Proposed Registration Decision PRD2011-20

Indaziflam

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Overview

Proposed Registration Decision for Indaziflam

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Indaziflam Technical Herbicide, Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide, containing the technical grade active ingredient indaziflam, to control both grassy and broadleaf weeds in pome fruit, stone fruit, tree nuts and grape.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Indaziflam Technical Herbicide, Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide.

What Does Health Canada Consider When Making a Registration Decision?

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

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

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

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

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

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

What Is Indaziflam?

Indaziflam belongs to the chemical class of alkylazines and acts in susceptible plants by inhibiting cell wall biosynthesis. Indaziflam acts only where cellulose synthesis is occuring such as in actively growing meristematic tissues, dividing cells, expanding cells, and growing roots. Fully developed leaves, tissues and plant organs are little affected, if at all, by the compound since cell wall formation has already been completed, and no new cellulose synthesis is required.

Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are selective, residual end-use products that contain the active ingredient indaziflam.

Health Considerations

Can Approved Uses of Indaziflam Affect Human Health?

Indaziflam is unlikely to affect your health when used according to label directions.

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

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

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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*.

In laboratory animals, indaziflam was of low acute oral, dermal and inhalation toxicity. Indaziflam was minimally irritating to the eyes and non-irritating to the skin, and did not cause an allergic skin reaction. Indaziflam 200 SC Herbicide was considered to have a similar toxicity profile to Indaziflam 500 SC Herbicide.

The acute toxicity of the end-use product Indaziflam 500 SC Herbicide containing indaziflam was low via the oral, dermal and inhalation routes of exposure. It was non-irritating to the eyes and skin and did not cause an allergic skin reaction.

Indaziflam did not cause cancer in animals and did not damage genetic material. There was no indication that indaziflam caused damage to the immune system. Indaziflam did not cause birth defects in animals. Health effects in animals given repeated doses of indaziflam included effects on body weight, and the liver, kidney, thyroid, nervous and reproductive systems.

When indaziflam was given to pregnant or nursing animals, there were effects on the developing fetus and juvenile animal. In rat reproductive toxicity studies, effects consisted of decreased body weights, decreased spleen, uterine and brain weights, decreased litter sizes, delayed sexual maturation, neurological effects, and diarrhea. In the rabbit developmental toxicity study, effects consisted of decreased body weights and increased skeletal variations. The effects were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to indaziflam than the adult animal.

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

Residues in Water and Food

Dietary risks from food and water are not of concern.

Chronic dietary (food plus water) estimates for the general population and infants less than one year old, the subpopulation which would ingest the most indaziflam relative to body weight, were less than six percent of the acceptable daily intake. Based on these estimates, the chronic dietary risk from indaziflam is not of concern for all population sub-groups. Indaziflam is not carcinogenic; therefore, a chronic cancer dietary exposure assessment is not required.

Acute dietary (food and water) estimates for the general population and all population subgroups was less than one percent of the acute reference dose, and is not of concern.

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

Residue trials conducted throughout the United States using indaziflam on apples, pears, sweet and tart cherries, peaches, plums, almonds, pecans and grapes, were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Occupational Risks From Handling Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

Occupational risks are not of concern when Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide to orchards, vineyards and nut trees can come in direct contact with indaziflam residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying indaziflam must wear a long-sleeved shirt and long pants, shoes, socks and chemical resistant gloves. The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the occupational exposure risk to these individuals is not of concern.

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

Environmental Considerations

What Happens When Indaziflam Is Introduced Into the Environment?

Indaziflam enters the environment when it is used as a herbicide for control of broadleaf weeds and grasses in pome fruit, stone fruit, tree nuts and grape grown in Eastern Canada and British Columbia.

In the aquatic environment, indaziflam is expected to partition from water to sediment where it is persistent. Soil biotransformation is expected to be the major route of transformation in the environment, with soil persistence ranging from slightly persistent to moderately persistent, depending on soil type. The major transformation products formed in soil include AE 1170437-carboxylic acid and AE 1170437- triazine indanone and AE 1170437-diaminotriazine, all of which are classified as non persistent, except diaminotriazine which ranges in persistence (from non persistent to persistent) depending on soil type. Indaziflam is moderately mobile and not expected to leach. In contrast, AE 1170437-diaminotriazine, AE 1170437-carboxylic acid and AE 1170437- triazine indanone are moderately to highly mobile and thus may leach to groundwater, once formed in the soil. Overall, levels of the parent and three transformation products in groundwater are low based on results of water modelling. Based on its low volatility, indaziflam residues are not expected in the air.

Indaziflam does not present a risk to wild mammals, birds, bees, invertebrates, freshwater or marine invertebrates and fish, and amphibians. However, indaziflam does affect terrestrial plants and aquatic plants. Therefore, to protect from the effects resulting from spray drift to non target terrestrial plants and aquatic plants, buffer zones of 15 metres and 1 metre are required for terrestrial plants and aquatic habitats, respectively. To protect aquatic plants from the potential effects of runoff, a label statement to minimize runoff will be required, as well as hazard based label statements for toxicity to terrestrial and aquatic plants.

Value Considerations

What is the Value of Indaziflam?

Indaziflam, as a pre-emergence treatment in pome fruit, stone fruit, grapes and tree nuts, provides control of annual grass and broadleaf weeds.

A single application of indaziflam provides effective residual control of annual grasses, including barnyard grass, giant foxtail, green foxtail, Italian ryegrass, large crabgrass, wild proso millet, yellow foxtail and annual broadleaf weeds, including annual sow-thistle, black mustard, common groundsel, field bindweed, lamb's-quarters, prickly lettuce (suppression only), redroot pigweed (suppression only), shepherd's purse, spotted spurge, stork's-bill, white sweet clover and wild mustard in pome fruit (apple, pear), stone fruit (apricot, cherry, nectarine, peach, plum), tree nuts (almond, hazelnut, filbert, walnut, chestnut, Japanese heartnut) and grapes that have been established for at least three full growing seasons in Eastern Canada and British Columbia only.

Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide provides an additional option for herbicide group rotation for controlling both grassy and broadleaf weeds in pome fruit, stone fruit, tree nuts and grape. The use of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide does not restrict the sequential use of other chemicals of alternate modes of action.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide on the skin or through inhalation of spray mists, anyone mixing, loading and applying Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide must wear a long-sleeved shirt and long pants, shoes, socks and chemical resistant gloves. In addition, standard label statements to protect against drift during application and to prevent use in greenhouses were added to the label.

Environment

- Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide can not be sprayed within 15 metres of susceptible non-target terrestrial plant species, and one metre from aquatic habitats. Use of hand-held or backpack sprayer, spot treatment or inter-row hooded sprayer do not require buffer zones.
- Hazard based label statements for toxicity will be required for terrestrial plants and aquatic plants.
- Run-off statements will be required on the label.

Next Steps

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

Other Information

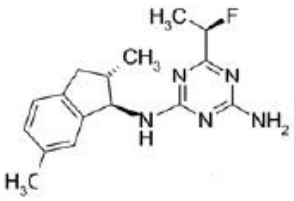
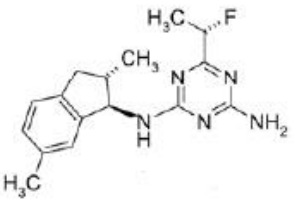
When the PMRA makes its registration decision, it will publish a Registration Decision on indaziflam (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s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

Science Evaluation

Indaziflam

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Indaziflam
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*N*-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-yl]-6-[(1*RS*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
2. Chemical Abstracts Service (CAS)	*N*-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-yl]-6-(1-fluoroethyl)-1,3,5-triazine-2,4-diamine
CAS number	950782-86-2 (*RS*) mixture 730979-19-8 (1*R*)-fluoroethyl diastereoisomer 730979-32-5 (1*S*)-fluoroethyl diastereroisomer
Molecular formula	$C_{16}H_{20}FN_5$
Molecular weight	301.36
Structural formula	  730979-19-8 (isomer A) 730979-32-5 (isomer B)
Purity of the active ingredient	95.8%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Indaziflam Technical

Property	Result
Colour and physical state	Technical is light beige powder (both isomers are white)
Odour	Odourless
Melting range	Isomer A: 183°C Isomer B: 178°C Technical: 177°C
Boiling point or range	Isomer A: 320°C; decomposes at 324°C Isomer B: N/A; decomposes at 329°C Technical: 293°C; decomposes at 317°C
Density	1.23 g/L at 20°C
Vapour pressure (Pa)	Isomer 20°C 25°C 50°C A $2.5x10^{-8}$ $6.8x10^{-8}$ $6.9x10^{-6}$ B $3.7x10^{-9}$ $1.1x10^{-8}$ $1.6x10^{-6}$
Ultraviolet (UV)-visible spectrum	No absorption was observed at λ>300 nm.
Solubility in water at 20°C (g/L)	Isomer pH 4 pH 9 Distilled water A 4.4 2.8 2.8 B 1.7 1.2 1.2
Solubility in organic solvents at 20°C (g/L)	Solvent Isomer A Isomer B Heptane 0.032 0.019 Toluene 4.3 1.3 Dichloromethane 150 28 Ethanol 13.0 5.1 Acetone 55 17.3 Acetonitrile 7.6 - Ethyl acetate 47 15 Dimethyl sulfoxide >250 -
n-Octanol-water partition coefficient (log K_{ow})	Isomer pH 2 pH 4 pH 7 pH 9 A 2.0 2.8 2.8 2.8 B 2.1 2.8 2.8 2.8
Dissociation constant (pK_a)	Isomer A: pKa = 3.5 Isomer B: pKa = 3.6
Stability (temperature, metal)	Chemically and stereo-chemically stable to temperature (54°C) and metals (steel, stainless steel, aluminum and brass).

End-Use Product—Indaziflam 500 SC Herbicide

Property	Result
Colour	Light beige
Odour	Medium aromatic odour
Physical state	Liquid
Formulation type	Suspension
Guarantee	500 g/L
Container material and description	1-20 L, plastic recyclable
Density	1.106 g/mL at 20°C
pH of 1% dispersion in water	4.9
Oxidizing or reducing action	The product does not contain any ingredient that is considered to be an oxidizing or reducing agent.
Storage stability	The product is stable in HDPE bottles for two years at room temperature.
Corrosion characteristics	No corrosion was observed to HDPE bottles in the 2-year study period.
Explodability	No impact explosive characteristics are expected on the basis of the chemical nature of the formulation ingredients.

End-Use Product—Indaziflam 200 SC Herbicide

Property	Result
Colour	Cream white
Odour	Medium acidulous odour
Physical state	Liquid
Formulation type	Suspension (SU)
Guarantee	200 g/L
Container material and description	1-20 L, plastic recyclable
Density	1.051 g/mL at 20°C
pH of 1% dispersion in water	5.1
Oxidizing or reducing action	The product does not contain any ingredient that is considered to be an oxidizing or reducing agent.
Storage stability	The product is stable in HDPE bottles for two years at room temperature.
Corrosion characteristics	No corrosion was observed to HDPE bottles in the 2-year study period.
Explodability	No impact explosive characteristics are expected on the basis of the chemical nature of the formulation ingredients.

1.3 Directions for Use

1.3.1 Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

Indaziflam 200 SC Herbicide (containing indaziflam at 200 g/L) and Indaziflam 500 SC Herbicide (containing indaziflam at 500 g/L), are selective pre-emergence herbicides for control of barnyard grass, giant foxtail, green foxtail, Italian ryegrass, large crabgrass, wild proso millet, yellow foxtail, annual sow-thistle, black mustard, common groundsel, field bindweed, lamb's-quarters, prickly lettuce (suppression only), redroot pigweed (suppression only), shepherd's purse, spotted spurge, stork's-bill, white sweet clover and wild mustard in pome fruit (apple, pear), stone fruit (apricot, cherry, nectarine, peach, plum), tree nuts (almond, hazelnut, filbert, walnut, chestnut, Japanese heartnut) and grapes that have been established for at least three full growing seasons. Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide may be applied once per growing season in the spring at a rate of 75 g a.i./ha (equivalent to 375 mL/ha or 150 mL/ha, respectively) (Table 1.3.1) with ground application equipment only.Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide may be tank mixed with either glyphosate (present as potassium salt) or glufosinate-ammonium for burndown of emerged weeds (refer to the glyphosate and glufosinate-ammonium herbicide labels for application rates and weed species controlled) (Table 1.3.2).

Table 1.3.1 Application rates and weed control claims for Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide in tank mixture with either glyphosate or glufosinate- ammonium herbicides

Products	Rates	Crop	Weeds Controlled	Remarks
Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide + Ignite SN Herbicide	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 2.7 – 5 L/ha	Apple, Pear, Peach, Plum, Grapes	Weed species controlled by Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide alone plus burndown control of emerged weeds.	Consult the label of the tank mix partner(s) for further instructions regarding directions for use, restrictions and precautions, and always observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.
Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide + Roundup Weathermax Roundup Ultra Roundup Ultra2 Roundup Ultra Max Roundup Transorb HC IPCO Factor 540 R/T 540 Liquid	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.5 - 8 L/ha	Apple, Pear, Apricot, Cherry (sweet/sour), Peach, Plum, Grapes, Chestnut, Walnut, Japanese heartnut		
	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.5-2.33 L/ha	Filbert, Hazelnut		
Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide + Touchdown Total	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.6 – 8.6 L/ha	Apple, Pear, Apricot, Cherry (sweet/sour), Peach, Plum, Grapes, Chestnut, Walnut, Japanese heartnut		
	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.8 – 2.5 L/ha	Filbert, Hazelnut		

1.4 Mode of Action

Indaziflam belongs to the chemical class of alkylazines. Indaziflam acts in susceptible plants by inhibiting the synthesis of cellulose, and thus, cell wall biosynthesis. Specifically, indaziflam inhibits crystalline cellulose deposition in the plant cell wall, severely affecting cell wall formation, cell division as well as cell elongation. Indaziflam acts only in plant cells and tissues where cellulose synthesis is actively taking place (germinating weed seeds and developing seedlings), for example, in actively growing meristematic tissues, dividing cells, expanding cells, as well as growing roots. Fully developed leaves, tissues and plant organs are not or hardly affected by the compound since cell wall formation already has been completed, and no new cellulose synthesis is required.

Indaziflam is classified as a Group 29 herbicide by the Weed Science Society of America and as a Group L herbicide by the Herbicide Resistance Action Committee.

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 the impurities in Indaziflam Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

Liquid chromatography methods with tandem mass spectrometry (LC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices and environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for indaziflam was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, a genotoxicity study and a special sexual maturation study were performed with the fluoroethyl diaminotriazine (FDAT) metabolite. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data was high and the database was considered adequate to define the majority of the toxic effects that may result from exposure to indaziflam.

Metabolism studies were performed with indaziflam radiolabelled at the indane ([indane-^{14}C]AE1170437) and triazine ([triazine-2,4-^{14}C]AE 1170437) rings. Indaziflam was well absorbed, extensively metabolized and mostly excreted within 24 hours. The main excretory pathways were the bile and urine with 5 – 16% excreted unmetabolized in the faeces. Absorption and phase I excretion were rapid ($t_{1/2}$ < 10 min); however, phase II excretion had a half-life ($t_{1/2}$) of 13 – 18 hours for the triazine ring and 31 – 33 hours for the indane ring. In females, roughly equivalent amounts were excreted in the urine and faeces. In males, faecal excretion was the primary route. Maximum concentrations (C_{max}) and area under the curve (AUC) values were similar in females dosed with the triazine-labelled compound to males dosed with either label. Both these values were lower in females given the indane-labelled ring, indicating that females metabolize indaziflam differently than males. This is supported by clearance values which were highest for females dosed with the indane-labelled compound, identical for males and lowest for females given the triazine-labelled compound.

Females retained less radioactivity in the tissues than males; tissue levels were highest in the gastrointestinal (GI) tract, liver and skin. There was proportionately less radioactivity left in the GI tract, liver, skin, thyroid gland and general carcass in high-dose males than low-dose males but proportionately equivalent amounts in the spleen. In the case of bone, brain, fat, heart, muscle, gonads and whole blood values, more of the indane ring was retained in the tissue at higher doses than the triazine label. The metabolites were well characterized with less than 11% of the metabolites unidentified.

The major metabolic pathways involved oxidation of indaziflam resulting in the formation of carboxylic acid as the main metabolite followed by the formation of dihydroxy, 3-hydroxyindane acid and the 3-hydroxyindane acid epimer and hydroxyl glutamic acid. There were quantitative differences in metabolism between the sexes. High-dose males excreted significantly more unchanged parent than low-dose males indicating a saturation of the uptake system. There were no significant qualitative differences between the low-dose male and female studies. A minor, but important, metabolite was FDAT as it is similar to the atrazine metabolite, diaminochlorotriazine (DACT), which is not a metabolite of indaziflam. DACT has been implicated in female reproductive toxicity. Small amounts of this metabolite were found in low-dose female and high-dose male studies.

Indaziflam 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.

Acute toxicity studies were performed with the Indaziflam 500 SC Herbicide formulation and bridged to the Indaziflam 200 SC Herbicide formulation. Indaziflam 500 SC Herbicide was of low acute oral, dermal and inhalation toxicity in rats. It was non-irritating to the eyes and skin of rabbits and not a dermal sensitizer in guinea pigs. In the acute inhalation toxicity study of the end-use product, animals exhibited a high-legged gait, a staggering gait, limp body, convulsions, tremors and mydriasis.

Neurotoxicity was a common finding in repeat dose oral studies and in the acute neurotoxicity study. Dogs were the most sensitive species to neurotoxicity, as evidenced by axonal degeneration of the dorsal spinal cord, sciatic nerve and brain stem at lower doses. At higher doses, seizures, aggression, tremors, ataxia, decreased activity, sluggish pupils and laboured breathing were noted. The only sign of neurotoxicity in the mouse was seen in a moribund animal at the high dose. Female rats were more sensitive than the males. Neurotoxicity was manifested by tremors and a decrease in activity, piloerection, hunched posture, anogenital and lacrimal/nasal staining, dilated pupils or loss of pupillary reflex, low alertness and gait changes. Histopathological changes to the nervous tissue, degeneration of gasserian ganglion, sciatic and tibial nerves in males and females occurred in the neurotoxicity studies. In the combined chronic and carcinogenicity study, degeneration of the pars nervosa in the pituitary gland and median eminence of the brain and retinal atrophy were noted in females. Histopathological changes were noted at doses greater than or equal to the LOAEL and at doses lower than clinical signs of neurotoxicity. In the developmental neurotoxicity (DNT) study, there were no neurological effects on the pups.

Effects on the reproductive potential were noted throughout the rodent studies. In male mice, there was focal tubular degeneration in the testes in the 90-day study and an increase in atrophy of the seminal vesicles at terminal sacrifice in the long-term study. In the 90-day rat study, epididymide weights were decreased at the high dose. In female mice, uterine weights were decreased in the 90-day study, at the interim sacrifice in the long-term study and in the parental (F_0) animals in the multi-generational reproductive toxicity study. There was an increase in atrophied uteri and endometrial atrophy and an increase in blood-filled cysts and follicles of the ovaries at terminal sacrifice of the long-term study and decreased ovarian weights in parental (F_0) dams and a decrease in pituitary weights in F_1 adult females in the multi-generational reproductive toxicity study. In the multi-generational reproductive toxicity study, dosing was decreased during the F_0/F_1 lactation phase due to excessive mortality in the pups. The deaths occurred after the animals were weaned so the absolute consumption would have been higher than the parental animals. In addition to the mortality, there was a delay in sexual maturation in males and females, a decrease in the number of implantation sites and litter sizes (F_0/F_1), a decrease in the corpora lutea (F_1) and a decrease in the F_1 pup uterine weights.

In the rabbit developmental toxicity study, there was one treatment-related abortion. In rabbits, developmental toxicity was limited to decreased fetal body weights and an increase in fetuses with 27 presacral vertebrae and detached 13th thoracic ribs at maternally toxic doses. In rats, fetal body weights were decreased at maternally toxic doses. There was no evidence of sensitivity of the young.

Also noted in the repeat dose studies were effects on body weight and the liver, kidney, spleen and, in the rat only, the thyroid. Body weight effects were seen in all but the 90-day dog and repeat dose dermal studies. In mice, liver effects consisted of increased darkened liver and increased albumin, hepatocellular vacuolation, lobulations, lobular torsion and decreased liver weights. In rats, additional findings were changes to clinical chemistry parameters and increased hepatocellular hypertrophy and increased liver size and weights. In male mice, kidney effects consisted of decreased weights in the 90-day study and, additionally, hyperplasia of the collecting ducts and pelvic epithelium, unilateral and bilateral papillary necrosis and intratubular yellow/brown materials, a decrease in corticoepithelial vacuolation and hyaline cases with tubular dilalation in the chronic and carcinogenicity study. Female mice exhibited an increase in pelvic epithelium hyperplasia in the long-term study. In rats, mononuclear cell infiltrate was noted in short-term oral and dermal studies, along with tubular cystic dilatation specific to the repeat-dose dermal toxicity study. In the reproductive toxicity studies, parental males exhibited increased kidney weights and increased hyaline degeneration and tubular regeneration. Kidney weights were also increased at terminal sacrifice in the 2-year rat study in males; however, the only evidence of kidney toxicity in females were macroscopic effects noted post mortem. In the rat, thyroid effects were dependent on administered dose and duration. The thyroid was affected as evidenced by increased thyroid stimulating hormone (TSH) at week three at similar doses in the 90-day and long-term studies along with diffuse follicular cell hypertrophy. While these and other thyroid effects were treatment-related and adverse, they were also highly variable, determined to be adaptive and did not progress to carcinogenicity of the thyroid. For example, T4 was decreased in the 90-day study at week three; however, at the higher dose, T4 was elevated at three months in male rats and TSH was decreased in females. Colloid alteration was noted in both sexes in the long-term study. In females, thyroid weights were unaffected during treatment but increased at the end of the recovery period of the 90-day study. Spleen weights were decreased in a number of studies, including at high-doses in the 90-day mouse, 90-day rat and rat multigenerational toxicity study. The immunotoxicity study was negative.

In the repeat dose dermal toxicity study in rats, signs of irritation consisting of skin thickening in males and skin reddening in females were observed at the mid-dose. At the high-dose there was an increase in mononuclear cell infiltrate in treated skin in males and females and in untreated skin of treated females. There was an increase in thymus weights, enlarged popliteal lymph nodes, inflammatory infiltrate and alveolar haemorrhage in the lungs and increased cellularity of the paracortex of popliteal lymph nodes in males.

There was no evidence of carcinogenicity in the rat or mouse and the battery of genotoxicity studies was negative.

Studies were performed on the select metabolites. Genotoxicity studies on the carboxylic acid and the FDAT metabolites were negative. A special study was performed with FDAT and DACT to compare reproductive toxicity. It was determined that FDAT caused increased salivation and delayed sexual maturation of the offspring at the LOAEL and urine staining, decreased body weight and body weight gain, decreased ovarian weights and a slight decrease in uterine weights at the high dose in pups. The reproductive toxicity of FDAT was less than that of DACT, but, in comparison to the reproductive toxicity study, FDAT produced greater delays in vaginal patency than indaziflam.

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

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. There were no health-related incident reports submitted to the PMRA for end use products containing indaziflam as of July 12th, 2011.

3.1.1 PCPA Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for indaziflam. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, a developmental neurotoxicity study in rats and a special study on the reproductive toxicity potential of the FDAT metabolite.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. Minor developmental effects (increased incidence of skeletal variations) were observed in the rabbit developmental toxicity studies; however, these effects occurred in the presence of maternal toxicity. In the 2-generation rat reproductive toxicity study, litter sizes were decreased, sexual maturation was delayed and offspring exhibited increased mortality when receiving higher doses than the dams at the highest dose tested by both nursing and consuming diet. However, this occurred in the presence of maternal toxicity (body weight, kidney and neurological effects). On the basis of this information, the PCPA factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

General Population

To estimate acute dietary risk (1 day), the acute neurotoxicity study with a NOAEL of 50 mg/kg bw was selected for risk assessment. At the LOAEL of 100 mg/kg bw, there was a decrease in activity in females. This effect was the result of a single exposure and is therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor has been reduced to 1-fold. **The composite assessment factor (CAF) is 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{50 \text{ mg/kg bw}}{100} = 0.5 \text{ mg/kg bw of indaziflam}$$

3.3 Acceptable Daily Intake (ADI)

To estimate dietary risk of repeat exposure, the 12-month dog study with a NOAEL of 2 mg/kg bw was selected for risk assessment. At the LOAEL of 6 mg/kg bw, an increase in axonal degeneration within the spinal cord, sciatic nerve and brain stem was 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 have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor has been reduced to 1-fold. **The composite assessment factor (CAF) is 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of indaziflam}$$

Cancer Assessment

There was no evidence of carcinogenicity and therefore, no cancer risk assessment was necessary.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal and Inhalation

Although a rat short-term dermal study was available, rats were not as sensitive to the critical effect (axonal degeneration) as the dog and therefore the dermal study was not appropriate for risk assessment. No repeat-dose inhalation toxicity study was available. For short- and intermediate-term dermal and inhalation risk assessment, the 90-day oral toxicity study in dogs

was selected. In this study, the NOAEL was determined to be 7.5 mg/kg bw/day based on an increase in axonal degeneration within the sensory tracts of the dorsal spinal cord, sciatic nerve and brain stem of males and females at the LOAEL of 15 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. The target margin of exposure (MOE) is 100.

Cancer Assessment
There was no evidence of carcinogenicity and therefore, no cancer risk assessment is necessary.

3.4.1.1 Dermal Absorption

In support of these submissions, a rat *in vivo* dermal absorption study as well as an *in vitro* study using human and rat skin were submitted. These studies were reviewed and considered for the triple pack approach in the selection of a dermal absorption value.

Although the studies were conducted under the same doses and conditions, they were found not to meet the criteria for the triple pack approach for the following reasons:

- High variability in the rat *in vivo* dermal absorption values (CV= 8.48 to 46.91%). A low coefficient of variation gives confidence in the results of the study and is included in the 'minimal standards' of the NAFTA Triple Pack Approach position paper (2008).
- The ratio of *in vivo* to *in vitro* dermal absorption in the rat was close to one for some time points, but ranged away from one for other time points (0.6 for the low dose to 2.25 for the high dose). Given that the ratio of *in vivo* to *in vitro* dermal absorption values has a large range that spans around one, there is reduced confidence in applying the triple pack approach to these studies.
- The coefficients of variation for the *in vitro* skin samples (human and rat) ranged from 25.47% to 83.21%. As human skin is generally found to be more variable than rat skin, the higher coefficient of variation is considered acceptable in the human skin samples. However, the coefficient of variation in the rat skin samples it expected to be lower.
- The rat *in vitro* dermal absorption values were lower than what was reported in the rat *in vivo* study for both the mid and high doses. This is unusual given that *in vitro* studies are usually considered to be 'overestimates' of *in vivo* dermal absorption. Given these results, there is some uncertainty regarding the representativeness of the human *in vitro* values.

Using a weight-of-evidence approach, taking into consideration all the studies submitted, the dermal absorption value of 25% from the rat *in vivo* study was selected.

A comparison of the *in vivo* and *in vitro* dermal penetration results is presented in Table 3.4.1.1.

Table 3.4.1 Summary of Percent of Dermally Absorbed Dose in *In Vivo* and *In Vitro* Penetration Studies for Indaziflam Following Eight Hour Exposure

	In vivo	***In vitro***	
Species	Rat	Rat	Human
High Dose (5000 µg a.i./cm^2)	3.1-5.6%	2.7%	0.3%
Intermediate Dose (2 µg a.i./cm^2)	13-27%	12%	2.4%
Low Dose (0.5 µg a.i./cm^2)	25-46%	42%	11%
In vivo = treated skin + tape strips (including s*tratum corneum*) + urine + feces + cage wash + blood + non-treated skin + carcass *In vitro* = receptor fluid + receptor chamber + skin (including tape strips and *stratum corneum*)			

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide during mixing, loading and application. Dermal and inhalation exposure estimates for workers mixing, loading and applying Indaziflam 500 and Indaziflam 200 SC Herbicide were generated from the Pesticide Handler Exposure Database (PHED) version 1.1.

Exposure to workers mixing, loading and applying Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide is expected to be short to intermediate in duration and to occur primarily by the dermal route. Exposure estimates were derived for mixer/loader/applicators applying Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide to orchard crops, vineyards and nut trees using groundboom application equipment. The exposure estimates are based on mixer/loader/applicators wearing a single layer of clothing (long sleeve shirt and long pants) and gloves during application.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. The amount handled per day was calculated using the highest application rate and the default area treated per day for groundboom application of herbicides to orchards (26 ha/day). Exposure was determined on a kilogram body weight basis assuming 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints to obtain the MOE; the target MOE is 100. Since the dermal and inhalation NOAEL are the same, a combined MOE is required.

Table 3.4.2 Mixer/Loader/Applicator Exposure Estimates and MOEs

Scenario	Method	Unit Exposure (µg/kg a.i. handled)	Exposure Estimates (µg a.i./kg bw/day[a])	MOE[b] (target 100)	Combined Exposure (µg a.i./kg bw/day)	Combined MOE (target 100)
Dermal Exposure					**Dermal + Inhalation**	
Mixer/loader	Open pour mixing/loading (liquid)	51.14	0.3561	21,058	0.40	18,750
Applicator	Groundboom application	32.98	0.2297	32,654	0.26	26,132
Mixer/loader/ applicator	Open pour mixing/loading (liquid) & groundboom application	84.12	0.5858	12,801	0.66	10,246
Inhalation Exposure						
Mixer/loader	Open pour mixing/loading (liquid)	1.60	0.045	166,667		
Applicator	Groundboom application	0.96	0.027	277,778		
Mixer/loader/ applicator	Open pour mixing/loading (liquid) & groundboom application	2.56	0.072	104,167		

[a] Exposure Estimates= PHED (µg a.i./kg a.i.handled) X Rate (0.075 kg a.i./ha) X Area treated per day (26 ha) X Dermal Absorption Factor (25%, dermal exposure only)

bw (70kg)

[b] MOE = NOAEL (7.5 mg/kg bw/day) ,
(Exposure estimates (µg/kg/day)/1000 µg/mg)

Acceptable margins of exposure (both dermal and inhalation) were obtained for workers who mix, load and apply Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide in orchard crops, grapes and tree nut crops using ground boom equipment.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Since both Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are applied to the ground at the base of the trees (orchards, grapevines and tree nuts) using groundboom equipment, residues are not expected to occur on the foliage. Therefore, post-application exposure is not expected to be of concern since contact with indaziflam treated soil is expected to be negligible. A post-application risk assessment is not required and a restrictive entry interval (REI) above 12 hours is not required.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. 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.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is indaziflam and the metabolite FDAT. A residue definition for risk assessment and enforcement in animal commodities has not been determined. The LC-MS/MS enforcement analytical method is valid for the quantification of indaziflam and FDAT residues in pome fruits, stone fruits, tree nuts, grapes, olives and citrus fruits. The residues of indaziflam and FDAT are stable when stored in a freezer at less than -20°C for up to 25 months in almond hulls, almond nutmeats, apples, cherries and oranges. Raw agricultural commodities were processed, but were not further analyzed due to the lack of quantifiable residues following exaggerated application rates in the unprocessed raw agricultural commodity. Quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Supervised residue trials conducted throughout the United States using end-use products containing indaziflam at exaggerated rates in or on apples, pears, sweet and tart cherries, peaches, plums, almonds, pecans and grapes are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following assumptions were made in a basic chronic analysis: 100% crop treated, default processing factors, and residues of indaziflam and FDAT in crops at MRL values. The basic chronic dietary exposure from all supported indaziflam food uses (alone) for the general population, including infants and children, and all representative population subgroups is 1.2% of the acceptable daily intake (ADI) or less. Chronic dietary exposure to indaziflam from food and water is 1.8% (0.000362 mg/kg bw/day) of the ADI for the general population. The highest exposure and risk estimate are for all infants (<1 year old) at less than 6% (0.001157 mg/kg bw/day) of the ADI, and is not of concern.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were made in a basic acute analysis: 100% crop treated, default processing factors, and residues of indaziflam and FDAT in crops at MRL values. The basic acute dietary exposure (food alone) for all supported indaziflam registered commodities is estimated to be less than 0.2% (0.001173 mg/kg/day) of the ARfD for all population subgroups (95^{th} percentile, deterministic). Aggregate exposure from food and water is 0.61% of the ARfD or less for all population subgroups, and is not of concern.

3.5.3 Aggregate Exposure and Risk

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

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRLs (ppm)
Pome Fruits (Crop Group 11-09)	0.01
Stone fruits (Crop Group 12-09)	0.01
Tree Nuts (Crop Group 14-11)	0.01
Small fruit vine climbing subgroup, except fuzzy kiwi (Crop Subgroup 13-07F)	0.01

For additional information on 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 methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Tables 5 and 6 in Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Indaziflam enters the environment when it is used as a herbicide for control of broadleaf weeds and grasses in pome fruit, stone fruit, tree nuts and grape grown in Eastern Canada and British Columbia. In the aquatic environment, indaziflam is expected to partition from water to sediment where it is persistent. Under field conditions relevant to Canada, the half life ranges from 13 to 22.5 days. Under laboratory conditions, indaziflam is slightly persistent to moderately persistent in aerobic soil at 20 to 25ºC (DT_{50} value range of 20.9 days to 96 days for a range of soils from Germany and the United States). Indaziflam dissipates to below 50% under laboratory and field conditions, where approximately 10 to 30% of the parent is present at study termination. The major transformation products, AE 1170437-triazine-indanone, and AE 1170437-carboxylic acid are not persistent. AE 1170437-diaminotriazine ranges from slightly persistent to persistent depending on soil type. The phototransformation half life of indaziflam on soil is 11.8 days. Therefore phototransformation on soil is not expected to be a major route of dissipation. Field and laboratory data indicate that indaziflam is more strongly bound to soil particles than its major transformation products (K_{OC} values ranging from 440 to 789 L/kg for parent and 10 to 307 L/kg for the transformation products), and are thus the parent is not expected to leach through the soil profile and enter groundwater, however, the transformation products may leach once formed in the soil. Taking into account the dissipation of the transformation products, the

potential concentrations of indaziflam and thus, its major transformation products in groundwater are expected to be low. This is supported by groundwater modelling.

Indaziflam could reach water systems by spray drift or runoff. It has low solubility in water, and therefore, transport may occur via runoff events (where indaziflam bound to soil particles may enter the aquatic environment). Indaziflam is stable to hydrolysis, but does transform to two major transformation products (AE 1170437-olefine and AE 1170437-hydroxyethyl) via photolysis (DT50 of 1.4 days). In the aerobic water/sediment systems, indaziflam partitions to the sediment where it remains relatively stable. Two major transformation products were formed, AE 1170437-triazine-indanone, and AE 1170437-carboxylic acid, which reached maximums of 10% throughout the study.

Based on low values for vapour pressure (2.5×10^{-8} Pa) and Henry's law constant (2.69×10^{-6} Pa m^3/mol), indaziflam is considered to be non-volatile in the environment. Therefore, indaziflam residues are not expected in the air, and long-range transport is not expected.

Data on the fate and behaviour of indaziflam and its major transformation products are summarized in Tables 6 to 9 of Appendix I.

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 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).

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 those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g. 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 = 1). 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

Risk of indaziflam (including end-use product and transformation products) to terrestrial organisms (see Table 10 to 12 in Appendix I) was based upon evaluation of toxicity data for the following:

- One mammal and three bird species (mallard duck, bobwhite quail and zebra finch) representing vertebrates (acute gavage, short- and long term (reproduction), dietary exposure)
- One bee species, two other arthropods and one earthworm species representing invertebrates (acute, short term and long term exposure with technical grade active ingredient, end-use product, and major soil transformation products)
- Ten crop species representing non-target plants

For terrestrial vertebrates indaziflam did not cause mortality or sublethal effects in Northern Bobwhite quail, or zebra finch upon acute exposure of concentrations up to 2000 mg/kg bw. In dietary studies with Northern Bobwhite quail and mallard ducks, body weight was lower in mallards treated with 5215 mg/kg feed (NOEC: 2518 mg/kg feed). No adverse effects were noted in Bobwhite quail (NOEC: 5007 mg/kg feed). Indaziflam did not adversely affect reproductive endpoints in Northern Bobwhite quail or mallard ducks exposed to maximum concentrations of up to 1023 and 1015 mg/kg feed, respectively. Screening level risk quotients did not exceed the trigger value of one for birds exposed to food contaminated with indaziflam on and off the field of application (Table 11, Appendix I) for acute, dietary and reproductive effects.

Following acute exposure of rats to indaziflam, no mortality was observed (LD_{50}>5000 mg/kg bw). Following short term dietary exposure of rats and mice to indaziflam, sublethal effects such was body weight loss and organ weight changes, were observed at concentrations of 14 mg/kg bw/day for rats (corresponding to a NOEL of 338 mg/kg bw/day). In the rat multigenerational study, effects such as increased mortality of F1 pups was observed during lactation. Sublethal reproductive endpoints included delayed sexual maturation, decreased litter size and decreased uterine weight in the Fo generation, as well as effects on offspring including reduced body weight, spleen weight in F2 generation and decreased uterine weight in the F1 generation (NOEL for parental effects, reproduction and offspring effects: 68.9 mg/kg bw/day). Screening level risk quotients did not exceed the trigger value of one for mammals exposed to food contaminated with indaziflam on and off the field (Table 12, Appendix I).

For terrestrial invertebrates, acute effects of indaziflam, its end-use product, Indaziflam 500 SC, and three major soil transformation products (AE 1170437-carboxylic acid, AE 1170437-triazine-indanone, and 1170437-diaminotriazine) were studied on earthworms (*Eisenia fetida*). After 14 days of exposure there were no mortalities from exposure (LC_{50}>1000 mg/kg soil) to the parent or transformation products, however, body weight was significantly lower in earthworms exposed to indaziflam (NOEC: 316 mg/kg soil), Indaziflam 500 SC (NOEC: 562 mg/kg soil) and AE 1170437-diaminotriazine (500 mg/kg soil). The chronic effects of Indaziflam 500 SC were also conducted over a 28 day period at concentrations up to 438 mg/kg soil. Although no mortalities were observed, there was a significant reduction in juveniles (NOEC: 78 mg/kg soil). Screening level risk quotients did not exceed the trigger value of one for earthworms (Table 10, Appendix I). The acute oral and contact effects of indaziflam, and its end-use product, Indaziflam 500 SC, on bees have also been studied. No mortality or signs of toxicity were observed at concentrations up to 100 and 120 µg a.i./bee (the highest dose tested) in the contact and oral studies, respectively. Screening level risk quotients did not exceed the trigger value of one for honeybees from either contact or oral exposure to indaziflam. Effects of the end-use product Indaziflam 500 SC to beneficial arthropod species, parasitoid wasps (*Aphidius rhopalosiphi*), and the predacious mite (*Typhlodromus pyri*) were studied in dose-response tests. Overall, there were no toxic effects in any studies with beneficial arthropods (LR_{50} >1000 g a.i., the highest doses tested). Screening level risk quotients did not exceed the trigger value of two for beneficial arthropod species from either contact or oral exposure to indaziflam.

Effects on vegetative vigour and seedling emergence of ten non-target terrestrial plants have been studied with the end-use product, Indaziflam 500 SC, up to 100 g a.i. / ha and 40 g a.i./ha, respectively. In the seedling emergence study, emergence, survival, dry weight and shoot length were all affected in many of the species tested at low concentrations. In the vegetative vigour study, survival and shoot length were affected in many of the species tested at low concentrations. To characterize the potential risk of indaziflam to non-target terrestrial plants a species sensitivity distribution SSD5 (i.e. cumulative distribution function CDF) was calculated for both the seedling emergence vegetative vigour studies. The SSD5 examines the concentration at which 95% of the species will not exhibit 50% effect, or in other words, the concentration at which 5% of the population may exhibit effects. The most sensitive $ER_{50}^{5th\ percentile(50\%)}$ is 0.167 g a.i./ha for seedling emergence. Based on the SSD5 for seedling emergence in comparison to the expected exposure for off-field drift (6%), the screening level risk quotients (RQ: 27) exceeded the value of one for non-target terrestrial plants exposed to indaziflam (Table 10, Appendix I). Since both end-use products are used as pre-emergent herbicides, the endpoint selection was considered relevant for the proposed use pattern. In order to mitigate for the potential adverse effects of indaziflam on non-target plants, a buffer zone and hazard statements will be required on the label.

4.2.2 Risks to Aquatic Organisms

Risk of indaziflam (including end-use product and transformation products) to freshwater aquatic organisms (see Table 13 Appendix I) was based upon evaluation of toxicity data for the following:

- two invertebrates; daphnid (acute and long term exposure), chironomid,
- three freshwater fish species (bluegill sunfish, rainbow trout and fathead minnow (acute and long term exposure))
- amphibian species using fish as a surrogate
- two algae, diatom and one vascular plant (duckweed)
- Macrophyte species in two outdoor mesocosm/microcosm studies

Risk of indaziflam to marine aquatic organisms (see Table 13 Appendix I) was based upon evaluation of toxicity data for the following:

- three invertebrates; amphipod (acute) and Eastern oyster (acute exposure), diatom
- one fish species (acute exposure)

For freshwater invertebrates indaziflam caused 35% immobilization to *Daphnia magna* at the highest test concentration (9.88 mg/L) in the acute technical grade active ingredient study compared to 5% mortality in the highest test concentration (38 mg a.i./L) in the acute end-use product study. Up to 100% of daphnids exposed to Indaziflam 500 SC Herbicide at concentrations ranging from 4.3 to 38 mg a.i./L exhibited sublethal effects including paleness and quiescence (48 hour EC_{50}: 2.96 mg a.i./L; LC_{50}> 38 mg/L). Chronic exposure to indaziflam led to a treatment related reduction in the number of offspring produced by daphnid as well as a reduction in adult weight and length at a concentration of 0.8 mg/L (NOEC: 0.34 mg/L). Since indaziflam is expected to partition to sediment based on its low solubility in water and moderately high K_{OC}, an additional toxicity study was conducted with sediment dwelling chironomid. Following acute exposure to indaziflam at concentrations up to 2.25 mg/L, no effects were observed on mortality, growth, or behaviour (LC_{50}>100 mg/kg sediment, >0.18 mg/L water). Screening level risk quotients did not exceed the trigger value of one for freshwater invertebrates.

For freshwater vertebrates indaziflam caused up to 100% mortality to Rainbow trout, bluegill sunfish and Fathead following acute exposure at concentrations ranging from 0.38 to 1.07 mg a.i./L (LC_{50}: 0.57 mg/L (rainbow trout; LC_{50}: 0.32 mg a.i./L (bluegill sunfish); LC_{50}: 0.77 mg a.i./L (fathead minnow)). Chronic exposure of fathead minnow to indaziflam also resulted in a high percentage of mortality of fry (97.5% mortality at the highest test concentration (1013 µg/L; NOEC: 465 µg/L)). As three major transformation products are also formed in soil and water/sediment systems, additional studies were conducted with AE 1170437-carboxylic acid and AE 1170437-diaminotriazine. Following acute exposure to the transformation products, there were no mortality or sublethal effects observed in fathead minnow (LC_{50}>103 and 101 mg transformation products /L, respectively). Using the most sensitive fish species as a surrogate for

amphibians, acute effects may occur at concentrations of 0.32 mg/L. Despite the high mortality observed in the fish studies, indaziflam is applied at low rates, and thus the expected exposure is low. As such, the screening level risk quotients did not exceed the trigger value of one for freshwater fish. The screening level risk quotient did exceed the trigger value of one for amphibian (RQ:1.6). To further characterize the risk, input from spray drift (6%) and runoff scenarios was also assessed. Considering drift and runoff, the tier I risk quotient did not exceed the trigger value of one (Table 14, Appendix I).

For algae (*Pseudokirchneriella subcapitata* and *Anabaena flos-aquae)* and the diatom (*Navicula pelliculosa*), indaziflam and/or its end-use product (Indaziflam 500 SC Herbicide) caused inhibition in biomass and/or cell density exceeding 97% at concentrations ranging from 76.5 to 3926 µg a.i./L (EC_{50}: 60.7 to 722 µg a.i./L). Exposure to transformation products including those formed in soil and water/sediment systems (AE 1170437 diaminotriazine, AE 1170437-carboxylic acid) and AE 1170437 hydroxyethyl and AE 1170437 olefine, which are formed primarily under photolytic conditions, resulted in > 80% inhibition in biomass and/or cell density. Despite the high inhibition of cell density and biomass observed in the algal and diatom studies, indaziflam is applied at low rates and, thus, the expected exposure is low. As such, the screening level risk quotients did not exceed the trigger value of one for algae and the diatom exposed to indaziflam and its transformation products (Table 6-7, Appendix I).

For vascular plants, *Lemna gibba*, indaziflam and/or its end-use product (Indaziflam 500 SC Herbicide) caused inhibition in frond area and/or growth rate exceeding 95% at concentrations ranging from 112 ng a.i./L to 200 ng a.i./L (EC_{50}: 58.5 to 68.1 ng a.i./L). Exposure to transformation products including those formed in soil and water/sediment systems (AE 1170437 triazine indanone, AE 1170437 diaminotriazine, AE 1170437-carboxylic acid) and AE 1170437 hydroxyethyl and AE 1170437 olefine, which are formed primarily under photolytic conditions, resulted in > 85% inhibition in frond area and/or growth rate. The screening level risk quotients did not exceed the trigger value of one for *Lemna gibba* exposed to the transformation products, AE 1170437 diaminotriazine, and AE 1170437 carboxylic acid. The screening level risk quotient did, however, exceed the trigger value of one for *Lemna gibba* exposed to indaziflam (RQ: 276), the end-use product (RQ: 321), and AE 1170437 triazine indanone (RQ: 1.6), AE 1170437 olefine (RQ:59)) and AE 1170437 hydroxyethyl (RQ:37). Additional higher tier mesocosm/microcosm studies were conducted to assess the toxicity of indaziflam to macrophyte species. A six week chronic study with emergent and submergent macrophytes exposed to indaziflam in outdoor ponds showed signs of chlorotic leaves and decreased biomass at concentrations of 1 µg/L (NOEC: 0.32 µg a.i. /L). A second ten week outdoor microcosm/mesocosm study conducted with a number of macrophyte species including *Lemna gibba* and *potamogetan* (in addition to zooplankton, and phytoplankton), showed effects to a number of species at different concentrations. The most sensitive species was the *Lemna gibba* (which showed a short term decrease in biomass and recovery) and *Spirodela polyhiza* (which showed a slight decrease in frond numbers) at 0.032 µg a.i./L (NOEC: 0.01 µg/L). To further examine the potential risk, the LOEL was also assessed. The level at which effects (with no recovery) occurred in 15 of the 29 species in the microcosm, was 1.0 µg/L (corresponding to a NOEC of 0.32 µg/L). The design of the test included exposure of *Lemna gibba* (called a parallel bioassay) to the test chemical in confined glass containers and, thus, increased exposure

compared to the free floating macrophytes is expected. Therefore, the effects to *Lemna gibba* in the test may have been exaggerated (or was conservative for the purpose of a higher tier study). Taking these factors into consideration, the NOEC of 0.32 µg/L was chosen to assess the potential risk under more realistic conditions. Based on the NOEC 0.32 µg/L the tier I risk quotient did exceed the trigger value of one (RQ: 29 (NOEC without recovery)). To further characterize this risk for the laboratory and higher tier mesocosm/microcosm studies, input from spray drift (6%) and/or runoff scenarios were also assessed. The tier I risk quotients were not exceeded for amphibian exposure to indaziflam, taking into consideration drift and potential runoff (Table 14, Appendix I). Since the higher tier mesocosm/microcosm studies examine the potential risk to a number of macrophyte species under relevant environmental conditions, taking into account, exposure to the transformation products, and was the lowest endpoint for the screening level risk assessment, further refinement of the risk was based on the results of the higher tier studies. The tier I risk quotients were still exceeded for the higher tier mesocosm studies (Table 14, Appendix I). In order to mitigate for the potential risk to aquatic plants from exposure to indaziflam, aquatic buffer zones (to mitigate for spray drift) and runoff statements will be required on the label.

For marine species, indaziflam did not cause adverse effects to marine amphipod (LC_{50}>1.4 mg/L). Following exposure to indaziflam, Eastern oyster (*Crassostrea virginica*) exhibited up to 91% shell reduction in the highest test concentration (1.8 mg/L)(EC_{50}: 0.92 mg/L). Indaziflam also caused up to 100% mortality in sheepshead minnow at the highest test concentration (96 hour LC_{50}: 0.96 mg/L), and a 90 to 98% inhibition in cell density following exposure of saltwater diatom (*Skeletonema costatum*) to indaziflam (EC_{50}: 23 µg/L). Despite the adverse effects noted in the toxicity studies, the expected concentration of indaziflam in water is low and, thus, the screening level risk quotients did not exceed the trigger value of one.

4.3 Incident reports / additional considerations

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the U.S. EPA Ecological Incident Information System (EIIS). Specific information regarding the mandatory reporting system regulations that came into force April 26 2007 under the PCP Act can be found at http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

As of July 11, 2011, no environmental incident reports were found for indaziflam.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims for Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

Efficacy data from 37 field trials conducted during a four year period (2005 to 2008) were submitted.

The trials were conducted in eight states of the U.S. and were of an appropriate experimental design. The trials were conducted on a wide range of soil types with organic matter content from 0.3% to 3.5% and pH varying from 5.3 to 8.3. The efficacy of multiple rates of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide (25-100 g a.i./ha) was assessed to determine the lowest effective rate (LER).

When applied as a pre-emergence treatment, the efficacy of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide, applied alone (37 trials) or in a tank mixture with glyphosate (12 trials) or glufosinate-ammonium (six trials) for the control of labelled weeds was visually assessed and reported as a percentage (%) in comparison to an untreated weedy check. Efficacy was evaluated at up to four times throughout the growing season.

5.1.1.1 Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide Applied as an Alone Treatment

The lowest effective rate was determined for seven of the 21 weed species evaluated. Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide applied at a rate of 50 g a.i./ha controlled stork's-bill. Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide applied at a rate of 75 g a.i./ha controlled large crabgrass, spotted spurge, giant foxtail, annual sow-thistle and suppressed prickly lettuce and redroot pigweed.

For the remaining 14 weed species, Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide applied at a rate of 50 g a.i./ha appeared to control lamb's-quarters, black mustard, shepherd's-purse, field bindweed, barnyard grass, Italian ryegrass, white sweet clover, yellow foxtail, common groundsel, wild mustard, wild proso millet and green foxtail. Data provided for wild carrot and velvetleaf were insufficient to support an efficacy claim for these two weed species.

The submitted data were adequate to support the efficacy claims summarized in Table 5.1.1 for both Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide applied pre-emergence at 75 g a.i./ha. Although certain weed species were controlled with a pre-emergence application of Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide at 50 g a.i./ha, it should be understood that it is very difficult to predict which weed species will emerge following a pre-emergence application (with respect to weeds) of Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide. Therefore, labelling and use of a rate lower than 75 g a.i./ha may result in unsatisfactory overall weed control, given that the objective in an orchard and vineyard setting is to control many weed species.

Table 5.1.1 Application rates and weed control claims for Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

Application Rate	Weed Species
Indaziflam 200 SC Herbicide 375 mL/ha (75 g a.i./ha) OR Indaziflam 500 SC Herbicide 150 mL/ha (75 g a.i./ha)	Barnyard grass Giant foxtail Green foxtail Italian ryegrass Large crabgrass Wild proso millet Yellow foxtail Annual sow-thistle Black mustard Common groundsel Field bindweed Lamb's-quarters Prickly lettuce (suppression only) Redroot pigweed (suppression only) Shepherd's-purse Spotted spurge Stork's-bill White sweetclover Wild mustard

5.1.1.2 Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide Applied in a Tank Mixture With Glyphosate or Glufosinate-Ammonium Herbicides

Adequate data were provided to support weed control claims for the herbicide tank mixture of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide with either glyphosate or glufosinate-ammonium (Table 5.1.2).

Table 5.1.2 Application rates and weed control claims for Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide in tank mixture with either glyphosate or glufosinate-ammonium herbicide

Products	Rates	Crop	Weeds Controlled	Remarks
Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide + Ignite SN Herbicide	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 2.7 – 5 L/ha	Apple, Pear, Peach, Plum, Grapes	Weed species controlled by Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide alone plus burndown control of emerged weeds.	Consult the label of the tank mix partner(s) for further instructions regarding directions for use, restrictions and precautions.
Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide + Roundup Weathermax Roundup Ultra Roundup Ultra2 Roundup Ultra Max Roundup Transorb HC IPCO Factor 540 R/T 540 Liquid	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.5 - 8 L/ha	Apple, Pear, Apricot, Cherry (sweet/sour), Peach, Plum, Grapes, Chestnut, Walnut, Japanese heartnut		
	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.5-2.33 L/ha	Filbert, Hazelnut		
Indaziflam (Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide) Herbicide + Touchdown Total	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.6 – 8.6 L/ha	Apple, Pear, Apricot, Cherry (sweet/sour), Peach, Plum, Grapes, Chestnut, Walnut, Japanese heartnut		
	375 mL/ha (Indaziflam 200 SC Herbicide) or 150 mL/ha (Indaziflam 500 SC Herbicide) + 1.8 – 2.5 L/ha	Filbert, Hazelnut		

5.2 Phytotoxicity to Host Plants

5.2.1 Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

Crop tolerance data were submitted from 30 field trials conducted on almond (three trials), apple (eight trials), apricot (three trials), grape (ten trials), peach (two trials), pistachio (two trials), sweet cherry (one trial) and walnut (one trial) during a three year period (2006 to 2008). These crops were representatives of the labelled crops: pome fruit (apple, pear), stone fruit (apricot, cherry, nectarine, peach, plum), tree nuts (almond, hazelnut, filbert, walnut, chestnut, Japanese heartnut) and grapes.

The trials were conducted in five states of the U.S. and were of an appropriate experimental design. The trials were conducted on a wide range of soil types with organic matter content from 0.3% to 3.5% and pH varying from 5.4 to 8.7. Treatments of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide at the supported application rate (i.e. 75 g a.i./ha) as well as at exaggerated rates of 100 g a.i./ha and 150 g a.i./ha were assessed to determine the degree of phytotoxicity.

5.2.1.1 Representative Crops Assessed

Crop tolerance was assessed after a directed spray of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide alone or in a tank mixture with glyphosate or glufosinate-ammonium to the ground in several representative pome, stone, nut tree crops (almond, apple, apricot, peach sweet cherry, walnut and pistachio) and grapes. Data showed that the representative crops were tolerant to a directed spray (without foliar contact) of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide alone or in a tank mixture with glyphosate or glufosinate-ammonium. Reported crop injury was 0% for all trials at all ratings for all crops assessed.

5.2.1.2 Supported Claims

Crop injury data support crop tolerance claims for pome fruit (apple, pear), stone fruit (apricot, cherry, nectarine, peach, plum), tree nuts (almond, hazelnut, filbert, walnut, chestnut, Japanese heartnut) and grapes that have been established for at least three full growing seasons with a directed spray of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide at 75 g a.i./ha alone or in tank mixture with glyphosate or glufosinate-ammonium.

Although the tolerance of pear, plum, filbert, chestnut, and Japanese heartnut was not specifically evaluated, it is anticipated that these crops would exhibit adequate tolerance to Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide since crop tolerance data made available for several representative pome, stone and nut tree crops (almond, apple, apricot, peach, sweet cherry, walnut and pistachio) demonstrated that these crops were tolerant of Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide applied at rates at or above the proposed rate of 75 g a.i./ha. Crop tolerance data also indicated that grapes can be expected to exhibit adequate tolerance to Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide

when applied in accordance with the proposed labels. Reported crop injury was 0% for all trials at all ratings for all crops assessed. Since indaziflam is applied directly to the soil and not to crop foliage, it is anticipated that injury would occur only if root uptake took place or precautions were not taken to control drift. There is a cautionary statement on the proposed label that indicates crop injury may occur if certain situations are present. Given the similar growth characteristics of tree crops, and given that these herbicides are not directly applied to trees or grape vines, and given that the proposed labels include a cautionary statement to not apply these products under certain conditions (e.g. where there is soil cracking), substantial differences in tolerance would not be expected among tree species. Therefore, the data support an application of 75 g a.i./ha of Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide alone, or in tank mixture with labeled rates of glyphosate products (where glyphosate is present as the potassium salt) or glufosinate-ammonium in all proposed tree crops and in grape vineyards.

5.3 Impact on Succeeding Crops

5.3.1 Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

It was indicated by the applicant that as labelled host crops are grown continuously for many years, the labelling of rotational cropping instructions should not be required. While orchard crops and grapes are grown continuously, there is a possibility that crops other than those labelled could be grown following the removal of an orchard or vineyard that was previously treated with indaziflam, residues from which may remain in soil. Therefore, a cautionary statement was added to the labels of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide in which it is advice from a Bayer CropScience representative should be sought prior to planting other crops (i.e. other than those appearing on the label) following removal of an orchard or vineyard that was previously treated with indaziflam.

5.4 Sustainability

5.4.1 Survey of Alternatives

5.4.1.1 Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide

Several herbicides are available for use in vineyards and orchards. These include products having modes of action (MOA) from the following MOA groups according to the WSSA classification:

- for grapes: 5, 7, 9, 10, 14, 15, 20, & 22, and
- for apples 1, 3, 4, 5, 6, 7, 9, 10, 11, 14, 15, 20, & 22

Both pre-emergence residual and post-emergence products are available.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide provides an additional option for herbicide group rotation for controlling annual grass and broadleaf weeds in pome fruit, stone fruit, tree nuts and grape. The use of Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide does not restrict the sequential use of other chemicals of alternate modes of action.

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

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of selecting naturally resistant biotypes. Therefore, Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide should be used in rotation with herbicides having different modes of action.

Both Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are alternative herbicides to those belonging to Group 2, 4, 5, 7, 9, and 22 chemistries for pome fruit, stone fruit, tree nut and grape growers. Herbicide-resistant populations from 15 weed species have been discovered and are variously resistant to atrazine & metribuzin (Group 5); imazethapyr, thifensulfuronmethyl, flumetsulam, imazamox, primisulfuron-methyl (Group 2); linuron, monolinuron, and prometryn (Group 7); glyphosate (Group 9); paraquat (Group 22); and 2,4-D (Group 4 synthetic auxins).

When applied at the labelled use-rate, Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are expected to control or suppress biotypes of labelled weeds that are resistant to other groups of chemistries. Consequently, indaziflam has the potential to delay the onset of herbicide resistance and to combat certain forms of resistance once present.

Both Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide labels include the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action.*

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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 [those that meet all four criteria outlined in the policy, i.e., 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*] (Table 15, Appendix I).

During the review of indaziflam and Indizaflam Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide, PMRA has taken into account the federal Toxic Substances Management Policy and has followed its Regulatory Directive DIR99-03. It has been determined that this product does not meet TSMP Track-1 criteria because:

- Indaziflam does meet the criteria for persistence in soil based on a half life calculation. Its values for half-life in soil (maximum DT_{50} of >1 year (lab), 22.5 days (field)), is above the TSMP Track-1 cut-off criteria for soil (≥ 182 days). It also meets the criteria for sediment (>365 days).

- Indaziflam is not bioaccumulative. The octanol-water partition coefficient (log K_{ow}) is 2.8, which is below the TSMP Track-1 cut-off criterion of ≥5.0, and the bioconcentration factor is 16 which is below the cut-off criterion of 5000.

- Indaziflam does meet the criteria for toxicity.

- Indaziflam does not form any major transformation products that meet the TSMP Track-1 criteria.

- Indaziflam (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

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

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for indaziflam is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after long-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. The primary effect was neurotoxicity. Other targets in short-term and chronic studies in laboratory animals were effects on the reproductive potential, body weights, liver, kidneys and thyroid glands. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residue in plants (apple, grape and sugarcane) is adequately understood. The residue definition for enforcement purposes in plant products is indaziflam and the metabolite 1-fluoroethyl diaminotriazine (FDAT). A residue definition for risk assessment and enforcement in animal commodities was not established. The domestic use of indaziflam on apples, pears, peaches, nectarines, plums, cherries, apricots, almonds, pecans and grapes does not result in risks of concern to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits (MRLs) to protect human health. The PMRA recommends that the following MRLs be specified for residues of indaziflam.

MRLs (ppm)	Foods
0.01	Pome Fruits (Crop Group 11-09)
0.01	Stone fruits (Crop Group 12-09)
0.01	Tree Nuts (Crop Group 14-11)
0.01	Small fruit vine climbing subgroup, except fuzzy kiwi (Crop Subgroup 13-07F)

Mixers, loaders and applicators handling Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide and workers re-entering treated orchards, vineyards and tree nut areas are not expected to be exposed to levels of indaziflam that will result in an unacceptable risk when Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are used according to label directions. The personal protective equipment on the product label is adequate to protect workers who mix, load and apply Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide.

7.2 Environmental Risk

Indaziflam does not present a risk to wild mammals, birds, bees, invertebrates, freshwater or marine invertebrates and fish, and amphibians. However, indaziflam does affect terrestrial plants and aquatic plants. Therefore, to protect from the effects resulting from spray drift to non target terrestrial plants and aquatic plants, buffer zones of 15 metres and one metre are required for terrestrial plants and aquatic habitats, respectively. To protect aquatic plants from the potential effects of runoff, a label statement to minimize runoff will be required, as well as hazard based label statements for toxicity to terrestrial and aquatic plants.

7.3 Value

The data submitted to register Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide are adequate to describe their efficacy for use in pome fruit, stone fruit, tree nuts and grapes. A single pre-emergence application of Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide at 75 g a.i./ha can be expected to result in the control of barnyard grass, giant foxtail, green foxtail, Italian ryegrass, large crabgrass, wild proso millet, yellow foxtail, annual sow-thistle, black mustard, common groundsel, field bindweed, lamb's-quarters, prickly lettuce (suppression only), redroot pigweed (suppression only), shepherd's purse, spotted spurge,

stork's-bill, white sweet clover and wild mustard. Efficacy data also demonstrated that either Indaziflam 200 SC Herbicide or Indaziflam 500 SC Herbicide may be applied in combination with either glyphosate or glufosinate-ammonium for burndown of emerged weeds. The submitted phytotoxicity data demonstrate an adequate margin of crop safety of pome fruit, stone fruit, tree nuts and grapes to Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide.

As indaziflam belongs to a new chemistry group (Weed Science Society of America Group 29, the akylazines) that inhibits the synthesis of cellulose (cell wall synthesis), it represents a mode of action that is different from those of registered herbicides, including herbicides that are currently registered for use in labelled crops and for which weed resistance has been reported (WSSA Groups 2, 4, 5, 7, 9 and 22). Indaziflam, therefore, has the potential to delay the onset of resistance of weeds to currently used herbicides of other chemistries and to mitigate resistance to currently used herbicides that may already be present.

7.4 Unsupported Uses

Certain claims originally proposed by the applicant were not supported by the PMRA because value was not adequately demonstrated. Efficacy data were inadequate to support efficacy claims for wild carrot and velvetleaf.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Indaziflam Technical Herbicide, Indaziflam 200 SC Herbicide and Indaziflam 500 SC Herbicide, containing the technical grade active ingredient indaziflam, to control both grassy and broadleaf weeds in pome fruit, stone fruit, tree nuts and grape.

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

List of Abbreviations

^{o}C	Celcius
µg	microgram(s)
a.i.	active ingredient
ADI	acceptable daily intake
Aq	aqueous
ARfD	acute reference dose
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDF	cumulative distribution factor
Chol	cholesterol
CV	coefficient of variation
cm^2	centimeter(s) squared
DACT	diaminochlorotriazine
DNT	devepomental neurotoxicity
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 50% (the dose required to observe a 90% decline in concentration)
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ER_{50}	effective rate for 50% of the population
FDA	Food and Drugs Act
FDAT	fluoroethyl diaminotriazine
F0	parental generation
FIR	food intake rate
g	gram(s)
GI	gastrointestinal
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene
HPLC	high pressure liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%

LER	lowest effective rate
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting
m^3	metre(s) cubed
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
min	minute(s)
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
ng	nanogram(s)
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand white
Pa	Pascals
PCPA	Pest Control Products Act
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
REI	re-entry interval
RQ	risk quotient
SC	soluble concentrate
SSD5	species sensitive distribution
$t_{1/2}$	half-life
T4	thyroxine
TGAI	technical grade active ingredient
TRR	total radioactive residue
TRT	treatment
TSH	thyroid stimulatory hormone
TSMP	Toxic Substances Management Policy
U.S.	United States
UV	ultraviolet
v/v	volume per volume dilution
WSSA	Weed Science Society of America
wt	weight(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant		*active*	1	*LOQ*	*specify matrix*	*PMRA #*
		metabolite				
Animal						
Soil	DH-002-S06-01	AE1170437 (parent)	LC-MS/MS	0.8 ppb		1769215
	DH-002-S06-01	AE1170437 diaminotriazine	LC-MS/MS	0.3 ppb		1769215
	DH-002-S06-01	AE2158968	LC-MS/MS	0.3 ppb		1769215
	DH-002-S06-01	AE2158969	LC-MS/MS	0.4 ppb		1769215
	DH-002-S06-01	AE2300077	LC-MS/MS	0.3 ppb		1769215
	DH-002-S06-01	BCS-AA10201	LC-MS/MS	0.5 ppb		1769215
Sediment	DH-002-S06-01	AE1170437 (parent)	LC-MS/MS	0.2 ppb		1769215
	DH-002-S06-01	AE1170437 diaminotriazine	LC-MS/MS	0.3 ppb		1769215
	DH-002-S06-01	AE2158968	LC-MS/MS	0.2 ppb		1769215
	DH-002-S06-01	AE2158969	LC-MS/MS	0.3 ppb		1769215
	DH-002-S06-01	AE2300077	LC-MS/MS	0.4 ppb		1769215
	DH-002-S06-01	BCS-AA10201	LC-MS/MS	0.4 ppb		1769215
Water	DH-005-W07-01	AE1170437 (parent)	LC-MS/MS	0.01 ppb		1769219
	DH-005-W07-01	AE1170437 diaminotriazine	LC-MS/MS	0.02 ppb		1769219
	DH-005-W07-01	AE2158968	LC-MS/MS	0.01 ppb		1769219
	DH-005-W07-01	AE2158969	LC-MS/MS	0.01 ppb		1769219
	DH-005-W07-01	AE2300077	LC-MS/MS	0.01 ppb		1769219
	DH-005-W07-01	BCS-AA10201	LC-MS/MS	0.02 ppb		1769219
Plant	DH-003-P07-01	Indaziflam and FDAT	LC-MS/MS (liquid chromatography with tandem mass spectrometry); these methods are procedurally identical	0.01 ppm for each analyte	Whole oranges and almond nutmeats	PMRA #1769479
	DH-003-P07-02 Enforcement Method			0.005 ppm for each analyte	Whole oranges and almond nutmeats	PMRA #s1769477 1769476 and 1769480
Animal	DH-007-A09-01	Indaziflam and FDAT	LC-MS/MS	0.01 ppm for each analyte	Chicken breast	PMRA #1769225

Table 2 Toxicity Profile of End-use Product(s) Containing Indaziflam

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute Toxicity Studies – Indaziflam 500 SC	
Acute Oral Toxicity (Gavage; DACO 4.6.1 – Acute Toxic Class Method) Wistar Rats PMRA 1769455	Oral LD_{50} = 2500 mg/kg bw **Low Toxicity** NB. Tremors were noted at day 2
Acute Dermal Toxicity (DACO 4.6.2) Wistar Rats PMRA 1769457	Dermal LD_{50} > 2000 mg/kg bw **Low Toxicity**
Acute Inhalation Toxicity (DACO 4.6.3) Wistar Rats PMRA 1769461	Inhalation LC_{50} > 1.937 mg/L or 1937 mg/m^3 **Low Toxicity** NB. Clinical signs of neurotoxicity noted (high-legged gait, staggering gait, limp, convulsions, tremors, mydriasis)
Primary Eye Irritation (DACO 4.6.4) NZW Rabbits PMRA 1769463	MAS (24, 48, 72 hours) = 0.44/110 **Non-irritating**
Primary Dermal Irritation (DACO 4.6.5) NZW Rabbits PMRA 1769465	MAS (24, 48. 72 hours) = 0/8 **Non-irritating**
Dermal Sensitization – Buehler Patch Test (DACO 4.6.6) Guinea Pigs PMRA 1769467	**Not a dermal sensitizer**

Table 3 Toxicity Profile of Technical Indaziflam

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Toxicokinetic Studies	
A preliminary series of metabolism studies were performed on male rats with [Indane-3-^{14}C]AE 1170437 and [Triazine-2,4-^{14}C] AE1170437 via single oral low dose (11.50 and 14.98 mg/kg bw, respectively) and single oral low dose (14.0 and 13.35 mg/kg bw, respectively) with bile cannulation. Following these studies, females were dosed with 4.84 and 8.85 mg/kg bw of [Indane-3-^{14}C]AE 1170437 and [Triazine-2,4-^{14}C] AE1170437, respectively, and male rats were dosed with 558.7 and 722.8 mg/kg bw of [Indane-3-^{14}C]AE 1170437 and [Triazine-2,4-^{14}C] AE1170437, respectively. In order to determine plasma curves, male and female rats implanted with jugular cannulae were dosed with 13.73 or 2.90 mg/kg bw of [Indane-3-^{14}C]AE 1170437 (♂/♀, respectively) or 16.29 or 13.12 mg/kg bw of [Triazine-2,4-^{14}C] AE1170437(♂/♀, respectively). In the single oral low dose studies on male rats, AE 1170437 was well absorbed, extensively metabolized and mostly excreted within 24 hours. In both the oral low dose and bile cannulation assays, the majority of the recovered radioactivity was found in the GI tract, with other tissues of note being the liver, kidneys, fat, skin, heart, bone, brain, lung, spleen and thyroid gland. In the bile cannulation assay, following 48 hours, more of the triazine-labelled AE 1170437 was found in the tissues than the indane-labelled AE 1170437 or in the low dose oral assay. The main excretory pathyways were via the bile and urine with between 5 and 16% parent compound excreted unmetabolized in the faeces. The uptake of AE 1170437 and phase I excretion ($t_{1/2}$ = 10 min) was rapid. Phase II excretion had a $t_{1/2}$ of between 13 – 18 hours for the triazine ring and 31 – 33 hours for the indane ring. Urinary excretion was primarily in the first 12 hours and faecal excretion in the first 24. In females, roughly equivalent amounts were excreted in the urine and faeces. In males, faecal excretion was the primary route. Maximum concentrations (C_{max}) and area under the curve (AUC) values were similar in females dosed with the triazine-labelled compound to males dosed with either label. Both these values were lower in females given the indane-labelled ring, indicating that females metabolize indaziflam differently than males. This is supported by clearance values which were highest for females dosed with the indane-labelled compound, identical for males and lowest for females given the triazine-labelled compound. Plasmakinetics were not performed in the high-dose experiments. Females retained less radioactivity in the tissues than males, tissue levels were highest in the GI tract, liver and skin. There was proportionately less radioactivity left in the GI tract, liver, skin, thyroid gland and general carcass in high-dose males than low-dose males but proportionately equivalent amounts in the spleen. In the case of bone, brain, fat, heart, muscle, gonads and whole blood values, there was an increase more of the indane ring was retained in the tissue at higher doses than the triazine label. The metabolic process was well characterized with less than 11% of the metabolites unidentified. The major metabolite was carboxylic acid in the faeces and urine in the low-dose females and high-dose males, with low-dose females excreting much less unchanged parent than low-dose males indicating a more extensive metabolism. High-dose males excreted significantly more unchanged parent than low-dose males indicating a saturation of the system. There were no qualitative differences between the low-dose male and female studies, though there was a male high-dose urinary metabolite, 3-ketohydroxymethyl, which only appeared in the bile cannulation studies at low-dose. The major metabolic pathways involved oxidation of indaziflam resulting in the formation of carboxylic acid as the main metabolite followed by the formation of dihydroxy, 3-hydroxyindane acid and the 3-hydroxyindane acid epimer and hydroxyl GA. A minor, but important, metabolite was fluoroethyl diaminotriazine (FDAT) as it is similar to the atrazine metabolite, diaminochlorotriazine (DACT), which is not a metabolite of indaziflam. DACT has been implicated in female reproductive toxicity. This was found in low-dose female and high-dose male studies at low levels.	
Acute Toxicity Studies - TGAI	
Acute Oral Toxicity Study (Gavage; DACO 4.2.1 – Acute	Oral LD_{50} ♀ ≥ 5000 mg/kg bw

Study Type/Animal/PMRA #	Study Results
Toxic Class Method) Wistar Rats PMRA 1769092	Low Toxicity
Acute Oral Toxicity Study (Gavage; DACO 4.2.1 – Acute Toxic Class Method) Wistar Rats PMRA 1769095	Oral LD_{50} = 2500 mg/kg bw Low Toxicity
Acute Dermal Toxicity Study (DACO 4.2.2) Wistar Rats PMRA 1769096	Dermal LD_{50} ♂ > 2000 mg/kg bw ♀ > 2000 mg/kg bw ♂♀ > 2000 mg/kg bw Low Toxicity
Acute Inhalation Toxicity (DACO 4.2.3) Wistar Rats PMRA 1769099	Inhalation LC_{50} ♂ > 2.3 mg/L ♀ > 2.3 mg/L ♂♀ > 2.3 mg/L Low Toxicity
Primary Eye Irritation (DACO 4.2.4) NZW Rabbits PMRA 1769100	MIS (1hour) 4/110 MAS (24, 48, 82 hours) 0.67/110 Minimally irritating
Primary Dermal Irritation (DACO 4.2.5) NZW Rabbit PMRA 1769103	MAS (24, 48, 72 hours) 0/8 Non-irritating
Dermal Sensitization – Local Lymph Node Assay (DACO 4.2.6) CBA/J Mice PMRA 1769104	Not a dermal sensitizer
Short-Term Toxicity Studies	
90-day Dietary (DACO 4.3.1) C57BL/6J Mice Non-guideline/ Acceptable PMRA 1769109	LOAEL = 218/256 mg/kg bw/day NOAEL = 91/118 mg/kg bw/day 218/256 mg/kg bw/day: 1 mortality ♀ (with hunched posture, wasted appearance, body weight loss and ↓ fc, emaciation, small thymus, black focus on spleen, dark liver, mottled red lungs, dilated gallbladder); ↓ bw, ↓ albumin, ↓ heart wts, plasmacytosis in submax. lymph nodes ♂♀; ↓ chol, ↓ kidney wts, ↑ lymphoid hyperplasia in submax. lymph nodes, focal tubular degeneration in testes ♂; ↓ protein, ↓ spleen wts, ↓ uterine wts ♀
90-day Dietary (DACO 4.3.1) Wistar Rats PMRA 1769108	LOAEL= 338/410 mg/kg bw/day NOAEL = 14/16 mg/kg bw/day 338/410 mg/kg bw/day: ↑ gross liver size ♂♀; ↑ liver wts, ↑TSH and ↓ T4 at 3 weeks, ↑ diffuse follicular cell hypertrophy in thyroid, ↑ interstitial mononuclear cell infiltrate in kidneys ♂; ↓ bwg wks 1, 7 and 13, ↑ chol, ↑ liver wts, ↑ prominent liver lobulation ♀ Recovery: ↓ bw and bwg ♂; ↑ thyroid wts ♀
90-day Toxicity (Gavage; DACO 4.3.2) Beagle dog PMRA 1769110	LOAEL = 15 mg/kg bw/day NOAEL = 7.5 mg/kg bw/day 15 mg/kg bw/day: ↑ axonal degeneration w/in sensory tract of dorsal spinal cord, sciatic nerve and brain stem ♂♀

Study Type/Animal/PMRA #	Study Results
12-month Dietary Toxicity (DACO 4.3.2) Beagle dog PMRA 1769112	LOAEL = 6/7 mg/kg bw/day NOAEL = 2 mg/kg bw/day 6/7 mg/kg bw/day: ↑ axonal degeneration w/in spinal cord, sciatic nerve and brain stem ♂♀
4 week dermal toxicity (DACO 4.3.5) Wistar Rats PMRA 1769116	Dermal LOAEL = 200 mg/kg bw/day Dermal NOAEL = 40 mg/kg bw/day Systemic LOAEL = 1000 mg/kg bw/day Systemic NOAEL = 200 mg/kg bw/day 200 mg/kg bw/day: skin thickening in ♂ and skin reddening in ♀
Chronic Toxicity/Oncogenicity Studies	
Carcinogenicity (Dietary; DACO 4.4.3) C57BL/6J Mice PMRA 1769128	LOAEL = 142/168 mg/kg bw/day NOAEL = 34/42 mg/kg bw/day 142/168 mg/kg bw/day: ↓ bw/bwg, ↓ fc, ↑ centrilobular hepatocellular vacuolation concurrent with ↓ generalized hepatocellular vacuolation, ↑ red and black foci in stomach and glandular erosion/necrosis ♂♀; ↑ hyperplasia of collecting ducts and pelvic epithelium, unilateral and bilateral papillary necrosis and intratubular yellow/brown materials, ↓ corticoepithelial vacuolation and hyaline cases with tubular dilatation , ↑ prominent lobulations in liver, ↑ atrophy at ter sac of adrenal glands, seminal vesicles and thymus ♂; ↑ pelvic epithelium hyperplasia, ↓ ter liver wts, ↑ brown foci in liver, ↑ in lobular torsion, ↓ uterine wts at int sac, ↑ atrophied uteri and endometrial atrophy, ↑ blood-filled cysts/follicles ♀ No evidence of carcinogenicity
Combined Chronic/Carcinogencity (Dietary; DACO 4.4.4) Wistar Rats PMRA 1769117	LOAEL = 118/167 mg/kg bw/day NOAEL = 12/17 mg/kg bw/day ≥ 118/167 mg/kg bw/day: ↑ dilated pupils and soiled anogenital region, ↑ phos, ↓ bilirubin, ↓ glucose, ↑ chol, ↑ trig in first year, ↑ dark liver, enlarged liver, hepatocellular hypertrophy, ↑ colloid alteration in thyroid ♂♀; ↑ rel liver wt @ int sac, ↑ follicular cell hypertrophy ♂; dilated pupils, tremors, low alertness, noisy respiration in the first year, limited use of limbs, tremors, splayed hindlimbs, low alertness, ↓ bw and bwg, ↑degenerative changes in pars nervosa in pituitary gland and median eminence in brain ♀ No evidence of carcinogenicity
Developmental/Reproductive Toxicity Studies	
One Generation Reproductive Toxicity (Dietary; DACO 4.5.1) Wistar Rats Range-finding PMRA 1769139	Parental: 188.7/211.7 mg/kg bw/day: ↓ bwg, fc, fe, ↑ liver and thyroid wts F0, ↓ spleen wts F1 ♀ 514.9/545.7 mg/kg bw/day: ↑ kidney, liver, adrenal wts F0♂; ↓ bw, ↓ # implantations/dam and litter size, ↓ uterine weights F0/F1 Offspring: 514.9/545.7 mg/kg bw/day: ↓ bw and bwg pups ♀ (day 21), ↓ spleen wts
Multi-Generation Reproductive Toxicity (Dietary; DACO 4.5.1) Wistar Rats PMRA 1769140	Parental LOAEL = 317.6/355.5 mg/kg bw/day Parental NOAEL = 68.9/83.2 mg/kg bw/day 317.6/355.5 mg/kg bw/day: ↓ bwg and fc (premating) F0/F1 ♂/♀; ↑ kidney wts F0, ↑ hyaline degeneration and tubular regeneration F0/F1; ↑ hair loss and hair thinning F0, ↑ coarse tremors F0, ↓ bw/bwg and fe F0/F1 (lactation and gestation), ↓ thymus wts F0/F1, ↓ adrenal wts w/ cytoplasmic vacuolation F0, ↓ spleen wts F0 ♀ Reproductive LOAEL = 317.6/355.5 mg/kg bw/day

Study Type/Animal/PMRA #	Study Results
	Reproductive NOAEL = 68.9/83.2 mg/kg bw/day 317.6/355.5 mg/kg bw/day: delayed sexual maturation ♂/♀; ↓ implantation sites and ↓ litter size F0/F1, ↓ corpora lutea F1, ↓ pituitary wt F1, ↓ uterine and ovarian wts F0 ♀ Offspring LOAEL = 317.6/355.5 mg/kg bw/day Offspring NOAEL = 69.6/87.2 mg/kg bw/day 317.6/355.5 mg/kg bw/day: ↓ bw and bwg ♂/♀F_1; ↓ mean litter sizes, delayed preputial separation and vaginal patency in F1/F2, ↓ spleen wts; ↑ tremors, morbidity/mortality, weakness, stains (perianal, urine, nasal), distended abdomen, ↑ activity, ↑ reactivity, ↑ diarrhea and soft stool F1 ♂♀; ↓ abs brain wts F1♂ No sensitivity to the young
Prenatal Developmental Toxicity (Gavage; DACO 4.5.2) SD Rats PMRA 1769164	Maternal LOAEL = 200 mg/kg bw/day Maternal NOAEL = 25 mg/kg bw/day 200 mg/kg bw/day: ↓ bw and fc GD 6 – 8 Offspring LOAEL = 200 mg/kg bw/day Offspring NOAEL = 25 mg/kg bw/day 200 mg/kg bw/day: ↓ bw
Prenatal Developmental Toxicity (Gavage; DACO 4.5.3) NZW Rabbits PMRA 1769167	Maternal LOAEL = 60 mg/kg bw/day Maternal NOAEL = 25 mg/kg bw/day 60 mg/kg bw/day: 1 abortion (GD 27), ↓ bwg and fc (GD 6-8, 22-26), ↓ corrected bwg Offspring LOAEL = 60 mg/kg bw/day Offspring NOAEL = 25 mg/kg bw/day 60 mg/kg bw/day: ↓ bw, ↑ presence of 27 presacral vertebrae,↑ detached 13th thoracic rib
Genotoxicity Studies	
Bacterial Reverse Mutation Assay (DACO 4.5.4) Salmonella typhimurium PMRA 1769168	Negative
Bacterial Reverse Mutation Assay (DACO 4.5.4) Salmonella typhimurium PMRA 1769176	Negative
In vitro mammalian cell assay (DACO 4.5.5) V79 cell cultures PMRA 1769180	Negative
In vitro mammalian clastogenicity (DACO 4.5.6) V79 cell cultures PMRA 1769185	Negative

Study Type/Animal/PMRA #	Study Results
In vivo cytogenetics (Intraperioneal; DACO 4.5.7) Hsd/Win:NMRI Mice PMRA 1769191	Negative
Neurotoxicity Studies	
Acute Neurotoxicity Study (Gavage; DACO 4.5.12) Wistar Rats PMRA 1769159	LOAEL = 100 mg/kg bw in ♀s and 500 mg/kg bw in ♂s NOAEL = 50 mg/kg bw in ♀s and 100 mg/kg bw in ♂s 100 mg/kg bw: ↓ session activity in ♀
Subchronic Neurotoxicity Study (Dietary; DACO 4.5.13) Wistar Rats PMRA 1769161	LOAEL = 585.7/580.9 mg/kg bw/day NOAEL = 243.6/306.9 mg/kg bw/day 585.7/580.9 mg/kg bw/day: tremors, ↓ fc ♂♀; ↑ red lacrimal and nasal staining and repetitive chewing, ↓ bw, ↑ red lacrimal and perianal staining and 1 incident of diarrhoea, repetitive chewing movements and tremors at FOB, ↑ lacrimation and ventral staining at necropsy ♂; urine and perianal staining, single incidences of perianal and urine staining and tremors at week 4 and ↓ urination at all time points at FOB, ↓ motor activity at weeks 2 – 8 and ↓ locomotor activity at all time points, ↑ nerve fibre degeneration of spinal nerve root ♀
Developmental Neurotoxicity Study (Dietary; DACO 4.5.14) Wistar Rats PMRA 1769163	Maternal LOAEL = 559.7/345.4 mg/kg bw/day Maternal NOAEL = 80.8 mg/kg bw/day Offspring LOAEL = 559.4/345.4 mg/kg bw/day Offspring NOAEL = 80.8 mg/kg bw/day Maternal Toxicity: 559.4/345.4 mg/kg bw/day: ↑ coarse tremors, repetitive jaw chewing, dilated pupils with and without pupil reflex, signs of lacrimal and nasal staining (all signs abated when dose reduced to 4000 mg/kg); ↓ bw to LD7, ↓ bwg GD 0 – 20; ↓ fc LD 0 – 7; ↑ elective sacrifices where dam produced fewer than 3 pups of each sex or less than 7 pups surviving to LD 4. Offspring Toxicity: 559.4/345.4 mg/kg bw/day: ↓ bw from PND 0 – 21 in litters and ♀ and from PND 0 – 17 and 28 – 49 in ♂
Special Studies (non-guideline)	
Immunotoxicity Feeding Study (DACO 4.8) Wistar Rats PMRA 1769200	LOAEL = 258.8/334.2 mg/kg bw/day NOAEL = 27.7/31.0 mg/kg bw/day 258.8/334.2 mg/kg bw/day: ↑ tremors ♀; ↓ bw throughout treatment ♂ and sporadically in ♀; ↓ fc in ♂; ↓ spleen cells available for assay No evidence of immunotoxicity
Metabolites – AE1170437-Carboxylic acid	
Bacterial Reverse Mutation Assay (DACO 4.5.4) Salmonella typhimurium PMRA 1769175 and 1769170	Negative

Study Type/Animal/PMRA #	Study Results
Metabolites – AE1170437-Diaminotraizine	
Bacterial Reverse Mutation Assay (DACO 4.5.4) Salmonella typhimurium PMRA 1769174	Negative
In vitro mammalian cell assay (DACO 4.5.5) V79 cell cultures PMRA #1769181	Negative
In vitro mammalian clastogenicity (DACO 4.5.6) V79 cell cultures PMRA #1769190	Negative
Special female sexual maturation study (Gavage; DACO 4.8) Wistar Rats Non-guideline/ Acceptable PMRA 1769198	72.9 mg/kg bw/day: ↑ salivation; delayed sexual maturation

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Indaziflam

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Acute neurotoxicity study	NOAEL = 50 mg/kg bw Reduced motor activity	100
	ARfD = 0.5 mg/kg bw		
Repeated dietary	12-month dog study	NOAEL = 2 mg/kg bw/day Axonal degeneration	100
	ADI = 0.02 mg/kg bw/day		
Short and Intermediate -term dermal[2]	90-day dog study	NOAEL = 7.5 mg/kg bw/day Axonal degeneration	100
Short and Intermediate -term inhalation[3]	90-day dog study	NOAEL = 7.5 mg/kg bw/day Axonal degeneration	100
Non-dietary oral ingestion (short-term)	N/A		
Aggregate	N/A		
Cancer	N/A		

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

[2]Since an oral NOAEL was selected, a dermal absorption factor 25% was determined based on a weight-of-evidence approach

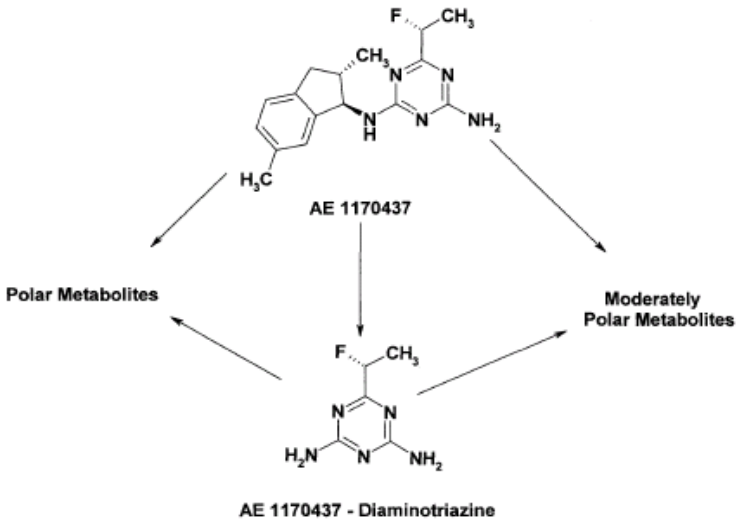
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN PLANTS - APPLES			PMRA # 1769206	
Radiolabel Position	**[Indane-3-^{14}C] and [triazine-2,4-^{14}C]**			
Test Site	Pots maintained outdoors			
Treatment	Soil applications to the base of the trees			
Rate	Split applications totalling 299-315 (TRT1) or 1462-1750 (TRT2) g a.i./ha			
Timing	At flowering and 30 days before sample collection			
Preharvest interval	30 days			
TRRs (expressed as indaziflam equivalents) in apple fruit from trees treated with [indane-3-^{14}C] AE 1170437 were 0.004 ppm and 0.011 ppm following TRT1 and TRT2, respectively. TRRs in apple fruit from trees treated with [triazine-2,4-^{14}C] AE 1170437 were 0.011 ppm and 0.054 ppm, following TRTs 1 and 2, respectively. Extractable residues of 78% and 85% were obtained with the indane label (TRT1 and TRT2, respectively) and 97% (both TRTs) with the triazine label in apple fruit. Overall accountabilities were 55% and 75% for TRT1 and TRT2, respectively (indane label), and 82% (both treatments, triazine label). While several polar compounds had formed (46-76% of TRRs; 0.002 ppm [both labels]), the only identified residue with the indane label was unmetabolized indaziflam, which accounted for 13% of the TRRs (<0.001 ppm) (TRT1) and 8% of the TRRs (<0.001 ppm) (TRT2). The major residue detected, and the only metabolite identified with the triazine label was FDAT, which accounted for 72% of the TRRs (0.008 ppm; TRT1) and 62% of the TRRs (0.033 ppm; TRT2).				
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**
Apple Fruit	Indaziflam	FDAT	--	--
NATURE OF THE RESIDUE IN PLANTS - GRAPES			**PMRA # 1769207**	
Radiolabel Position	**[Indane-3-^{14}C] and [triazine-2,4-^{14}C]**			
Test Site	Pots maintained outdoors			
Treatment	TRT1 and 2: Soil applications at the base of the vines			
Rate	TRT1: Split applications for total rates of 243-277 g a.i./ha TRT2: A single application at a total rate of 974-995 g a.i./ha			
Timing	TRT1: At flowering and 30 days before sample collection TRT2: At flowering; due to phytotoxicity, the second application was not given.			
Preharvest interval	TRT1: 30 days TRT2: 59 days ([Indane-3-^{14}C] label); 46 days ([triazine-2,4-^{14}C] label)			
TRRs (expressed as indaziflam equivalents) in fruit from plants treated with [indane-3-^{14}C] indaziflam were 0.006 ppm and 0.019 ppm, for TRT1 and TRT2, respectively. TRRs in grape fruit from plants treated with [triazine-2,4-^{14}C] indaziflam from TRT1 and TRT2 groups were 0.015 ppm and 0.040 ppm, respectively. Grapes treated with [indane-3-^{14}C] indaziflam from the TRT1 and TRT2 groups had extractable residues of 71 % and 66%, respectively. Grapes with [triazine-2,4-^{14}C] indaziflam from TRT1 and TRT2 groups had extractable residues of 81 % and 96%, respectively. Overall accountability for both labels ranged from 85 to 99%. The major and only residues detected were FDAT; for 43% of the TRRs, 0.006 ppm [TRT1] and 47% of the TRRs; 0.019 ppm [TRT2]) with the triazine label and unmetabolized indaziflam (19% of the TRRs, 0.001 ppm [TRT1] and 24% of the TRRs, 0.005 ppm; TRT2) with the indane label.				

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**
Grape Fruit	Indaziflam	FDAT	--	--
NATURE OF THE RESIDUE IN PLANTS - SUGARCANE			**PMRA # 1769210**	
Radiolabel Position	**[Indane-3-^{14}C] and [triazine-2,4-^{14}C]**			
Test Site	Pots maintained in a greenhouse environment			
Treatment	TRT1: First application to the whole plant and surrounding soil and the second directed to the base of the stalk of mature plants and to the soil TRT2: A single application to both the plant and the surrounding soil when plants were 25-30 cm high			
Rate	Total rates of 296-300 g a.i./ha (TRT1) (950-1020 g a.i./ha [TRT 2])			
Timing	TRT1: The first application was made when the plants were 25-30 cm in height and the second was made 30 days prior to sample collection. TRT2: When plants were 25-30 cm high.			
Preharvest interval	30 days			
TRRs (expressed as indaziflam equivalents) in sugarcane plants stripped of the outer leaves were 0.004 ppm and 0.005 ppm for the indane and triazine labels respectively. Due to extreme phytotoxicity, experiments for TRT2 were terminated without sample collection. With the indane label, 65% of the residues were extractable, while 68% of the residues were extractable with the triazine label. While there were several polar compounds formed, the only identified residue with the indane label was unmetabolized indaziflam (22% of the TRRs, <0.001 ppm) label; the diaminotriazine metabolite (FDAT) (30% of the TRRs, 0.002 ppm) and indaziflam (17% of the TRRs; <0.001 ppm) were observed with the triazine label.				
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**
Sugarcane - whole plant with outer leaves removed	Indaziflam	FDAT Indaziflam	--	--
CONFINED ROTATIONAL CROP STUDY			**PMRA # --**	
Not required as the requested crops are all orchard crops and are therefore, not rotated.				

Proposed metabolic scheme in apples, grapes and sugarcane



The translocation of indaziflam from soil at the base of the plant (apple, grape and sugarcane) and from foliar and soil applications (sugarcane) into the plant is limited. When taken up, the metabolic pathways in the three crops investigated appear to be similar and consist of the metabolic degradation of indaziflam by oxidative hydrolysis of the nitrogen-indane bond to form the metabolite FDAT. No other metabolites were identified.

Based on the results of the plant metabolism studies, the residue definition for both enforcement and risk assessment in apple, grape and sugarcane is indaziflam and the metabolite 1-fluoroethyl diaminotriazine (FDAT).

NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA # 1769201 and 1769202**

Triazine label study: Two lactating goats were dosed orally by capsule with [triazine-2,4-^{14}C] indaziflam at a rate of 47 ppm once daily for five consecutive days. Urine and feces were collected for days 1 to 5 and milk was collected twice daily throughout the study period. The goats were sacrificed 23 hours after the last dose, and edible tissues (liver, kidney, perirenal fat, omental fat, round muscle and loin muscle) were collected. TRRs in milk and tissues were determined using LSC. Residues in extracts were identified and quantitated by reverse-phase HPLC and LC-MS/MS. Although daily urine and fecal samples were collected, they were not analysed to determine how much of the administered dose was excreted.

TRRs (expressed as indaziflam equivalents) in milk samples ranged from 0.037 ppm in day 1 morning milk to 0.067 ppm in day 3 evening milk. TRRs found in tissue samples were 0.816 ppm in liver, 0.022 ppm in loin muscle, 0.025 ppm in round muscle, 0.044 ppm in perirenal fat, 0.032 ppm in omental fat and 0.405 ppm in kidney. The majority of residues (95-100% of the TRRs) were extractable, with <1% to 4% (<0.001 to 0.012 ppm) of the residues remaining unextractable.

Indane radiolabel study: Two lactating goats were dosed orally by capsule with [indane-3-^{14}C] AE 1170437 at a rate of 57 ppm once daily for five consecutive days. Urine and feces were collected for days 1 to 5 and milk was collected twice daily throughout the study period. The goats were sacrificed 23 hours after the last dose, and edible tissues (liver, kidney, perirenal fat, omental fat, round muscle and loin muscle) were collected. TRRs in milk and tissues were determined using LSC. Residues in extracts were identified and quantitated by reverse-phase HPLC and LC-MS/MS. Although daily urine and fecal samples were collected, they were not analysed to determine how much of the administered dose was excreted.

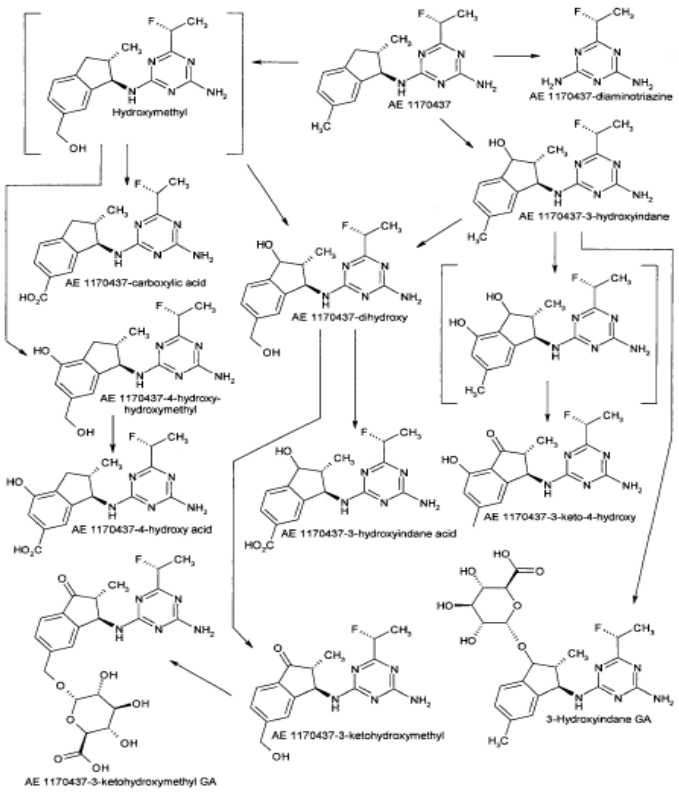
TRRs (expressed as indaziflam equivalents) in milk samples ranged from 0.011 ppm in day 1, day 3 and day 5 morning milk to 0.048 ppm in day 2 evening milk. TRRs found in tissue samples were 0.368 ppm in liver, 0.006 ppm in loin muscle, 0.007 ppm in round muscle, 0.013 ppm in perirenal fat, 0.015 ppm in omental fat and 0.153 ppm in kidney. The majority of residues (85-100% of the TRRs) were extractable, with 2% to 15% (<0.001 to 0.023 ppm) of the residues remaining unextractable. TRRs in the loin and round muscle samples were not further characterized since the TRRs were <0.01 ppm.

Matrices	**TRRs (ppm)**	
	[Indane-3-^{14}C]	**[Triazine-2,4-^{14}C]**
Muscle - loin	0.006	0.022
Muscle - round	0.007	0.025
Fat - perirenal	0.013	0.044
Fat - omental	0.015	0.032
Kidney	0.153	0.405
Liver	0.368	0.816
Milk (maximum residues) – day 3, triazine label; day 2, indane label	0.048	0.067

Metabolites identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**	**[Indane-3-^{14}C]**	**[Triazine-2,4-^{14}C]**
Muscle	None	AE 1170437 dihydroxy	None	AE 1170437-diaminotriazine, AE 1170437-4-hydroxy hydroxymethyl, AE 1170437-3-keto-4-hydroxy, AE 1170437-3-ketohydroxymethyl, AE 1170437-3-ketohydroxymethyl GA, AE 1170437-3-hydroxyindane, AE 1170437-carboxylic acid

Fat	None	None	AE 1170437 (indaziflam), AE 1170437-4-hydroxy hydroxymethyl, AE 1170437-4-hydroxy acid, AE 1170437-3-keto-hydroxymethyl, AE 1170437-3-hydroxyindane GA, AE 1170437-carboxylic acid	AE 1170437 (indaziflam), AE 1170437-diaminotriazine, AE 1170437-4-hydroxy hydroxymethyl, AE 1170437- dihydroxy, AE 1170437- 4-hydroxy acid, AE 1170437-3-hydroxyindane acid, AE 1170437-3-keto-hydroxymethyl, AE 1170437-3-keto-hydroxymethyl GA, AE 1170437-3-hydroxyindane GA, AE 1170437-carboxylic acid
Kidney	AE 1170437-dihydroxy, AE 1170437-carboxylic acid, AE 1170437-3-hydroxyindane GA	AE 1170437-carboxylic acid, AE 1170437-4-hydroxy acid, AE 1170437-3-hydroxyindane GA	AE 1170437-4-hydroxy hydroxymethyl, AE 1170437-3-keto-4-hydroxy, AE 1170437-3-keto-hydroxymethyl, AE 1170437-3-keto-hydroxymethyl GA, AE 1170437-3-hydroxyindane GA	AE 1170437-diaminotriazine, AE 1170437-4-hydroxy hydroxymethyl, AE 1170437-dihydroxy, AE 1170437-3-hydroxyindane, AE 1170437-3-keto-hydroxymethyl,
Liver	AE 1170437-carboxylic acid, AE 1170437-3-keto-hydroxymethyl GA	AE 1170437-carboxylic acid, AE 1170437-3-hydroxyindane GA	AE 1170437 (indaziflam), AE 1170437-4-hydroxy hydroxymethyl, AE 1170437-4-hydroxy acid, AE 1170437-3-keto-hydroxymethyl	AE 1170437 (indaziflam), AE 1170437-4-hydroxy hydroxymethyl, AE 1170437-dihydroxy, AE 1170437-4-hydroxy acid, AE 1170437-3-keto-hydroxymethyl, AE 1170437-3-keto-hydroxymethyl GA
Milk	AE 1170437-4-hydroxy hydroxymethyl, AE 1170437 dihydroxy, AE 1170437-3-keto-hydroxymethyl, AE 1170437-3-hydroxyindane	FDAT, AE 1170437-4-hydroxy hydroxymethyl, AE 1170437 dihydroxy, AE 1170437-3-keto-hydroxymethyl, AE 1170437-3-hydroxyindane	AE 1170437-3-keto-4-hydroxy, AE 1170437-3-ketohydroxymethyl GA, AE 1170437-carboxylic acid	AE 1170437 (indaziflam), AE 1170437-3-hydroxyindane acid, AE 1170437-3-keto-4-hydroxy, AE 1170437-3-keto-hydroxymethyl GA, AE 1170437-carboxylic acid

Proposed Metabolic Scheme in Lactating Goat



CROP FIELD TRIALS ON POME FRUITS	**PMRA# 1769485**

During the 2007 and 2008 growing seasons, 12 trials on apples in zones 1 (3 trials), 2 (1 trial), 5 (2 trials), 9 (1 trial), 10 (1 trial) and 11 (4 trials), and six trials on pears in zones 1 (1 trial), 10 (2 trials) and 11 (3 trials) were conducted in the U.S.. Each site consisted of one untreated and three treated plots. The treated plots received a single soil-surface application of indaziflam to the base of the trees at a rate of 146-157 g a.i./ha on apples and 145-161 g a.i./ha on pears. Applications were made using ground-based equipment in a volume of 110-191 L/ha. The formulation used in all applications was AE 1170437Indaziflam 500 SC Herbicide (a soluble concentrate [SC] formulation of indaziflam; 500 g a.i./L). Mature apples were collected at PHIs of 13-14, 43-46 and 157-209 days, and mature pears were collected at PHIs of 13-14, 39-45 and 157-184 days.

Commodity	**Total Rate (g a.i./ha)**	**PHI (days)**	**Combined Residues of Indaziflam + FDAT (ppm)**						
			n	**Min.**	**Max.**	**HAFT**	**Median**	**Mean**	**Std. Dev.**
Apples	147-155	13-14	24	<0.01	<0.01	<0.01	<0.01	<0.01	--
	146-154	43-46	24	<0.01	<0.01	<0.01	<0.01	<0.01	--
	147-157	157-209	20	<0.01	<0.01	<0.01	<0.01	<0.01	--
Pears	150-154	13-14	11	<0.01	<0.01	<0.01	<0.01	<0.01	--
	149-161	39-45	11	<0.01	<0.01	<0.01	<0.01	<0.01	--
	145-155	157-184	11	<0.01	<0.01	<0.01	<0.01	<0.01	--

CROP FIELD TRIALS ON STONE FRUITS | **PMRA# 1769484**

During the 2007 and 2008 growing seasons, 3 trials in tart cherries in zones 1 (1 trial) and 5 (2 trials), 3 trials in sweet cherries in zones 5, 10 and 11 (1 trial each), 9 trials in peaches in zones 1 (1 trial), 2 (3 trials), 5 (1 trial), 6 (1 trial) and 10 (3 trials), and 6 trials in plums in Zones 5 (1 trial), 10 (4 trials) and 12 (1 trial) were conducted in the U.S.. Each site consisted of one untreated and one treated plot. The treated plots at each site received a single soil-surface application of indaziflam to the base of the trees at a rate of 148-162 g a.i./ha on cherries, 144-157 g a.i./ha on peaches and 146-150 g a.i./ha on plums. Applications were made using ground-based equipment in a volume of 121-194 L/ha. The formulation used in all applications was AE 1170437Indaziflam 500 SC Herbicide (indaziflam; 500 g a.i./L). Mature cherries were collected at PHIs of 14-20, 45 and 83-115 days, mature peaches were collected at PHIs of 13-14, 43-45 and 120-211 days, and mature plums were collected at PHIs of 14, 45 and 160-210 days.

Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues of Indaziflam + FDAT (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Cherries	150-158	14-20	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
	148-162	45	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
	148-159	83-115	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
Peaches	145-157	13-14	18	<0.01	<0.01	<0.01	<0.01	<0.01	--
	144-152	43-45	18	<0.01	<0.01	<0.01	<0.01	<0.01	--
	149-156	120-211	18	<0.01	<0.01	<0.01	<0.01	<0.01	--
Plums	148-152	14	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
	148-156	45	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
	146-153	160-210	12	<0.01	<0.01	<0.01	<0.01	<0.01	--

CROP FIELD TRIALS ON TREE NUTS | **PMRA# 1769483**

During the 2007 growing season, five trials in almonds in zone10 and 5 trials in pecans in zones 2 (two trials), 4 (one trial), 6 (one trial) and 8 (one trial) were conducted in the U.S.. Each site consisted of one untreated and one treated plot. The treated plots at each site received a single soil-surface application of indaziflam to the base of the trees at rates of 148-152 g a.i./ha on almonds and 146-150 g a.i./ha on pecans. Applications were made using ground-based equipment in a volume of 93-189 L/ha. The formulation used in all applications was AE 1170437Indaziflam 500 SC Herbicide (indaziflam; 500 g a.i./L). Samples of almond nutmeats and almond hulls were collected at a PHI of 14 days, and samples of pecans were collected at a PHI of 12-13 days.

Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues of Indaziflam + FDAT (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Almond nutmeats	148-152	14	10	<0.01	<0.01	<0.01	<0.01	<0.01	--
Almond hulls	148-152	14	10	<0.01	0.153	0.149	0.023	0.050	0.059
Pecans	146-150	12-13	10	<0.01	<0.01	<0.01	<0.01	<0.01	--

CROP FIELD TRIALS ON GRAPES | **PMRA# 1769486**

During the 2007 and 2008 growing seasons, 12 field trials were conducted in the U.S. in Zones 1 (2 trials), 10 (8 trials) and 11 (2 trials). Each site consisted of one untreated and three treated plots. The treated plots received a single soil-surface application of indaziflam to the base of the vines and extending to the row centres at a rate of 145-157 g a.i./ha**.** Applications were made using ground-based equipment in a volume of 100-186 L/ha. The formulation used in all applications was AE 1170437Indaziflam 500 SC Herbicide (indaziflam; 500 g a.i./L). Mature grapes were collected at PHIs of 13-14, 43-45 and 143-240 days.

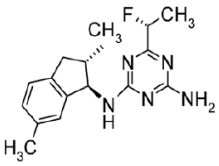
Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues of Indaziflam + FDAT (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Grapes	145-157	13-14	24	<0.01	<0.01	<0.01	<0.01	<0.01	--
	147-155	43-45	24	<0.01	<0.01	<0.01	<0.01	<0.01	--
	148-159	143-240	24	<0.01	0.0115	0.0113	<0.01	<0.01	0.0029
FREEZER STORAGE STABILITY							**PMRA #s 1769492 and 2065430**		
Residues of indaziflam and FDAT were shown to be stable at <-20°C for up to 26 months in almond hulls, 25 months in almond nutmeat, 26 months in apples, 25 months in cherries and 26 months in oranges.									
PROCESSED FOOD AND FEED							**PMRA #1769496, 1769498, 1769497**		
Processing studies were conducted on plums, apples and grapes treated with a single ground application of indaziflam (suspension concentrate formulation) directed to the base of the plant at an exaggerated rate of 738-754 g a.i./ha. Residues of indaziflam and FDAT were below the combined LOQ of 0.01 ppm in all raw agricultural commodities. Residues were not determined in any commodities processed from plums and apples. Residues determined in grape juice and raisins were all < the combined LOQ.									
LIVESTOCK FEEDING							**PMRA # --**		
The only feed item is apples (processed into wet apple pomace), which is considered an "alternative feedstuff" for dairy cattle only. There are no poultry feed items among the requested crops. Results of the reviewed apple processing studies (apples pomace) showed that maximum total indaziflam residues (sum of indaziflam + FDAT) were below the combined LOQ (<0.01 ppm) following exaggerated applications of indaziflam at 738 g a.i./ha with mature apples harvested at a long PHI of 181 days to ensure maximum residue translocation and accumulation to the mature fruit (proposed PHI is 14 days). As residues were non quantifiable in the apple fruit, residue determination was not conducted in wet apple pomace in the processing study. The dietary burden determined using the More Balanced Diet calculator (Version A) was calculated to be 0 ppm for dairy cattle. Therefore, no quantifiable residues of indaziflam + FDAT are expected in dairy cattle tissues or milk from feeding wet apple pomace processed from treated apples according to the Canadian use pattern. As a result, feeding studies are not required at this time.									

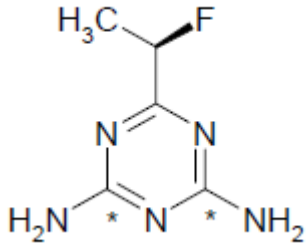
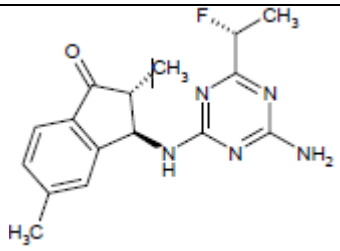
Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

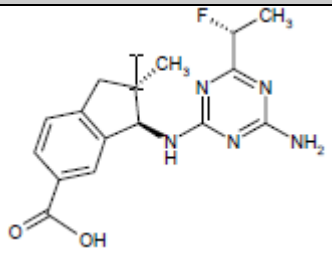
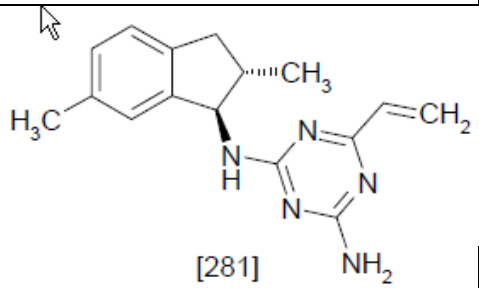
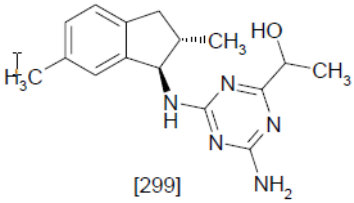
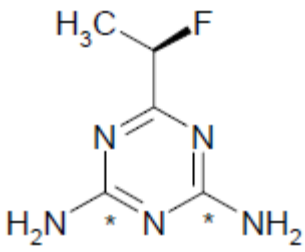
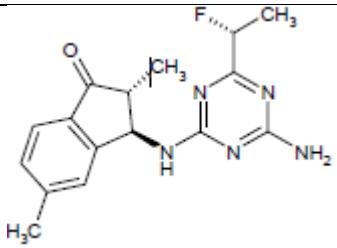
PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (apple, grapes and sugarcane)**	Indaziflam and the metabolite, 1-fluoroethyl diaminotriazine (FDAT)
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (apple, grapes and sugarcane)**	Indaziflam and the metabolite, 1-fluoroethyl diaminotriazine (FDAT)
METABOLIC PROFILE IN DIVERSE CROPS	The metabolic profile is similar in two fruits (apples and grapes) and one miscellaneous crop (sugarcane).
ANIMAL STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT	Not determined.
RESIDUE DEFINITION FOR RISK ASSESSMENT	Not determined.
METABOLIC PROFILE IN ANIMALS	The metabolic profile was determined in lactating goats. Indaziflam metabolism observed in goats and rats was similar.
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Basic chronic non-cancer dietary risk: **ADI = 0.02 mg/kg bw/day** **Estimated chronic drinking water concentration = 15 μg/L**	All infants < 1 year	0.2	5.8
	Children 1–2 years	1.2	3.5
	Children 3 to 5 years	0.8	3.0
	Children 6–12 years	0.4	1.9
	Youth 13–19 years	0.2	1.3
	Adults 20–49 years	0.1	1.6
	Adults 50+ years	0.1	1.7
	Total population	0.1	1.8
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
Acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 15 μg/L** **ARfD = 0.5 mg/kg bw/day**	All Infants (<1 year old)	0.10	0.61
	Children 1-2 years old	0.15	0.32
	Children 3-5 years old	0.10	0.27
	Children 6-12 years old	0.05	0.18
	Youth 13-19 years old	0.03	0.14
	Adults 20-49 years old	0.02	0.15
	Adults 50+ years old	0.02	0.14
	Females 13-49 years old	0.03	0.15
	General Population	0.04	0.18

Table 7 Major transformation products in environmental media

Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)
PARENT					
AE 1170437	Indaziflam				

Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)
MAJOR (>10%) TRANSFORMATION PRODUCTS					
AE 1170437-diaminotriazine	6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine		Aerobic soil (120 days, German soils))	31.6 (study termination)	31.6 (study termination)
			Aerobic soil (368 days, U.S. soils)	37.9 (study termination)	37.9 (study termination)
			Anaerobic soil		
			Soil photolysis		
			Aqueous photolysis		
			Hydrolysis		
			Aerobic aquatic (120 days, Angler Weiher system)	10.5 (study termination)	10.5 (study termination)
			Anaerobic aquatic		
			Field studies (Washington, 531 days)	18 (day 59)	
AE 1170437-triazine indanone	(*2R*, *3R*)3-{4-amino-6-[(*1R*)1-fluoroethyl]-1,3,5-triazin-2-ylamino}-2,5-dimethyl-indan-1-one		Aerobic soil (120 days, German soils)	15.8 (day 38)	11.6
			Aerobic soil (368 days, U.S. soils)	16.7 (day 122)	8.8
			Anaerobic soil (flooded, 30 aerobic days + 180 anaerobic days)	10 (day 30 aerobic phase)	7.0 to 9.2% (throughout anaerobic phase – stable)
			Soil photolysis	-	
			Aqueous photolysis	-	
			Hydrolysis	-	
			Aerobic aquatic (120 days, Angler Weiher system)	10.5 (study termination)	
			Anaerobic aquatic		
			Field studies (Washington, 531 days)	10.1 (day 28)	<1

Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)
AE 1170437-carboxylic acid	(2S,3R)-3-({4-amino-6-[(lR)-l-fluoroethyl]-l,3,5-triazin-2-yl} amino)-2-methylindane-5-carboxylic acid		Aerobic soil (120 days, German soils)	21.7 (day 30)	17.5
			Aerobic soil (368 days, U.S. soils)	17.9 (day 123)	9.9
			Anaerobic soil (flooded, 30 aerobic days + 180 anaerobic days)	10.2 (day 30 aerobic phase)	9.1 to 11 (throughout anaerobic phase – relatively stable)
			Soil photolysis	-	
			Aq. photolysis	-	
			Hydrolysis		
			Aerobic aquatic (120 days, Angler Weiher system)	10.5	
			Field studies (Washington, 531 days)		
AE 1170437 - olefine		 [281]	Aerobic soil		
			Anaerobic soil		
			Soil photolysis		
			Aq. Photolysis (72 hours)	53.5 (study termination)	53.5 (study termination)
			Hydrolysis -pH7 Hydrolysis -pH9		
			Aerobic aquatic		
			Anaerobic aquatic		
			Field studies		
AE 1170437 -1-hydroxyethyl		 [299]	Aerobic soil		
			Anaerobic soil		
			Soil photolysis		
			Aq. photolysis (72 hours)	20.3 (study termination)	20.3 (study termination)
			Hydrolysis -pH7 Hydrolysis -pH9		
			Aerobic water	--	--
			Anaerobic water	--	--
			Field studies		
MINOR (<10%) TRANSFORMATION PRODUCTS					
AE 1170437-diaminotriazine	6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine		Aerobic soil		
			Anaerobic soil		
			Soil phototransformation	6.9	
			Anaerobic soil (flooded, 30 aerobic days + 180 anaerobic days)	4 (day 30 aerobic phase)	4 to 6 (throughout anaerobic phase – relatively stable)
			Hydrolysis –pH7 Hydrolysis –pH9		
			Aerobic aquatic (120 days, Hoenniger Weiher system)	2.5 (day 62)	2.3
			Anaerobic water		
			Field studies (New York, 545 days)	8.1	
AE 1170437-triazine indanone	(*2R, 3R*)3-{4-amino-6-[(*1R*)1-fluoroethyl]-1,3,5-triazin-2-ylamino}-2,5-dimethyl-indan-1-one		Aerobic soil		
			Anaerobic soil		
			Soil phototransformation	6.9	
			Aq. Photolysis		
			Hydrolysis –pH7 Hydrolysis –pH9		
			Aerobic aquatic (120 days, Hoenniger Weiher system)	5.3	5.3
			Anaerobic water		

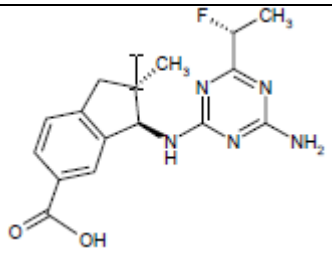
Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)
			Field studies (New York, 545 days)	4.3	
AE 1170437-carboxylic acid	(2S,3R)-3-({4-amino-6-[(lR)-l-fluoroethyl]-l,3,5-triazin-2-yl} amino)-2-methylindane-5-carboxylic acid		Aerobic soil		
			Anaerobic soil		
			Soil phototransformation	2	
			Aq. Photolysis		
			Hydrolysis		
			Aerobic aquatic (120 days, Hoenniger Weiher system)	4 (day 30)	3.7
			Anaerobic water		
			Field studies (Washington, 531 days)	5.4 (day 14)	
			Field studies (New York, 545 days)	2.6	

Table 8 Fate and behaviour in the terrestrial environment

Property	PMRA number	Value (days)	Comments
Abiotic transformation			
Hydrolysis	1873490	Half life: stable	Not an important route of transformation
Phototransformation on soil	1769231	Continuous dark control corrected (for Alberta irradiance) half life (triazine label): 47.1 days Continuous dark control corrected (for Alberta irradiance) half life (indane label): 53.4 days	Not an important route of transformation (> 3 days)

Property		PMRA number	Value (days)	Comments
Biotransformation				
Biotransformation in aerobic soil with parent (AE 1170437)	German soils (triazine label)	1769235	LH AXXa sandy loam : DT_{50}: (IORE): 51.6 days (characterization) DT_{50}: (IORE DT_{90} x 0.301): 120 days (modelling) DT_{90}: 400 days	EPA classification (Goring et al. 1975): slightly to moderately persistent
			LH AIIIa loam: DT_{50}: (IORE): 29.8 days (characterization) DT_{50}: (IORE DT_{90} x 0.301): 51.9 days (modelling) DT_{90}: 172 days	
			Wurmwiese sandy loam DT_{50}: (DFOP): 20.9 days (characterization) DT_{50}: (DFOP slow rate): 98 days (modelling) DT90: 214	
			Hoefchen a. H.loam : DT_{50}: (IORE): 42.2 days (characterization) DT_{50}: (IORE DT_{90} x 0.301): 55.7 days (modelling) DT_{90}: 185 days	
	German soils (indane label)	1769238	LH AXXa sandy loam DT_{50} (IORE DT90x0.301): 130 days (modelling) DT_{50} (IORE): 42.6 days (characterization) DT90: 434 days	EPA classification (Goring et al. 1975): slightly persistent
			LH Allla Loam: DT_{50} (IORE DT90x0.301): 52.9 days (modelling) DT_{50} (IORE): 28.2 days (characterization) DT90: 176 days	
			Wurmwiese sandy loam: DT_{50} (DFOP slow rate): 90.1 days (modelling) DT_{50} (DFOP): 28 days (characterization) DT90: 212 days	
			Hoefchen loam: DT_{50} (IORE DT90x0.301): 71 days (modelling) DT_{50} (IORE): 36.7 days (characterization)	

Property		PMRA number	Value (days)	Comments
			DT90: 237 days	
	U.S. soils (indane label)	1769239	Carolina sandy loam DT_{50} (IORE DT90x0.301): 202.6 days (modelling) DT_{50} (IORE): 59.9 days (characterization) DT90: 673 days	EPA classification (Goring et al. 1975): moderately persistent
			North Carolina sandy loam DT_{50} (DFOP slow rate): 348 days (modelling) DT_{50} (DFOP): 95.7 days (characterization) DT90: 902 days	
	U.S. soils (triazine label)	1769240	California sandy loam DT_{50} (IORE DT90x0.301): 193 days (modelling) DT_{50} (IORE): 52.9 days (characterization) DT90: 642 days	EPA classification (Goring et al. 1975): moderately persistent
			North Carolina DT_{50} (IORE DT90 x 0.301): 2648 days (modelling) DT_{50} (IORE): 61.1days (characterization) DT90: 8797 days	
Biotransformation in aerobic soil with transformation product (AE 1170437 diaminotriazine)	German soils	1769237	LH AXXa sandy loam DT_{50} (DFOP slow rate): 80 days (modelling) DT_{50} (DFOP): 31 days (characterization) DT90: 199 days	EPA classification (Goring et al. 1975): non-persistent to persistent
			Hoefchen sandy loam: DT_{50} (IORE) 13.7 days (modelling) DT_{50} (IORE) 15.6 days (characterization) DT90: 45.5 days	
			Wurmwiese sandy loam DT_{50} (DFOP slow rate): 265 days (modelling) DT_{50} (DFOP): 189 days (characterization) DT90: 803	

Property		PMRA number	Value (days)	Comments
Mobility				
Adsorption / desorption in soil	Parent (AE 1170437)	1769256	AXXa Kf ads: 8.8 mL/g Hoefchen Kf ads: 9.39 mL/g Wurmweise Kf ads: 6.2 mL/g Pikeville Kf ads: 11.2 mL/g Stanley Kf ads: 10.14 mL/g AXXa Kfoc ads: 440 mL/g Hoefchen Kfoc ads: 391 mL/g Wurmweise Kfoc ads: 477 mL/g Pikeville Kfoc ads: 745 mL/g Stanley Kfoc ads: 441 mL/g	EPA classification (McCall et al. 1981): Moderate mobility
	Transformation product (AE 1170437-Diaminotriazine)	1769257	AXXa Kf ads: 0.17 mL/g Hoefchen Kf ads: 0.26 mL/g Wurmweise Kf ads: 0.30 mL/g Pikeville Kf ads: 0.48 mL/g Stanley Kf ads: 0.78 mL/g AXXa Kfoc ads: 10 mL/g Hoefchen Kfoc ads: 12 mL/g Wurmweise Kfoc ads: 15 mL/g Pikeville Kfoc ads: 48 mL/g Stanley Kfoc ads: 37 mL/g	EPA classification (McCall et al. 1981): Very high mobility
	Transformation product (AE 1170437-Triazine indanone)	1769258	Pikeville Kf ads: 3.04 ml/g Stanley Kf ads: 5.96 ml/g Hoefchen Kf ads: 5.17 ml/g AXXa Kf ads: 3.0 ml/g Wurmwiese Kf ads: 3.04 ml/g Pikeville Kfoc ads: 304 ml/g Stanley Kfoc ads: 284 ml/g Hoefchen Kfoc ads: 250 ml/g AXXa Kfoc ads: 183 ml/g Wurmwiese Kfoc ads: 146 ml/g	EPA classification (McCall et al. 1981): Moderate to high mobility
	Transformation product (AE 1170437-carboxylic acid)	1769263	Pikeville Kf ads: 1.01 ml/g Stanley Kf ads: 1.07 ml/g Hoefchen Kf ads: 0.66 ml/g AXXa Kf ads: 0.49 ml/g Wurmwiese Kf ads: 0.65 ml/g Pikeville Kfoc ads: 103 ml/g Stanley Kfoc ads: 51 ml/g Hoefchen Kfoc ads: 32 ml/g AXXa Kfoc ads: 30 ml/g Wurmwiese Kfoc ads: 31 ml/g	EPA classification (McCall et al. 1981): High to very high mobility

Property		PMRA number	Value (days)	Comments
Field studies				
Field dissipation (with AE 1170437 Indaziflam 500 SC Herbicide end-use product) on bare ground applied at 150 g a.i./ha	Washington	1769520	DT_{50} (IORE): 22.5 days DT90: 302 days 9% carry over.	Slightly persistent
	New York	1769521	DT_{50} (DFOP): 13 days DT90: 1334 days 17% carry over.	Non-persistent

Persistence of pesticide in soil (Goring et al. 1975) or water (McEwen and Stephenson 1979)
Adsorption/Desorption and Mobility (McCall et al. 1981)

Table 9 Fate and behaviour in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis (7 days at 50ºC)	1873490	Half life: stable	Not an important route of transformation
Phototransformation in water	1769233	Continuous dark control corrected half life (for triazine and indane label): 1.4 days	Potentially an important route of transformation (> 1 week)
Biotransformation			
Biotransformation in aerobic water systems (119 days in a water/sediment system)	1769254	DT_{50} (using SFO) entire system: 4938 days (characterization and modelling) DT90 (using SFO) entire system: 16404 days (characterization and modelling)	Not an important route of dissipation. AE 1170437 partitions from water to sediment and is then relatively stable. AE 1170437 is classified as persistent according to the criteria of McEwan and Stephenson 1979.

Property	Test material	Value	Comments
Biotransformation in aerobic water systems	1769249	Angler Weiher: DT_{50} (Angler Weiher) water: 4.8 days (IORE)(combined for label A and B) DT_{50} (Angler Weiher) whole system: 161 days (DFOP slow rate)(modelling) DT_{50} (Angler Weiher) whole system: 127 days (DFOP)(characterization) DT90 (Angler Weiher) whole system (from DFOP): 500 days Hoenniger Weiher: DT_{50} (Hoenniger Weiher) water: 2.67 days (IORE) (combined for label A and B) DT_{50} (Hoenniger Weiher) whole system: 976 days (DFOP slow rate) (modelling) DT_{50} (Hoenniger Weiher) whole system: 636 days (DFOP) (characterization) DT90 (Hoenniger Weiher) whole system (from DFOP): 2902 days	Not an important route of dissipation. AE 1170437 partitions from water to sediment and is then relatively stable. AE 1170437 is classified as moderately persistent to persistent according to the criteria of McEwan and Stephenson 1979.
Biotransformation in anaerobic water systems (30 days of aerobic system and then flooded for 180 days under anaerobic conditions))	1769247	Label A entire system DT_{50}: 1176 days (SFO) (modelling and characterization) DT90: 3907 days Label A water DT_{50} (SFO): 718 days Label B entire system DT_{50}: 1029 days (SFO) (modelling and characterization) DT90: 3417 days Label B water DT_{50} (SFO): 1900 days	Not an important route of dissipation. AE 1170437 is classified as persistent according to the criteria of McEwan and Stephenson 1979.

Property	Test material	Value	Comments
Bioaccumulation in fish	1769300	Steady-state bioconcentration factors for parent BCF (whole fish): 16 Lipid normalized: 11	Not likely to bioconcentrate in the environment

Table 10 Effects on terrestrial organisms (screening level assessment)

Organism	Exposure [PMRA number]	Test substance	Endpoint value	EEC	RQ (EEC/ Endpoint)	LOC exceeded
Terrestrial organisms						
Earthworm	Acute (14 d) [1769265]	Indaziflam	LC_{50}> 1000 mg/kg/2=500 mg/kg soil	0.033 mg a.i./kg soil	<1 (0.00007)	no
	Acute (14 d) [1769267]	Transformation product: AE 1170437-diaminotriazine	LC_{50}> 1000 mg/kg=500 mg/kg soil	0.017 mg/kg soil	<1 (0.00007)	no
	Acute (14 d) [1769266]	Transformation product: AE 1170437-triazine-indanone	LC_{50}> 1000 mg/kg/2=500 mg/kg	0.035 mg/kg soil	<1 (0.00007)	no
	Acute (14 d) [1769268]	Transformation product: AE 1170437-carboxylic acid	LC_{50}> 1000 mg/kg/2=500 mg/kg	0.036 mg/kg soil	<1 (0.00007)	no
	Acute (14 d) [1769524]	End-use product, Indaziflam 500 SC (43% TGAI)	LC_{50}> 1000 mg /kg/2=500 mg EU/kg (215 mg a.i./kg)	0.033 mg a.i./kg soil	<1 (0.002)	no
	Chronic [1769525]	End-use product, Indaziflam 500 SC (43% TGAI)	NOEC (based on reproduction): 78 mg/kg (34 mg a.i./kg)	0.033 mg a.i./kg soil	<1 (0.002)	no

Organism	Exposure [PMRA number]	Test substance	Endpoint value	EEC	RQ (EEC/ Endpoint)	LOC exceeded
Bee	Oral (96 hour) [1769273]	Indaziflam	LD_{50}: >120 µg a.i./bee (x 1.12) = 134.4 kg a.i./ha	0.075 kg a.i./ha (one application only)	<1 (0.0006)	no
	Contact (96 hour) [1769273]	Indaziflam	LD_{50}: >100 µg a.i./bee (x 1.12)= 112 kg a.i./ha	0.075 kg a.i./ha (one application only)	<1 (0.0007)	no
	Oral (96 hour) [1769528]	End-use product, Indaziflam 500 SC (43% TGAI)	LD_{50}: >119.7 µg a.i./bee (256 µg product/bee) (x1.12)=134.1 kg a.i./ha	0.075 kg a.i./ha (one application only)	<1 (0.0006)	no
	Contact (96 hour) [1769528]	End-use product, Indaziflam 500 SC (43% TGAI)	LD_{50}: >100 µg a.i./bee (214 µg product/bee) (x1.12)= 112 kg a.i./ha	0.075 g a.i./ha (one application only)	<1 (0.0007)	no
Aphid parasitoid (*Aphidius rhopalosiphi*)	Contact	End-use product, Indaziflam 500 SC (43% TGAI)	LR_{50}: >1000 g a.i./ha	In field: 1 application: 75 g a.i./ha	<1 (0.075)	no
				Off field: (6% drift): 4.5 g a.i./ha	<1 (0.0045)	no
Predacious mite (*T. pyri*)	Contact	End-use product, Indaziflam 500 SC (43% TGAI)	LR_{50}: >1000 g a.i./ha	In field: 1 application: 75 g a.i./ha	<1 (0.075)	no
				Off field: (6% drift): 4.5 g a.i./ha	<1 (0.0045)	no

Organism	Exposure [PMRA number]	Test substance	Endpoint value	EEC	RQ (EEC/ Endpoint)	LOC exceeded
Terrestrial plants						
Vascular plant	Seedling emergence [1170437]	End-use product, AE 1170437 SC 500 (43% TGAI)	Dicot (oilseed rape emergence) and monocot (onion emergence) SSD5 (most sensitive endpoint: seedling emergence): 0.167 g a.i./ha.	Off field (6% drift): 4.5 g a.i./ha	**27**	**Yes**
	Vegetative vigour [1769337]	End-use product, AE 1170437 SC 500 (43% TGAI)	SSD5: 5.2	Off field (6% drift): 4.5 g a.i./ha	0.86	No

Table 11 Screening level risk assessment: Effects of indaziflam on birds on field.

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	LOC Exceeded
Small Bird (0.02 kg)					
Acute	200.00	Insectivore (small insects)	3.78	0.02	No
Reproduction	111.00	Insectivore (small insects)	3.78	0.03	No
Medium Sized Bird (0.1 kg)					No
Acute	200.00	Insectivore (small insects)	2.95	0.01	No
Reproduction	111.00	Insectivore (small insects)	2.95	0.03	No
Large Sized Bird (1 kg)					No
Acute	200.00	Herbivore (short grass)	3.08	0.02	No
Reproduction	111.00	Herbivore (short grass)	3.08	0.03	No

Table 12 Screening level risk assessment: Effects of indaziflam on birds on field.

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ	LOC Exceeded
Small Mammal (0.015 kg)					
Acute	500.00	Insectivore (small insects)	2.17	0.00	No
Reproduction	68.90	Insectivore (small insects)	2.17	0.03	No
Medium Sized Mammal (0.035 kg)					No
Acute	500.00	Herbivore (short grass)	6.81	0.01	No
	500.00	Herbivore (leafy foliage) **	12.83	0.03	Not applicable
Reproduction	68.90	Herbivore (short grass)	6.81	0.10	No
	68.90	Herbivore (leafy foliage) **	12.83	0.19	Not applicable
Large Sized Mammal (1 kg)					No
Acute	500.00	Herbivore (short grass)	3.64	0.01	No
	500.00	Herbivore (leafy foliage) **	6.86	0.01	Not applicable
Reproduction	68.90	Herbivore (short grass)	3.64	0.05	No
	68.90	Herbivore (leafy foliage) **	6.86	0.10	Not applicable

** Leafy foliage is not relevant for the current submission as this scenario is only for pesticides which are applied to lettuce type crops (eg. cabbage, lettuce etc).

1. Estimated daily exposure (EDE) = FIR/BW*EEC

Note: As there was no risk with on field exposure, there will be no risk from 6% drift for estimation of off-field exposure.

Table 13 Effects on aquatic organisms (screening level)

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Daphnia magna	Acute (48 hour) [1769275]	Indaziflam	48H EC_{50}: >9.88 mg a.i./L / 2 = 4.9 mg a.i./L (35% immobility in 9.88 mg/L treatment group)	9.4 µg a.i./L	0.002	No
	Acute (48 hour) [1769530]	Indaziflam 500 SC (end-use product)	48 hour LC_{50} (based on mortality): >38 mg a.i./L/2 = 19 mg a.i./L 48 hour EC_{50} (based on sublethal effects, including lying on the bottom of the aquaria): 2.96 mg a.i./L/2 = 1.48 mg a.i./L	9.4 µg a.i./L	0.0005	No
	Chronic (21 d) [1769276]	Indaziflam	NOAEC (based on dry weight and length): 0.34 mg a.i./L	9.4 µg a.i./L	0.03	No
Chironomus tentans	Acute (10 d) [1769278]	Indaziflam	LC_{50}: > 0.18 mg/L/2 = 0.09 mg a.i./L in overlying water (no effects observed) LC_{50}: > 100 mg/kg in sediment (no effects observed)	9.4 µg a.i./L	0.10	No
Rainbow trout (*Oncorhynchus mykiss)*	Acute (96 hour) [1769286]	Indaziflam	LC_{50}: 0.57 mg a.i/L /10 = 0.057 mg a.i./L (100% mortality in the 0.78 mg/L treatment level, second highest treatment level)	9.4 µg a.i./L	0.16	No

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Bluegill sunfish *(Lepomis macrochirus)*	Acute (96 hour) [1769288]	Indaziflam	LC_{50}: 0.32 mg a.i/L /10 = 0.032 mg a.i./L (100% mortality at 24 hours in the 0.75 and 1.54 mg/L treatment levels (two highest test concentrations))	9.4 µg a.i./L	0.29	No
Fathead minnow (*Pimephales promelas*)	Acute (96 hour) [1769290]	Indaziflam	LC_{50}: 0.77 mg a.i./L/10 = 0.077 mg a.i./L (100% mortality by 24 hours in the two highest concentrations, 1.07 and 2.19 mg/L, no other mortality in other treatment groups, however, 100% of fish in the 0.55 mg a.i./L group exhibited loss of equilibrium and erratic behaviour)	9.4 µg a.i./L	0.12	No
Fathead minnow (*Pimephales promelas*)	Acute (96 hour) [1769291]	AE 1170437-Carboxylic acid (transformation product)	LC_{50}: > 103/10= 10.3 mg/L (no effects noted at any concentration)	10 µg a.i./L	0.001	No
Fathead minnow (*Pimephales promelas*)	Acute (96 hour) [1769292]	AE 1170437-Diaminotriazine (transformation product)	LC_{50}: > 101/10=10.1 mg/L (no effects noted at any concentration)	4.9 µg a.i./L	0.0005	No

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Fathead minnow (*Pimephales promelas*)	Chronic (35 d) [1769298]	Indaziflam	NOEC (based on 35 day fry survival): 465.3 µg a.i./L (97.5% mortality in the highest test concentration (1013 µg a.i./L), but only 1.2% mortality in the next lowest test concentration (286 µg a.i./L)	9.4 µg a.i./L	0.02	No
Amphibians	Acute (96 hour) [1769288]	Indaziflam	LC_{50}: 0.32 mg a.i/L /10 = 0.032 mg a.i./L	15 cm ** 50 µg a.i./L	**1.6**	**yes**
	Chronic (35 d) [1769298]	Indaziflam	NOEC (based on 35 day fry survival): 465.3 µg a.i./L	15 cm ** 50 µg /L	0.0001	No
	Acute (96 hour) [1769291]	AE 1170437-Carboxylic acid (transformation product)	LC_{50}: > 103/10=10.3 mg/L (no effects noted at any concentration)	15 cm**: 55 µg /L	0.005	No
	Acute (96 hour) [1769292]	AE 1170437-Diaminotriazine (transformation product)	LC_{50}: > 101/10=10.1 mg/L (no effects noted at any concentration)	15 cm**: 26 µg /L	0.003	No
Blue-green alga (*Anabaena flos-aquae*)	Acute (96 hour) [1769333]	Indaziflam	96 hour Cell density EC_{50}: 722 µg a.i./L/2 = 361 µg a.i./L (up to 92% inhibition in cell density in the highest test concentration)	9.4 µg a.i./L	0.03	No
Green alga (*Pseudokirchneriella subcapitata*)	Acute (96 hour) [1769325]	Indaziflam	EC_{50} (biomass): 76.1 µg a.i./L/2 = 38 µg a.i./L (up to 99% inhibition in biomass in the highest test concentration)	9.4 µg a.i./L	0.25	No

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Green alga (*Pseudokirchneriella subcapitata*)	Acute (72 hour) [1769326]	AE 1170437 Diaminotriazine (transformation product)	EC_{50} cell density: 11.28 mg/L/2 = 5.6 mg/L (97 and 98% inhibition in the two highest concentrations)	4.9 µg /L	0.0009	No
Green alga (*Pseudokirchneriella subcapitata*)	Acute (72 hour) [1769322]	AE 1170437-Carboxylic Acid (transformation product)	EC_{50} (cell density, biomass and growth rate):>9.4 mg/L/2 = 4.7 mg/L (up to 39% inhibition in highest concentration for cell density and biomass)	10 µg /L	0.002	No
Green alga (*Pseudokirchneriella subcapitata*)	Acute (72 hour) [1769321]	AE 1170437-1-hydroxyethyl (transformation product)	EC_{50} (cell density): 0.65 mg/L/2 = 0.325 mg/L (most sensitive endpoint, but very similar to biomass) (94 to 97% inhibition in the three highest concentrations)	9.3 µg /L	0.029	No
Green alga (*Pseudokirchneriella subcapitata)*	Acute (72 hour) [1769318]	AE 1170437-olefine (a photolytic transformation product)	EC_{50} (biomass): 65.9 µg/L/2 = 32.9 µg/L (81 and 98% inhibition in the two highest test groups)	8.8 µg/L	0.27	No
Green alga (*Pseudokirchneriella subcapitata*)	Acute (72 hour) [1769534]	Indaziflam 500 SC (End-Use Product)	EC_{50} (cell density): 60.7 µg a.i./L/2 = 30.4 µg a.i./L (97 to 99% inhibition in the 3 highest test concentrations)	9.4 µg a.i./L	0.31	No
Diatom (*Navicula pelliculosa)*	Acute (96 hour) [1769317]	Indaziflam	72 hour EC_{50} (biomass): 76.5 µg a.i./L/2 = 38 µg a.i./L 96 hour EC_{50} (biomass): 102 µg a.i./L/2 = 51 µg a.i./L (97 and 99% inhibition in the two highest test concentrations)	9.4 µg a.i./L	0.25	No

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769342]	Indaziflam	Yield based on frond number EC_{50}: 68.1 ng a.i./L/2= 34 ng a.i./L (100% inhibition at the highest concentration)	9.4 µg a.i./L	**276**	**Yes**
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769434]	AE 1170437-triazine-indanone (transformation product)	EC_{50} (frond area yield): 12.5 µg/L/2 = 6.25 µg/L (100% inhibition in the 2 highest concentrations)	9.8 µg/L	**1.6**	**Yes**
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769346]	AE 1170437-diaminotriazine (transformation product)	EC_{50} (frond number based on growth rate): 51 µg/L /2 = 25.5 µg/L (100% inhibition in the 3 highest test concentrations)	4.9 µg/L	0.19	No
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769347]	AE 1170437-1-hydroxyethyl (transformation product)	Frond area (yield) EC_{50}: 502 ng/L/2 = 251 ng/L (up to 100% inhibition in the highest test concentration)	9.3 µg/L	**37**	**Yes**
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769348]	AE 1170437-carboxylic acid (transformation product)	EC_{50} (frond number): 4.0 mg/L/2= 2 mg/L (95 to 100% inhibition in the three highest test concentrations)	10 µg /L	0.005	No
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769351]	AE 1170437-olefine (photolytic transformation product)	Frond area EC_{50}: 0.3 µg/L/2 = 0.15 µg/L (85 to 100% inhibition in the 3 highest concentrations)	8.8 µg /L	**59**	**Yes**
Vascular plant, duckweed (*Lemna gibba* G3)	Acute (7 d) [1769536]	Indaziflam 500 SC (End-Use Product, 43% TGAI)	EC_{50} based on frond number (yield): 58.5 ng a.i./L/2= 29.3 ng/L [130 ng form./L] (92 to 100% inhibition in the two highest concentrations)	9.4 µg a.i./L	**321**	**Yes**

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Outdoor experiment with *macrophytes*	Chronic (6 weeks) [1769356]	Indaziflam	NOEC: 0.32 µg a.i./L (based on survival and dry weight, growth for water lily and water milfoil)	9.4 µg a.i./L	**29**	**Yes**
Freshwater experiment with *macrophytes*	Chronic (10 weeks) [1769355]	Indaziflam 500 SC (End-Use Product)	NOEC: 0.01 µg a.i./L (with recovery) NOEC: 0.32 ug/L for lemna considering no recovery LOEC: 1.0 ug/L for lemna considering no recovery	9.4 µg a.i./L	**940** **29** **9**	**Yes**
Marine species						
Marine amphipod (*Leptocheirus plumulosus)*	Acute (10 d) [1769284]	Indaziflam	Based on Mean-measured Overlying Water Concentrations: LC_{50} mortality: > 1.4 mg /L/2=0.7 mg/L (no effects during the study)	9.4 µg a.i./L	0.01	No
Eastern oyster (*Crassostrea virginica*)	Acute (96 hour) [1769282]	Indaziflam	EC_{50}: 0.92 mg a.i./L/2= 0.46 mg a.i./L (based on shell reduction up to 91% compared to controls in highest test concentration (1.8 mg/L))	9.4 µg a.i./L	0.02	No
Sheepshead minnow (*Cyprinodon variegates)*	Acute (96 hour) [1969296]	Indaziflam	96-hour LC_{50}: 0.96 mg a.i/L/10= 0.096 mg a.i./L (20% mortality in the 0.77 mg/L test group and 100% mortality in the highest test concentration)	94 µg a.i./L	0.098	No

Organism	Exposure [PMRA number]	Test Substance	Endpoint value	EEC (80 cm depth unless stated otherwise)	RQ (EEC/ Endpoint)	LOC exceeded
Saltwater diatom (*Skeletonema costatum)*	Acute (96 hour) [1769331]	Indaziflam	72 hour cell density EC_{50}: 23 µg a.i./L/2=11.5 µg a.i./L (90 to 98% inhibition in the 2 highest concentrations) 96 hour cell density EC_{50}: 36 µg a.i./L/2 = 18 µg a.i./L	9.4 µg a.i./L 9.4 µg a.i./L	0.82 0.52	No No

Table 14 Tier I level risk to aquatic organisms from spray drift and runoff inputs

				Spray Drift		Runoff		
Organism	**Exposure**	**Test substance**	**Endpoint value**	**EEC**	**RQ**	**EEC**	**RQ**	**LOC exceeded?**
Freshwater species								
Amphibians	Acute (96 hour) [1769288]	Indaziflam	LC_{50}: 0.32 mg a.i/L /10 = 0.032 mg a.i./L	15 cm ** 3 µg a.i./L	0.094	15 cm: 3.7 µg a.i./L	0.12	No
Outdoor experiment with *macrophytes*	Chronic (6 weeks) [1769356]	Indaziflam	NOEC: 0.32 µg a.i./L (based on survival and dry weight, growth for water lily and water milfoil)	0.564 µg a.i./L	**1.8**	80 cm (using combined residue): 2.2 µg a.i./L	**6.9**	Yes

				Spray Drift		Runoff		
Organism	**Exposure**	**Test substance**	**Endpoint value**	**EEC**	**RQ**	**EEC**	**RQ**	**LOC exceeded?**
Freshwater experiment with *macrophytes*	Chronic (10 weeks) [1769355]	AE 1170437 SC500 (End-Use Product)	NOEC: 0.01 µg a.i./L (with recovery)	0.564 µg a.i./L	**56.4**	80 cm (using combined residue): 2.2 µg a.i./L	**220** **6.9**	Yes
			NOEC: 0.32 ug/L for lemna considering no recovery, many species affected)	0.564 µg a.i./L	**1.8**		**6.9**	
			LOEL: 1.0 µg a.i./L (15 macrophyte species affected out of 29. Many effects were not recovered by study termination)	0.564 µg a.i./L	0.56		**2.2**	

Table 15 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
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes.	na
Predominantly anthropogenic[2]	Yes		Yes	na
Persistence[3]:	Soil	Half-life ≥ 182 days	Half-life: 52 to >182 days (based on SFO) (yes)	AE 1170437 triazine-indanone half life: <182 days AE 1170437 carboxylic acid half life: <182 days AE 1170437 diaminotriazine half life: 13.7 to 265 days (yes)
	Water	Half-life ≥ 182 days	Half-life: stable to hydrolysis. Indaziflam partitions to sediment in the aquatic environment.	
	Sediment	Half-life ≥ 365 days	Half-life: stable (yes)	

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (2.5 x 10^{-8}) and Henry's Law Constant (2.69 x 10^{-8} Pa xm^3/mol).	
Bioaccumulation[4]	Log $K_{OW} \geq 5$		2.8 (no)	
	BCF ≥ 5000		16	
	BAF ≥ 5000		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 toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion 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}).

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

All of the specified Canadian MRLs are the same as those in the U.S., except for crop subgroup 13-07F for which only "grapes" (the representative crop) has a tolerance established in the U.S. (40 CFR Part 180). Codex MRLs are not currently established for indaziflam on any commodities.

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Small fruit vine climbing subgroup, except fuzzy kiwifruit (Crop Subgroup 13-07F)	0.01	0.01 (for grape only)	Not reviewed by Codex
Pome Fruits (Crop Group 11-09)	0.01	The U.S. tolerance is the same for these Crop Groups	
Stone fruits (Crop Group 12-09)	0.01		
Tree Nuts (Crop Group 14-11)	0.01		

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

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

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

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2.0 Human and Animal Health

PMRA Document Number **Reference**

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1769327 2008, BCS DER for toxicity of the metabolite BCS-AA10365 (AE 1170437-1-diaminotriazine) to the green alga Pseudokirchneriella subcapitata, DACO: 9.8.2

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1769343 2008, Lemna gibba G3 Growth inhibition test with AE 2158968 (AE 1170437-triazine-indanone) under static conditions, DACO: 9.8.5

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