↓ food efficiency, ↑ liver wt., ↑ periacinar hepatocytic hypertrophy, ↑ focal necrosis with inflammatory infiltrate (♂); ↓ bw/bwg, ↓ food efficiency (♀)
28-day oral toxicity range-finding study (diet) Wistar rats PMRA No. 3200989	Supplemental Range-finding ≥27 mg/kg bw/day: ↓ thymus wt (♂/♀) ≥129/134 mg/kg bw/day: ↓ bw/bwg, ↓ FC, ↓ food efficiency (♀) 674/669 mg/kg bw/day: ↓ bw/bwg (♂/♀)
90-day oral toxicity study with high dose recovery group (diet) Wistar rats FOB	NOAEL = 57/64 mg/kg bw/day (♂/♀) LOAEL = 280/312 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg (♂/♀) Recovery group: evidence of recovery

Study type/ Animal/PMRA No.	Study results
PMRA No. 3200975	
90-day oral toxicity study (diet) CD rats PMRA No. 3200977	NOAEL = 33/38 mg/kg bw/day (♂/♀) LOAEL = 335/383 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg, ↓ FC (♂/♀)
90-day oral toxicity study CD rats PMRA No. 3200978	NOAEL = 38.1/44.3 mg/kg bw/day (♂/♀) LOAEL – not established No treatment-related effects observed
90-day oral toxicity study with 2 recovery groups for each dose (diet) F-344 rats PMRA No. 3200979 and 3200908 (electron microscopy results)	NOAEL = 19/21 mg/kg bw/day (♂/♀) LOAEL = 185/208 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg (♂♀) Recovery: Effects on bw/bwg recovered after 4 weeks
90-day oral toxicity study (gavage) Beagle dogs PMRA No. 3200982	NOAEL = 250 mg/kg bw/day (♂/♀) LOAEL = 500 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ vomiting (♂/♀); ↓ bw/bwg, food efficiency (♀) Limitations: ophthalmological results were not reported, epididymis and uterus not weighed
1-yr oral toxicity study (capsule) Beagle dogs PMRA No. 3200983 and 3200984 (impurity analysis)	NOAEL = 100 mg/kg bw/day (♂/♀) LOAEL = 300 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ liver wt ♂/♀; ↑ cholesterol ♂; ↑ AP, ↓secretory activity in caudal and cranial mammary gland ♀
Waiver request for dermal toxicity study	Submitted waiver request based on low acute oral and dermal toxicity of the active ingredient and dermal absorption studies that indicate that the potential for dermal absorption being low and not

Study type/ Animal/PMRA No.	Study results
PMRA No. 3200991	rapid. Waiver considered acceptable and dermal study not required.
Chronic toxicity/Oncogenicity studies	
2-year oral combined chronic and oncogenicity study (diet) B6C3F1 mice PMRA No. 3201002	NOAEL = 62/74 mg/kg bw/day (♂/♀) LOAEL = 322/384 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg ♂♀ **No evidence of tumourigenicity**
2-yr oral combined chronic and oncogenicity study F-344 rats PMRA No. 3200995	NOAEL 23/28 mg/kg bw/day (♂/♀) LOAEL 120/143 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg (♂/♀); ↓ FC (♀) **No evidence of tumourigenicity**
Developmental/ Reproductive Toxicity Studies	
2-generation reproductive toxicity study (diet) Sprague Dawley rats PMRA No. 3201004	Parental NOAEL = 36/42 mg/kg bw/day (♂/♀) Parental LOAEL = 176 /206 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg, ↓ FC (♂/♀); ↓ thymus wt (♀) Reproductive NOAEL = 888/206 mg/kg bw/day (♂/♀) Reproductive LOAEL = Not determined/1042 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ Dystocia and mortality, ↓ birth wt all generations Offspring NOAEL = 42 mg/kg bw/day Offspring LOAEL = 206 mg/kg bw/day Effects at LOAEL: ↓ mean pup wts No evidence of sensitivity of the young Study acceptable according to the guidelines of the time, however, missing parameters according to current guidelines such as various histopathological parameters, pup parameters including weight, anogenital distance and sexual maturity, food consumption, estrus cyclicity.

Study type/ Animal/PMRA No.	Study results
Rat developmental toxicity study (gavage) Sprague Dawley rats PMRA No. 3201009	Maternal NOAEL= 50 mg/kg bw/day Maternal LOAEL= 500 mg/kg bw/day Effects at LOAEL: ↓bwg GD 6–14 Developmental NOAEL= 500 mg/kg bw/day Developmental LOAEL= not determined No fetal findings at the highest dose tested. No evidence of sensitivity of the young
Rat developmental toxicity study Wistar rats PMRA No. 3201011	Maternal NOAEL =1000 mg/kg bw/day Maternal LOAEL = not determined Developmental NOAEL = 1000 mg/kg bw/day Developmental LOAEL = not determined No findings at the highest dose tested. No evidence of sensitivity of the young.
Rabbit developmental toxicity study New Zealand White rabbit PMRA No. 3201010	Maternal NOAEL = 350 mg/kg bw/day Maternal LOAEL = 2500 mg/kg bw/day Effects at the LOAEL: pale faeces and red discoloured urine, ↓bwg, ↓ FC Developmental NOAEL = 2500 mg/kg bw/day Developmental LOAEL = Not established No fetal findings at the highest dose tested. No evidence of sensitivity of the young.
Waiver request Evaluation of potential reproductive toxicity PMRA No. 3201005 PMRA No. 3201006	Authors proposed that studies were adequate as the effects have been characterized and that there would be no information gained from further investigations into and modernization of the reproductive and developmental toxicity studies. The reviewer agrees with the author's conclusions. Decreased pup viability indices and increased pup deaths occurred in the presence of maternal toxicity up to and including dystocia. Additionally, the changes in the offspring, other than decreased mean pup weights, did not occur at the LOAEL. Further study into sperm counts and implantation sites would not be required at this time.

Study type/ Animal/PMRA No.	Study results
	It was concluded that, as apparent uterine and testicular effects were not treatment-related and there were no flags for endocrine effects in the published literature, there was sufficient evidence to determine that further investigations into endocrine effects would not be required at this time to characterize the most appropriate endpoints in the database. Additional reproductive toxicity and developmental toxicity studies would not be required.
Genotoxicity Studies	
Bacterial reverse mutation assay S. Typhimurium PMRA No. 3201012	Negative ± metabolic activation Tested up to the limit concentration.
Bacterial reverse mutation assay S. Typhimurium PMRA No. 3201014	Supplemental Negative ± metabolic activation Test up to the limit concentration. Limitations: Only one strain was used.
Bacterial reverse mutation assay S. Typhimurium PMRA No. 3201015	Negative ± metabolic activation Tested up to the limit concentration.
In vitro forward mutation assay in mammalian cells Mouse lymphoma L5178Y cells PMRA No. 3201019	Negative ± metabolic activation No increase in mutations in the presence of metabolic activation Increase in mutations without metabolic activation only at cytotoxic doses.
In vitro forward mutation assay in mammalian cells Chinese Hamster V78 cell PMRA No. 3201021 and 3201023	Negative ± metabolic activation Tested up to precipitating concentration.

Study type/ Animal/PMRA No.	Study results
In vitro forward mutation assay in mammalian cells Mouse lymphoma L5178Y cells PMRA No. 3201022	Negative ± metabolic activation Tested up to cytotoxic concentration.
In vitro chromosomal aberrations assay Human lymphocytes PMRA No. 3201025	Supplemental No evidence of chromosomal aberrations above threshold. Tested up to precipitating concentration. Limitations: purity not provided, no positive control for S9
In vivo Chromosomal aberrations Sprague Dawley rats PMRA No. 3201026	Supplemental No evidence of chromosomal aberrations above threshold. Clinical signs included piloerection, hunched posture, lethargy, decreased respiratory rate, and increased lacrimation. Limitations: Purity of test substance not provided.
In vivo Micronucleus Assay NMRI mice PMRA No. 3201027	Negative Tested up to a limit dose. No clinical signs of toxicity.
In vitro unscheduled DNA synthesis Rat primary hepatocyte PMRA No. 3201029	Supplemental Tested up to cytotoxic concentrations. No evidence of unscheduled DNA synthesis. Limitations: purity of test substance not provided.
Neurotoxicity studies	
Waiver request PMRA No. 3201007	Waiver submitted based on lack of neurotoxicity findings in the rest of the submitted toxicology database or in the available literature in the 30 plus years since the initial registration of diflufenican in Europe. Waiver considered acceptable on the basis of the lack of neurotoxicity flags and an additional study is not required.

Study type/ Animal/PMRA No.	Study results
Special studies (non-guideline)	
Immunotoxicity study Waiver request PMRA No. 3201008	Waiver submitted based on lack of immunotoxicity findings in the rest of the database or in the available literature in the 30 plus years since the initial registration of diflufenican in Europe. Waiver considered acceptable on the basis of the lack of immunotoxicity flags, and an additional study is not required.
High-throughput evaluation of endocrine toxicity PMRA No. 3201038	In a review of the ToxCast and Tox21 assays with diflufenican, there were no positive results in estrogen receptor assays, androgen receptor assays, thyroid-related assays, or steroidogenesis assays.
Diflufenican – In silico modelling	
In silico reports and discussion document PMRA No. 3201041 PMRA No. 3201049 PMRA No. 3201050 PMRA No. 3201051	Study contains in silico predictions for diflufenican, BCS-BT38895 and 2,4-difluoroaniline. Results for metabolites are in the following table entries. Diflufenican had no in silico alerts for genotoxicity, bacterial mutation or gene mutations, but a positive alert for methaemoglobinaemia based on the simple anilines. Plausible alerts for methaemoglobinaemia for anilines or precursors and equivocal for nephrotoxicity for halogenated benzenes. No matching alerts for bacterial mutation. No evidence of chromosomal aberrations above threshold.
Metabolite - BCS-BT38895 (soybean seed metabolite)	
Acute oral toxicity Sprague-Dawley rats PMRA No. 3200964	LD_{50} > 2000 mg/kg bw – (♀) Low acute toxicity
14-day oral toxicity study (diet) Han Wistar rats PMRA No. 3201037	NOAEL = Not determined (♂/♀) LOAEL = 17/16 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ methemoglobin (♂♀)
28-day oral toxicity study (diet) Han Wistar rats PMRA No. 3200986	NOAEL = Not determined (♂/♀) LOAEL = 4.7/4.0 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ methemoglobin (♂♀); ↑ spleen wt, ↑ spleen extramedullary hemopoiesis (♂)

Study type/ Animal/PMRA No.	Study results
Bacterial reverse mutation assay S. Typhimurium and *E. coli* PMRA No. 3201013	Negative ± metabolic activation Tested up to the limit concentration
In vitro forward mutation assay in mammalian cells Chinese Hamster Ovary Cells PMRA No. 3201020	Negative ± metabolic activation Tested up to cytotoxic concentration.
In vitro micronucleus test Human lymphocytes PMRA No. 3201039	Negative ± metabolic activation Tested up to limit concentration.
In vitro micronucleus test Human lymphocytes PMRA No. 3201039	Negative ± metabolic activation Tested up to limit concentration.
In silico modelling report PMRA No. 3201045 PMRA No. 3201046 PMRA No. 3201048	No alerts identified for bacterial mutation; however, there are positive alerts for chromosomal aberration and plausible alerts for hepatotoxicity and methaemoglobinaemia for anilines or precusors and equivocal alerts for nephrotoxicity for halogenated benzenes.
Metabolite - M&B 38,181	
Acute oral and dermal toxicity Sprague-Dawley rats PMRA No. 3200967	Supplemental LD_{50} > 2000 mg/kg bw - ♀/♂ Low acute toxicity LD_{50} > 1000 mg/kg bw - ♀/♂ Slight dermal toxicity Limitations: no fasting in the oral portion, no top dose and use of aluminium jacket to hold test item in place in the dermal portion

Study type/ Animal/PMRA No.	Study results
Bacterial reverse mutation assay S. Typhimurium PMRA No. 3201017 DACO 4.5.4	Negative± metabolic activation Tested up to the limit concentration
In vitro chromosome Aberration Human lymphocytes PMRA No. 3201024 DACO 4.5.6	Weakly positive ± metabolic activation
Mammalian micronucleus test NMRI mice - Mouse peripheral blood cells PMRA No. 3201028 DACO 4.5.7	Negative Clinical signs of toxicity at ≥ 500 mg/kg bw included reduced spontaneous activity, recubency, ataxia, piloerection, bradykinesia and half eye lid closure.
Metabolite - 2,4-difluoroaniline, M&B 40,401	
Bacterial reverse mutation assay S. Typhimurium PMRA No. 3201016 DACO 4.5.4	Supplemental No increase in mutations ± metabolic activation Tested up to cytotoxic dose. Limitations: Batch details in PMRA No. 3201018, but no purity
In silico modelling report PMRA No. 3201043 PMRA No. 3201044	Positive bacterial mutation alert for aromatic amines and positive chromosomal aberration, bacterial mutation and salmonella mutation alerts. Plausible alerts for hepatotoxicity and methaemoglobinaemia and equivocal for bone marrow toxicity, carcinogenicity, nephrotoxicity, skin sensitization and splenotoxicity for anilines or precursors.

Table 6 Toxicity profile of end-use product(s) containing Diflufenican

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study Type/Animal/PMRA No.	Study Results
SC500 - AE F088657 00 SC42 A2 (2021-0639)	
Acute oral toxicity Wistar rats PMRA No. 3200125	$LD_{50} \geq 5000$ mg/kg bw – (♀) Low acute toxicity
Acute dermal toxicity Wistar rats PMRA No. 3200126	$LD_{50} > 4000$ mg/kg bw - (♂♀) Low acute toxicity
Acute inhalation toxicity Sprague-Dawley derived, albino rats PMRA No. 3200127	$LC_{50} > 5.05$ mg/L - (♂♀) Low acute toxicity
Eye Irritation New Zealand White Rabbits PMRA No. 3200128	MAS 2/110 MIS 6/110 at 1 hour Minimally irritating Note: Did not score for discharge
Skin Irritation New Zealand White Rabbits DACO 4.6.5	MAS = 0.2/8 MIS = 0.7/8 at 1 and 24 hours Minimally irritating
Skin sensitization - LLNA CBA/J mice PMRA No. 3200130	Negative

SC617 - DFF+IFT+CSA SC617 (2021-0695)	
Acute oral toxicity Sprague-Dawley derived, albino rats PMRA No. 3201640	LD_{50} > 2000 mg/kg bw – (♀) Low acute toxicity
Acute dermal toxicity PMRA No. 3210641	Waiver submitted based on low acute oral and dermal toxicity. Waiver considered acceptable and dermal study not required.
Acute inhalation toxicity Sprague-Dawley derived, albino rats PMRA No. 3201642	LC_{50} > 2.19 mg/L – (♂♀) Low acute toxicity
Eye irritation New Zealand White rabbits PMRA No. 3201643	MAS = 13.1/110 MIS = 25.3/110 at 24hrs Non-zero scores at 72 hrs Mildly irritating
Skin irritation New Zealand White rabbits PMRA No. 3201644	MAS = 0.2/8 MIS = 1/8 at 1h Minimally irritating
Skin sensitization - LLNA CBA/J mice PMRA No. 3201645 DACO 4.6.6	Negative
SC600 - AE F088657 + metribuzin SC600 (200 + 400 g/L) (2021-0697)	
Acute oral toxicity Sprague-Dawley derived, albino rats PMRA No. 3201827	LD_{50} = 1098 mg/kg bw (♀) Slightly acutely toxic Clinical signs included: hypoactivity, irregular respiration, hunched posture and piloerection

Acute dermal toxicity PMRA No. 3201828 DACO 4.6.2	Waiver submitted based on slight acute oral toxicity and minimal dermal irritation of the end-use product. Waiver considered acceptable and dermal study not required.
Acute inhalation toxicity Sprague-Dawley derived, albino rats PMRA No. 3201829	LC_{50} > 2.71 mg/L – (♂♀) Low acute toxicity
Eye irritation New Zealand White rabbits PMRA No. 3201830	MAS = 0.9/110 MIS = 6/110 at 1h Non-zero scores at 24 hrs Minimally irritating
Skin irritation New Zealand White rabbits PMRA No. 3201831	MAS = 0.3/8 MIS = 2/8 at 1h Minimally irritating
Skin sensitization - LLNA CBA/J mice PMRA No. 3201832 DACO 4.6.6	Negative

Table 7 Amount of ^{14}C-Diflufenican in each matrix after a single dermal application of SC500 formulation in rat in vivo study.

Matrix Analysed	Mean (n=4) Residues in Matrix (% of applied dose)[1]								
	5000 µg/cm^2			20 µg/cm^2			8 µg/cm^2		
	8-hour Exposure			8-hour Exposure			8-hour Exposure		
	Sacrifice time			Sacrifice time			Sacrifice time		
	8 hours	24 hours	120 hours	8 hours	24 hours	120 hours	8 hours	24 hours	120 hours
Urine	<0.1	<0.1	<0.1	<0.1	<0.1	0.4	<0.1	<0.1	0.5
Cage wash	<0.1	ND	ND	<0.1	ND	<0.1	ND	ND	<0.1
Feces	<0.1	ND	ND	<0.1	0.3	4.2	ND	0.7	7.3
Carcass including	0	0.1	0.1	0.3	0.7	1.3	0.4	1.1	2.2

Matrix Analysed	Mean (n=4) Residues in Matrix (% of applied dose)[1]								
	5000 µg/cm²			20 µg/cm²			8 µg/cm²		
	8-hour Exposure			8-hour Exposure			8-hour Exposure		
	Sacrifice time			Sacrifice time			Sacrifice time		
	8 hours	24 hours	120 hours	8 hours	24 hours	120 hours	8 hours	24 hours	120 hours
blood (cells + plasma)									
Untreated skin	ND	ND	ND	ND	<0.1	<0.1	<0.1	<0.1	<0.1
Application site skin (treated skin minus skin strips)	0.3	<0.1	<0.1	1	0.2	0.2	0.9	0.3	0.4
Surrounding skin	0.2	0.1	0.1	0.3	0.3	1.5	0.7	0.3	1.1
Percent absorbed (based on sum of urine + cage wash + feces + blood + carcass + surrounding skin + application site)	**0.5**	**0.2**	**0.2**	**1.6**	**1.5**	**7.6**	**2**	**2.4**	**11.5**
Skin strips (1-2)	1	2.6	1.5	5.6	11.6	16.5	8.2	14.6	7.9
Skin strips (3-17)	4.2	5.5	4.7	35.3	27.5	20.1	33.4	24.8	15.3
All skin strips (1-17)	5.2	8.1	6.2	40.9	39.1	36.6	41.6	39.4	23.2
Absorbable (biological samples including surrounding skin + application site skin + all skin strips)	**5.7**	**8.3**	**6.4**	**42.5**	**40.6**	**44.2**	**43.6**	**41.8**	**34.7**
First skin wash (radioactivity in skin swabs)	89.1	89.2	93.1	54.1	55	53.6	53.3	55.7	58.7
Non-occlusive protective cover (saddle and tape extracts) at termination.	0.3	0.4	0.6	0.6	0.4	0.7	0.5	0.4	2.4
Total non-absorbed	**89.4**	**89.6**	**93.7**	**54.7**	**55.4**	**54.3**	**53.8**	**56.1**	**61.1**
Recovery (sum of all matrices above)	**95.1**	**97.9**	**100.1**	**97.2**	**96**	**98.5**	**97.4**	**97.9**	**95.8**

Limit of detection (LOD) is twice the background radioactivity level in each sample type.

ND = Not detected (<LOD).
ND and <0.1% values were considered zero for calculation of means.

Table 8 AHETF Unit exposure estimates for mixers/loaders and applicators handling SC500, SC617 and SC600.

Scenario		AHETF unit exposure (µg/kg a.i. handled)[1]			
		Dermal	Dermal absorbed[2]	Inhalation[3]	Total unit exposure[4]
PPE: Single layer clothing and chemical-resistant gloves					
Mixer/Loader AHETF estimates					
A	Open Mix/Load (M/L) Liquid	58.5	25.74	0.63	26.37
Applicator AHETF estimates					
B	Open-cab groundboom application	25.4	11.18	1.68	12.86
Mixer/Loader + Applicator AHETF estimates					
A + B	Open M/L + Open-cab groundboom application	83.9	36.92	2.31	39.23

[1] No MEA adjustment
[2] Adjusted with dermal absorption factor 44%
[3] Light inhalation rate and 100% inhalation absorption
[4] Total unit exposure = Dermal unit exposure + inhalation unit exposure

Table 9 Mixer/Loader/Applicator exposure and risk assessment for SC500, SC617 and SC600

Crop	Worker type and Task	PPE[1]	Total unit exposure (µg/kg a.i. handled)[2] Dermal + inhalation	Maximum rate (kg a.i./ha)	ATPD (ha/day)[3]	Total daily exposure (mg/kg bw/day)[4]	Combined MOE[5]
Corn (SC500, SC617)	Farmer M/L/A	SL + CR gloves	39.23	0.15	107	0.0079	2923
	Custom M/L/A	SL + CR gloves	39.23	0.15	360	0.0265	869
Soybean (SC500, SC600)	Farmer M/L/A	SL + CR gloves	39.23	0.18	107	0.0094	2436
	Custom M/L/A	SL + CR gloves	39.23	0.18	360	0.0318	724

[1] Personal Protective Equipment (PPE): SL = Single layer of clothing: long-sleeved shirt and long pants. CR = Chemical-resistant
[2] Total AHETF unit exposures (dermal + inhalation) from Table 8.
[3] Standard Area Treated per day (ATPD table, 20-9-2017)
[4] Total Daily Exposure = [(total unit exposure, dermal adjusted for 44% dermal absorption + inhalation) × ATPD × rate)]/(80 kg bw × 1000 µg/mg).

[5] For diflufenican, a NOAEL of 23 mg/kg bw/day based on decreased body weight and body weight gain in rat, target MOE = 100.

Table 10 Integrated food residue chemistry summary

Nature of the residue in laying hen				PMRA No. 3201058		
Species and numbers	16 laying hen (Gallus gallus domesticus)					
Radiolabel position	[Difluorophenyl-UL-14C]-diflufenican (Specific activity: 3.2 MBq/mg)					
Average dose	0.68 and 14.3 mg/kg feed (ppm)					
Treatment Regimen	A single oral dose via capsule in the morning at 24-hour intervals.					
Study period	14 consecutive days					
Collection time	Eggs: 2/day (morning and evening); Excreta: 1/day					
Tissues/Samples collected	Whole blood, plasma, liver, kidneys, skin with fat, abdominal fat pad, thigh muscle, breast muscle and pre-lay eggs.					
Interval from last dose to sacrifice	23 hours					
Plateau of residues in eggs	240 h following administration of the first dose, both concentrations in egg yolks. 96 h after the first dose, both concentrations, egg whites.					
Matrices:	Extraction solvents:					
Fat, skin with fat and muscle	Acetonitrile followed by hexane partitioning.					
Liver and kidney	Sequential extraction using aqueous methanol.					
Egg yolks	Methanol then acetonitrile, followed by hexane partitioning					
Excreta	Acetone:water					
Post-extraction solids (PES)	Liver, kidney and egg yolk PES samples were treated with pepsin enzyme extraction; liver and kidney PES were further treated with hydrochloric acid (HCl) reflux.					
Matrices	**[Difluorophenyl-UL-14C]-diflufenican**					
	Low dose (0.7 ppm)			**High dose (14.3 ppm)**		
	TRRs (ppm)	**% of Administered dose**	**Transfer factor, TF[1]**	**TRRs (ppm)**	**% of Administered dose**	**Transfer factor, TF[1]**
Excreta (0–335 hr)	6.13	86.05	-	6.04	83.84	-
Cage Wash (0–335 hr)	-	1.49	-	-	1.41	-
Pooled Egg Yolk (0-335 hr)	0.030	0.20	0.032	0.342	0.10	0.015
Pooled Egg White (0–335 hr)	<0.001	<0.001	<0.001	0.003	0.00	<0.001

Eggs from ovary/oviduct	0.026	0.07	-	0.265	0.04	-
Liver	0.033	0.06	0.048	0.306	0.03	0.021
Kidney	0.006	<0.01	0.009	0.070	<0.01	0.005
Abdominal Fat	0.053	0.13	0.078	0.727	0.10	0.051
Skin with fat	0.024	0.04	0.036	0.375	0.04	0.026
Muscle, breast	0.002	0.01	0.004 (total)	0.011	<0.01	0.002 (total)
Muscle, thigh	0.004	0.01		0.069	0.01	
Total recovery	-	87.87		-	85.42	
Total of organs/tissues	-	0.76		-	0.46	

Summary of major identified metabolites in hen matrices		
Radiolabel position	[Difluorophenyl-UL-14C]-diflufenican	
Metabolites identified	Major metabolites	
Liver	Diflufenican	
Breast muscle		
Thigh muscle		
Abdominal fat		
Egg yolk		
Nature of the residue in lactating goat		PMRA No. 3201059
Species and numbers	Two goats (Saanen)	
Radiolabel position	[Pyridine-2-14C]-diflufenican (PY-label; Specific activity: 6.1 MBq/mg) [Difluorophenyl-UL-14C]-diflufenican (DFP-label; Specific activity: 6.8 MBq/mg)	
Average dose	10.9 (PY-label) and 8.9 (DFP-label) mg/kg feed (ppm)	
Treatment regimen	Once, orally, at 24 hour intervals via gelatin capsule	
Study period	5 consecutive days	
Collection time	Urine and faeces samples: 24 hours preceding the first dose and then at 24-hour intervals afterwards, up to 23 hours after the last dose. Milk samples: in the morning immediately prior to each administration, about six hours later in the afternoon, twice a day during the dosing phase, and before sacrifice. Cage wash: collected at the end of each 24-hour collection period, immediately prior to dosing.	
Tissues collected	Muscle (foreleg and rump muscle), fat (omental, subcutaneous and peritoneal/perirenal), liver and kidneys.	
Interval from last dose to sacrifice	23 hours	

Plateau of residues in milk	Plateau concentrations of 0.003 ppm (PY-label, corresponding to 0.007-0.008% of the AD) and 0.004–0.005 ppm (DFP-label, corresponding to 0.012 to 0.015% of the AD) by Days 2–3 after administration.	
Extraction solvents	Urine and faeces	Urine was analyzed directly without work-up. Faeces were extracted 3-fold with acetonitrile followed by 2–3-fold with acetonitrile/water.
	Liver	Acetonitrile (three times) followed by two or three extractions with acetonitrile:water (1:1, v/v).
	Omental fat	Hexane followed acetonitrile
	Peritoneal fat	Hexane followed by acetonitrile
PES	Liver	Post-extracted liver residues were incubated with a mixture of proteases in 0.01 M phosphate buffer at pH 7.5 for 18 hours at 37°C. Following incubation, samples were extracted 3-fold with acetonitrile and the extract was subsequently sonicated and centrifuged, and samples of the supernatant were taken for radioassay. Protease-treated liver residues were incubated with 1 M HCl for 18 hours at 37°C and subsequently centrifuged. Supernatant samples were neutralized with base (1 M NaOH for approximately 18 hours at 37°C), centrifuged and homogenized twice with acetone, prior to radioassay.

Matrices	**[Pyridine-2-14C] (10.9 ppm)**			**[Difluorophenyl-UL-14C] (8.9 ppm)**		
	TRRs (ppm)	**% of Administered Dose**	**Transfer factor, TF[1]**	**TRRs (ppm)**	**% of Administered Dose**	**Transfer factor, TF[1]**
Faeces (0–119 hr)	-	1.9	-	-	0.68	-
Urine (0–119 hr)	-	67.0	-	-	89.4	-
Cage wash (0–119 hr)	-	<0.1	-	-	<0.1	-
Liver	0.058	0.08	0.005	0.080	0.11	0.009
Kidney	0.003	<0.01	<0.001	0.006	<0.01	<0.001
Foreleg muscle	0.001	-	<0.001 (total)	0.002	-	<0.001 (total)
Thigh/rump muscle	<0.001	-		<0.002	-	
Omental fat	0.010	-	<0.001 (total)	0.010	-	0.001 (total)
Subcutaneous fat	0.005	-		0.005	-	
Peritoneal fat	0.007	-		0.010	-	
Milk, total	0.003	<0.1	<0.001	0.004	<0.1	<0.001

[1]The transfer factors were calculated by dividing the mean TRR value of the respective group by the feeding level (milligrams of active ingredient per kilograms feed per day).		
Summary of major identified metabolites in goat matrices		
Radiolabel position	[Pyridine-2-14C]-diflufenican, [Difluorophenyl-UL-14C]-diflufenican	
Metabolites identified	Major metabolites	
Faeces	Diflufenican	
Omental fat		
Peritoneal fat		
Liver, kidney, muscle, milk, subcutaneous fat	None	
Nature of the residue in lactating cattle - 2000 Study		PMRA No. 3201056
Species and numbers	Two cows (Holstein/Friesian)	
Radiolabel position	[Difluorophenyl-UL-14C]-diflufenican (Specific activity: 3.28 MBq/mg)	
Average dose	1 and 20.7 mg/kg feed (ppm)	
Treatment Regimen	A single gelatin capsule, via bolus gun, every 12 hours (twice daily)	
Study period	7 consecutive days	
Collection time	Urine and faeces samples: 24 hours preceding the first dose and then during 24-hour intervals afterwards, up to 23 hours after the last dose. Milk samples: in the morning prior to administration of the first dose and twice daily, immediately prior to the morning and afternoon doses. The final collection was made immediately prior to sacrifice.	
Tissues collected	Liver, kidneys, omental and renal fat, and skeletal muscle from the hind and fore quarters	
Interval from last dose to sacrifice	23 hours	
Plateau of residues in milk	High- and low-dose cow: reached at the end of the dosing period	
Extraction solvents	Urine and faeces	Urine was analyzed directly without work-up. Faeces were extracted three times with acetone.
	Liver and kidney	Distilled water and methanol
	Omental and renal fat	Warmed acetonitrile (three times)
	Milk	5% (w/v) potassium oxalate, ethanol, diethyl ether with partitioning against hexane
PES	Liver and kidney	The PES (PES 1) was processed by enzyme hydrolysis, macerated with 0.1 M HCl and pepsin. The sample was then neutralized with 6 M NaOH, methanol was added, and the sample was frozen overnight. Following centrifugation, the PES was retained (PES 2), the extract was concentrated and further purified (methanol, overnight frozen storage). Additional centrifugation generated a final pellet (PES 3) that was subjected to HPLC analysis.

Matrices	[Difluorophenyl-UL-14C]-Diflufenican					
	1 ppm			20.7 ppm		
	TRRs (ppm)	% of Administered dose	Transfer factor, TF[1]	TRRs (ppm)	% of Administered dose	Transfer factor, TF[1]
Urine, 0–176 h	-	0.70	-	-	0.70	-
Faeces, 0–176 h	-	73.5	-	-	71.5	-
Cage wash, 176 h	-	0.73	-	-	0.40	-
Kidneys	0.002	<0.01	0.002	0.026	<0.01	0.001
Liver	0.019	0.12	0.019	0.259	0.07	0.013
Muscle (composite)	0.001	-	0.001	0.003	-	<0.001
Renal fat	0.007	-	0.007 (composite)	0.084	-	0.004 (composite)
Omental fat	0.006	-		0.071	-	
Milk, total (0–176 hr)	-	0.09	0.013	-	0.02	0.006
[1]The transfer factors were calculated by dividing the mean TRR value of the respective group by the feeding level (milligrams of ai per kilograms feed per day).						

Summary of major identified metabolites in cattle matrices	
Radiolabel position	[Difluorophenyl-UL-14C]-diflufenican (1 and 20.7 ppm)
Metabolites identified	Major metabolites
Faeces	Diflufenican
Urine	2,4-Difluoroaniline
All other matrices	None

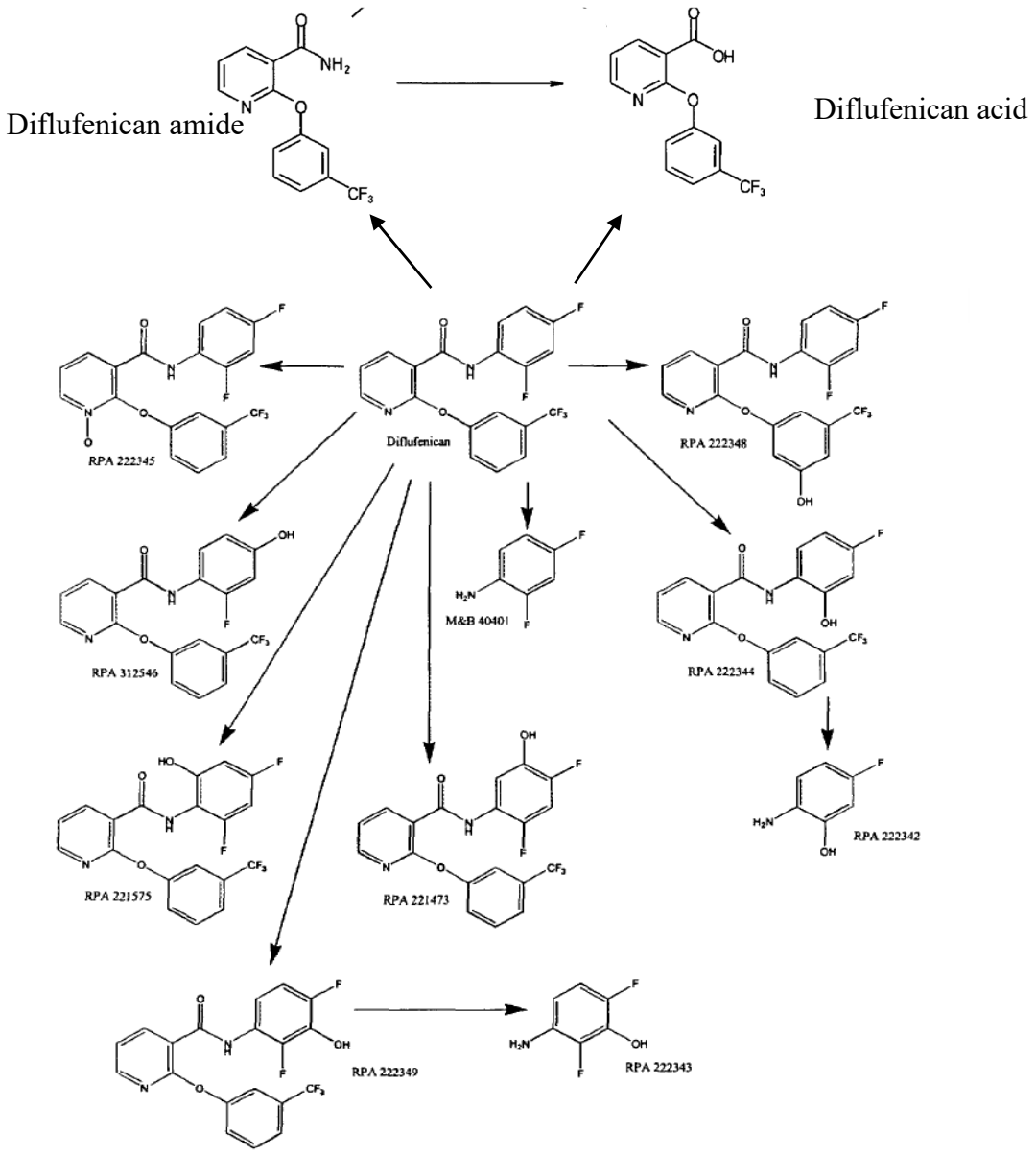
Nature of the residue in lactating cattle - 1989 Study	PMRA No. 3201057
Species and numbers	Two cows (Holstein/Friesian)
Radiolabel position	[Pyridine-2-14C]-diflufenican (Specific activity: 2.04 MBq/mg)
Average dose	5 and 50 mg/kg feed (ppm)
Treatment regimen	A single gelatin capsule, via bolus gun, every 12 hours (twice daily)
Study period	7 consecutive days
Collection time	Urine and faeces samples: 24 hours preceding the first dose and then during 24-hour intervals afterwards, up to 18 hours after the last dose. Milk samples: collected in the morning prior to administration of the first dose and twice daily, immediately prior to the morning and afternoon doses. The final milk collection was made immediately prior to sacrifice.
Tissues collected	Liver, kidneys, skeletal muscle (fore and hind), renal fat, and subcutaneous fat
Interval from last dose to sacrifice	18 hours

Plateau of residues in milk	TRRs in milk from the high-dose cow were low, with an increase in concentration from 0.001 ppm at 6 h post first dose to a maximum 0.031 ppm at 78 h post first dose. Levels declined until the end of the study period, indicating plateau levels (~0.018 ppm) had been reached.		
Extraction solvents	Urine and faeces	Urine was analyzed directly without work-up. Faeces were extracted with methanol.	
	Liver	Twice with methanol and twice with methanol containing 5% acetic acid	
	Renal fat	Hexane soak followed by methanol extraction	
	Milk	5% (w/v) potassium oxalate, ethanol, diethyl ether with partitioning against hexane	

Matrices	[Pyridine-2-14C]-diflufenican					
	5 ppm			50 ppm		
	TRRs (ppm)	% of Administered dose	Transfer factor, TF[1]	TRRs (ppm)	% of Administered dose	Transfer factor, TF[1]
Faeces, 0–168 h	-	69.75	-	-	85.84	-
Urine, 0–168 h	-	0.39	-	-	0.30	-
Milk	0.002	0.02	<0.001	0.016	0.02	<0.001
Liver	0.05	0.05	0.009	0.40	0.05	0.008
Kidney	<0.01	<0.01	0.002	0.04	<0.01	0.001
Muscle (composite)	<0.01	0.21	0.002	0.003	-	<0.001
Renal fat	0.04	-	0.005 (total)	0.06	-	0.001
Subcutaneous fat	0.02	-		0.07	-	
[1]The transfer factors were calculated by dividing the mean TRR value of the respective group by the feeding level (milligrams of ai per kilograms feed per day).						

Summary of major identified metabolites in cattle matrices	
Radiolabel position	[Pyridine-2-14C]-diflufenican (5 and 50 ppm)
Metabolites identified	Major metabolites
Faeces	Diflufenican
Renal fat	
Milk	
All other matrices	None

Proposed Metabolic Scheme in Livestock



Freezer storage stability in animal matrices		
Tested matrices	Analyte	Tested intervals (months)
Given that feeding studies were not submitted for review (and none are required), freezer storage stability data were not required.		

Anticipated residues in poultry matrices[1]			
Matrices	Residue definition[2]	Dietary burden (ppm)	Anticipated residues of diflufenican (ppm)
Eggs	Diflufenican	0.01	<LOQ

Fat			
Liver			
Muscle			
[1]The hen metabolism study was used to estimate the anticipated residues in the relevant poultry matrices. [2]Diflufenican is the residue definition for enforcement and dietary exposure purposes.			
Anticipated residues in animal matrices			
Matrices	Residue definition	Dietary burden (ppm)	Anticipated residues (ppm)
Dairy cattle			
Whole milk	Diflufenican	0.02	<LOQ
Fat			
Liver			
Kidney			
Muscle			
Swine			
Fat	Diflufenican	0.01	<LOQ
Liver			
Kidney			
Muscle			
The cattle metabolism studies were used to estimate the anticipated residues in the relevant livestock matrices.			

Nature of the residue in soybeans – Preemergent application			PMRA No. 3201060, 3201061
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific activity: 3.31 Bq/mg) [Difluorophenyl-UL-14C]-diflufenican (specific activity: 3.07 Bq/mg)		
Treatment			
Test site	Metal tubs containing gravel in the bottom followed by sandy loam soil located outdoors at the test facility		
Treatment	A single preemergent soil application one day after planting soybean seed		
Total rate	[Pyridine-2-14C]-label: 170.2 g a.i./ha [Difluorophenyl-UL-14C]-label: 166.2 g a.i./ha		
Formulation	Both labels: Suspension concentrate (SC) formulation (guarantee: 500 g/L)		
Harvest	Soybean forage and hay: BBCH growth stages 65-69, 101-102 day PHI. Hay was allowed to dry outdoors for up to 6 days prior to collection. Soybean seed: BBCH growth stage 89, 181-182 day PHI. Soybean early forage: BBCH growth stages 18-49, 80-81 day PHI.		
Extraction solvents	Early forage: acetonitrile (ACN)/H2O (4:1) (4 times) Forage, hay and seed: ACN/H2O (4:1) (four times) followed by ACN (two times)		
Matrices	PHI (days)	[Pyridine-2-14C]-Diflufenican	[Difluorophenyl-UL-14C] - Diflufenican
		TRR (ppm)	TRR (ppm)
Early Forage	80–81	0.026	0.017
Forage	101–102	0.023	0.016
Hay		0.050	0.040

Seed	181–182	0.013	0.017
Summary of major identified metabolites in soybean matrices – Preemergent treatment			
Radiolabel position	[Pyridine-2-14C]-Diflufenican [PY] and [Difluorophenyl-UL-14C]-Diflufenican [DFP]		
Metabolites identified	Major metabolites		
Early forage	Diflufenican (PY, DFP) Diflufenican amide (PY)		
Forage			
Hay			
Seed	Malonyl adduct of 2,4-difluoroaniline (DFP)		

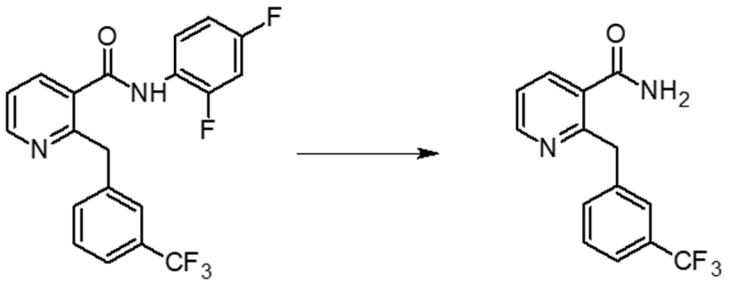
Nature of the residue in wheat – Early postemergent application	PMRA No. 3201062, 3201063
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific activity: 1.82 Bq/mg) (PY-label) [Difluorophenyl-UL-14C]-diflufenican (specific activity: 1.3 Bq/mg) (DFP-label) [Trifluoromethylphenyl-UL-14C]-diflufenican (specific activity: 1.5 Bq/mmol) (TFP-label)
Treatment	
Test site	Vessels with bases buried in the ground and filled with loam soil and fitted with a plastic tube connected to the base of the vessel to facilitate drainage and leachate removal at the test facility in the UK.
Treatment	Single early postemergence foliar spray application to winter wheat crop at BBCH13–14
Total rate	[Pyridine-2-14C]-label: 172.5 g a.i./ha [Difluorophenyl-UL-14C] and [Trifluoromethylphenyl-UL-14C]-labels: Low rate: 191.4 [DFP-label] and 182.4 [TFP-label] g a.i./ha High rate: nominal 400 g a.i./ha (both labels; actual rate was not reported)
Formulation	Not indicated
Harvest	[Pyridine-2-14C]-label: Immature hay samples: BBCH41–43 (116 days after the last application [DALA]). Wheat straw, chaff and grain samples: BBCH92 (251 DALA). [Difluorophenyl-UL-14C] and [Trifluoromethylphenyl-UL-14C]-labels: Immature wheat plants: BBCH57 (134 DALA). Wheat straw, chaff and grain samples: BBCH92 (201 DALA).

Extraction solvents	[Pyridine-2-14C]-label: TRR were too low in immature hay and grain to characterize further. Wheat straw: sequential extraction using acetonitrile, methanol and acetone following 72 hours of soaking in water. [Difluorophenyl-UL-14C] and [Trifluoromethylphenyl-UL-14C]-labels: Immature plant material: sequential extraction with acetonitrile and methanol. Grain: soaked overnight in 1% NaCl. Straw: sequential extraction with acetonitrile/water, acetonitrile and methanol.					
Matrices	PHI (days)	[Pyridine-2-14C]-Diflufenican	[Difluorophenyl-UL-14C]-Diflufenican		[Trifluoromethylphenyl-UL-14C]-Diflufenican	
		172.5 g a.i./ha	191.4 g a.i./ha	400 g a.i./ha	182.4 g a.i./ha	400 g a.i./ha
		TRR (ppm)				
Immature hay	116-134	0.002	<0.001	0.004	0.0015	0.011
Straw	201-251	0.012	0.007	0.035	0.010	0.047
Chaff		0.006	0.003	0.017	0.011	0.055
Grain		0.003	<0.001	0.002	0.003	0.011
Summary of major identified metabolites in wheat matrices – Early postemergent treatment						
Radiolabel position	[Pyridine-2-14C]- / [Difluorophenyl-UL-14C]- / [Trifluoromethylphenyl-UL-14C]-Diflufenican					
Metabolites identified	Major metabolites					
Immature hay	None					
Grain						
Chaff						
Straw	Diflufenican (all labels)					
Nature of the residue in winter wheat – Preemergent application					PMRA No. 3201064	
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific activity: 5.20 Bq/mg) [Difluorophenyl-UL-14C]-diflufenican (specific activity: 3.28 Bq/mg) [Trifluoromethylphenyl-UL-14C]-diflufenican (specific activity: 3.74 Bq/mmol)					
Treatment						
Test site	Cylindrical containment vessels with bases were buried in the ground, filled with loam soil and fitted with a plastic tube connected to the base of the vessel to facilitate drainage and leachate removal at the UK test facility.					
Treatment	A single preemergent soil application 5 days after planting wheat seed.					
Total rate	Low Rate: [Pyridine-2-14C]-label: 188.6 g a.i./ha [Difluorophenyl-UL-14C]-label: 183.7 g a.i./ha [Trifluorophenyl-UL-14C]-label: 173.9 g a.i./ha High Rate: All labels - 937.5 g a.i./ha					

Formulation	Not indicated						
Harvest	Immature plants: BBCH65 (215 DALA). Mature harvest samples: BBCH92 (272 DALA), separated into bottom portion of the straw and top straw. Ears were threshed into grain and chaff. The chaff and ear stalks were combined and identified as chaff.						
Extraction solvents	Grain (trifluoromethylphenyl-label) - high rate treatment: methanol/water, centrifuged and soaked in 1% NaCl. Chaff (trifluoromethylphenyl-label) - low and high rate treatments: sequential extraction with acetonitrile/water, acetonitrile and methanol. Top straw (trifluoromethylphenyl- and pyridine-labels - low and high rate treatments: sequential extraction with acetonitrile/water, acetonitrile, and methanol. Bottom straw (all radiolabels) - low and high rate treatments: sequential extraction with acetonitrile/water, acetonitrile and methanol.						
Matrices	PHI (days)	[Pyridine-2-14C] -Diflufenican		[Difluorophenyl-UL-14C] -Diflufenican		Trifluorophenyl-UL-14C]-Diflufenican	
		188.6 g a.i./ha	937.5 g a.i./ha	183.7 g a.i./ha	937.5 g a.i./ha	173.9 g a.i./ha	937.5 g a.i./ha
		TRR (ppm)					
Immature plants	215	0.002	0.004	0.001	0.008	0.003	0.018
Grain	272	0.002	0.008	<0.001	<0.001	0.002	0.101
Chaff		0.004	0.021	0.003	0.019	0.008	0.157
Top straw		0.010	0.046	0.006	0.026	0.009	0.141
Bottom straw		0.024	0.102	0.012	0.088	0.015	0.137
Summary of major identified metabolites in winter wheat matrices – Preemergent treatment; 173.9-188.6 g a.i./ha							
Radiolabel position	[Pyridine-2-14C]-Diflufenican [PY], [Difluorophenyl-UL-14C]-Diflufenican [DFP], [Trifluorophenyl-UL-14C]-Diflufenican [DFP]						
Metabolites identified	Major metabolites						
Grain	None						
Chaff							
Top straw							
Bottom straw	Diflufenican (PY-label)						
Nature of the residue in spring wheat – Preemergent application						PMRA No. 3201065	
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific activity: 20.39 mCi/mmol)						
Treatment							

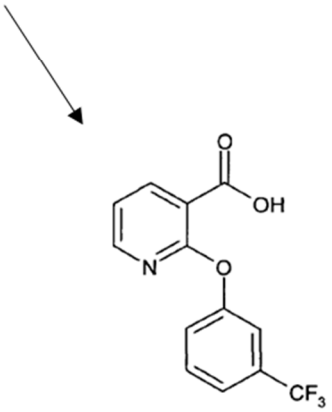
Test Site	Plastic pots standing in individual plastic trays, filled with soil. After dosing, the pots in their trays were placed in a glasshouse directly on the concrete slabbed floor. The glasshouse was not equipped with either heating or lighting, but temperature fluctuations were moderated by automatically adjusting roof vents.	
Treatment	Soil surface using a Hamilton syringe, preemergent to wheat.	
Total Rate	499.7 g a.i./ha	
Formulation	Not indicated	
Harvest – grain	At maturity 129 days after sowing	
Extraction solvents	Sequentially with hexane, chloroform, acetone, methanol, methanol/water (50:50 v/v), water, methanol/water (50:50 v/v), methanol/water/glacial acetic acid (47.5:47.5:5 v/v), and methanol/water (50:60 v/v).	
Matrices	PHI (days)	[Pyridine-2-14C]-Diflufenican
		499.7 g a.i./ha
		TRR (ppm)
Grain	Not reported; 129 days after sowing	0.07
Radiolabel position	[Pyridine-2-14C]-Diflufenican [PY	
Metabolites identified	Major metabolites	
Grain	None	

Proposed metabolic scheme in plants: Pre- and early postemergent application



Diflufenican

DFF-amide



DFF-acid (tentative)

Freezer storage stability in plant matrices					PMRA No. 3200368, 3200369, 3200370, 3200371
Tested matrices	Analytes	Tested intervals (days)	Demonstrated stability (days)	Temperature (°C)	Category
Sugar beet tops	Diflufenican	0, 29, 90, 180, 362, 540 and 722	722	-18°C	High-water
Dry bean (seed)		0, 28, 83, 175, 352, 532 and 715	715		High-protein
Potato tuber Sugar beet root		0, 29, 90, 180, 362, 540 and 722	722		High-starch
Rape (seed)		0, 28, 82, 174, 354, 536 and 712	712		High-oil

Grapes		0, 28, 82, 174, 354, 536 and 712	712		High-acid

Crop field trials on soybeans	PMRA No. 3200373

Field trials on soybeans were conducted in 2017 in North American growing regions 2 (2 trials), 4 (3 trials) and 5 (17 trials) for a total of 22 trials. SC500 (a suspension concentrate [SC] formulation) was applied as a single preplant or postplant, preemergent broadcast spray at a rate of 170-190 g a.i./ha/application. Samples of forage and hay, and soybean seed were harvested at 41–78 day PHIs and 112–164 PHIs, respectively. Hay samples were cut and dried in the field or under cover if rain was expected for 1–12 days prior to being placed in frozen storage. The number and geographic distribution of trials were in accordance with Health Canada's SPN2017-02 for Joint Canada/United States Field Trial Requirements. Independence of trials was assessed. Adequate storage stability data are available on diverse crop types to support the storage intervals of the soybean field trials. Samples were analyzed using a validated analytical method.

Commodity	Total application rate (g a.i./ha)	PHI (days)	Analyte	Residue levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Soybean forage	170–190	41–78	Diflufenican	22	<0.010	<0.010	<0.010	<0.010	0
Soybean hay		40–78		22	<0.010	0.015	0.010	0.010	0.0011
Soybean seed		112–164		22	<0.010	<0.010	<0.010	<0.010	0

n = number of independent trials. Values based on per trial averages. HAFT = Highest Average Field Trial, SDEV = Standard Deviation. For computation of the HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.

Crop field trials on field corn	PMRA No. 3200373

Field trials on field corn were conducted in 2018 in North American growing regions 1 (1 trial), 2 (1 trial), 5 (18 trials), 7 (1 trial) and 8 (1 trial) for a total of 22 trials. SC500 (SC formulation) was applied as a single preplant or postplant, preemergent broadcast spray at a rate of 150–160 g a.i./ha/application. Forage samples were collected at 75- to 114-day PHIs, and grain and stover samples were harvested at 110- to 160-day PHIs for. At one trial, grain samples were not collected due to wildlife damage. The number and geographic distribution of trials were in accordance with Health Canada's SPN2017-02 for Joint Canada/United States Field Trial Requirements. Independence of trials was assessed. Adequate storage stability data are available on diverse crop types to support the storage intervals of the field corn field trials. Samples were analyzed using a validated analytical method.

Commodity	Total application rate (g a.i./ha)	PHI (days)	Analyte	Residue levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Corn forage	150–160	75–114	Diflufenican	21	<0.010	<0.010	<0.010	<0.010	0
Corn grain[1]		110–160		20	<0.010	<0.010	<0.010	<0.010	0
Corn stover				21	<0.010	<0.010	<0.010	<0.010	0

n = number of independent trials. Values based on per trial averages. HAFT = Highest Average Field Trial, SDEV = Standard Deviation. For computation of the HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.
[1] Although 18 trials were conducted in region 5, grain samples at one of the trials were not collected due to excessive wildlife damage to the plot. However, forage and stover were collected from this plot for residue analysis.

Processed food and feed – Soybeans	PMRA No. 3200384
Processing studies were conducted in 2 distinct North American growing regions using SC500 (SC formulation) at rates of 900–930 g a.i./ha (equivalent to 5-fold the supported maximum single seasonal rate) in/on soybeans. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed commodities. Samples were analyzed using a validated analytical method. Residues of diflufenican were all <LOQ (<0.01 ppm) in the bulk soybean seed and all processed commodities. Therefore, processing factors for diflufenican could not be calculated.	
Processed food and feed – Field corn	PMRA No. 3200385
Processing studies were conducted in 2 distinct North American growing regions using SC500 (SC formulation) at 750 g a.i./ha (5-fold the maximum single seasonal use rate) in/on field corn. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method. Residues of diflufenican were all <LOQ (<0.01 ppm) in the bulk field corn grain commodities. Therefore, further analyses were not conducted on the processed commodities.	

Confined accumulation in rotational crops – Cabbage, spring wheat and sugar beet	PMRA No. 3200375
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific radioactivity: 1.011 Bq/mmol) [Difluorophenyl-UL-14C]-diflufenican (specific radioactivity: 1.215 Bq/mmol) [Trifluoromethylphenyl-UL-14C]-diflufenican (specific radioactivity: 1.391 Bq/mmol)
Treatment	
Test site	Outdoor plots located in the UK consisting of open top, sealed bottom, containers buried so that the soil surface was flush with the outside soil surface.
Soil type	Sandy silt loam
Treatment	Bare soil (surface) was treated at application rates of 387, 350 and 401 g a.i./ha, respectively, for each of [pyridine-2-14C]-, [difluorophenyl-UL-14C]- and [trifluoromethylphenyl-UL-14C]-diflufenican, and at exaggerated rates of 668 and 680 g a.i./ha for the difluorophenyl-UL- and the 3-trifluoromethyl phenyl-labelled rings only. The soil was subsequently aged for 12 weeks (~84 days) prior to planting cabbage, spring wheat and sugar beet seeds.
Formulation	Not reported.

Extraction solvents	Immature and mature cabbage samples, immature sugar beet plants and mature sugar beet leaves and roots, and immature wheat plant samples: acetonitrile and acetonitrile/water (1:1, v/v). Extracted residue from mature cabbage, mature sugar beet leaves and roots and immature wheat plants were further subjected to Soxhlet extraction with acetonitrile/water (80:20, v/v). Wheat grain: soaking in 1% NaCl for two days, sonicated, and centrifuged. The solid grain residue was extracted with acetonitrile/water (1:1, v/v) and the extract was subjected to Soxhlet extraction with acetonitrile/water (80:20 v/v). Wheat straw samples: sequential extraction with acetonitrile and acetonitrile/water (1:1 v/v) followed by Soxhlet extraction with acetonitrile/water (80:20 v/v).					
Matrices	PBI (days)	[Pyridine-2-14C]	[Difluorophenyl-UL-14C]		[Trifluoromethylphenyl-UL-14C]	
		386.98 g a.i./ha	349.68 g a.i./ha	668.13 g a.i./ha	400.92 g a.i./ha	679.88 g a.i./ha
		TRR (ppm)				
Immature cabbage	84	0.011	0.003	0.005	0.018	0.028
Immature sugar beet		0.014	0.009	0.014	0.023	0.041
Immature wheat		0.034	0.031	0.031	0.028	0.091
Mature cabbage		0.010	0.003	0.004	0.012	0.025
Mature sugar beet leaves		0.040	0.016	0.020	0.050	0.084
Mature sugar beet roots		0.049	0.014	0.016	0.055	0.085
Mature wheat grain		0.035	0.012	0.018	0.037	0.084
Mature wheat straw		0.174	0.152	0.156	0.081	0.313
Mature wheat chaff		0.081	0.046	0.050	0.077	0.235
Mature wheat stubble		0.181	0.172	0.263	0.126	0.360
Summary of major identified metabolites in rotated crops						
Plantback intervals (PBI)	84 days					
Radiolabel position	[Pyridine-2-14C]-diflufenican		[Difluorophenyl-UL-14C]- diflufenican		[Trifluoromethylphenyl-UL-14C]-diflufenican	
Matrix	Major metabolites identified					
Immature cabbage	Diflufenican DFF-acid DFF-amide		None		DFF-acid	
Mature cabbage	Diflufenican DFF-acid		None		DFF-acid	
Immature sugar beet plants	Diflufenican DFF-acid DFF-amide		Diflufenican		Diflufenican DFF-amide	
Sugar beet leaves	Diflufenican		Diflufenican		None	
Sugar beet roots	None		None		None	

Immature wheat plants	DFF-amide	None	None
Wheat grain	None	None	None
Wheat straw	None	None	None
Confined accumulation in rotational crops – Winter wheat, spring barley, cabbage, onions and sugarbeets			PMRA No. 3200376
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific activity: 718.3 MBq/mmol)		
Treatment			
Test site	Outdoor contained circular plots located in the UK (Essex).		
Soil type	Sandy loam.		
Treatment	Winter wheat seeds were planted 30 days after application in soil treated at 206 g a.i./ha. After the wheat was harvested, autumn sown onions (winter onions) were planted at 330 days after the application. Spring barley seeds were planted 140 days (20 weeks) after a single soil application at 206 g a.i./ha. After the barley was harvested, spring green (oxheart cabbage) seeds were planted 330 days after application. Cabbage seeds were planted 140 days after a single application to soil at 206 g a.i./ha. After the cabbage was harvested, winter wheat seeds were planted 330 days after application. Sugar beets seeds were planted 140 days after a soil application of 206 g a.i./ha. After sugar beet harvest, winter wheat seeds were planted 330 days after the soil application. These same sub-plots were subsequently treated with 283 g a.i./ha, two days after the winter wheat seeds were planted. Winter wheat seeds were planted 30 days after a single application of 283 g a.i./ha.		
Formulation	Not reported.		

Extraction solvents	Wheat straw: acetonitrile and acetonitrile/water (1:1 v/v). Selected remaining straw residue was further extracted with 0.5 M NaOH at 70°C. Wheat grain: water and acetonitrile Barley straw: sequentially with acetonitrile, acetonitrile/water (1:1 v/v), water, and acetonitrile. Selected barley straw samples were further extracted sequentially with 1% NaCl, water, 1 M HCl at 70°C, and 1 M NaOH. Barley grain: sequentially with acetonitrile, water, and acetonitrile Selected sugar beet top and root samples: acetonitrile and acetonitrile/water (1:1 v/v) Selected onion peel samples: acetonitrile and acetonitrile/water (1:1 v/v)	
Matrices	PBI (days)	[Pyridine-2-14C] TRR (ppm)
Immature wheat plants	31	0.014
Mature wheat grain	31	0.007
Mature wheat chaff	31	0.028
Mature wheat straw	31	0.050
Immature barley plants	140	0.007
Mature barley grain	140	0.016
Mature barley chaff	140	0.034
Mature barley straw	140	0.036
Immature cabbage plants	140	0.004
Mature cabbage outer leaves	140	0.004
Mature cabbage heart	140	0.004
Immature sugar beet leaves	140	0.006
Immature sugar beet roots	140	0.018
Mature sugar beet leaves	140	0.016
Mature sugar beet roots	140	0.019
Immature onion leaves	330	0.002
Immature onion peel	330	0.020
Immature onion bulb	330	0.001
Mature onion leaves	330	0.002
Mature onion peel	330	0.009
Mature onion bulb	330	0.002
Immature greens plants	330	0.002
Mature greens plants	330	0.002
Immature wheat plants	330	0.014
Mature wheat grain	330	0.007
Mature wheat chaff	330	0.031

Mature wheat straw	330	0.0499		
Immature wheat plants[1]	330/-2	0.0291		
Mature wheat grain[1]	330/-2	0.0167		
Mature wheat chaff[1]	330/-2	0.0504		
Mature wheat straw[1]	330/-2	0.1025		
1 Planted 330 days after first treatment at 206 g a.i./ha and two days prior to second treatment at 283 g a.i./ha.				
Summary of major identified metabolites in rotated crops				
Matrix	PBI (days)	Major metabolites identified		
Sugar beet roots	140	Diflufenican		
Confined accumulation in rotational crops – Winter wheat			PMRA No. 3200377	
Radiolabel position	[Pyridine-2-14C]-diflufenican (specific activity: 2056.1 MBq/mmol)			
Treatment				
Test site	Outdoor confined plots located in the UK (Essex).			
Soil type	Sandy silt loam			
Treatment	A rate of 187.5 g a.i./ha was applied to Plots 1 and 2; two applications of 187.5 g a.i./ha, one year apart, were made to Plot 3 for a total rate of 375 g a.i./ha, and a single exaggerated rate of 937.5 g a.i./ha was made to Plot 4. Winter wheat seeds were planted to the test plots as follows: Plot 1: 30 days postapplication Plot 2: 1 year postapplication Plot 3: 1 year after the first application, one day before the 2nd application Plot 4: 1 year postapplication. Prior to planting the winter wheat, a cover crop was grown in Plots 2, 3 and 4 postapplication, during the ageing period between test substance application until harvest. The cover crop was not analysed for residues.			
Formulation	Not reported.			
Extraction solvents	Wheat straw and stubble only: acetonitrile/water (3:1, v/v) and twice with acetonitrile/ water (1:3, v/v).			
Matrix	[Pyridine-2-14C]-diflufenican			
	TRR [ppm]			
	Treatment 1: 187.5 g a.i./ha	Treatment 2: 187.5 g a.i./ha	Treatment 3: 2x 187.5 g a.i./ha [Total: 375 g a.i./ha]	Treatment 4: 937.5 g a.i./ha
	30 day PBI	342 day PBI	342/-1[1] day PBI	342 day PBI

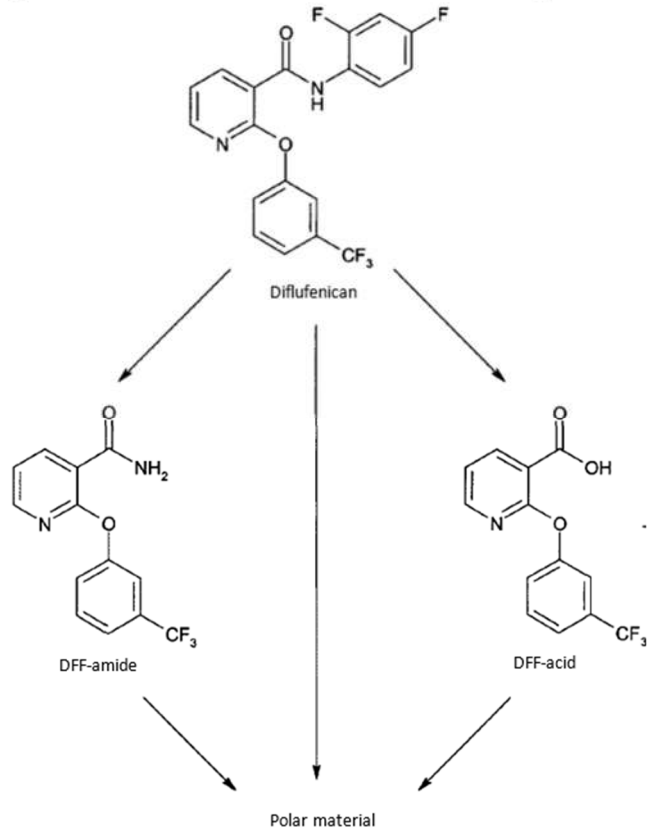
Wheat straw	0.016	0.009	0.018	0.068
Wheat stubble	0.026	0.013	0.036	0.106

[1] Winter wheat seeds at this plot were planted 1 year after the first application and one day before the second application.

Summary of major identified metabolites in rotated crops

No major metabolites were observed in any wheat sample.

Proposed metabolic scheme in rotational crops



Residue data in rotational crops – Mustard greens, turnips and wheat (spring)	PMRA No. 3200378, 3200379, 3200380

Nine trials (three each for mustard greens, turnips and spring wheat) were conducted during the 2017-2018 growing season in North American growing regions 2 (1 mustard green trial), 3 (1 turnip trial), 5 (1 mustard green, 1 turnip and 1 spring wheat trial), 7 (1 spring wheat trial), 8 (1 spring wheat trial) and 10 (1 mustard green and 1 turnip trial). One broadcast application was made to bare soil with Diflufenican SC500 (500 g a.i./L) at a rate of 180–190 g a.i./ha. No adjuvants were used at any trial sites. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commo-dity	Total applica-tion rate (g a.i./ha)	PBI (days)	Residue levels (ppm)					
			n	LAFT	HAFT	Median	Mean	SDEV
Diflufenican								
Mustard greens	180	25–30	3	<0.010	<0.010	<0.010	<0.010	0
		113–138	3	<0.010	<0.010	<0.010	<0.010	0
		336–358	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Turnip - tops	180	29–30	3	<0.010	<0.010	<0.010	<0.010	0
		110–120	3	<0.010	<0.010	<0.010	<0.010	0
		339–365	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Turnip - roots	180	29–30	3	<0.010	<0.010	<0.010	<0.010	0
		110–120	3	<0.010	<0.010	<0.010	<0.010	0
		339–365	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Wheat - forage	180-190	23-29	3	<0.010	<0.010	<0.010	<0.010	0
		105–-115	3	<0.010	<0.010	<0.010	<0.010	0
		339–364	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Wheat - grain	180-190	23–29	3	<0.010	<0.010	<0.010	<0.010	0
		105–115	3	<0.010	<0.010	<0.010	<0.010	0
		339–364	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Wheat - hay	180-190	23–29	3	<0.010	<0.010	<0.010	<0.010	0
		105–115	3	<0.010	<0.010	<0.010	<0.010	0
		339–364	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Wheat - straw	180-190	23–29	3	<0.010	<0.010	<0.010	<0.010	0
		105–115	3	<0.010	<0.010	<0.010	<0.010	0
		339–364	Due to residues being <LOQ at the earlier PBIs, these samples were not analyzed.					
Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ. n = number of independent field trials.								

Residue data in rotational crops – Carrots, potatoes and sugar beets (EU Trials)								PMRA No. 3200381, 3200382, 3200383
Three trials each for carrots, potatoes and sugar beets were conducted during the 2009–2010 growing season in Europe (Northern France, Spain and the Netherlands). One broadcast application was made to bare soil with Diflufenican SC500 (500 g a.i./L) at a rate of 150 g a.i./ha. No adjuvants were used at any trial sites. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.								
Commo-dity	Total applica-tion Rate (g a.i./ha)	PBI (days)	Residue Levels (ppm)					
			n	LAFT	HAFT	Median	Mean	SDEV
Diflufenican								
Carrot (root)	150	89–92	3	<0.010	<0.010	<0.010	<0.010	0
		357–378	3	<0.010	<0.010	<0.010	<0.010	0
Carrot (tops)		89–92	3	<0.010	<0.010	<0.010	<0.010	0
		357–378	3	<0.010	<0.010	<0.010	<0.010	0
Potato (tuber)	150	89–91	3	<0.010	<0.010	<0.010	<0.010	0
		359–379	3	<0.010	<0.010	<0.010	<0.010	0
Sugar beet root	150	89–91	3	<0.010	<0.010	<0.010	<0.010	0
		356–379	3	<0.010	<0.010	<0.010	<0.010	0
Sugar beet tops	150	89–91	3	<0.010	<0.010	<0.010	<0.010	0
		356–379	3	<0.010	<0.010	<0.010	<0.010	0
Based on the results of the field accumulation studies, a plantback interval of 30 days is adequate for all unlabelled crops (in other words, all crops except field corn and soybeans).								

Table 11 Food residue chemistry overview of metabolism studies and risk assessment

Plant studies	
Residue definition for enforcement **Primary crops (cereal grains [wheat] and pulses/oilseeds [soybean])** **Rotational crops (Wheat, barley, cabbage, sugar beet, onions, potato)**	Diflufenican

Residue definition for risk assessment	**Human food and animal feed commodities:** **Primary food crops -Cereal grains (wheat), pulses/oilseeds (soybean)** **Rotational crops - Wheat, barley, cabbage, sugar beet, onions, potato**	Diflufenican
	Pulses/oilseeds (soybean) seed	Metabolite BCS-BT38895 (Unique soybean seed metabolite)
Metabolic profile in diverse crops		The profile in diverse crops cannot be determined, because only 2 crop categories (wheat [cereal grain] and soybean [pulses and oilseeds]) were investigated and a unique metabolite was observed in soybean seed.
Animal studies		
Animals		**Ruminant and poultry**
Residue definition for enforcement		Diflufenican
Residue definition for risk assessment		
Metabolic profile in animals (goat, hen, cattle, rat)		The metabolic profile is similar in the animals investigated.
Fat soluble residue		Yes

Dietary risk from food and drinking water - Diflufenican

Basic chronic dietary exposure analysis **ADI = 0.2 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.149 ppm**	**Population**	**Estimated risk % of acceptable daily intake (ADI)**	
		Food alone	**Food and drinking water**
	All infants <1 year	0.1	5.7
	Children 1–2 years	0.3	2.3
	Children 3–5 years	0.2	1.8
	Children 6–12 years	0.1	1.3
	Youth 13–19 years	0.1	1.1
	Adults 20–49 years	0.1	1.5
	Adults 50+ years	0.1	1.5

	Females 13–49 years	0.1	1.5
	Total population	0.1	1.6
Dietary risk from food – Metabolite BCS-BT38895 (Unique soybean seed metabolite)			
Refined acute dietary exposure analysis, 95th percentile **ARfD = 0.05 mg/kg bw**	**Population**	**Estimated risk % of acute reference dose (ARfD)**	
		Soybean Seed Alone	
	All infants <1 year	0.2	
	Children 1–2 years	0.1	
	Children 3–5 years	0.1	
	Children 6–12 years	0.1	
	Youth 13–19 years	0.05	
	Adults 20–49 years	0.05	
	Adults 50+ years	0.04	
	Females 13–49 years	0.04	
	Total population	0.06	
Refined chronic (non-cancer) dietary exposure analysis **ADI = 0.01 mg/kg bw/day**	**Population**	**Estimated risk % of acceptable daily intake (ADI)**	
		Soybean seed alone	
	All infants <1 year	0.1	
	Children 1–2 years	0.2	
	Children 3–5 years	0.1	
	Children 6–12 years	0.1	
	Youth 13–19 years	0.1	
	Adults 20–49 years	0.1	
	Adults 50+ years	0.1	
	Females 13–49 years	0.1	
	Total population	0.1	
Refined cancer dietary exposure	**Population**	**Estimated lifetime cancer risk**	
		Food alone	

analysis **q_1^* = 0.0638 (mg/kg bw/day)$^{-1}$**	Total population	4×10^{-7}

Table 12 Fate and behaviour in the environment

Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
Abiotic transformation						
Hydrolysis	[pyridine-2-^{14}C] diflufenican	pH 5, 7 and 9 at 50 and 70 °C	Stable	None	Not a route of dissipation for diflufenican	3201085
	[pyridine-2-^{14}C] DFF-acid	pH 4, 5, 7 and 9 at 25 and 50 °C	Stable	None	Not a route of dissipation for DFF-acid	3201086
Aqueous Photolysis	[pyridine-2-^{14}C] diflufenican	pH 7 buffer, 25 °C, Equivalent time at 50 °N	Stable	Minor, pH 7 DFF-acid; M&B 44085; DFF-amide; Unknowns	Not a route of dissipation for diflufenican	3201091
	[pyridine-2-^{14}C] DFF-acid	pH 7 buffer, 25 °C, Equivalent time at 50 °N	Stable	None	Not a route of dissipation for DFF-acid	3201090
Soil Photolysis	[pyridine-2-^{14}C] diflufenican	Suffolk, UK Sandy loam soil (23 °C, pH 6.67)	Stable	Minor Unknowns; UR	Not a route of dissipation for diflufenican	3201087
	[trifluoromethyl phenyl-UL-^{14}C]diflufenican	Derbyshire, UK Sandy loam soil (20 °C, pH 5.2)	Stable	Minor DFF-acid; DFF-amide; CO_2; Unknowns; UR	Not a route of dissipation for diflufenican	3201088
Biotransformation						
Aerobic Soil	[pyridine-2-^{14}C] diflufenican	Essex, UK Loam soil (20 °C, pH 6.9) %OM: 3.1	All labels combined: DT_{50}: 235 d; DT_{90}: 782 d (SFO)	Major DFF-amide; UR; CO_2 Minor DFF-acid; Unknowns	Diflufenican is persistent	3201092

Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
	[difluorophenyl UL ^{14}C]diflufenican and [trifluoromethyl phenyl UL^{14}C]diflufenican	Essex, UK Loam soil (20 °C, pH 6.9) %OM: 3.1		Major UR; CO_2 Minor DFF-acid; DFF-amide; Unknowns		3201093
	[trifluoromethyl phenyl UL^{14}C]diflufenican	Hertfordshire, UK Clay loam soil (20 °C, pH 8.1) %OM: 5.3	DT_{50}: 40.3 d; DT_{90}: 241.8 d (IORE) $T_{R\ IORE}$ = 72.8 d	Major DFF-acid; UR; CO_2; Minor DFF-amide; Unknowns	Diflufenican is slightly persistent	3201094
		Suffolk, UK Loamy sand soil (20°C, pH 5.9) %OM: 3.4	DT_{50}: 110 d; DT_{90}: 668.6 d (DFOP) Slow $t_{1/2}$ = 258.8 d	Major DFF-acid; DFF-amide; UR; CO_2; Minor Unknowns	Diflufenican is moderately persistent	
		Suffolk, UK Sandy loam soil (20°C, pH 7.4) %OM: 5.5	DT_{50}: 79.9 d; DT_{90}: 488.6 d (IORE) $T_{R\ IORE}$ = 147d	Major UR; CO_2; Minor DFF-amide; DFF-acid; Unknowns	Diflufenican is moderately persistent	
		Suffolk, UK Sandy loam soil (10°C, pH 7.4) %OM: 5.5	DT_{50}: 191.9 d; DT_{90}: 637.5 d (SFO)	Major DFF-acid; DFF-amide; UR; CO_2; Minor Unknowns	Diflufenican is persistent	
	[pyridine-2-^{14}C] diflufenican	Porterville, California Sandy loam soil (20°C, pH 7.8) %OM: 1.2	DT_{50}: 85 d; DT_{90}: 282.3 d (SFO)	Major UR; CO_2;	Diflufenican is moderately persistent	3201098
		Louisville, Nebraska Silt loam soil (20°C, pH 6.7) %OM: 4.4	DT_{50}: 26.38 d; DT_{90}: 104.6 d (IORE) $T_{R\ IORE}$ = 31.5 d	Major UR; CO_2;	Diflufenican is slightly persistent	
	[difluorophenyl UL ^{14}C]diflufenican	Porterville, California Sandy loam soil	DT_{50}: 145.8 d; DT_{90}: 484.3 d (SFO)	Major UR; CO_2;	Diflufenican is moderately persistent	3201099

Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
		(20°C, pH 7.6) %OM: 1.2				
		Louisville, Nebraska Silt loam soil (20°C, pH 6.9) %OM: 5.3	DT_{50}: 15.8 d; DT_{90}: 70.4 d (IORE) $T_{R\ IORE}$ = 21.2 d	Major UR; CO_2	Diflufenican is slightly persistent	
Aerobic Soil	[pyridine-2-^{14}C]DFF-acid	Hattersheim, Germany Silt loam soil (SLS) (20°C, pH 7.03) %OM: 2.84	DT_{50}: 9.1d; DT_{90}: 30.28 d (SFO)	Major UR; CO_2 Minor Unknown Others	DFF-acid is non persistent	3201095
		Frankfurt, Germany Sandy loam soil (SLV) (20°C, pH 6.16) %OM: 1.4	DT_{50}: 17.2d; DT_{90}: 57.2 d (SFO)	Major UR; CO_2 Minor Unknown Others	DFF-acid is slightly persistent	
		Royston, UK Silt loam soil (Flint Hall) (20°C, pH 7.35) %OM: 4.74	DT_{50}: 14.6 d; DT_{90}: 48.5 d (SFO)	Major UR; CO_2 Minor Unknown Others	DFF-acid is non persistent	
Aerobic Soil	[pyridine-2-^{14}C]DFF- amide	Hattersheim, Germany Silt loam soil (SLS) (20°C, pH 7.03) %OM: 2.84	DT_{50}: 9.5 d; DT_{90}: 31.58 d (SFO)	Major DFF-acid; UR; CO_2 Minor Others	DFF-amide is non persistent	3201096
		Frankfurt, Germany Sandy loam soil (SLV) (20°C, pH 6.16) %OM: 1.4	DT_{50}: 60 d; DT_{90}: 290 d (IORE) $T_{R\ IORE}$ = 87.4 d	Major UR; CO_2 Minor DFF-acid; Others	DFF-amide is moderately persistent	
		Royston, UK Silt loam soil (Flint Hall) (20°C, pH 7.35) %OM: 4.74	DT_{50}: 21.8 d; DT_{90}: 111.3 d (IORE) $T_{R\ IORE}$ = 33.5 d	Major UR; CO_2 Minor DFF-acid; Others	DFF-amide is slightly persistent	

Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
Aerobic Soil	[difluorophenyl-UL-^{14}C]2,4-DFA	Monheim, Germany Sandy loam soil (20°C, pH 5.9) %OM: 2.6	DT_{50}: 0.03 d; DT_{90}: 0.26 d (IORE) $T_{R\ IORE}$ = 0.079 d	Major UR; sum of unidentified Minor CO_2	2,4-DFA is non persistent	3201097
		Burscheid, Germany Silt loam soil (20°C, pH 6.4) %OM: 2.9	DT_{50}: 0.047 d; DT_{90}: 0.22 d (IORE) $T_{R\ IORE}$ = 0.065 d	Major UR; CO_2; sum of unidentified	2,4-DFA is non persistent	
		Blankenheim, Germany Clay loam soil (20°C, pH 7.5) %OM: 8.6	DT_{50}: 0.045 d; DT_{90}: 0.29 d (IORE) $T_{R\ IORE}$ = 0.087 d	Major UR; sum of unidentified Minor CO_2	2,4-DFA is non persistent	
		Monheim, Germany Loam soil (20°C, pH 5.8) %OM: 2.8	DT_{50}: 0.038 d; DT_{90}: 0.30 d (IORE) $T_{R\ IORE}$ = 0.089 d	Major UR; sum of unidentified Minor CO_2	2,4-DFA is non persistent	
Anaerobic Soil	[difluorophenyl-UL-^{14}C]diflufenican and [trifluoromethylphenyl-UL-^{14}C]diflufenican	Essex, United Kingdom Loam soil (20°C, pH 6.9)	Not determined	Major UR; 2,4-DFA; DFF-acid (trifluoro label) Minor Unknown	NA: study was acceptable with restriction	3201101
Anaerobic Soil	[pyridine-2-^{14}C]DFF- acid	Essex, United Kingdom Loam soil (20°C, pH 7.2)	Not determined	Major UR	NA: study was acceptable with restriction	3201102
Aerobic aquatic systems	[pyridine-2-^{14}C] diflufenican	Bickenbach Germany Water:sand sediment (20°C, water pH 8.2, sediment pH 7.8)	DT_{50}: 223 d; DT_{90}: 25470 d (IORE) $T_{R\ IORE}$ = 7747 d	Major DFF-acid Minor UR; CO_2	Persistent Partition 74.8% in sediment	3201103
		Unter Widdersheim Germany Water:sandy	DT_{50}: 79 d; DT_{90}: 541 d (DFOP) Slow $t_{1/2}$ =	Major UR; DFF-acid Minor	Moderately persistent Partition	

Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
		silt sediment (20°C, water pH 8.2, sediment pH 7.5)	200 d	CO_2	59.2% in sediment	
	[difluorophenyl-UL-^{14}C]diflufenican	Row Pond United Kingdom Water:clay sediment (20°C, water pH 7.84, sediment pH 6.3)	DT_{50}: 606 d; DT_{90}: 3505 d (DFOP) Slow $t_{1/2}$ = 1248 d	Major UR Minor 2,4-DFA; CO_2	Persistent Partition 56.2% in sediment	3201104
		Swiss Lake United Kingdom Water:sand sediment (20°C, water pH 6.75, sediment pH 5.4)	DT_{50}: 187 d; DT_{90}: 2167 d (IORE) $T_{R\ IORE}$ = 652 d	Major UR Minor 2,4-DFA; CO_2	Persistent Partition 56.2% in sediment	
	[pyridine-2-^{14}C]diflufenican	Hatton Lake North Dakota Water:sand sediment (19.3°C, water pH 8.5, sediment pH 8.1)	DT_{50}: 126 d; DT_{90}: 420 d (SFO)	Major DFF-acid; UR Minor Sum of unidentified; CO_2	Moderately persistent Partition 53.8% in sediment	3201106
		Northwood River North Dakota Water:silt loam sediment (19.3°C, water pH 8.3, sediment pH 7.8)	DT_{50}: 135 d; DT_{90}: 590 d (DFOP) Slow $t_{1/2}$ = 196 d	Major DFF-acid; UR Minor CO_2	Moderately persistent Partition 58.1 % in sediment	
	[Difluorophenyl-UL-^{14}C] diflufenican	Louisburg Pond North Carolina Water:loamy sand sediment (19.4°C, water pH 7.1, sediment pH	DT_{50}: 407 d; DT_{90}: 1353 d (SFO)	Major UR Minor CO_2	Persistent Partition 77.5 % in sediment	3201105

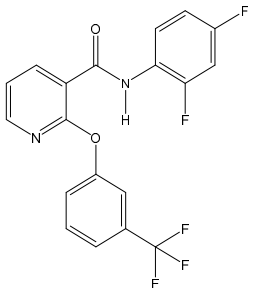
Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
		5.9)				
		Northwood River North Dakota Water:silt loam sediment (19.4°C, water pH 8.3, sediment pH 8.1)	DT_{50}: 145 d; DT_{90}: 605 d (DFOP) Slow $t_{1/2}$ = 198 d	Major UR Minor CO_2	Moderately persistent Partition 59.9% in sediment	
Anaerobic Aquatic	[Difluorophenyl-UL-^{14}C] diflufenican	Goose River North Dakota Water:silt loam sediment (19.8 °C, water pH 8.3, sediment pH 8.1)	DT_{50}: 1065 d; DT_{90}: >1000 d (IORE) $T_{R\ IORE}$: >1000 d	Major UR Minor Sum of unidentified CO_2	Persistent 76.6% partition in sediment	3201107
	[pyridine-2-^{14}C]diflufenican	Golden Lake North Dakota Water:loamy sand sediment (19.8 °C, water pH 8.6, sediment pH 8.1)	DT_{50}: 517 d; DT_{90}: 1716 d (SFO)	Major Minor UR DFF-acid Sum of unidentified	Persistent 57.2 % partition in sediment	3201108
		Goose River North Dakota Water:silt loam sediment (19.8 °C, water pH 8.5, sediment pH 8.1)	DT_{50}: 156 d; DT_{90}: 766 d (DFOP) Slow $t_{1/2}$ = 203 d	Major UR Minor DFF-acid Sum of unidentified	Moderately persistent 57.8 % partition in sediment	
Mobility						
Adsorption/desorption in soil (6 soils)	[difluorophenyl-UL-^{14}C]diflufenican	K_d = 50.4–259.1 mL/g K_{oc} = 4732–8591 mL/g $K_{F(ads)}$ = 39.7–264.8 (mL/g-soil)$^{-1/n}$ $K_{F,\ OC(ads)}$ = 3045–7354 (mL/g-OC)$^{-1/n}$ 1/n = 0.88–0.99 $K_{F(des)}$ = 6.9–11.3 (mL/g-soil)$^{-1/n}$ 1/n = 0.37–0.54			Diflufenican is immobile based on McCall et al., (1981) classification [1]	3201111
4 soils	[pyridine-2-^{14}C]DFF-acid	K_d = 0.13–0.28 mL/g K_{oc} = 4.56–15.38 mL/g $K_{F(ads)}$ = 0.11–0.43 (mL/g-soil)$^{-1/n}$ $K_{F,\ OC(ads)}$ = 7–24 (mL/g-OC)$^{-1/n}$			DFF-acid is very highly mobile based on McCall et	3201109

Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
		1/n = 0.54–0.72 $K_{F(des)}$ = 0.13–0.93 (mL/g-soil)$^{-1/n}$ $K_{F, OC(des)}$ = 8–2748 (mL/g-OC)$^{-1/n}$ 1/n = 0.22–1.01			al., (1981) classification	
4 soils	[pyridine-2-^{14}C]DFF-amide	K_d = 0.54–3.63 mL/g K_{oc} = 67.36–116.49 mL/g $K_{F(ads)}$ = 1.09–4.01 (mL/g-soil)$^{-1/n}$ $K_{F, OC(ads)}$ = 103–138 (mL/g-OC)$^{-1/n}$ 1/n = 0.74–0.85 $K_{F(des)}$ = 2.27–6.88 (mL/g-soil)$^{-1/n}$ 1/n = 0.27–0.42			DFF-amide is highly mobile based on McCall et al., (1981) classification	3201110
4 soils	[difluorophenyl-UL-^{14}C]2,4-DFA	K_d = 2.25–7.64 mL/g K_{oc} = 118.15–184.84 mL/g $K_{F(ads)}$ = 2.10–6.43 (mL/g-soil)$^{-1/n}$ $K_{F, OC(ads)}$ = 110.4–179.6 (mL/g-OC)$^{-1/n}$ 1/n = 0.89–0.97			2,4-DFA has medium to high mobility based on McCall et al., (1981) classification	3201112
Volatilization	Not required. Diflufenican is not expected to be volatile under field conditions based on its low vapour pressure.					
Field dissipation studies						
New York Bare ground soil (510 days)	SC500 (AE F088657 500 g/L42.10 % a.i.	Silt loam (180 g a.i. /ha) pH: 4.5	DT_{50}: 35 d; DT_{90}: 629 d (IORE) $T_{R\ IORE}$: 189 d	Minor TPs AE 0542291 (1.2%, 267 d) AE B107137 (1.6%, 267 d)	Slightly persistent. No residues below 30 cm soil depth for parent, and below 15 cm soil depth for TP	3200390
Iowa Bare ground soil (468 days)	SC500 (AE F088657 500 g/L) 42.10 % a.i.	Silty clay loam (180 g a.i. /ha) pH: 6.2	DT_{50}: 110 d; DT_{90}: 366 d (SFO)	Minor TPs AE 0542291 (1.96%, 27 d) AE B107137 (<LOD of 0.4 ppb)	Persistent. No residues below 30 cm soil depth for parent, and below 15 cm soil depth for TP	3200392
Washington Bare ground soil (269-364 days)	SC500 (AE F088657 500 g/L) 42.10 % a.i.)	Sand (180 g a.i. /ha) pH 7.6	DT_{50}: 15.6 d; DT_{90}: 163.7 d (DFOP) Slow $t_{1/2}$: 77.9 d	Minor TPs AE 0542291 (2.23%, 122 d) AE B107137 (0.96%, 14 d)	Slightly persistent. No residues below 30 cm soil depth for parent,	3200393

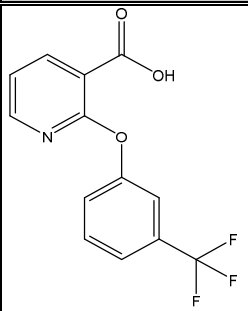
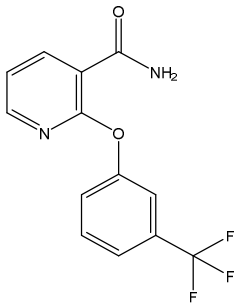
Study	Test substance	System	Value[1]	Transformation products	Comments	PMRA No.
					and below 15 cm soil depth for TP	
Bioaccumulation/Bioconcentration						
Bioconcentration and Metabolism with rainbow trout (*Oncorhynchus mykiss*)	[Pyridine-2-^{14}C]diflufenican	Whole body BCF= 1571 - 1772		No other major radioactive component was found in both water and fish	Depuration half-life for the total radioactive residues 2.4 -3.0 days	3201185

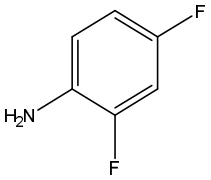
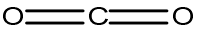
[1]Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel; T_R = representative half-life (IORE); Slow t½= representative half-life (DFOP);
Legends: UR, unextracted residues; AE 0542291, DFF-acid; AE B107137, DFF-amide

Table 13 Transformation products formed in the environment

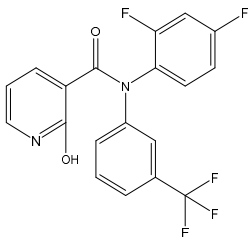
Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
Parent						
Chemical Name: Diflufenican (M&B 38544; AE F088657) **IUPAC:** 2',4'-Difluoro-2-[(α,α,α-trifluoro-m-tolyl)oxy]nicotinanilide **CAS:** N-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]- 3-pyridinecarboxamide **CAS No.:** 83164-33-4 **Formula:** $C_{19}H_{11}F_5N_2O_2$ **MW:** 394.3 g/mol **SMILES:** n1c(Oc2cc(C(F)(F)F)ccc2)c(C(=O)Nc3c(F)cc(F)cc3)ccc1		Hydrolysis (50 and 70°C)	3201085	pH 5.0	102.0% (14 d)	**100.1%** (30 d)
				pH 7.0	101.5% (30 d)	**101.5%** (30 d)
				pH 9.0	105.2% (30 d)	**105.2%** (30 d)
		Aqueous Photolysis	3201091	Buffer pH 7.0	99.7% (1 d)	**92.1%** (17 d)
		Soil Photolysis	3201087	SL, pH 6.67	99.84% (1 d)	**95.50%** (31 d)
			3201088	SL, pH 5.7	103.0 (0 d)	**90.0%** (10 d)
		Aerobic soil	3201092	Loam, pH 6.9	92.2% (7 d)	**37.12%** (365 d)
			3201093	Loam, pH 6.9	97.04% (7 d)	**41.72%** (269 d)
			3201094	CL, pH 8.1	95.83% (0 d)	6.85% (365 d)
				LS, pH 5.9	100.21% (0 d)	**25.05%** (365 d)
				SL, pH 7.4 (20°C)	94.75% (0 d)	**14.80%** (365 d)
				SL, pH 7.4 (10°C)	100.46% (0 d)	**33.42%** (365 d)
			3201098	SL, pH 7.8	100.3% (3	**34.3%** (120

Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
					d)	d)
				SiL, pH 6.7	97.5% (0 d)	**9.9%** (120 d)
			3201099	SiL, pH 6.9	100.6% (0 d)	5.54% (120 d)
				SL, pH 7.6	94.0% (2 d)	**52.45%** (120 d)
		Anaerobic soil[1]	3201101	Loam, pH 6.9	97.67% (0 d)	**36.48%** (272 d)
		Aerobic aquatic	3201103	Brook: Sand, pH 7.8	95.7% (3 d)	**62.3%** (121 d)
				Brook: SSi, pH 7.5	96.3% (3 d)	**38.8%** (121 d)
			3201104	Pond: Clay, pH 7.8	99.3% (0 d)	**56.2%** (365 d)
				Lake: Sand, pH 6.7	100.5% (0 d)	**34.9%** (365 d)
			3201106	Lake: Sand, pH 7.8	95.4% (0 d)	**51.2%** (105 d)
				River: SiL, pH 7.6	94.9% (0 d)	**51.5%** (105 d)
			3201105	Pond: LS, pH 5.3	97.6% (0 d)	**81.3%** (100 d)
				River: SiL, pH 7.9	99.7% (0 d)	**62.0%** (100 d)
		Anaerobic aquatic	3201107	River: SiL, pH 7.9	99.2% (0 d)	**76.9%** (100 d)
			3201108	Lake: LS, pH 7.9	96.3% (3 d)	**80.9%** (100 d)
				River: SiL, pH 7.9	99.6% (1, 3 d)	**57.8%** (100 d)
		Terrestrial Field Dissipation	3200390	New York	78.1 (3 d)	**12.7%** (510 d)
			3200392	Iowa	39.96 (0 d)	4.86% (468 d)
			3200393	Washington	70.93 (0 d)	0.0% (269 d)
Major (>10% AR) transformation products						
Chemical Name: M&B 38181 (AE B107137; AE 0650274; Diflufenican acid) **IUPAC:** 2-[3-(Trifluoromethyl)phenox		Aqueous Photolysis	3201091	Buffer pH 7.0	2.0% (7 d)	ND (17 d)
		Soil Photolysis	3201088	SL, pH 5.7	2.6% (10 d)	2.6% (10 d)
		Aerobic soil	3201092	Loam, pH 6.9	8.79% (286 d)	8.5% (365 d)

Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
y]nicotinic acid **CAS:** 2-(3-Trifluoromethyl)phenoxy -3-pyridinecarboxylic acid **CAS No.:** 36701-89-0 **Formula:** $C_{13}H_8F_3NO_3$ **MW:** 283.2 g/mol **SMILES:** OC(C1=CC=CN=C1OC2 =CC=CC(C(F)(F)F)=C2) =O			3201093	Loam, pH 6.9	**11.32%** (60 d)	5.82% (269 d)
				CL, pH 8.1	**11.38%** (14 d)	ND (365 d)
			3201094	LS, pH 5.9	**14.06%** (120 d)	8.29% (365 d)
				SL, pH 7.4 (20°C)	6.79% (56 d)	1.36% (365 d)
				SL, pH 7.4 (10°C)	**16.78%** (180 d)	1.09% (365 d)
			3201098	SL, pH 7.8	7.75% (58 d)	4.95% (120 d)
				SiL, pH 6.7	8.3% (29 d)	0.4% (120 d)
		Anaerobic soil[1]	3201101	Loam, pH 6.9	**70.94%** (272 d)	**70.94%** (272 d)
		Aerobic aquatic	3201103	Brook: Sand, pH 7.8	**28.8%** (89 d)	**25.6%** (121 d)
				Brook: SSi, pH 7.5	**45.9%** (30 d)	**35.7%** (121 d)
			3201106	Lake: Sand, pH 7.8	**32.2%** (105 d)	**32.2%** (105 d)
				River: SiL, pH 7.6	**15.7%** (105 d)	**15.7%** (105 d)
		Anaerobic aquatic	3201108	Lake: LS, pH 7.9	3.3% (100 d)	3.3% (100 d)
				River: SiL, pH 7.9	9.1% (100 d)	9.1% (100 d)
		Terrestrial Field Dissipation	3200390	New York	1.6% (267 d)	0.6% (510 d)
			3200392	Iowa	0.0%	0.0 (468 d)
			3200393	Washington	0.96% (14 d)	0.0% (269 d)
Chemical Name: M&B 43625 (AE 0542291; Diflufenican amide) **IUPAC:** 2-(3-Trifluoromethyl)phenoxy nicotinamide **CAS:** 2-(3-Trifluoromethyl)phenoxy -3-pyridinecarboxamide **Formula:** $C_{13}H_9F_3N_2O_2$		Aqueous Photolysis	3201091	Buffer pH 7.0	0.3% (4 d)	ND (17 d)
		Soil Photolysis	3201088	SL, pH 5.7	1.9% (5, 10 d)	1.9% (10 d)
		Aerobic soil	3201092	Loam, pH 6.9	**15.69%** (286 d)	**14.53%** (365 d)
			3201093	Loam, pH 6.9	4.45% (119 d)	4.34% (269 d)
			3201094	CL, pH 8.1	0.62% (253 d)	ND (365 d)

Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
MW: 282.2 g/mol **SMILES:** NC(C1=C(OC2=CC=CC(C(F)(F)F)=C2)N=CC=C1)=O				LS, pH 5.9	**26.26%** (320 d)	**15.67%** (365 d)
				SL, pH 7.4 (20°C)	0.83% (253 d)	ND (365 d)
				SL, pH 7.4 (10°C)	**15.55%** (320 d)	0.80% (365 d)
		Terrestrial Field Dissipation	3200390	New York	1.2% (267 d)	0.0% (510 d)
			3200392	Iowa	1.96% (27 d)	0.0% (468 d)
			3200393	Washington	2.23% (122 d)	0.0 (269 d)
Chemical Name: 2,4-Difluoroaniline (M&B 40401) **IUPAC:** 2,4-Difluoroaniline **CAS No.:** 367-25-9 **Formula:** $C_6H_5F_2N$ **MW:** 129.1 g/mol **SMILES:** FC1=CC=C(N)C(F)=C1		Anaerobic soil[1]	3201101	Loam, pH 6.9	**12.28%** (90 d)	4.03% (272 d)
		Aerobic aquatic	3201104	Pond: Clay, pH 7.8	2.5% (59 d)	0.3% (365 d)
				Lake: Sand, pH 6.7	6.8% (30 d)	ND (365 d)
Chemical Name: Carbon dioxide **IUPAC:** Carbon dioxide **CAS No.:** 124-38-9 **Formula:** CO_2 **MW:** 44 g/mol **SMILES:** C(=O)=O		Soil Photolysis	3201088	SL, pH 5.7	4.9% (10 d)	4.9% (10 d)
		Aerobic soil	3201092	Loam, pH 6.9	**26.48%** (365 d)	**26.48%** (365 d)
			3201093	Loam, pH 6.9	**25.87%** (269 d)	**25.87%** (269 d)
			3201094	CL, pH 8.1	**50.49%** (253 d)	**46.31%** (365 d)
				LS, pH 5.9	**14.29%** (365 d)	**14.29%** (365 d)
				SL, pH 7.4 (20°C)	**35.80%** (180 d)	**34.96%** (365 d)
				SL, pH 7.4 (10°C)	**16.88%** (365 d)	**16.88%** (365 d)
			3201098	SL, pH 7.8	**31.1%** (120 d)	**31.1%** (120 d)
				SiL, pH 6.7	**68.0%** (120 d)	**68.0%** (120 d)
			3201099	SiL, pH 6.9	**33.0%** (120 d)	**33.0%** (120 d)
				SL, pH 7.6	**10.1%** (120 d)	**10.1%** (120 d)

Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
		Aerobic aquatic	3201103	Brook: Sand, pH 7.8	0.2% (121 d)	0.2% (121 d)
				Brook: SSi, pH 7.5	0.6% (121 d)	0.6% (121 d)
			3201104	Pond: Clay, pH 7.8	0.8% (365 d)	0.8% (365 d)
				Lake: Sand, pH 6.7	6.8% (365 d)	6.8% (365 d)
			3201106	Lake: Sand, pH 7.8	0.8% (105 d)	0.8% (105 d)
				River: SiL, pH 7.6	1.5% (105 d)	1.5% (105 d)
			3201105	Pond: LS, pH 5.3	1.9% (100 d)	1.9% (100 d)
				River: SiL, pH 7.9	1.6% (100 d)	1.6% (100 d)
		Anaerobic aquatic	3201107	River: SiL, pH 7.9	0.1% (22, 42 d)	0.0% (100 d)
			3201108	Lake: LS, pH 7.9	0.0% (100 d)	0.0% (100 d)
Volatile organics	NA	Anaerobic soil (acceptable with restriction)	3201101	Loam, pH 6.9	**29.42%** (272 d)	**29.42%** (272 d)
Unextracted residues	NA	Aerobic soil	3201092	Loam, pH 6.9	**9.97%** (286 d)	**9.97%** (365 d)
			3201093	Loam, pH 6.9	**21.61%** (269 d)	**21.61%** (269 d)
			3201094	CL, pH 8.1	**32.30%** (320 d)	**31.20%** (365 d)
				LS, pH 5.9	**24.41%** (365 d)	**24.41%** (365 d)
				SL, pH 7.4 (20°C)	**31.50%** (365 d)	**31.50%** (365 d)
				SL, pH 7.4 (10°C)	**30.30%** (365 d)	**30.30%** (365 d)
			3201098	SL, pH 7.8	**13.3%** (90 d)	**13.0%** (120 d)
				SiL, pH 6.7	**19.8%** (58 d)	**19.1%** (120 d)
			3201099	SiL, pH 6.9	**58.3%** (63,	**58.3%** (120

Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
					120 d)	d)
				SL, pH 7.6	**31.3%** (120 d)	**31.3%** (120 d)
		Anaerobic soil (acceptable with restriction)	3201101	Loam, pH 6.9	**19.39%** (272 d)	**19.39%** (272 d)
		Aerobic aquatic	3201103	Brook: Sand, pH 7.8	**9.0%** (61 d)	8.6% (121 d)
				Brook: SSi, pH 7.5	**11.1%** (121 d)	**11.1%** (121 d)
			3201104	Pond: Clay, pH 7.8	**35.2%** (365 d)	**35.2%** (365 d)
				Lake: Sand, pH 6.7	**27.4%** (212 d)	**22.7%** (365 d)
			3201106	Lake: Sand, pH 7.8	**10.3%** (105 d)	**10.3%** (105 d)
				River: SiL, pH 7.6	**22.4%** (105 d)	**22.4%** (105 d)
			3201105	Pond: LS, pH 5.3	**17.9%** (100 d)	**17.9%** (100 d)
				River: SiL, pH 7.9	**35.6%** (100 d)	**35.6%** (100 d)
		Anaerobic aquatic	3201107	River: SiL, pH 7.9	**25.2%** (100 d)	**25.2%** (100 d)
			3201108	Lake: LS, pH 7.9	8.9% (70 d)	8.5% (100 d)
				River: SiL, pH 7.9	**32.7%** (100 d)	**32.7%** (100 d)
Minor (<10% AR) transformation products						
Chemical Name: M&B 44085 **IUPAC:** N-(2,4-difluorophenyl)-2-hydroxy-N-(3-(trifluoromethyl)phenyl)nicotinamide **Formula:** $C_{19}H_{11}F_5N_2O_2$ **MW:** 394.3 g/mol **SMILES:** O=C(N(C1=CC=CC(C(F)(F)F)=C1)C2=CC=C(F)C		Aqueous Photolysis	3201091	Buffer pH 7.0	2.1% (14 d)	0.9% (17 d)

Chemical name/ Synonym and properties	Chemical structure	Study type	PMRA	System	Maximum %AR (day)	Final %AR (day)
=C2F)C3=CC=CN=C3O						

CL, clay loam; SL, sandy loam; SiL, silt loam; LS, loamy sand; SSi, sandy silt; NA, not available; ND, not detected.

Table 14 Toxicity to non-target terrestrial species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Invertebrates					
Earthworm *Eisenia fetida*	14-d Acute, artificial soil (mortality, body weight and behavioural abnormality)	SC500 G 43.8 % w/w	LC_{50} >438 mg a.i./kg dw soil (nominal), the highest concentration tested	NA	3200395
	56-d Chronic, artificial soil (growth and reproduction)	Diflufenican Technical 96.8 % w/w	**NOEC = 1000 mg a.i./kg dw soil**	NA	3201138
	56-d Chronic, artificial soil (survival, growth and reproduction)	SC500 G; 502.6 g/L 42.6 % w/w	**NOEC = 426 mg a.i./kg dw soil** (nominal), the highest concentration tested	NA	3200396
Collembolan *Folsomia candida*	28-d Chronic, artificial soil (reproduction)	Diflufenican Technical 99.6 % w/w	NOEC = 10,000 mg a.i./kg dw soil	NA	3201147
Aphid parasitoid *Aphidius rhopalosiphi*	48-h and 14-d Acute contact, Glass plates (mortality and fecundity)	SC500 (500 g/L) (43.8 % w/w)	**LR_{50} and 14-d ER_{50} > 606.01 g** a.i./ha (nominal)	NA	3200402
Predatory mite *Typhlodromus pyri*			LR_{50}/ER_{50} > 606.01 g a.i./ha (nominal)	NA	3200400

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Predatory mite *Hypoaspis aculeifer*	14-d Chronic, artificial soil (adult mortality and reproduction)	Diflufenican Technical 97.3 % w/w	NOEC= 1000 mg a.i./kg dw soil (nominal)	NA	3201145
		SC500 G; 502.6 g/L (42.6 % w/w)	**NOEC = 438 mg a.i./kg dw soil** (nominal)	NA	3200401
Pollinators					
Honey bee *Apis mellifera* L.	48-h Acute Oral 48-h Acute Contact	Diflufenican Technical 97.3 % w/w	**LD_{50} > 107.4 µg a.i./bee** (measured). **LD_{50} > 100 µg a.i./bee** (nominal).	Relatively non-toxic	3201139
	72-h Acute larva	Diflufenican Technical 98.74 % w/w	**LD_{50} = 63.36 µg a.i./larva**	Relatively non-toxic	3202661
	22-d Chronic larva (adult emergence)	Diflufenican Technical 97.3 % w/w	**NOEDD = 6.75 µg a.i./larva/day**	NA	3201140
	10-d Chronic Oral	Diflufenican Technical 98.74 % w/w	**NOEDD = 113.0 µg a.i./bee/ day**	NA	3202662
	48-h Acute Oral 48-h Acute Contact	SC500 G 43.8 % w/w	**LD_{50} > 98.0 µg a.i./bee** (measured). **LD_{50} > 87.6 µg a.i./bee** (measured).	Relatively non-toxic	3200397
	21-d Chronic brood, treated sugar solution (adult bee mortality, bee brood development, abnormal behaviour)	SC500A G (500 g/L) 42.2% w/w	No effect on bee brood development at a rate of 0.30 g a.i./L	NA	3200398
	10-d Chronic Oral (mortality, sub-lethal effects, abnormal behaviour)	SC500A G (500 g/L) 41.9% w/w; 493.8 g /L (analysed)	**NOEDD = 0.46 µg a.i./bee/day**	NA	3200399
Bumble bee *Bombus terrestris L.*	48-h Acute Contact	Diflufenican Technical 97.3 % w/w	LD_{50} > 100 µg a.i./bumble bee.	Relatively non-toxic	3201143

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	48-h Acute Oral	Diflufenican Technical 97.3 % w/w	LD_{50}>122.0 µg a.i./bumble bee.	Relatively non-toxic	3201144
Birds					
Bobwhite quail *Colinus virginianus*	14-d Acute Oral (mortality and toxicological signs)	SC500 (500 g/L) 41.7 % w/w (492.3 g/L)	**14-d LD_{50} > 834 mg a.i./kg bw** (nominal), highest dose tested	No adverse effects up to the highest dose tested.	3200406
		Diflufenican M&B 38 544 technical (purity not reported)	LD_{50} > 2150 mg a.i./kg bw, the highest dose tested	Practically non-toxic	3201187
Mallard duck *Anas platyrhynchos*	14-d Acute Oral (mortalities, clinical observations, individual bodyweights, group mean food consumption, gross macroscopic *post mortem* examination)	Diflufenican M&B 38 544 technical (purity not reported)	LD_{50} > 4000 mg a.i./kg bw, the highest dose tested	Practically non-toxic	3201188
Canary *Serinus canaria*	5-d Acute Dietary (mortality, body weight, feed consumption, clinical signs and necropsy)	Diflufenican Technical 99.2 % w/w	14-d LDD_{50} > 724.4 mg a.i./kg bw/day (measured), the highest dose tested	No adverse effects up to the highest dose tested.	3201193
Bobwhite quail *Colinus virginianus*		Diflufenican (AE F088657), 99.2 % w/w	14-d LDD_{50} > 1083 mg a.i./kg bw/day (measured), the highest dose tested	Practically non-toxic	3201190
	20-w Reproduction (survival, eggs laid, eggs damaged, egg shell thickness, viable embryos, normal	Diflufenican Technical, 98–98.5 % w/w)	**NOEDD = 9.42 mg a.i./kg bw/day** (measured), (body weight)	NA	3201195

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	hatchlings)		NOEDD = 93.28 mg a.i./kg bw/day (measured), (reproduction)		
Mallard duck *Anas platyrhynchos*	5-d Acute Dietary (mortality, body weight, food consumption and behaviour)	Diflufenican (AE-F088657-01-16), 99.2 % w/w	14-d LDD_{50} > 1205.2 mg a.i./kg bw/day (measured), the highest dose tested	Practically non-toxic	3201191
	21-w Reproduction (number of eggs laid, fertility of the eggs, viability and survival of the embryos, hatchability, offspring survival and egg shell thickness)	Diflufenican Technical, 99.5 % w/w)	NOEDD = 162 mg a.i./kg bw/day (measured), the highest dose tested (reproduction)	NA	3201200
	23-w Reproduction (number of eggs laid, eggshell thickness and egg fertility, embryo viability, hatch rates, offspring survival, offspring weight, and signs of toxicosis among offspring)	Diflufenican Technical, 99.2 % w/w	NOEDD <8.6 mg a.i./kg bw/day (measured), the lowest dose tested (eggs laid per hen)	NA	3201197
Mammals					
Rat, Sprague-Dawley	Acute	Diflufenican (98.0%) technical	**LD_{50}> 5000 mg/kg bw**	Practically non-toxic	3200965
	Reproduction		**NOAEL $_{body\ weight}$ = 41.9 mg/kg bw/day**	NA	3201005
Vascular plants					
Vascular plants: 10 species	21-d Seedling emergence (emergence, plant survival, visual symptoms of phytotoxicity, plant	SC500 (500 g/L) 41.7 % w/w (492.3 g/L)	**ER_{25} = 4.18 g a.i./ha** (onion: shoot dry weight)	NA	3200411

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	growth stage, shoot length and shoot dry weight)				
	21-d Vegetative vigour (plant survival, shoot height, shoot dry weight, visual symptoms of phytotoxicity and plant growth stage)	SC500 (500 g/L) 41.7 % w/w (492.3 g/L)	**ER_{25} = 51.66 g a.i./ha** (tomato: shoot dry weight)	NA	3200410
	21-d Seedling emergence (plant emergence, survival and visual phytotoxicity symptoms)	SC600: Diflufenican (DAN) + Metribuzin (BAX) (200 + 400 g/L)	**ER_{25} = 1.3 g DAN** + 2.6 g BAX/**ha** (sugar beet: shoot dry weight)	NA	3201836
	21-d Vegetative vigour (plant survival, shoot height, shoot dry weight and visual symptoms of phytotoxicity)		**ER_{25} = 6.2 g DAN** + 12.4 g BAX/**ha** (sugar beet: shoot dry weight)	NA	3201833
	21-d Seedling emergence (emergence, plant survival, visual symptoms of phytotoxicity, plant growth stage and shoot dry weight)	SC617: Diflufenican (DAN) + Isoxaflutole (IXF) + Cyprosulfamide (CSA) (257 + 182 + 181 g/L)	ER_{25} = 1.05 g DAN + 0.74 g IXF/ha (sugar beet: survival)	NA	3201648
2 Species	21-d Seedling emergence (emergence, plant survival, visual injuries, plant growth stage, plant height and shoot dry weight)		**ER_{25} = 0.53 g DAN** + 0.47 g IXF/**ha** (butterhead lettuce: survival)	NA	3201649
10 Species	21-d Vegetative vigour (plant survival, shoot height, shoot dry weight, visual symptoms of		**ER_{25} = 0.27 g DAN** + 0.236 g IXF/**ha** (butter head lettuce: shoot dry	NA	3201647

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	phytotoxicity and plant growth stage)		weight)		

[a] Atkins et al.(1981) for bees and USEPA classification for others, where applicable; NA, not applicable

Table 15 Toxicity of Diflufenican and transformation products to non-target aquatic species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Freshwater species					
Invertebrates					
Daphnia magna	48-h Acute	Diflufenican 98.8 % w/w	**EC_{50}> 42.0 µg a.i./L** (geomean measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201149
	48-h Acute	DFF-acid (TFMP-NA (acid)) 99.5% w/w	**EC_{50} > 85.5 mg DFF-acid /L** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201150
	48-h Acute	DFF-amide (M&B 43,625) > 98 % w/w	**EC_{50} > 10 mg DFF-amide /L** (nominal), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201148
	48-h Acute	2,4-difluoroaniline 97.8 % w/w	**EC_{50} = 198.8 µg 2,4-DFA /L** (measured)	Highly toxic	3201151
	48-h Acute	SC500, 41.7 % w/w; 492.3 g/L (analytised)	**EC_{50} > 4.46 mg a.i./L** (geomean measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3200403
	21-d Chronic	Diflufenican	NOEC = 52 µg	NA	320115

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
		968 g/kg (analysed)	a.i./L. (measured TWA)		3
	21-d Chronic	Diflufenican 98.8 % w/w	**NOEC = 22.2 µg a.i./L.** (geometric mean measured)	NA	3201154
Midge *Chironomus dilutus*	42-d Chronic (developmen t)	Diflufenican 99.2 % w/w	**NOEC = 44.1 mg a.i./kg dw sediment** (measured) NOEC in overlying and pore water (not determined)	NA	3201160
Freshwater amphipod *Hyalella azteca*	42-d Chronic (life cyle) survival, growth and reproduction	Diflufenican 99.2 % w/w	**NOEC = 88.5 mg a.i./kg dw sediment** (measured) NOEC in overlying and pore water not determined	NA	3201156
Midge *Chironomus riparius*	28-d Chronic (emergence)	DFF-acid (TFMP-NA) 99.5 ± 0.5 %	**NOEC = 100 mg DFF-acid /kg dw sediment**; highest concentration tested equivalent to **22.7 mg DFF-acid / L pore water** and **21.84 mg DFF-acid / L overlying water**	NA	3201155
Fish					
Rainbow trout *Oncorhynchus mykiss*	96-h Acute	Diflufenican Technical 98.8 % w/w	**LC_{50} > 32.8 µg a.i./L** (geometric	No adverse effects up to the highest	3201170

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
			mean measured), highest concentration tested.	concentration tested.	
	28-d Chronic (sublethal effect)	Diflufenican 967 g/kg (analysed)	**NOEC = 19.2 µg a.i/L** (measured)	NA	3201184
	96-h Acute	M&B 38544 ~ 98% diflufenican	LC_{50} = 73.5 mg a.i./L (nominal)	Slighty toxic	3200405
	96-h Acute	DFF- acid (TFMP-NA acid) 99.5 ±0.5 %)	**LC_{50} >89.1 mg DFF-acid /L** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201171
	96-h Acute	DFF- amide (AE 0542291) 99.0 % w/w	**LC_{50} >8.46 mg DFF-amide /L** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201172
Fathead minnow *Pimephales promelas*	96-h Acute	Diflufenican Technical 98.8 % w/w	**LC_{50} > 39.8 µg a.i./L** (geometric mean measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201174
	35-d Chronic (ELS) - growth	Diflufenican 968 g /kg (analysed)	NOEC = 15 µg a.i./L (measured)	NA	3201180
	34-d Chronic (ELS)-body length	Diflufenican 98.8 % w/w	**NOEC = 3.05 µg a.i./L.** (geometric mean measured)	NA	3201181
	96-h Acute	DFF- acid 99.5 %	**LC_{50} >88.5 mg DFF-acid**	No adverse effects up to	3201175

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
			/L (measured), highest concentration tested.	the highest concentration tested.	
	96-h Acute	2,4-difluoroaniline (AE C522392) 97.8 % w/w	**LC_{50} = 40.0 mg 2,4-DFA /L** (nominal)	Slightly toxic	3201176
African clawed frog *Xenopus laevis*	48-h Acute	Diflufenican 99.2 % w/w	**LC_{50} > 70.5 µg a.i./L** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201232
Algae					
Green alga *Raphidocelis subcapitata*	96-h Acute (AUC, growth rate and yield)	Diflufenican 99.2 % w/w	E_bC_{50}= 0.25 µg a.i./L (TWA)	Very highly toxic	3201204
Freshwater diatom, *Navicula pelliculosa*	96-h Acute (AUC, growth rate and yield)	Diflufenican 99.2 % w/w	E_bC_{50}= 1.2 µg a.i./L (TWA)	Very highly toxic	3201206
Green alga *Desmodesmus subspicatus*	72-h Acute (AUC and growth rate)	Diflufenican 96.7 % w/w	E_bC_{50} = 0.25 µg a.i./L (measured)	Very highly toxic	3201218
Freshwater alga, *Selenastrum capricornutum*	72-h Acute (AUC and growth rate)	Diflufenican 96.7 % w/w	E_bC_{50} = 0.27 µg a.i./L (measured)	Very highly toxic	3201219
Green alga, *Pseudokirchneriella subcapitata*	72-h Acute (AUC and growth rate)	Diflufenican 98.8 % w/w	**E_bC_{50} = 0.22 µg a.i./L (measured)**; algistatic effect up to 1.0 µg a.i. /L.	Very highly toxic	3201214
Freshwater diatom, *Navicula pelliculosa*	72-h Acute (AUC and growth rate)	Diflufenican 96.7 % w/w	E_bC_{50} = 3.5 µg a.i./L (measured)	Very highly toxic	3201211
		Diflufenican 98.8 % w/w	E_bC_{50} = 2.59 µg a.i./L (measured) - algistatic effect up to 10 µg	Very highly toxic	3201216

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
			a.i./L		
Green alga, *Desmodesmus subspicatus*	72-h Acute (AUC and growth rate)	Diflufenican 96.8 % w/w	E_bC_{50} = 0.46 µg a.i./L (measured) - algistatic effect up to 3.9 µg a.i./L	Very highly toxic	3201220
	72-h Acute (AUC and growth rate) - sediment-water system	Diflufenican 96.8 % w/w	E_bC_{50} = 2.44 µg a.i./L (nominal) - overlying water	Very highly toxic	3201221
Freshwater blue-green alga (Cyanobacteria), *Anabaena flos-aquae*	96-h Acute (AUC, growth rate and yield)	Diflufenican 99.2 % w/w	E_bC_{50} > 41 µg a.i./L (TWA), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201208
	72-h Acute (AUC and growth rate)	Diflufenican 96.8 % w/w	E_bC_{50} = 51 µg a.i./L (measured)	Very highly toxic	3201212
Blue-green alga (Cyanobacteria), *Microcystis aeruginosa*	72-h Acute (AUC and growth rate)	Diflufenican 96.8 % w/w	E_bC_{50} = 51 µg a.i./L (measured)	Very highly toxic	3201213
Blue- green alga (Cyanobacteria) *Anabaena sp.*	72-h Acute (AUC and growth rate)	Diflufenican 98.8 % w/w	E_rC_{50} > 43.7 µg a.i./L (geomean measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201215
Green alga, *Pseudokirchneriella supspicatus*	72-h (AUC and growth rate)	DFF-acid 99.5 ± 0.5 % w/w	**E_rC_{50} > 90.3 mg/L** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201217
Green alga, *Desmodesmus subspicatus*	72-h Acute (AUC and growth rate)	DFF-amide 99.4 % w/w	**EbC_{50} = 36 mg/L** (nominal)	Slightly toxic	3201202
Green alga, *Pseudokirchneriella supspicatus*	72-h Acute (cell densities,	2,4-difluoroaniline (2,4-DFA, AE	**EC_{50} = 2.9 mg/L** (measured)	Moderately toxic	3201203

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	AUC and growth rate)	C522392) 98.3 % w/w			
Green alga *Desmodesmus subspicatus*	72-h Acute (AUC and growth rate)	SC500 (500 g/L) 43.8 % w/w	**E_bC50 = 1.8 µg a.i./L** (nominal)	Very highly toxic	3200408
	72-h Acute (AUC and growth rate)	SC500 (500 g/L) 43.8 % w/w	E_bC50 = 2.89 µg a.i./L (measured)	Very highly toxic	3200409
Vascular plant					
Duckweed *Lemna gibba*	14-d growth inhibition (frond number, frond biomass)	Diflufenican Technical 96.8 % w/w	**EC_{50} = 39 µg a.i./L** (measured)	Very highly toxic	3201224
	7-d growth inhibition (frond number, biomass and AUC)	Diflufenican Technical 98.8 % w/w	EC_{50} > 45.4 µg a.i./L (geomean measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201225
	7-d growth inhibition (frond number, frond area)	DFF-acid (AE B107137) 97.6 % w/w	**EC_{50} > 100 mg/L** (nominal), highest concentration tested.	Practically non toxic	3201227
	7-d growth inhibition (frond number)	DFF-amide (AE 0542291) 99.0 % w/w	**E_yC_{50} = 63.5 mg/L** (nominal)	Slightly toxic	3201226
	7-d growth inhibition (frond number, frond area and yield)	2,4-difluoroaniline (AE C522392; 2,4-DFA) 97.8 % w/w	**EC_{50} >100 mg/L** (nominal), highest concentration tested.	Practically non toxic	3201228
Myriophyllum spicatum	14-d growth inhibition - water-sediment system with	Diflufenican Technical (AE F088657) 97.3 % w/w	EC_{50} > 101 µg a.i./L, (geo mean measured), highest	No adverse effects up to the highest concentration tested.	3201229

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	spiked water (growth and yield based on shoot length, fresh weight and dry weight)		concentration tested.		
Marine species					
Eastern Oyster *Crassostrea virginica*	96-h Acute (shell deposition)	Diflufenican 99.2 % w/w	**IC_{50} > 42 µg a.i./L** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201163
Saltwater mysid *Americamysis bahia*	96-h Acute	Diflufenican 99.2 % w/w	LC_{50} > 43 µg a.i./L. (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201165
	28-d Chronic (reproduction, number of young produced per reproductive day)	Diflufenican 99.2 % w/w	**NOEC = 5.9 µg a.i./L** (measured)	NA	3201167
Marine amphipod *Leptocheirus plumulosus*	28-d Chronic (growth, survival and reproduction)	Diflufenican 99.2 % w/w	**NOEC = 75.1 mg a.i./kg dw** sediment (measured), highest concentration tested.	NA	3201166
Sheepshead minnow *Cyprinodon variegatus*	96-h Acute	Diflufenican 99.2 % w/w	**LC_{50} > 35.2 µg a.i./L.** (measured), highest concentration tested.	No adverse effects up to the highest concentration tested.	3201178
	34-d Chronic (ELS) - time to hatch and	Diflufenican 99.2 % w/w	**NOEC = 4.6 µg a.i./L.** (measured)	NA	3201182

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
	survival				
Marine diatom, *Skeletonema costatum*	96-h Acute (AUC, growth rate and yield)	Diflufenican 99.2 % w/w	**E_bC_{50} = 3.7 µg a.i./L** (TWA)	Very highly toxic	3201222

[a] USEPA classification, where applicable; AUC, area under the growth curve. Bolded values were carried forward to the risk assessment.

Table 16 Endpoints and uncertainty factors used to establish effects metrics for the risk assessment

Organism	Exposure	Test substance	Endpoint value	UF applied[1]	Effect metric	LOC[2]
Terrestrial organisms						
Invertebrates						
Earthworm, *Eisenia fetida*	56-d Chronic	Diflufenican Technical 96.8 % w/w	NOEC = 1000 mg a.i./kg dw soil	1	1000 mg a.i./kg dw soil	1.0
	56-d Chronic	SC500 G; 502.6 g/L 42.6 % w/w	NOEC = 426 mg a.i./kg dw soil	1	426 mg a.i./kg dw soil	1.0
Honeybee, *Apis mellifera*	48-h Oral	Diflufenican Technical 97.3 % w/w	LD_{50} > 107.4 µg a.i./bee	1	>0.1074 mg a.i./bee	0.4
		SC500 G 43.8 % w/w	LD_{50} > 98.0 µg a.i./bee	1	>0.098 mg a.i./bee	0.4
	48-h-Contact	Diflufenican Technical 97.3 % w/w	LD_{50} > 100 µg a.i./bee	1	>0.100 mg a.i./bee	0.4
		SC500 G 43.8 % w/w	LD_{50} > 87.6 µg a.i./bee	1	>0.0876 mg a.i./bee	0.4
	Adult 10-d Chronic Oral	SC500A G (500 g/L) 41.9% w/w; 493.8 g /L	NOED = 4.6 µg a.i./bee	1	0.0046 mg a.i./bee	1.0
	Adult 10-d Chronic Oral	Diflufenican Technical 98.74 % w/w	NOED = 113 µg a.i./bee	1	0.003 mg a.i./bee	1.0

Organism	Exposure	Test substance	Endpoint value	UF applied[1]	Effect metric	LOC[2]
	72-h Oral – larva single exposure	Diflufenican Technical 98.74 % w/w	LD_{50} = 63.36 µg a.i./larva	1	0.06336 mg a.i./larva	0.4
	22-d Chronic larva	Diflufenican Technical 97.3 % w/w	NOEDD = 6.75 µg a.i./larva/day	1	0.00675 mg a.i./larva/day	1.0
Aphid parasitoid, *Aphidius rhopalosiphi*	48-d Contact	SC500 (500 g/L) (43.8 % w/w)	LR_{50} > 606.01 g a.i./ha	1	>606,010 mg a.i./ha	2.0
Predatory mite *Hypoaspis aculeifer*	14-d Chronic	SC500 G; 502.6 g/L (42.6 % w/w)	$NOEC_{reproduction}$ = 438 mg a.i./kg dw soil	1	438 mg a.i./kg dw	1.0
Birds						
Bobwhite quail, *Colinus virginianus*	14-d Acute-Oral	SC500 (500 g/L) 41.7 % w/w (492.3 g/L)	LD_{50} > 834 mg a.i./kg bw	10	>83.4 mg a.i./kg bw	1.0
	20-w Reproduction	Diflufenican Technical, purity: 98–98.5 % w/w)	NOEDD = 9.42 mg a.i./kg bw/day	1	9.42 mg a.i./kg bw/day	1.0
Mammals						
	Acute-Oral	Diflufenican (98.0%) Technical	LD_{50} > 5000 mg a.i./kg bw/day	10	>500 mg a.i./kg bw/day	1.0
	Reproduction		NOAEL= 41.9 mg a.i./kg bw/day	1	41.9 mg a.i./kg bw/day	1.0
Vascular plants						
Vascular plants, 10 species	21-d Seedling emergence	SC500 (500 g/L) 41.7 % w/w (492.3 g/L)	ER_{25} = 4.18 g a.i./ha	1	4180 mg a.i./ha	1.0
	21-d Vegetative vigour		ER_{25} = 51.66 g a.i./ha	1	51 660 mg a.i./ha	1.0
	21-d Seedling emergence	SC600: Diflufenican (DAN) + Metribuzin (BAX) (200 + 400 g/L)	ER_{25} = 1.3 g DAN/ha	1	1300 mg a.i./ha	1.0
	21-d Vegetative vigour		ER_{25} = 6.2 g DAN/ha	1	6200 mg a.i./ha	1.0
2 species	21-d Seedling emergence	SC617: Diflufenican (DAN) +	ER_{25} = 0.53 g DAN/ha	1	530 mg a.i./ha	1.0

Organism	Exposure	Test substance	Endpoint value	UF applied[1]	Effect metric	LOC[2]
10 species	21-d Vegetative vigour	Isoxaflutole (IFT) + Cyprosulfamide (CSA) (257 + 182 + 181 g/L)	ER_{25} = 0.27 g DAN/ha	1	270 mg a.i./ha	1.0
Freshwater organisms						
Invertebrates						
Daphnia magna	48-h Acute	Diflufenican 98.8 % w/w	EC_{50}> 42.0 µg a.i./L	2	>0.021 mg a.i./L	1.0
		DFF-acid (TFMP-NA (acid)) 99.5% w/w	EC_{50}> 85.5 mg DFF-acid /L	2	>42.75 mg /L	1.0
		DFF-amide (M&B 43,625) > 98 % w/w	EC_{50}> 10 mg DFF-amide /L	2	>5 mg/L	1.0
		2,4-difluoroaniline 97.8 % w/w	EC_{50} = 198.8 µg 2,4-DFA /L	2	0.0994 mg/L	1.0
		SC500, 41.7 % w/w; 492.3 g/L (analytised)	EC_{50}> 4.46 mg a.i./L	2	>2.23 mg a.i./L	1.0
	21-d Chronic	Diflufenican 98.8 % w/w	NOEC = 22.2 µg a.i./L.	1	0.0222 mg/L	1.0
Midge *Chironomus dilutus*	42-d Chronic – spiked sediment: sediment*	Diflufenican 99.2 % w/w	NOEC = 44.1 mg a.i./kg dw	1	44.1 mg a.i./kg dw	1.0
Amphipod *Hyalella azteca*	42-d Chronic (life cycle)– spiked sediment: sediment*	Diflufenican 99.2 % w/w	NOEC = 88.5 mg a.i./kg dw	1	88.5 mg a.i./kg dw	1.0
Midge *Chironomus riparius*	28-d Chronic – spiked sediment: sediment	DFF -acid (TFMP-NA) 99.5 ±0.5 %	$NOEC_{emergence}$ = 100 mg DFF-acid /kg dw	1	100 mg /kg dw	1.0
	28-d Chronic – spiked sediment: pore water	DFF -acid (TFMP-NA) 99.5 ±0.5 %	$NOEC_{emergence}$ = 22.7 mg DFF-acid / L	1	22.7 mg / L	1.0

Organism	Exposure	Test substance	Endpoint value	UF applied[1]	Effect metric	LOC[2]
	28-d Chronic – spiked sediment: overlying water	DFF -acid (TFMP-NA) 99.5 ±0.5 %	$NOEC_{emergence}$ = 21.84 mg DFF-acid / L	1	21.84 mg / L	1.0
Fish						
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Diflufenican Technical 98.8 % w/w	LC_{50} > 32.8 µg a.i./L	10	>0.00328 mg a.i./L	1.0
		DFF- acid (TFMP-NA acid) 99.5 %	LC_{50} >89.1 mg /L	10	>8.91 mg /L	1.0
		DFF- amide (AE 0542291) 99.0 % w/w	LC_{50} >8.46 mg /L	10	>0.846 mg /L	1.0
	28-d Chronic	Diflufenican 967 g/kg	NOEC = 19.2 µg a.i/L	1	0.0192 mg a.i./L	1.0
Fathead minnow, *Pimephales promelas*	96-h Acute	Diflufenican Technical 98.8 % w/w	LC_{50} > 39.8 µg a.i./L	10	>0.00398 mg a.i./L	1.0
	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{body\ length}$ = 3.05 µg a.i./L.	1	0.00305 mg a.i./L	1.0
	96-h Acute	DFF- acid 99.5 %	LC_{50} >88.5 mg /L	10	>8.85 mg /L	1.0
	96- h Acute	2,4-difluoroaniline (AE C522392) 97.8 % w/w	LC_{50} = 40.0 mg /L	10	4.0 mg /L	1.0
Amphibians						
African clawed frog *Xenopus laevis*	48-h Acute	Diflufenican 99.2 % w/w	LC_{50} > 70.5 µg a.i./L	10	>0.00705 mg a.i./L	1.0
Fathead minnow, *Pimephales promelas*[3]	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{body\ length}$ = 3.05 µg a.i./L.	1	0.00305 mg a.i./L	1.0

Organism	Exposure	Test substance	Endpoint value	UF applied[1]	Effect metric	LOC[2]
Plants						
Green alga, *Pseudokirchnerella subcapitata*	72-h Acute	Diflufenican 98.8 % w/w	EbC50 = 0.22 µg a.i./L	2	0.00011 mg a.i./L	1.0
		DFF-acid 99.5 ± 0.5 % w/w	E_rC_{50} > 90.3 mg/L	2	45.15 mg/L	1.0
		2,4-difluoroaniline (2,4-DFA, AE C522392) 98.3 % w/w	EC_{50} = 2.9 mg/L	2	1.45 mg/L	1.0
Green alga, *Desmodesmus subspicatus*	72-h Acute	DFF- amide 99.4 % w/w	E_bC_{50} = 36 mg/L	2	18 mg/L	1.0
		SC500 (500 g/L) 43.8 % w/w	E_bC_{50}= 1.8 µg a.i./L	2	0.0009 mg a.i./L	1.0
Duckweed, *Lemna gibba*	14-d Dissolved	Diflufenican Technical 96.8 % w/w	EC_{50} = 39 µg a.i./L	2	0.0195 mg a.i./L	1.0
	7-d Dissolved	DFF-acid (AE B107137) 97.6 % w/w	EC_{50} >100 mg /L	2	>50 mg /L	1.0
		DFF-amide (AE 0542291) 99.0 % w/w	E_yC_{50} = 63.5 mg /L	2	31.75 mg /L	1.0
		2,4-difluoroaniline (AE C522392; 2,4-DFA) 97.8 % w/w	EC_{50} >100 mg /L	2	>50 mg /L	1.0
Marine organisms						
Invertebrates						
Eastern oyster, *Crassostrea virginica*	96- h Acute	Diflufenican 99.2 % w/w	IC_{50} >42 µg a.i./L	2	>0.021 mg a.i./L	1.0
Saltwater mysid, *Americamysis bahia*	28-d Chronic	Diflufenican 99.2 % w/w	NOEC = 5.9 µg a.i./L	1	0.0059 mg a.i./ L	1.0
Amphipods, *Leptocheirus plumulosus*	28-d Chronic – spiked sediment: sediment*	Diflufenican 99.2 % w/w	NOEC = 75.1 mg a.i./kg dw	1	75.1 mg a.i./kg dw	1.0

Organism	Exposure	Test substance	Endpoint value	UF applied[1]	Effect metric	LOC[2]
Fish						
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	Diflufenican 99.2 % w/w	LC_{50} > 35.2 µg a.i./L.	10	>0.00352 mg a.i./L.	1.0
	34-d Chronic	Diflufenican 99.2 % w/w	NOEC = 4.6 µg a.i./L	1	0.0046 mg a.i./L	1.0
Plants						
Marine diatom, *Skeletonema costatum*	96- h Acute	Diflufenican 99.2 % w/w	E_bC_{50}= 3.7 µg a.i./L	2	0.00185 mg a.i./L	1.0

[1] UF = uncertainty factor; as per the Guidance Manual; [2]LOC = Level of Concern; [3]used as a surrogate for amphibians; * NOEC in overlying and pore water (not determined).

Table 17 Screening level risk assessment on non-target species

Organism	Exposure	Test substance	Effect metric	EEC[1]	RQ[2]	Level of Concern exeeded
Invertebrates						
Earthworm *Eisenia fetida*	56-d chronic	Diflufenican Technical	NOEC = 1000 mg a.i./kg dw soil	0.08 mg a.i./kg dw soil	0.0	No
		SC500	NOEC = 426 mg a.i./kg dw soil		0.0	No
Bee adult *Apis mellifera*	48-h contact	Diflufenican Technical	LD_{50} >100 µg a.i./bee	0.432 µg a.i./bee	<0.0	No
		SC500	LD_{50}>87.6 µg a.i./bee		<0.0	No
	48-h oral	Diflufenican Technical	LD_{50} >107.4 µg a.i./bee	5.15 µg a.i./bee	<0.0	No
		SC500	LD_{50} >98 µg a.i./bee		<0.0	No
	10-d chronic	SC500	NOED = 4.6 µg a.i./bee	5.15 µg a.i./bee	**1.1**	Yes
		Diflufenican Technical	NOED = 113 µg a.i./bee	5.15 µg a.i./bee	0.0	No
Bee larva *Apis mellifera*	72-h acute	Diflufenican Technical	LD_{50} = 63.36 µg a.i./larva	2.187 µg a.i./bee	0.0	No
	22-d chronic (adult emergence)	Diflufenican Technical	NOEDD = 6.75 µg a.i./larva/day	2.187 µg a.i./bee	0.3	No
Aphid parasitoid, *Aphidius rhopalosiphi*	48-d acute contact, glass plate	SC500	LR_{50} > 606.01 g a.i./ha	180 g a.i./ha	<0.3	No

Organism	Exposure	Test substance	Effect metric	EEC[1]	RQ[2]	Level of Concern exeeded
Predatory mite *Hypoaspis aculeifer*	14-d Chronic	SC500	NOEC = 438 mg a.i./kg dw soil	0.08 mg a.i./kg dw soil	0.2	No
Vascular plants						
Vascular plants: 10 species	21-d seedling emergence	SC500	ER_{25} = 4.8 g a.i./ha	180 g a.i./ha	**43.1**	Yes
10 species		SC600	ER_{25} = 1.3 g a.i./ha	180 g a.i./ha	**138.5**	Yes
2 species		SC617	ER_{25} = 0.53 g a.i./ha	150 g a.i./ha	**283.0**	
10 species	21-d vegetative vigour	SC500	ER_{25}= 51.66 g a.i./ha	180 g a.i./ha	**3.5**	Yes
		SC600	ER_{25} = 6.2 g a.i./ha	180 g a.i./ha	**29.0**	Yes
		SC617	ER_{25} = 0.27 g a.i./ha	150 g a.i./ha	**555.5**	

[1]EEC = Estimated Environmental concentration. The soil EEC of 0.08 mg a.i./kg dw soil was calculated based on the maximum proposed foliar rate of maximum single application of 180 g a.i./ha was used for soil dwelling organisms effects metrics. This concentration was calculated assuming that the product is evenly distributed in the top 0 to 15 cm depth of soil with a bulk density of 1.5 g/cm^3.

The terrestrial plants EECs were equal to a single ground application at 180 g a.i./ha, except for Diflufenican SC617 (150 g a.i./ha).
The pollinator EECs were calculated using the single maximum application rate of 180 g a.i./ha as follows:
Estimated contact exposure = 2.4 µg a.i./bee × 0.18 g a.i./ha;
Estimated dietary exposure = 98 µg a.i./g × 0.292 g/day × 0.18 g a.i./ha; and
Estimated brood exposure = 98 µg a.i./g × 0.124 g/day × 0.18 g a.i./ha.
[2]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the effect metric (RQ = EEC/effect metric). The RQ is then compared to the level of concern (LOC = 2.0 for beneficial arthropods, 0.4 for acute exposures to bees, and 1.0 for everything else). If the screening level RQ is below the LOC, the risk is considered acceptable and no further risk characterization is necessary. For groups where the LOC is exceeded (RQ > 1), further characterization of the risk is conducted.

Table 18 Risk to birds and mammals

Organisms	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw) [1]	RQ	LOC	LOC Exceeded
Small Bird (0.02 kg)						
Acute	83.40	Insectivore	14.65	0.2	1	No
Reproduction	<8.6	Insectivore	14.65	**>1.7**	1	Yes
Medium-Sized Bird (0.1 kg)						
Acute	83.40	Insectivore	11.43	0.1	1	No
Reproduction	<8.6	Insectivore	11.43	**>1.3**	1	Yes
Large-Sized Bird (1 kg)						
Acute	83.40	Herbivore (short grass)	7.39	0.1	1	No

Organisms	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw) [1]	RQ	LOC	LOC Exceeded
Reproduction	<8.6	Herbivore (short grass)	7.39	**>0.9**	1	-*
Small Mammal (0.015 kg)						
Acute	>500.00	Insectivore	8.43	<0.0	1	No
Reproduction	41.9	Insectivore	8.43	0.2	1	No
Medium-Sized Mammal (0.035 kg)						
Acute	>500.00	Insectivore	16.34	<0.0	1	No
Reproduction	41.9	Herbivore (short grass)	16.34	0.4	1	No
Large-Sized Mammal (1 kg)						
Acute	>500.00	Herbivore (short grass)	8.73	<0.0	1	No
Reproduction	41.9	Herbivore (short grass)	8.73	0.2	1	No

([1]) EDE = Estimated daily exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398(bw in g) 0.850.
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(bw in g) 0.651.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(bw in g) 0.822.
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.
*Not determined

Table 19 Refined avian risk assessment using maximum and mean diflufenican residue values on the highest crop application rate (considering 6% drift)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Reproduction	<8.60	Insectivore	14.65	**>1.7**	1.61	>0.2	10.12	**>1.2**	1.11	>0.1
		Granivore (grain and seeds)	2.27	>0.3	0.25	>0.0	1.08	>0.1	0.12	>0.0
		Frugivore (fruit)	4.53	>0.5	0.50	>0.1	2.16	>0.2	0.24	>0.0

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
Medium-Sized Bird (0.1 kg)										
Reproduction	<8.60	Insectivore	11.43	**>1.3**	1.26	>0.1	7.89	**>0.9**	0.87	>0.1
		Granivore (grain and seeds)	1.77	>0.2	0.19	>0.0	0.84	>0.1	0.09	>0.0
		Frugivore (fruit)	3.54	>0.4	0.39	>0.0	1.69	>0.2	0.19	>0.0
Large-Sized Bird (1 kg)										
Reproduction	<8.60	Insectivore	3.34	>0.4	0.37	>0.0	2.30	>0.3	0.25	>0.0
		Granivore (grain and seeds)	0.52	>0.1	0.06	>0.0	0.25	>0.0	0.03	>0.0
		Frugivore (fruit)	1.03	>0.1	0.11	>0.0	0.49	>0.1	0.05	>0.0
		Herbivore (short grass)	7.39	**>0.9**	0.81	>0.1	2.62	>0.3	0.29	>0.0
		Herbivore (long grass)	4.51	>0.5	0.50	>0.1	1.47	>0.2	0.16	>0.0
		Herbivore (Broadleaf plants)	6.83	**>0.8**	0.75	>0.1	2.26	>0.3	0.25	>0.0

Table 20 Refined risk to terrestrial plants from spray drift

Organism	Exposure	Test substance	Effect metric	EEC[1]	RQ[2]	Level of Concern exeeded
Vascular plants						
Vascular plants: 10 species	21-d seedling emergence	SC500	ER_{25} = 4.8 g a.i./ha	10.8 g a.i./ha	2.6	Yes
10 species		SC600	ER_{25} = 1.3 g a.i./ha	10.8 g a.i./ha	8.3	Yes
2 species		SC617	ER_{25} = 0.53 g a.i./ha	9 g a.i./ha	17	
10 species	21-d vegetative vigour	SC500	ER_{25}= 51.66 g a.i./ha	10.8 g a.i./ha	0.2	No
		SC600	ER_{25} = 6.2 g a.i./ha	10.8 g a.i./ha	1.7	Yes
		SC617	ER_{25} = 0.27 g a.i./ha	9 g a.i./ha	33.3	

[1]EEC (Estimated Environmental Concentration) was calculated based on 6% spray drift factor for ground application.

[2]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the effect metric (RQ = EEC/effect metric).

Table 21 Screening level risk to aquatic organisms

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[3]	LOC exceeded
Freshwater Organisms						
Invertebrates						
Daphnia magna	48-h Acute	Diflufenican 98.8 % w/w	½ EC_{50} >0.021 mg a.i./L	0.0225	<1.1	Yes
		DFF-acid (TFMP-NA (acid)) 99.5% w/w	½ EC_{50} > 42.75 mg DFF-acid /L	0.0162	<0.0	No
		DFF-amide (M&B 43,625) > 98 % w/w	½ EC_{50} > 5 mg DFF-amide /L	0.0161	<0.0	No
		2,4-difluoroaniline 97.8 % w/w	½ EC_{50} = 0.0994 mg 2,4-DFA /L	0.0074	0.0	No
		SC500, 41.7 % w/w; 492.3 g/L (analytised)	½ EC_{50} > 2.23mg a.i./L	0.0225	<0.0	No
	21-d Chronic	Diflufenican 98.8 % w/w	NOEC =: 0.0222 mg a.i./L	0.0225	1.0	Yes
Midge *Chironomus dilutus*	42-d Chronic – spiked sediment: sediment	Diflufenican 99.2 % w/w	NOEC = 44.1 mg a.i./kg dw	0.08	0.0	No
	28-d Chronic – spiked sediment: sediment	DFF -acid (TFMP-NA) 99.5 ±0.5 %	$NOEC_{emergence}$ = 100 mg DFF-acid /kg dw	0.057	0.0	No
	28-d Chronic – spiked sediment: pore water	DFF -acid (TFMP-NA) 99.5 ±0.5 %	$NOEC_{emergence}$ = 22.7 mg DFF-acid / L	0.0162	0.0	No
	28-d Chronic – spiked sediment: overlying water	DFF -acid (TFMP-NA) 99.5 ±0.5 %	$NOEC_{emergence}$ = 21.84 mg DFF-acid / L	0.0162	0.0	No
Amphipod, *Hyalella Azteca*	42-d Chronic (life cycle)– spiked	Diflufenican 99.2 % w/w	NOEC = 88.5 mg a.i./kg dw	0.08	0.0	No

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[3]	LOC exceeded
	sediment: sediment[2]					
Fish						
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Diflufenican Technical 98.8 % w/w	1/10 LC_{50} >0.00328 mg a.i./L	0.0225	<6.9	Yes
		DFF- acid (TFMP-NA acid) 99.5 %	1/10 LC_{50} >8.91 mg /L	0.0162	<0.0	No
		DFF- amide (AE 0542291) 99.0 % w/w	1/10 LC_{50} > 0.846 mg /L	0.0161	<0.0	No
Fathead minnow, *Pimephales promelas*	96-h Acute	Diflufenican Technical 98.8 % w/w	1/10 LC_{50} > 0.00398 mg a.i./L	0.0225	<5.6	Yes
	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{body\ length}$ = 0.00305 mg a.i./L	0.0225	7.4	Yes
	96-h Acute	DFF- acid, 99.5 %	1/10 LC_{50} >8.85 mg /L	0.0162	<0.0	No
	96-h Acute	2,4-difluoroaniline (AE C522392) 97.8 % w/w	1/10 LC_{50} = 4.0 mg /L	0.0074	0.0	No
Amphibians						
African clawed frog, *Xenopus laevis*	48-h Acute	Diflufenican 99.2 % w/w	1/10 LC_{50} = 0.00705 mg a.i./L	0.12	17.0	Yes
Fathead minnow, *Pimephales promelas*[4]	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{growth}$ = 0.00305 mg a.i./L	0.12	39.3	Yes
Plants						
Green alga, *Pseudokirchneriella subcapitata*	72-h Acute	Diflufenican 98.8 % w/w	½ E_bC_{50}> 0.00011 mg a.i./L	0.0225	<204.5	Yes
		DFF-acid 99.5 ± 0.5 % w/w	½ E_rC_{50} > 45.15 mg/L	0.0162	<0.0	No
		2,4-difluoroaniline (2,4-DFA, AE C522392) 98.3 % w/w	½ EC_{50} = 1.45 mg/L	0.0074	0.0	No

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[3]	LOC exceeded
Green alga, *Desmodesmus subspicatus*	72-h Acute	DFF- amide 99.4 % w/w	½ E_bC_{50}= 18 mg/L	0.0161	0.0	No
		SC500 (500 g/L) 43.8 % w/w	½ E_bC_{50}= 0.0009 mg/L	0.0225	25.0	Yes
Duckweed, *Lemna gibba*	14-d Dissolved	Diflufenican Technical 96.8 % w/w	½ EC_{50} = 0.0195 mg a.i./L	0.0225	1.1	Yes
	7-d Dissolved	DFF-acid (AE B107137) 97.6 % w/w	½ EC_{50} > 50 mg /L	0.0225	<0.0	No
		DFF-amide (AE 0542291) 99.0 % w/w	½ E_yC_{50} = 31.75 mg /L	0.0161	0.0	No
		2,4-difluoroaniline (AE C522392; 2,4-DFA) 97.8 % w/w	½ EC_{50} > 50 mg /L	0.0074	<0.0	No
Marine Organisms						
Invertebrates						
Eastern oyster, *Crassostrea virginica*	96-h Acute	Diflufenican 99.2 % w/w	½ IC_{50} > 0.021 mg a.i./L	0.0225	<1.1	Yes
Saltwater mysid, *Americamysis bahia*	28-d Chronic	Diflufenican 99.2 % w/w	NOEC = 0.0059 mg a.i./ L	0.022	3.8	Yes
Amphipods, *Leptocheirus plumulosus*	28-d Chronic – spiked sediment: sediment	Diflufenican 99.2 % w/w	NOEC = 75.1 mg a.i./kg dw	0.08	0.0	No
Fish						
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	Diflufenican 99.2 % w/w	1/10 LC_{50} = 0.00352 mg a.i./L	0.0225	6.4	Yes
	34-d Chronic	Diflufenican 99.2 % w/w	NOEC = 0.0046 mg a.i./L	0.0225	4.9	Yes
Plants						
Marine diatom, *Skeletonema costatum*	96-h Acute	Diflufenican 99.2 % w/w	½ E_bC_{50}= 0.00185 mg a.i./L	0.0225	12.2	Yes

[1]EEC = Estimated Environmental Concentration. An EEC of 0.0225 mg a.i./L for a waterbody at a depth of 80 cm was used to evaluate risks to all organisms except amphibians, where an EEC of 0.12 mg a.i./L for a waterbody at a depth of 15 cm was used.

[2]The sediment and pore water concentrations were conservatively assumed to be equal to the soil and 80 cm water EECs of 0.08

mg a.i./kg dry weight soil and 0.0225 mg a.i./L, respectively. EECs for transformation products were calculated conservatively assuming 100% of the applied diflufenican was instantly transformed into the transformation product on a molecular weight/weight basis.
[3]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the effect metric (RQ = EEC/effect metric). The RQ is then compared to the level of concern (LOC = 1.0 for all aquatic organisms). If the screening level RQ is below the LOC, the risk is considered acceptable and no further risk characterization is necessary. For groups where the LOC is exceeded (RQ > 1), further characterization of the risk is conducted.
[4]used as a surrogate for amphibians.

Table 22 Refined risk to aquatic organisms from spray drift

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[2]	LOC exceeded
Freshwater Organisms						
Invertebrates						
Daphnia magna	48-h Acute	Diflufenican 98.8 % w/w	½ EC_{50} >0.021 mg a.i./L	0.00135	<0.1	No
	21-d Chronic	Diflufenican 98.8 % w/w	NOEC =: 0.0222 mg a.i./L	0.00135	0.1	No
Fish						
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Diflufenican Technical 98.8 % w/w	1/10 LC_{50} >0.00328 mg a.i./L	0.00135	<0.4	No
Fathead minnow, *Pimephales promelas*	96- h Acute	Diflufenican Technical 98.8 % w/w	1/10 LC_{50} > 0.00398 mg a.i./L	0.00135	<0.3	No
	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{body\ length}$ = 0.00305 mg a.i./L	0.00135	0.4	No
Amphibians						
African clawed frog *Xenopus laevis*	48-h Acute	Diflufenican 99.2 % w/w	1/10 LC_{50} = 0.00705 mg a.i./L	0.0072	1.0	Yes
Fathead minnow, *Pimephales promelas*[3]	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{growth}$ = 0.00305 mg a.i./L	0.0072	2.4	Yes
Plants						
Green alga, *Pseudokirchneriella subcapitata*	72-h Acute	Diflufenican 98.8 % w/w	½ E_bC_{50}> 0.00011 mg a.i./L	0.00135	<12.3	Yes
Green alga, *Desmodesmus subspicatus*	72-h Acute	SC500 (500 g/L) 43.8 % w/w	½ E_bC_{50}= 0.0009 mg/L	0.00135	1.5	Yes

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[2]	LOC exceeded
Duckweed, *Lemna gibba*	14-d Dissolved	Diflufenican Technical 96.8 % w/w	½ EC_{50} = 0.0195 mg a.i./L	0.00135	0.1	No
Marine Organisms						
Invertebrates						
Eastern oyster, *Crassostrea virginica*	96-h Acute	Diflufenican 99.2 % w/w	½ IC_{50} > 0.021 mg a.i./L	0.00135	<0.1	No
Saltwater mysid, *Americamysis bahia*	28-d Chronic	Diflufenican 99.2 % w/w	NOEC = 0.0059 mg a.i./ L	0.00135	0.2	No
Fish						
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	Diflufenican 99.2 % w/w	1/10 LC_{50} = 0.00352 mg a.i./L	0.00135	0.4	No
Plants						
Marine diatom, *Skeletonema costatum*	96-h Acute	Diflufenican 99.2 % w/w	½ EbC50 = 0.00185 mg a.i./L	0.00135	0.7	No

[1]EEC (Estimated Environmental Concentration) was calculated based on 6% spray drift factor for ground application.
[2]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the effect metric (RQ = EEC/effect metric).

Table 23 Refined risk to aquatic organisms from run-off

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[2]	LOC exceeded
Freshwater Organisms						
Invertebrates						
Daphnia magna	48-h Acute	Diflufenican 98.8 % w/w	½ EC_{50} >0.021 mg a.i./L	0.0019	<0.1	No
	21-d Chronic	Diflufenican 98.8 % w/w	NOEC =: 0.0222 mg a.i./L	0.00136	0.1	No
Fish						
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Diflufenican Technical 98.8 % w/w	1/10 LC_{50} >0.00328 mg a.i./L	0.0017	<0.5	No
Fathead minnow, *Pimephales promelas*	96- h Acute	Diflufenican Technical 98.8 % w/w	1/10 LC_{50} > 0.00398 mg a.i./L	0.0017	<0.4	No

Organism	Exposure	Test substance	Effect metric	EEC[1] (mg a.i./L)	RQ[2]	LOC exceeded
	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{body\ length}$ = 0.00305 mg a.i./L	0.00136	0.4	No
Amphibians						
African clawed frog *Xenopus laevis*	48-h Acute	Diflufenican 99.2 % w/w	1/10 LC_{50} = 0.00705 mg a.i./L	0.00325	0.5	No
Fathead minnow, *Pimephales promelas*[3]	34-d Chronic	Diflufenican 98.8 % w/w	$NOEC_{growth}$ = 0.00305 mg a.i./L	0.00143	0.5	No
Plants						
Green alga, *Pseudokirchneriella subcapitata*	72-h Acute	Diflufenican 98.8 % w/w	½ E_bC_{50}> 0.00011 mg a.i./L	0.0019	<17.3	Yes
Green alga, *Desmodesmus subspicatus*	72-h Acute	SC500 (500 g/L) 43.8 % w/w	½ E_bC_{50}= 0.0009 mg/L	0.0019	2.1	Yes
Duckweed, *Lemna gibba*	14-d Dissolved	Diflufenican Technical 96.8 % w/w	½ EC_{50} = 0.0185 mg a.i./L	0.0017	0.9	No
Marine Organisms						
Invertebrates						
Eastern oyster, *Crassostrea virginica*	96-h Acute	Diflufenican 99.2 % w/w	½ IC_{50} > 0.021 mg a.i./L	0.0017	<0.1	No
Saltwater mysid, *Americamysis bahia*	28-d Chronic	Diflufenican 99.2 % w/w	NOEC = 0.0059 mg a.i./ L	0.00136	0.2	No
Fish						
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	Diflufenican 99.2 % w/w	1/10 LC_{50} = 0.00352 mg a.i./L	0.0017	0.5	No
Plants						
Marine diatom, *Skeletonema costatum*	96-h Acute	Diflufenican 99.2 % w/w	½ E_bC_{50}= 0.00185 mg a.i./L	0.0017	0.9	No

*****EECs representing the 90th percentile of 96-hour concentration (acute assessment) and 21-day concentration (chronic assessment) as predicted by PRZM-EXAMS.
[2]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the effect metric (RQ = EEC/effect metric).

Table 24 Toxic substances management policy considerations-Comparison to TSMP Track 1 criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes $t_{1/2}$: 21.2 – 256 days	No. DFF-acid: 9.1 – 17.2 days DFF-amide: 9.5 – 87.4 days 2,4-DFA: 0.065 – 0.089 days
	Water	Half-life ≥ 182 days	Not applicable, diflufenican is insoluble	Not available
	Whole system (water + sediment)	Half-life ≥ 365 days	Yes $t_{1/2}$: 126 – >1000 days	Not available
	Air	Half-life ≥ 2 days or evidence of long-range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (4.25×10^{-6} Pa, at 25ºC) and Henry's Law Constant (3.3×10^{-7} atm m^3/mol, at 20ºC).	• Volatilization and long-range atmospheric transport are unlikely to occur for DFF-acid and DFF-amide based on the vapour pressure (3.5×10^{-4} and 8.9×10^{-7} Pa, at 20ºC respectively) and Henry's Law Constant (6.99×10^{-9} and 2.81×10^{-11} atm m^3/mol, at 20ºC, respectively). • Volatilization and long-range atmospheric transport are likely to occur for 2,4-DFA based on the vapour pressure (125 Pa, at 25ºC) and Henry's Law Constant (9.05×10^{-6} atm m^3/mol, at 25ºC).

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active Ingredient Endpoints	Transformation Products Endpoints
Bioaccumulation[4]	Log $K_{OW} \geq 5$	4.2	2.5 (DFF-acid); 1.7 (DFF-amide); 1.7 (2,4-DFA)
	BCF ≥ 5000	1571 - 1772	Not available
	BAF ≥ 5000	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}).

Table 25A List of supported uses for SC500 Herbicide

Items	Label claims that are supported
Region	National
Rates and efficacy claims	➢ 120 mL/ha: early-season control of redroot pigweed and green pigweed ➢ 180 mL/ha: early-season control of tall waterhemp and palmer amaranth and season-long control of redroot pigweed and green pigweed ➢ 240 mL/ha: season-long control of tall waterhemp ➢ 360 mL/ha: season-long control of palmer amaranth Only controls non-emerged weeds and emerged green and redroot pigweeds up to 5 cm in height.
Host crops	Field corn, seed corn, and soybean.
Application timing	Pre-plant surface or pre-emergence to the crops in all tillage systems
Tank mixtures	Pre-emergence in field corn: ➢ Aatrex Liquid 480 ➢ XtendiMax with VaporGrip Technology ➢ XtendiMax 2 with VaporGrip Technology
	Pre-plant surface and pre-emergence in field corn and seed corn: ➢ Converge Flexx ➢ Roundup WeatherMax with Transorb 2 Technology
	Pre-plant surface and pre-emergence in field corn: ➢ Roundup Transorb HC ➢ R/T 540 Liquid ➢ Co-op Vector 540 Liquid

Items	Label claims that are supported	
	➢ Roundup Xtend with VaporGrip Technology ➢ Roundup Xtend 2 with VaporGrip Technology	
	Pre-plant surface and pre-emergence in soybean: ➢ Sencor 75 DF or Sencor 480 F ➢ Roundup WeatherMax with Transorb 2 Technology ➢ Roundup Transorb HC	
	Pre-plant surface and pre-emergence in Roundup Ready 2 Xtend soybean: ➢ Roundup Xtend with VaporGrip Technology ➢ Roundup Xtend 2 with VaporGrip Technology ➢ XtendiMax with VaporGrip Technology ➢ XtendiMax 2 with VaporGrip Technology	
Application method	Ground application only in a minimum of 100 L/ha of total spray volume. Sprayable fluid nitrogen fertilizer may replace all or part of the water as a carrier.	
Rotational crops	Up to 360 mL/ha	Immediate plant back: soybean 30 days: field corn 4 months: winter wheat Following year: wheat (spring and durum), triticale, barley, oat, rye, timothy, red fescue, bromegrass, field pea, processing pea, lentil, lupin, clover, potato, and tomato (transplanted)
	Up to 300 mL/ha	Immediate plant back: field corn
	Up to 240 mL/ha	The following year: canola and sugar beet

Table 25B List of supported uses for SC600 Herbicide

Items	Label claims that are supported
Region	National
Rates and efficacy claims	Early-season control: ➢ 375 mL/ha: ball mustard, carpetweed†, cocklebur, common chickweed, common ragweed, dandelion (seedling), green pigweed, green smartweed, jimsonweed†, lady's-thumb, lamb's-quarter, prickly mallow†, prostrate pigweed, redroot pigweed, Russian thistle, shepherd's purse, stinkweed, tartary buckwheat, velvetleaf, volunteer non-triazine tolerant canola, wild buckwheat, wild mustard, wild potato vine, and yellow woodsorrel†. ➢ 450 mL/ha: the above weeds plus tall waterhemp and palmer amaranth. ➢ 600 mL/ha: the above weeds plus corn spurry, common groundsel, and hempnettle. ➢ 750 mL/ha: the above weeds plus henbit and scentless chamomile. ➢ 900 mL/ha: the above weeds plus barnyard grass, crabgrass (smooth and large), foxtail (giant, green, and yellow), fall panicum, and witchgrass.
	Season-long control: ➢ 450 mL/ha: green pigweed, lamb's-quarters, and redroot pigweed. ➢ 600 mL/ha: the above listed weeds plus tall waterhemp†. ➢ 900 mL/ha: the above listed weeds plus palmer amaranth†. † Non-emerged weeds only. Use higher rates within the labelled rate range for more consistent control and

Items	Label claims that are supported	
	when there are higher weed pressures. Only controls non-emerged weeds at the application and emerged weeds up to 4 cm in height.	
Timing and crop	Pre-plant surface and pre-emergence to soybean in all tillage systems	
Tank mixtures	Pre-plant surface and pre-emergence to soybean: ➢ Roundup WeatherMax with Transorb 2 Technology ➢ Roundup Transorb HC	
	Pre-plant surface and pre-emergence to Roundup Ready 2 Xtend soybean: ➢ Roundup Xtend with VaporGrip Technology ➢ Roundup Xtend 2 with VaporGrip Technology ➢ XtendiMax with VaporGrip Technology ➢ XtendiMax 2 with VaporGrip Technology	
Application method	Ground application in 100 – 300 L/ha of total spray volume.	
Rotational crops	Up to 900 mL/ha	Immediate plant back: soybean 30 days: field corn 4 months: winter wheat Following year: wheat (spring), triticale, barley, oat, timothy, field pea, processing pea, lentil, lupin, potato, and tomato (transplanted)
	Up to 750 mL/ha	Immediately plant back: field corn
	Up to 600 mL/ha	The following year: canola

Table 25C List of supported uses for SC617 Herbicide

Items	Label claims that are supported
Region	Eastern Canada and British Columbia
Rates and efficacy claims	➢ 292 mL/ha: early-season control of barnyard grass, large crabgrass, smooth crabgrass, green foxtail, (suppression), witchgrass, lamb's-quarters, common ragweed, dandelion (seedling), eastern black nightshade, plantain (seedling), annual sowthistle, spiny annual sowthistle, velvetleaf, wild mustard, wormseed mustard, redroot pigweed, green pigweed, tall waterhemp, and palmer amaranth. ➢ 438 mL/ha: season-long control of the above weeds except for barnyard grass and green foxtail. ➢ 585 mL/ha: season-long control of the above weeds plus barnyard grass and green foxtail. Use higher rates within the labelled rate range for more consistent control and longer residual control. Only controls non-emerged weeds at the application and emerged weeds up to 5 cm in height.
Host crops	Field corn and seed corn
Timing	Pre-plant surface or pre-emergence to the crop in all tillage systems
Tank mixtures	A minimum 292 mL/ha SC617 Herbicide + 1.1 L/ha Aatrex Liquid 480: early-season control of weeds listed for SC617 Herbicide plus fall panicum, lady's thumb, proso millet, wild buckwheat, and yellow foxtail.
	A minimum 438 mL/ha SC617 Herbicide + 1.67 L/ha Aatrex Liquid 480: season-long control of weeds listed for SC617 Herbicide plus lady's thumb, wild

Items	Label claims that are supported	
	buckwheat, and yellow foxtail.	
	585 mL/ha SC617 Herbicide + 2.21 L/ha Aatrex Liquid 480: season-long control of weeds listed for SC617 Herbicide plus fall panicum, lady's thumb, proso millet, wild buckwheat, yellow foxtail, giant ragweed, and Canada fleabane.	
	Pre-plant surface and pre-emergence to field and seed corn: ➢ Roundup WeatherMax with Transorb 2 Technology	
	Pre-plant surface and pre-emergence to field corn: ➢ Roundup Transorb HC ➢ R/T 540 Liquid ➢ Co-op Vector 540 Liquid ➢ Roundup Xtend with VaporGrip Technology ➢ Roundup Xtend 2 with VaporGrip Technology	
	Pre-emergence to field corn: ➢ Aatrex Liquid 480 ➢ XtendiMax with VaporGrip Technology ➢ XtendiMax 2 with VaporGrip Technology	
Application method	Ground application only in a minimum of 150 L/ha of total spray volume. Sprayable fluid nitrogen fertilizer may replace all or part of the water as a carrier	
Rotational crops	Up to 585 mL/ha	Immediate plant back: field corn 4 months: winter wheat Following year: wheat (spring), barley, oat, timothy, field pea, processing pea, potato, soybean, and tomato (transplanted)
	Up to 467 mL/ha	The following year: canola

Appendix II Supplemental maximum residue limit information—International situation and trade implications

Diflufenican is an active ingredient that is concurrently being registered in Canada and the United States for use on field corn and soybeans. The MRLs proposed for diflufenican in Canada are the same as corresponding tolerances to be promulgated in the United States, except for livestock commodities, for which an exemption from a tolerance exists.

Once established, the American tolerances for diflufenican will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[12] listed for diflufenican in or on any commodity on the Codex Alimentarius Pesticide Index website.

[12] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of studies/Information submitted by registrant

1.0 Chemistry

PMRA Document Number	Reference
3200936	2021, Tier II summary: Diflufenican TC - Product chemistry evaluation (based on OECD dossier numbering) - Identity, physical and chemical properties, analytical methods - Confidential information, DACO: 2.1, 2.10, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9,8.2.1 CBI
3200937	2020, Diflufenican - Description of the manufacturing process of the technical grade active substance, DACO: 2.11.1, 2.11.2, 2.11.3 CBI
3200938	2020, Diflufenican - Description of the manufacturing process of the technical grade active substance, DACO: 2.11.1, 2.11.2, 2.11.3 CBI
3200939	2020, Diflufenican (AE F088657) - Technical grade active substance - Discussion on the formation of impurities, DACO: 2.11.4 CBI
3200940	2020, Diflufenican Technical grade active substance - Justification of certified limits for USA and Canada, DACO: 2.12.1 CBI
3200941	2000, Technical diflufenican: HPLC determination of active ingredient, DACO: 2.13.1 CBI
3200942	2012, Validation of the HPLC analytical method AM035412FP1 - Determination of by-products in technical grade and pure diflufenican (AE F088657) by high performance liquid chromatography (HPLC), DACO: 2.13.1 CBI
3200943	2012, Determination of by-products in technical grade and pure diflufenican (AE F088657) by high performance liquid chromatography (HPLC), DACO: 2.13.1 CBI
3200944	2016, Validation of the GC analytical method AM046116FP1 - Determination of [CBI REMOVED] in technical grade and pure AE F088657 (Diflufenican) by gas chromatography (GC), DACO: 2.13.1 CBI
3200945	2016, Determination of [CBI REMOVED] in technical grade and pure AE F088657 (diflufenican) by gas chromatography (GC), DACO: 2.13.1 CBI
3200946	2015, Material accountability of technical diflufenican (AE F088657), DACO: 2.13.2, 2.13.3 CBI

PMRA Document Number	Reference
3200947	2016, Five batch analysis of technical diflufenican (AE F088657) - Analysis of [CBI REMOVED], DACO: 2.13.2, 2.13.4 CBI
3200948	2015, Diflufenican (AE F088657), technical substance: Physical characteristics colour, physical state and odour, DACO: 2.14.1, 2.14.2, 2.14.3 CBI
3200949	2002, Statement to the dissociation constant - Diflufenican (AE F088657), DACO: 2.14.10 CBI
3200950	2002, Partition coefficient 1-octanol / water (HPLC-method) - Diflufenican - AE F088657 00 1B99 0001, DACO: 2.14.11 CBI
3200951	1998, Diflufenican: NMR, IR, MS and UV-visible spectra, DACO: 2.13.2, 2.14.12 CBI
3200952	2014, Stability to elevated temperature, metals, and metal ions and corrosion characteristics to plastic containers of diflufenican (AE F088657) according to OCSPP 830.6313 and 830.6320, DACO: 2.14.13, 2.14.14 CBI
3200953	2020, Diflufenican (AE F088657), pure substance: Determination of the pH-value in distilled water, DACO: 2.14.15,830.7000 CBI
3200954	1998, Diflufenican: Physical characteristics, DACO: 2.14.4, 2.14.5, 2.14.6 CBI
3200955	2015, Diflufenican (AE F088657), pure substance: Solubility in distilled water (column elution method), DACO: 2.14.7 CBI
3200956	1998, Diflufenican - Water and solvent solubility, DACO: 2.14.7, 2.14.8 CBI
3200957	1992, Determination of the vapour pressure of diflufenican in accordance with USEPA 63-9 and OECD 104/EEC A.4 guidelines, DACO: 2.14.9 CBI
3201068	2019, Amendment no. 01: Independent laboratory validation of analytical method DC-002-S18-01 for the determination of residues of diflufenican and its metabolites AE 0542291 and AE B107137 in soil, DACO: 8.2.2.1,8.2.2.2
3201069	2018, An analytical method for the determination of residues of diflufenican and its metabolites AE 0542291 and AE B107137 in soil and sediment using LC/MS/MS, DACO: 8.2.2.1,8.2.2.2
3201070	2019, In house laboratory validation of analytical method for the determination of AE F088657 and its metabolites: AE 0542291 and AE B107137 in soil and sediment by LC/MS/MS, DACO: 8.2.2.1,8.2.2.2
3201071	2019, An analytical method for the determination of residues of AE F088657 and its metabolites AE 0542291 and AE B107137 in water using LC/MS/MS, DACO: 8.2.2.3

PMRA Document Number	Reference
3201072	2019, In house laboratory validation of an analytical method for the determination of residues of AE F088657 and its metabolites AE 0542291 and AE B107137 in water using LC/MS/MS, DACO: 8.2.2.3
3201073	2019, Independent laboratory validation of analytical method DC-004-W19-01 for the determination of residues of AE F088657 and its metabolites AE 0542291 and AE B107137 in water, DACO: 8.2.2.3
3200116	2021, Product chemistry data to support the registration of diflufenican SC500 herbicide (Product identity and composition), DACO: 3.2.1, 3.2.3, 3.3.1 CBI
3200117	2020, Manufacturing procedure - Plant protection product for USA - Diflufenican SC500 (500 g/L) - Brodal, DACO: 3.2.2 CBI
3200118	2005, Determination of diflufenican in formulations HPLC-UV, external standard, DACO: 3.4.1 CBI
3200119	2020, Validation of analytical method AM005305FF2 - Determination of diflufenican in the formulation diflufenican SC500 (500 g/L), DACO: 3.4.1 CBI
3200120	2005, Physical, chemical and technical properties of diflufenican suspension concentrate 500 g/litre - Identification Code: AE F088657 00 SC42 A203, DACO: 3.5.1, 3.5.2, 3.5.3, 3.5.4, 3.5.6, 3.5.7, 3.5.9 CBI
3200121	2005, 2. Amendment - Storage stability at elevated temperature and cold stability of diflufenican SC500 (500 g/L) - Packaging material: HDPE, DACO: 3.5.10, 3.5.14, 3.5.5 CBI
3200122	2005, Safety relevant technical properties of diflufenican suspension concentrate 500 g/litre - Identification code: AE F088657 00 SC42 A203, DACO: 3.5.11, 3.5.12, 3.5.8 CBI
3200123	2020, Waiver summary report for diflufenican SC500, DACO: 3.5.13, 3.5.15, 3.5.8 CBI
3200124	2020, Waiver summary report for diflufenican SC500, DACO: 3.5.13, 3.5.15, 3.5.8 CBI
3201632	2021, Product chemistry data to support the registration of diflufenican SC617 herbicide (Product identity and composition), DACO: 3.2.1, 3.2.3, 3.3.1 CBI
3201633	2020, Manufacturing procedure - Plant protection product for USA - Diflufenican + isoxaflutole [CBI REMOVED] SC617 (257+180+180g/L) - Convintro Xtron, DACO: 3.2.2 CBI
3201634	2019, Determination of diflufenican, isoxaflutole [CBI REMOVED] in formulations - HPLC-UV, external standard, DACO: 3.4.1 CBI

PMRA Document Number	Reference
3201635	2020, Validation of analytical method AM034319MF1 - Determination of diflufenican, isoxaflutole [CBI REMOVED] in the formulation diflufenican + isoxaflutole [CBI REMOVED] SC617 (257+180+180 g/L), DACO: 3.4.1 CBI
3201636	2019, Characterization of the formulation diflufenican + isoxaflutole [CBI REMOVED] SC617 (257+180+180 g/L), DACO: 3.5.1, 3.5.2, 3.5.6, 3.5.7 CBI
3201637	2020, Storage stability at elevated temperature and corrosion characteristics of diflufenican + isoxaflutole [CBI REMOVED] SC617 (257+180+180 g/L) - Packaging material: HDPE - Final report (14 days), DACO: 3.5.10, 3.5.14, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.9 CBI
3201638	2020, Safety-relevant data of diflufenican + isoxaflutole [CBI REMOVED] SC617 (257+180+180 g/L), DACO: 3.5.11, 3.5.12, 3.5.8 CBI
3201639	2020, Waiver summary report for diflufenican + isoxaflutole [CBI REMOVED] SC617, DACO: 3.5.13, 3.5.15, 3.5.8 CBI
3201820	2021, Product chemistry data to support the registration of diflufenican SC600 herbicide (Product identity and composition), DACO: 3.2.1, 3.2.3, 3.3.1 CBI
3201821	2020, Manufacturing procedure - Plant protection product for USA - Diflufenican + metribuzin SC600 (200+400 g/L), DACO: 3.2.2 CBI
3201822	2019, Validation of analytical method AM031117MF1 - Determination of diflufenican and metribuzin in the formulation diflufenican + metribuzin SC600 (200+400 g/L), DACO: 3.4.1 CBI
3201823	2017, Determination of diflufenican and metribuzin in formulations - HPLC-UV, external standard, DACO: 3.4.1 CBI
3201824	2018, Storage stability (14 days) at elevated temperature and corrosion characteristics of diflufenican + metribuzin SC600 (200+400 g/L) - Packaging material: HDPE, DACO: 3.5.1, 3.5.10, 3.5.14, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.9 CBI
3201825	2018, Safety-relevant data of diflufenican+metribuzin SC600 (200+400 g/L), DACO: 3.5.11, 3.5.12, 3.5.8 CBI
3201826	2020, Waiver summary report for diflufenican + metribuzin SC600, DACO: 3.5.13, 3.5.15, 3.5.8 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
3200125	2005, AE F088657 00 SC42 A2 - Acute toxicity in the rat after oral administration, DACO: 4.6.1
3200126	2005, AE F088657 00 SC42 A2 - Acute toxicity in the rat after dermal application, DACO: 4.6.2
3200127	2018, AE F088657 SC500: Acute inhalation toxicity in rats, DACO: 4.6.3
3200128	2005, AE F088657 00 SC42 A2 - Acute eye irritation on rabbits, DACO: 4.6.4
3200129	2005, AE F088657 00 SC42 A2 - Acute skin irritation/corrosion on rabbits, DACO: 4.6.5
3200130	2005, AE F088657 00 SC42 A203 - (Diflufenican 500 g/l, new brodal-NPE-free) - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse, DACO: 4.6.6
3200964	2020, BCS-BT38895: Acute oral toxicity - Up-and-down procedure in rats, DACO: 4.2.1
3200965	1992, Diflufenican: Acute oral toxicity (Limit test) in the rat, DACO: 4.2.1
3200967	1985, Herbicides: Diflufenican (M&B 38,544): Metabolite M&B 38,181: Acute toxicity studies in the rat, DACO: 4.2.1,4.2.2
3200968	1988, Diflufenican - Acute toxicity and primary irritation studies, DACO: 4.2.1,4.2.2,4.2.4,4.2.5
3200969	1985, Herbicides: M&B 38,544: Acute toxicity and local tolerance studies in various species, DACO: 4.2.1,4.2.2,4.2.4,4.2.5,4.2.6
3200971	1992, Diflufenican: Acute dermal toxicity (limit test) in the rat, DACO: 4.2.2
3200973	2018, Amendment no. 1: AE F088657: Acute inhalation toxicity in rats, DACO: 4.2.3
3200974	1997, Diflufenican: Magnusson-Kligman maximisation test in guinea pigs, DACO: 4.2.6
3200975	2002, Diflufenican Technical: Repeated dose 90 day oral toxicity study in Wistar rats, DACO: 4.3.1
3200976	1993, Diflufenican: Toxicity study by dietary administration to B6C3F1 mice for 13 weeks, DACO: 4.3.1

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3200977	1984, M&B 38,544: 13 week toxicity study in rats by the dietary route, DACO: 4.3.1
3200978	1985, M&B 38,544: Repeat 13 week dietary toxicity study in rats., DACO: 4.3.1
3200979	1987, M&B 38544: Toxicity study by dietary administration to F-344 rats for 13 weeks followed by 4 and 8 week reversibility periods, DACO: 4.3.1
3200980	1987, M&B38544: Toxicity study by dietary administration to F-344 rats followed by 4 and 8 weeks reversibility periods First supplement to LSR Report 87/MBL/026/708 - Electron microscopy report of selected hepatic tissues from the 13 week sacrifice, DACO: 4.3.1
3200982	1984, Herbicide - M&B 38544: 13-week oral toxicity in dogs, DACO: 4.3.2
3200983	1987, M+B 38544: 52-week toxicity study in oral administration to beagle dogs, DACO: 4.3.2,4.4.5
3200986	2021, BCS-BT38895: Toxicity study by dietary administration to Han Wistar rats for 4 weeks, DACO: 4.3.3
3200989	2001, Diflufenican Technical: 28 day dietary range finding study in Wistar rats, DACO: 4.3.3
3200991	2020, Diflufenican - Waiver request of the data requirements for a repeat dose dermal toxicity study, DACO: 4.3.5
3200993	2021, Diflufenican: Combined chronic toxicity and carcinogenicity (OCSPP 870.4300) studies cover OCSPP data requirement 870.4200: Carcinogenicity, DACO: 4.4.1,4.4.2,4.4.3,4.4.4
3200995	1987, M&B 38,544: Combined oncogenicity and toxicity study in rats, DACO: 4.4.4
3201002	1987, MB38544: Combined oncogenicity and toxicity study in mice, DACO: 4.4.4
3201003	1987, Addendum to M&B198/851080 - Effect of M&B38544 on reproductive function of multiple generations in the rat - Histopathology of the reproductive tract in F0 and F1A adult rats, DACO: 4.5.1
3201004	1985, Effect of M+B 38544 on reproductive function of multiple generations in the rat, DACO: 4.5.1
3201005	2019, Evaluation of the potential reproductive toxicity of diflufenican in males and females, DACO: 4.5.1

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3201006	2017, Weight of evidence to support utilization of reproductive toxicity and developmental toxicity studies run in accordance with 1982 guidelines, DACO: 4.5.1,4.5.2
3201007	2020, Waiver request of the data requirements for acute, subchronic and developmental neurotoxicity studies - Diflufenican, DACO: 4.5.10,4.5.11,4.5.12,4.5.13,4.5.14
3201008	2020, Waiver request of the data requirements for an immunotoxicity study - Diflufenican, DACO: 4.5.15,870.78
3201009	1984, Effect of M&B38544 on pregnancy of the rat, DACO: 4.5.2
3201010	1984, MB 38544 - Effect of pregnancy of the rabbit, DACO: 4.5.3
3201011	2002, Teratogenicity study in Wistar rats with diflufenican technical, DACO: 4.5.2
3201012	1984, Ames metabolic activation test to assess the potential mutagenic effect of M&B 38,544, DACO: 4.5.4
3201013	2020, BCS-BT38895: Bacterial reverse mutation test, DACO: 4.5.4
3201014	2006, Diflufenican (tested as AE F088657 techn. getrocknet) (Project: Diflufenican) - *Salmonella*/microsome test - Plate incorporation and preincubation method using *Salmonella* Typhimurium TA 102, DACO: 4.5.4
3201015	2006, Diflufenican (tested as diflufenican TGAS) - *Salmonella*/microsome test - Plate incorporation and preincubation method, DACO: 4.5.4
3201016	1985, M&B 40,401 (42 083 R.P.) In vitro mutagenic activity on five Ames tester strains of *Salmonella* Typhimurium, using the mammalian-microsomes / plate incorporation assay, DACO: 4.5.4
3201017	2003, MB38181: Reverse mutation assay "Ames test" using *Salmonella* Typhimurium, DACO: 4.5.4
3201019	1984, An assessment of the mutagenic potential of M& B 38,544 using an in vitro mammalian cell test system, DACO: 4.5.5
3201020	2020, BCS-BT38895: In vitro HPRT mutation test using Chinese hamster ovary cells, DACO: 4.5.5
3201021	1990, Diflufenican: Investigation of mutagenic activity at the HGPRT locus in a Chinese hamster V79 cell mutation system, DACO: 4.5.5
3201022	2007, Forward cell mutation assay with diflufenican at the thymidine kinase locus (TK+-) in mouse lymphoma L5178Y cells, DACO: 4.5.5

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3201024	2004, MB38181: Chromosome aberration test in human lymphocytes in vitro, DACO: 4.5.6
3201025	1984, Metaphase analysis of human lymphocytes treated with M & B 38,544, DACO: 4.5.6
3201026	1984, Analysis of metaphase chromosomes obtained from bone marrow of rats treated with M&B 38,544, DACO: 4.5.7
3201027	2014, Diflufenican: Micronucleus assay in bone marrow cells of the mouse, DACO: 4.5.7
3201028	2013, Mammalian micronucleus test of murine peripheral blood cells with 2-(3-trifluoromethyl-phenoxy)-nicotinic acid, DACO: 4.5.7
3201029	1984, Evaluation of M&B 38,544 in the rat primary hepatocyte unscheduled DNA synthesis assay, DACO: 4.5.8
3201030	1994, (14C)-diflufenican: Tissue distribution study in the rat, DACO: 4.5.9
3201031	2001, (2,4-difluorophenyl-U-14C)-diflufenican - Repeat oral low dose A.D.M.E. study in the rat, DACO: 4.5.9
3201032	1984, Diflufenican - Absorption, distribution and elimination in the male and female rat following a single oral dose, DACO: 4.5.9
3201033	1985, Diflufenican - Metabolism in the male and female rat following a single oral dose, DACO: 4.5.9
3201034	1985, Diflufenican-(14C) - Elimination in the bile of rats after a single oral dose, DACO: 4.5.9
3201035	1984, Diflufenican-14C - Absorption in control and pre-treated male and female rats, DACO: 4.5.9
3201036	2001, Diflufenican: Rat A.D.M.E. and kinetics study using (difluorophenyl-U-14C)-DFF and [trifluoromethylphenyl-U-14C]-DFF, DACO: 4.5.9
3201037	2020, Amendment no. 01: BCS-BT38895: Preliminary toxicity study by dietary administration to Han Wistar rats for 2 weeks, DACO: 4.8
3201038	2020, An evaluation of endocrine-associated ToxCast and Tox21 data for diflufenican, DACO: 4.8
3201039	2020, BCS-BT38895: In vitro micronucleus test in human lymphocytes, DACO: 4.8
3201041	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8

PMRA Document Number	Reference
3201042	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201043	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201044	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201045	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201046	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201047	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201048	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201049	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201050	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201051	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201052	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201053	2021, Toxicology profile for diflufenican soybean seed metabolite, BCS-BT38895, DACO: 4.8
3201640	2020, DFF+IFT+CSA SC617: Acute oral toxicity - Up-and-down procedure in rats, DACO: 4.6.1
3201641	2020, Waiver for an acute dermal toxicity study on the mixture formulation diflufenican + isoxaflutole + cyprosulfamide SC617, DACO: 4.6.2
3201642	2020, DFF+IFT+CSA SC617: Acute inhalation toxicity in rats, DACO: 4.6.3
3201643	2020, DFF+IFT+CSA SC617: Primary eye irritation in rabbits, DACO: 4.6.4
3201644	2020, DFF+IFT+CSA SC617: Primary skin irritation in rabbits, DACO: 4.6.5

PMRA Document Number	Reference
3201645	2020, DFF+IFT+CSA SC617: Local lymph node assay (LLNA) in mice, DACO: 4.6.6
3201827	2018, AE F088657 + metribuzin SC600 (200 + 400 g/L): Acute oral toxicity - Up-and-down procedure in rats, DACO: 4.6.1
3201828	2020, Waiver for an acute dermal toxicity study on the mixture formulation AE F088657 + metribuzin SC600, DACO: 4.6.2
3201829	2018, AE F088657 + metribuzin SC600 (200 + 400 g/L): Acute inhalation toxicity in rats, DACO: 4.6.3
3201830	2018, AE F088657 + metribuzin SC600 (200 + 400 g/L): Primary eye irritation in rabbits, DACO: 4.6.4
3201831	2018, AE F088657 + metribuzin SC600 (200 + 400 g/L): Primary skin irritation in rabbits, DACO: 4.6.5
3201832	2018, AE F088657 + metribuzin SC600 (200 + 400 g/L): Local lymph node assay (LLNA) in mice, DACO: 4.6.6
3243511	2021, Waiver request of the data requirement for a 90-day inhalation study - Diflufenican, DACO: 4.3.6
3302089	2021, Historical histopathology data - B6C3F1 mice - long term studies - studies starting between January 1985 and Sep 1997, DACO: 4.4.4
3302092	2021, Regulatory response to the toxicology 90-day technical screen for diflufenican, DACO: 4.8
3200132	2019, Diflufenican: In vitro dermal absorption of diflufenican in the DFF SC500 formulation using human and rat skin, DACO: 5.8 (B)
3200133	2019, Diflufenican: In vivo dermal absorption of diflufenican in the DFF SC500 formulation in the rat, DACO: 5.8 (A)
3201056	2000, The distribution and metabolism of (^{14}C)-diflufenican in the lactating cow. DACO 6.2.
3201057	1989, (^{14}C)-diflufenican - Absorption, tissue retention, metabolism, and excretion in lactating cow. DACO 6.2.
3201058	2000, The distribution and metabolism of (^{14}C)-diflufenican in the laying hen. DACO 6.2.
3201059	2008, Diflufenican - Metabolism in the lactating goat. DACO 6.2.
3201060	2019, The metabolism of [pyridine-2-^{14}C] AE F088657 in soybean. DACO 6.3.

PMRA Document Number	Reference
3201061	2019, The metabolism of [difluorophenyl-UL-^{14}C] AE F088657 in soybean. DACO 6.3.
3201062	2000, (^{14}C)-Pyridine labelled diflufenican: Metabolism in post emergence treated wheat. DACO 6.3.
3201063	2003, (^{14}C)-Diflufenican: Metabolism, distribution and expression of residues in winter wheat, with 2,4-difluorophenyl-ring-labelled and 3-trifluoromethylphenyl-ring-labelled compound following post-emergence treatment. DACO 6.3.
3201064	2003, Metabolism, distribution and expression of residues in winter wheat, with compound labelled in each of the three rings: following preemergence application (^{14}C)-Diflufenican. DACO 6.3.
3201065	1987, Diflufenican: Metabolites in wheat grain at harvest following preemergence application. DACO 6.3.
3201074 & 3200136	2019, An analytical method for the determination of residues of AE F088657 in animal matrices using LC/MS/MS. DACO 7.2.1/7.2.2/7.2.3.
3200140 & 3201075	2020, Independent laboratory validation of an analytical method for the determination of residues of AE F088657 in animal matrices using LC/MS/MS. DACO 7.2.1/7.2.2/7.2.3.
3200141 & 3201080	2020, Amendment 01 to final report of RADC0107 - Validation of an analytical method DC-005-A19-01 for the determination of residues of AE F088657 in poultry and DC-005-A19-02 for the determination of residues of AE F088657 in beef liver and milk using LC/MS/MS. DACO 7.2.1/7.2.2/7.2.3.
3200134	2010, Analytical method 01143 for the determination of residues of diflufenican and its metabolite MB 38181 and the glycerol conjugates of MB 38181 in/on plant material. DACO 7.2.1/7.2.2/7.2.3.
3200139	2020, Independent laboratory validation of analytical method DC-003-P18-02 for the determination of residues of AE F088657 and its metabolites BCS-BT 38895, AE 0542291 and AE B107137 and the glycerol conjugates of AE B107137 in soybean seed. DACO 7.2.1/7.2.2/7.2.3.
3200138	2020, Extraction efficiency testing of Bayer CropScience residue analytical method DC-003-P18-02 for the determination of residue of AE F088657 and its metabolites AE B107137, AE 0542291 and BCS-BT38895 in soybean seed, forage and hay and storage stability of BCS-BT38895 in soybean seed with metabolism procedure of MEDC0005 using aged radioactive residues. DACO 7.2.1/7.2.2/7.2.3.

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PMRA Document Number	Reference
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3200378	2019, Amendment 01 to final report of RADC0044 - AE F088657 - Magnitude of the residue in limited rotational crops - Mustard greens. DACO 7.4.4.
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3.0 Environment

PMRA Document Number	Reference
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3200115	2021, Summary of the ecotoxicology studies for diflufenican SC500 (500 g/L), DACO: 12.7.9, Document M,Document N
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3201102	1999, (14C)-M&B 38181 - Anaerobic soil degredation, DACO: 8.2.3.4.4
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3201172	2015, BCS-AI56853 (AE 0542291) - Acute toxicity to fish (*Oncorhynchus mykiss*) under static conditions, DACO: 9.5.2.1
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3201215	2007, Diflufenican Technical - Algal growth inhibition assay *Anabaena* Sp., DACO: 9.8.2
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3201220	1998, Diflufenican - Freshwater algal growth inhibition study and recovery phase (*Scenedesmus subspicatus*), DACO: 9.8.2
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3201225	2007, Diflufenican Technical - Higher plant (*Lemna minor*) growth inhibition test, DACO: 9.8.5
3201226	2015, *Lemna gibba* G3 - Growth inhibition test with AE 0542291 (BCS-AI56853) under static conditions, DACO: 9.8.5
3201227	2015, *Lemna gibba* G3 - Growth inhibition test with AE B107137 (BCS-AB27392) under static conditions, DACO: 9.8.5
3201228	2015, *Lemna gibba* G3 - Growth inhibition test with AE C522392 (BCS-BC35087) under semi-static conditions, DACO: 9.8.5
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4.0 Value

PMRA Document Number	Reference
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B. Additional information considered

i) Published information

1.0 Human and animal health

PMRA Document Number	Reference
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