Proposed Registration Decision PRD2021-03

Fluazaindolizine and Salibro Nematicide

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Overview

Proposed registration decision for fluazaindolizine and Salibro Nematicide

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Reklemel Technical and Salibro Nematicide, containing the technical grade active ingredient fluazaindolizine, to control root-knot nematodes in tuberous and corm vegetables (Crop Subgroup 1C), carrot, cucurbit vegetables (Crop Group 9) and fruiting vegetables (Crop Group 8-09).

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

This Overview describes the key points of the evaluation, while the Science evaluation provides detailed technical information on the human health, environmental and value assessments of fluazaindolizine and Salibro Nematicide.

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

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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 fluazaindolizine and Salibro Nematicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on fluazaindolizine and Salibro Nematicide, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What is fluazaindolizine?

Fluazaindolizine is a nematicide that protects vegetable crops from root-knot nematodes, which induce galls on roots, stunt plants and cause yield losses. Fluazaindolizine results in paralysis of root-knot nematodes followed by mortality.

Health considerations

Can approved uses of fluazaindolizine affect human health?

Salibro Nematicide, containing fluazaindolizine, is unlikely to affect your health when used according to label directions.

Potential exposure to fluazaindolizine may occur through the diet (food and drinking water), when handling and applying the end-use products, or when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, the technical grade active ingredient fluazaindolizine was of low acute toxicity via the dermal and inhalation routes of exposure. It was minimally irritating the skin, and did not cause an allergic skin reaction.

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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*.

Fluazaindolizine was of moderate acute toxicity via the oral route of exposure and mildly irritating to the eyes; consequently, the signal word “WARNING” and hazard statements “POISON” and “EYE IRRITANT” are required on the label.

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

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of fluazaindolizine to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the kidney, adrenal glands and liver. There was no evidence of increased sensitivity of the young compared to adult animals. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in food and drinking water

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

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and all infants, the subpopulation which would ingest the most fluazaindolizine relative to body weight, are expected to be exposed to less than 30% of the acute reference dose. Based on these estimates, the acute dietary risk from fluazaindolizine is not of health concern for all population subgroups.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and all infants, the subpopulation which would ingest the most fluazaindolizine relative to body weight, are expected to be exposed to less than 74% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from fluazaindolizine is not of health concern for all population subgroups.

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

Residue trials conducted throughout Canada (and the United States) using fluazaindolizine on the primary crops of carrots, potatoes (Crop Subgroup 1C), fruiting vegetables (Crop Group 8-09), and cucurbit vegetables (Crop Group 9) and field accumulation trials (limited and extended) conducted in various North American and European regions on several crops/crop groups are acceptable. The MRLs for this active ingredient can be found in the Science evaluation section of this Consultation Document.

Risks in residential and other non-occupational environments

A residential risk assessment was not required since the product is not a domestic class product and is not permitted for use in residential areas.

Occupational risks from handling Salibro Nematicide

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

Farmers and custom applicators who mix, load or apply Salibro Nematicide can come in direct contact with fluazaindolizine on the skin and through inhalation. In addition, there is the potential for workers to be exposed during postapplication activities when they come in direct contact with Salibro Nematicide residues in treated soil and when moving irrigation lines during or after chemigation. Therefore, the label specifies that anyone mixing, loading and applying Salibro Nematicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Gloves are not required during application while in a closed cab. In addition, for chemigation application, workers are required to wear personal protective equipment as defined in the personal protective equipment (PPE) section of the label for mixers/loaders/applicators when making adjustments or repairs on the chemigation system when this product is in the irrigation water. The label also requires that workers not enter treated fields for twelve (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, risks to these individuals are not a concern.

For bystanders, exposure is expected to be negligible. Therefore, health risks to bystanders are not of concern.

Environmental considerations

What happens when fluazaindolizine is introduced into the environment?

When used according to label directions, environmental risks associated with fluazaindolizine and its associated end-use product are acceptable.

Fluazaindolizine enters the environment when Salibro Nematicide is used to control nematodes in labelled crops. Fluazaindolizine is broken down by microorganisms in the environment. On land, fluazaindolizine and its transformation products may move through soil and reach groundwater. Fluazaindolizine is not expected to be found in air or to travel long distances in the atmosphere from where it is applied. It is also not expected to accumulate in the tissues of plants or animals.

When used according to label directions, the risks from fluazaindolizine to terrestrial and aquatic organisms are acceptable. A precautionary label statement to inform users of the potential for leaching will be required.

Value considerations

What is the value of Salibro Nematicide?

Fluazaindolizine is the active ingredient in Salibro Nematicide. The registration of Salibro Nematicide will provide Canadian vegetable growers with a new product to manage root-knot nematodes, which can cause serious crop and economic losses.

Salibro Nematicide is applied to soil or by chemigation to protect tuberous and corm vegetables (Crop Subgroup 1C), cucurbit vegetables (Crop Group 9), fruiting vegetables (Crop Group 8-09) and carrots from root damage caused by parasitic root-knot nematodes.

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 Reklemel Technical Nematicide, and Salibro Nematicide to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

Because users may come into direct contact with Salibro Nematicide on the skin and through inhalation, anyone mixing, loading and applying Salibro Nematicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Chemical-resistant gloves are not required during application while in a closed cab. For chemigation application, workers are required to wear personal protective equipment as defined in the PPE section of the label for mixers/loaders/applicators when making adjustments or repairs on the chemigation system when this product is in the irrigation water.

In addition, standard label statements to protect against drift during application was added to the label. For postapplication re-entry activities, workers must not enter into treated areas during the restricted-entry interval (REI) of 12 hours.

Environment

A label statement to inform users of the potential for leaching, and to provide mitigation measures to reduce leaching.

Additional information being requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as postmarket information after registration.

Next steps

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

Other information

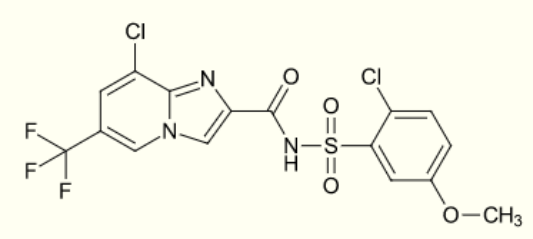
When the Health Canada makes its registration decision, it will publish a Registration Decision on fluazaindolizine and Salibro Nematicide (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science evaluation

Fluazaindolizine

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Fluazaindolizine
Function	Nematicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	8-chloro-*N*-[(2-chloro-5-methoxyphenyl)sulfonyl]-6-(trifluoromethyl)imidazo[1, 2-α]pyridine-2-carboxamide
2. Chemical Abstracts Service (CAS)	8-chloro-*N*-[(2-chloro-5-methoxyphenyl)sulfonyl]-6-(trifluoromethyl)imidazo[1, 2-α]pyridine-2-carboxamide
CAS number	1254304-22-7
Molecular formula	$C_{16}H_{10}Cl_2F_3N_3O_4S$
Molecular weight	468.2 g/mol
Structural formula	
Purity of the active ingredient	97.3%

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

Technical product—Reklemel Technical

Property	Result
Colour and physical state	Off-white to brown solid
Odour	None
Melting point	218.5 °C
Boiling point or range	Not applicable to a solid
Bulk density	0.515–0.85 g/cm^3

Property	Result
Vapour pressure at 20 °C	2.12×10^{-4} mPa
Ultraviolet (UV)-visible spectrum	λ_{max} at 202 and 235 nm, with no absorption at >350 nm
Solubility in water at 20 °C	pH — Solubility (g/L) distilled water — 0.0561 4.0 — 0.02210 7.0 — 2.1479 9.0 — 2.8455
Solubility in organic solvents at 20 °C	Solvent — Solubility (g/L) Acetonitrile — 35.05 Methanol — 3.47 Acetone — 99.76 Ethyl acetate — 27.62 1, 2-dichloroethane — 19.29 o-Xylene — 1.247 n-Octanol — 2.00 n-Hexane — 0.002
n-Octanol-water partition coefficient (K_{ow})	pH — log K_{ow} distilled water — 0.81 4.0 — 2.24 7.0 — -0.16 9.0 — -0.71
Dissociation constant (pK_a)	5.60
Stability (temperature, metal)	Stable to metals and metal ions (iron, aluminum and their acetate salts); stable to elevated temperature (54 °C for 2 weeks); no oxidizing properties.

End-use product—Salibro Nematicide

Property	Result
Colour	Off-white
Odour	Mild acidic
Physical state	Liquid
Formulation type	Suspension concentrate
Label concentration	500 g/L
Container material and description	HDPE bottle, jug, tote or drum, 0.5 L to bulk
Density	1.205–1.215 g/mL
pH of 1% dispersion in water	3–5 for a 1% dilution
Oxidizing or reducing action	Not an oxidizing or reducing agent

Property	Result
Storage stability	Stable after storage in HDPE for 2 years at 20–30 °C and for 14 days at 54 °C.
Corrosion characteristics	Not corrosive to its HDPE packaging
Explodability	Not explosive

1.3 Directions for use

Salibro Nematicide is applied as a soil treatment prior to planting or at planting of tuberous and corm vegetables (Crop Subgroup 1C), fruiting vegetables (Crop Group 8-09), cucurbit vegetables (Crop Group 9), and carrots. Salibro Nematicide may be applied pre-plant incorporated, broadcast followed by soil incorporation, in-furrow (tuberous and corm vegetables only), or by chemigation (fruiting vegetables and cucurbit vegetables only) prior to or at planting. Salibro Nematicide is applied at rates of 1.12–2.24 L product/ha to cucurbit vegetables and 2.24–4.48 L product/ha to all other labelled crops. Chemigation treatments during the crop season may be made at 0.56–1.12 L to cucurbit vegetables or at 1.12–2.24 L product/ha to all other labelled crops, where Salibro Nematicide was applied prior to or at planting or where the soil was treated with a fumigant prior to planting.

1.4 Mode of action

Fluazaindolizine is taken up by root-knot nematodes from water in the soil, which causes them to become immobile 24 to 48 hours after treatment. As a result, they are unable to feed on plant roots and eventually die. This represents a novel mode of action against root-knot plant parasitic nematodes, but the actual mechanism of action of fluazaindolizine is unknown.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

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

2.2 Method for formulation analysis

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

2.3 Methods for residue analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; DuPont-33861 and DuPont-47054 in plant matrices and DuPont-39226 and Charles River AV.225144.02 in animal matrices) were developed and proposed for data gathering and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limits of quantitation. In general, acceptable average recoveries (70–120%) were obtained in plant and animal matrices. The

proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples from the soybean plant metabolism (soybean hay and seeds), and from the confined crop rotation studies (wheat hay, radish roots, and mature spinach) analyzed with the enforcement method. Extraction solvents used in the method for animal matrices were similar to those used in the livestock metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled animal matrices was not required for the enforcement method.

Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on human and animal health

3.1 Toxicology summary

Fluazaindolizine, also identified as Reklemel Technical (brand name) or DPX-Q8U80 (code name), is a sulfonamide nematicide. Its pesticidal mode of action is not known, although it is expected to protect against plant parasitic nematode damage by rendering nematodes immobile and unable to feed on plant roots.

A detailed review of the toxicological database for fluazaindolizine was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies conducted with fluazaindolizine included an in vitro study investigating the comparative metabolism by mouse, rat, rabbit, dog and human hepatocytes as well as studies assessing potential hormonal perturbation. Several studies conducted with various transformation products of fluazaindolizine were also available for review, including acute oral toxicity studies, repeat-dose oral toxicity studies, developmental and reproductive toxicity studies, and genotoxicity studies. The required studies in the fluazaindolizine database were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with fluazaindolizine.

Metabolism and toxicokinetic studies were conducted in rats via the oral route. In these studies, fluazaindolizine was carbon (C)^{14}-radiolabelled on the phenyl ring ([Ph-^{14}C]fluazaindolizine) or the imidazopyridine ([IP-2-^{14}C]fluazaindolizine) portion of the molecule. Fluazaindolizine was rapidly absorbed and widely distributed to tissues following single low- or high-dose gavage administration, with plasma elimination half-lives of 8–13 hours. Following oral administration of both radiolabels to bile duct-cannulated rats, the total absorption was 44% to 59% of the administered dose, based on the recovery in the bile, urine, cage wash, plasma, red blood cells and carcass at 48 hours postdosing.

The highest levels of radioactivity at 1-24 hours postdosing were generally observed in the plasma, followed by the liver, the urinary bladder, the pituitary, and the kidneys with the [IP-2-^{14}C] label or the [Ph-^{14}C] label.

The highest levels of radioactivity at 168 hours postdosing were in liver, red blood cells and skin with the [IP-2-^{14}C] label, and were in pituitary, liver, skin and adrenal glands with the [Ph-^{14}C] label. Concentrations of radioactivity in tissues were generally slightly greater in females than in males.

Radioactivity was readily excreted within 48–72 hours of administration of a single dose. There was a slightly higher proportion of radioactivity excreted via the feces when compared to the amount excreted via the urine. Results from bile duct-cannulated rats suggested that biliary excretion accounted for a small fraction of the eliminated radioactivity when compared to the excretion via feces and urine. The levels of radioactivity in feces, urine and bile appeared to be similar between the high- and low-dose groups with both radiolabels and between sexes.

Tissue distribution and excretion measurements were also conducted after repeated oral administration via gavage of non-radiolabelled test material to rats for 14 days followed by a single gavage dose of the [Ph-^{14}C] labelled test material. Findings were similar to those observed in single-dosing experiments.

Fluazaindolizine was partially metabolised in the rat with no significant sex differences identified. Following single gavage dosing with a low or high dose of C^{14}-radiolabelled test material, unchanged fluazaindolizine was the major component in urine, feces, and cage wash extracts. In urine, IN-QEK31 and a sulphate conjugate of IN-A5760 were the most prominent metabolites. Other metabolites in urine included IN-UHD20, IN-REG72, a glucuronide conjugate of IN-A5760, IN-A5760, and IN-F4106. In feces, IN-UHD20 and IN-REG72 were most prominent. Other metabolites in feces included IN-QEK31.

The metabolic pathway of fluazaindolizine in the rat was proposed based on metabolites identified in the tissues, bile, urine and feces. The primary biotransformation pathways of fluazaindolizine involved O-demethylation, hydroxylation of the phenyl ring and hydrolysis of the amide bond. The metabolite IN-UHD20 was formed via direct hydroxylation of the phenyl ring of fluazaindolizine. Fluazaindolizine and IN-UHD20 underwent O-demethylation to form IN-REG72 and IN-UHD21, respectively. Direct hydrolysis of fluazaindolizine, IN-REG72 or IN-UHD20 produced metabolites IN-F4106 and IN-A5760, which contained only the phenyl ring, and IN-QEK31, which contained the imidazopyridine moiety. The identities of metabolites that were sufficiently characterized are presented in Appendix I, Table 3.

Supplemental pilot studies examining the rate of metabolism and elimination were also conducted in rats and mice that were administered a single gavage dose of [Ph-^{14}C]fluazaindolizine or [IP-5,8a-^{14}C]fluazaindolizine. Highest residues of radioactivity were detected in the liver of both species at 168 hours postdosing. Excretion was slightly faster in mice than rats.

In a non-guideline comparative in vitro metabolism study, the extent to which hepatocytes from mice, rats, rabbits, dogs, and humans metabolized [Ph-^{14}C]fluazaindolizine and [IP-5,8a-^{14}C]fluazaindolizine was investigated. Metabolism was observed in all tested species with the highest rates observed in human hepatocytes followed by mouse, rat, rabbit and dog.

The toxicokinetics of fluazaindolizine was also investigated in a supplemental study where female rats were gavage dosed with unlabelled test material for 14 days. The results of this study suggested that steady state plasma concentrations were achieved within the first few days of dosing, and that preferential partitioning into fat was not observed with repeated oral exposure.

Plasma concentrations of non-radiolabelled fluazaindolizine and a number if its metabolites were measured in select repeat-dose oral toxicity studies conducted in mice, rats, and dogs. Fluazaindolizine levels increased with increasing dose levels, in a mostly dose-proportional manner, and were generally higher in female animals. Fluazaindolizine was detected at much higher concentrations than any of the measured metabolites. Among the identified metabolites, the highest concentrations were measured for IN-UHD20, IN-REG72, IN-QEK31, and IN-F4106 in mice, IN-QEK31, IN-F4106, IN-REG72, REG72-OH, and Q8U80-OH in rats, and IN-QEK31 and IN-F4106 in dogs.

In acute toxicity testing, fluazaindolizine was of moderate acute toxicity to rats via the oral route of exposure, and was of low acute toxicity to rats via the dermal and inhalation routes of exposure. It was non- to mildly irritating to the eyes and non- to minimally irritating to the skin of rabbits. Fluazaindolizine demonstrated negative results for skin sensitization in guinea pigs using the Maximization test protocol, and in mice in a supplemental local lymph node assay.

The end-use product Salibro Nematicide, containing fluazaindolizine, was of low acute toxicity to rats via the oral, dermal, and inhalation routes of exposure; was minimally irritating to the eyes and skin of rabbits; and tested negative for skin sensitization in mice using the local lymph node assay.

Repeat-dose dietary toxicity studies with fluazaindolizine were available in mice, rats, and dogs. In these studies, which involved short-term to long-term testing, the most sensitive species, based on the evaluated toxicology endpoints, appeared to be the dog, followed very closely by the rat and then the mouse. The kidney was the primary target tissue following repeated oral dosing in mice and rats. Kidney toxicity in these species was evidenced by increased organ weight, kidney infarctions, hypertrophy, hyperplasia, fibrosis, necrosis, pyelonephritis, pyelitis, dilation, mineralization, discolouration and abnormal shape of the organ. In dogs, the liver and the adrenal were the primary target tissues following repeat oral dosing. Liver toxicity was evidenced by increased organ weight, single cell necrosis, vacuolation, and increased metabolic enzymes, while adrenal toxicity was evidenced by increased organ weight and corticomedullary pigmentation. Other common findings in the database included decreased body weight and effects on hematology parameters (reductions in red blood cell parameters in particular) in mice, rats and dogs, with dogs also exhibiting hemopoiesis of the liver, spleen and bone marrow. Affected clinical chemistry parameters included altered cholesterol levels and elevated serum alanine aminotransferase in particular, and changes in urinalysis parameters, such as decreased specific gravity and protein levels, and increased volume, were also observed. Following chronic dietary dosing in mice, effects on the pituitary gland (cysts), lymph nodes (plasmacytosis, inflammation), salivary gland (atrophy), and pancreas (mononuclear cell infiltration), along with an increase in the degree of amyloidosis of several tissues, were noted. In the long-term dietary study in rats, additional tissues affected included the nasal cavity (eosinophilic globules), stomach (hyperplasia, erosion), and uterus (metaplasia).

There was evidence to suggest that there was a slight increase in toxicity with extended duration of dosing in the rat and dog studies. In rats, kidney hyperplasia was observed at lower dose levels in the 24-month dietary chronic toxicity/oncogenicity study when compared to studies of shorter duration. Additionally in rats, a number of renal findings were only observed after lifetime dosing in the 24-month dietary study, such as kidney cysts, kidney interstitial fibrosis, and kidney papilla necrosis. In the dog, there were also a number of findings observed at lower dose levels in the 12-month dietary study when compared to studies of shorter duration, such as changes in the liver/gallbladder and adrenal weight. Additionally in dogs, there were findings only observed in the 12-month study, such as adrenal corticomedullary pigmentation.

In a supplemental 28-day dermal toxicity study in rats, there was no indication of systemic toxicity up to the limit dose of testing, although it should be noted the study was deemed supplemental since the test compound was only applied to a relatively small skin surface area. A request to waive the requirement for a repeat-exposure inhalation toxicity study was submitted for fluazaindolizine. The waiver request was supported for the proposed uses on the basis of the low volatility and low acute inhalation toxicity of fluazaindolizine, as well as the magnitude of the margins of exposure obtained for the inhalation exposure scenarios when oral endpoints were used in the risk assessment.

There was no treatment-related effect on neurotoxicity parameters that were assessed as part of the subchronic 90-day dietary study in rats, which included functional observations and measurements, motor activity testing, and neuropathology evaluation. In an acute neurotoxicity study in rats conducted via oral gavage, there were slight decreases in motor activity, in terms of duration of movement and ambulatory activity counts, as well as a decrease in habituation to the testing environment. This decreased activity was only observed in males on the day of dosing. Given the lack of other neurotoxicity-related findings in the database, the results of the acute neurotoxicity study were not considered to be an indication of selective neurotoxicity.

In a 28-day dietary immunotoxicity study in rats dosed with fluazaindolizine, there was no treatment-related effect on antibody response. There was no evidence of immune system dysregulation noted in this study, or in other studies in the fluazaindolizine database.

The potential for fluazaindolizine to impact reproductive performance was assessed in rats in both 1- and 2-generation dietary reproductive toxicity studies. In the 1-generation reproductive toxicity study, kidney hyperplasia was observed in parental animals of both sexes, with additional effects on the kidney and urinary bladder observed at a higher dose level in parental females.

No treatment-related effects were noted in weanling offspring. In offspring that were maintained on study into adulthood, similar effects on the kidney were noted at dose levels comparable to those causing effects in the parental generation.

In the 2-generation dietary reproductive toxicity study, the systemic toxicity observed in parental animals was generally consistent with findings reported in other repeat-dose dietary studies in rats, and included hyperplasia, dilation, and deformity of the kidney, as well as chronic progressive nephropathy. There were no effects on reproductive performance or in tissues of the

reproductive system, with the exception of inflammation of the prostate gland. At the same dose level at which F1 parental males exhibited renal hyperplasia, there were effects noted in F2 pups such as mucosal hyperplasia in the kidneys, ureters, and urinary bladder, as well as mucosal hyperplasia of the urethra and cystitis of the urinary bladder. Similar findings were observed in F1 pups and F1 maternal animals at the next higher dose level. The findings identified in the 1-generation and 2-generation reproductive toxicity studies in rats suggested that there was no increased sensitivity of the young animal when compared to the adult animal.

Developmental toxicity studies were conducted via oral gavage in rats and rabbits. In both species, maternal toxicity was noted at the same dose level at which developmental effects were noted. Developmental toxicity in the rat was evidenced by an increased incidence of short cervical ribs (classified as a variation) and decreased fetal weight, while developmental toxicity in the rabbit was evidenced by increased incidences of small gallbladders and sternebrae with thread-like attachments (classified as a variation). A slight increase in the number of abortions was observed at the high-dose level relative to controls. However, these abortions occurred after maternal animals lost a significant amount of body weight. Single incidences of abortion in the control and mid-dose groups were also observed after significant body weight loss in maternal animals. The relationship to treatment for the minimal increase in abortions at the high-dose level (three litters) was therefore considered equivocal. The findings identified in the developmental toxicity studies suggested that there was no increased sensitivity of the young animal when compared to the adult animal.

A series of three supplemental studies were conducted to investigate the potential for fluazaindolizine to cause hormonal perturbations. In an in vitro steroidogenesis assay conducted in human adrenocortical carcinoma cells, decreases in testosterone and estradiol were observed but only at the highest concentration tested, which, as per the guidelines for this assay, was considered an equivocal result for the inhibition of steroid biosynthesis. In a 3-day gavage uterotrophic assay in ovariectomized female rats, there were no treatment-related effects indicative of estrogen agonism. In a 15-day gavage study conducted in intact male rats, a number of hormones were measured. However, the assessment of hormonal alteration was difficult to interpret given small sample sizes and large inter- and intra-group variability, as well as excessive toxicity at the highest dose level. In this assay, treatment-related effects included reductions in epididymal and testes weights, and elevations in hepatic aromatase activity.

Although there were effects noted in some of these studies, they were likely not specific to the endocrine system given the lack of confirmatory findings in the available guideline toxicity studies. Notably, there were no reproductive effects noted in the 2-generation dietary reproductive toxicity study, which assessed vaginal patency, preputial separation, sperm parameters, and estrous cycle parameters.

Fluazaindolizine was negative for genotoxicity in several studies, including bacterial reverse mutation assays in *S. Typhimurium* and E. *coli*, an in vitro forward mutation assay in Chinese hamster ovary cells, in vivo micronucleus assays in mice, and a supplemental 14-day gavage study in rats.

A positive response was observed in the in vitro chromosomal aberration assay with human peripheral blood lymphocytes in the presence and absence of metabolic activation. Based on the weight of evidence, fluazaindolizine is considered negative overall for genotoxic potential.

There were no treatment-related tumours in an 18-month dietary oncogenicity study conducted in mice or in a 24-month chronic toxicity/oncogenicity study in rats. Given the lack of evidence of tumorigenicity in the database, a cancer risk assessment was not required.

A number of toxicity studies were provided for nine fluazaindolizine metabolites identified as potentially contributing to residues in the diet or drinking water: IN-A5760, IN-F4106, IN-QEK31, IN-REG72, IN-QZY47, IN-TMQ01, IN-TQD54, IN-UJV12, and IN-VM862. Of these, IN-A5760, IN-F4106, IN-QEK31, and IN-REG72 were also identified as metabolites formed in the rat, mouse and dog, while IN-QZY47, IN-TMQ01, IN-TQD54, IN-UJV12, and IN-VM862 were identified as unique transformation products in crop matrices, livestock, or environmental media.

In acute oral toxicity testing in rats, IN-QEK31 was found to be of slight toxicity, and metabolites IN-F4106, IN-QZY47, IN-TMQ01, IN-TQD54, and IN-UVJ12 were determined to be of low toxicity.

In vitro chromosomal aberration assays using human peripheral blood lymphocytes produced negative results for IN-REG72, IN-QZY47, IN-TMQ01, IN-TQD54, and IN-VM862, while IN-A5760, IN-F4106, IN-QEK31, and IN-UJV12 tested positive. IN-UJV12 tested positive in a bacterial reverse mutation assay using a high purity test material, and tested negative in the same assay using a lower purity test material. Bacterial reverse mutation assays yielded negative results for IN-A5760, IN-F4106, IN-QEK31, IN-REG72, IN-QZY47, IN-TMQ01, IN-TQD54, and IN-VM862. In vitro forward mutation assays using Chinese hamster ovary cells were negative for IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-UJV12, and IN-VM862. In vivo micronucleus assays in mice were negative for IN-A5760, IN-F4106, IN-QEK31, IN-REG72, and IN-UJV12. IN-QZY47 was also negative for unscheduled DNA synthesis in hepatocytes collected from rats following oral gavage dosing. Metabolites IN-A5760, IN-F4106, IN-QEK31, and IN-UJV12 tested positive in the chromosomal aberration assays; however, there were also negative results for each of these metabolites in the micronucleus assays, tempering concerns regarding the positive findings in the chromosomal aberration assays. Overall, there was no genotoxicity concern for any of the tested metabolites.

Repeat-dose dietary toxicity studies in rats of 28 days duration were conducted with IN-QZY47 and IN-TMQ01, and 90-day dietary toxicity studies were provided for IN-F4106 and IN-QEK31. For IN-VM862, a 90-day gavage toxicity study in rats was provided. The effects from these studies were compared with those observed in the toxicity studies with fluazaindolizine. IN-QZY47, IN-TMQ01, IN-F4106, and IN-QEK31 produced toxic effects at similar dose levels, and targeted similar tissues (liver, kidney, urinary bladder), as fluazaindolizine. IN-VM862 produced toxic effects at lower dose levels than fluazaindolizine, and targeted the liver and lymph nodes in addition to the kidney. It should be highlighted that the IN-VM862 study was administered via gavage while the fluazaindolizine study was administered via the diet, which slightly confounds the comparison to fluazaindolizine.

Reproductive and developmental toxicity screening studies, conducted via the diet in rats, were provided for IN-F4106 and IN-QEK31. For both compounds, the parental animals exhibited effects on the kidney at the same dose level at which decreased offspring body weights occurred. Effects on reproductive toxicity were not noted in these studies. The findings and effect levels observed in parental animals were similar to those in the 1-generation reproductive toxicity study in rats with fluazaindolizine, which identified the kidney as the target organ in parents, and did not identify reproductive or offspring effects.

A 2-generation reproductive toxicity study was provided for IN-F4106. Decreased body weight was observed in offspring at the same dose level that resulted in reduced body weight in parental animals. Reproductive toxicity was not noted in this study. The parental and offspring effect levels were similar to those in the 2-generation reproductive toxicity study in rats conducted with fluazaindolizine. However, it should be noted that the liver, kidney and urinary bladder were not examined microscopically in the parental animals in the 2-generation reproductive toxicity study with IN-F4106, resulting in some uncertainty as to the true magnitude of the parental effect level. Furthermore, the kidneys and urinary bladders of offspring were examined microscopically in the 2-generation study conducted with fluazaindolizine, and histopathology of these tissues formed the basis of the point of departure for offspring toxicity in that study. A similar assessment was not conducted in the 2-generation study with IN-F4106, and although not part of the standard protocol for reproductive toxicity studies, the lack of histological examination of these tissues results in uncertainty regarding the offspring effect level as well. However, when considering the results from the 90-day dietary toxicity study in rats using IN-F4106, in which the liver, kidney and urinary bladder were examined microscopically in adult animals, coupled with the fact that offspring were not more sensitive than the adult animal to kidney pathology in the 2-generation study with fluazaindolizine, it is unlikely that the lack of similar investigations in the 2-generation reproductive toxicity study with IN-F4106 would have a significant impact on the points of departure.

Developmental toxicity studies in rats, conducted via gavage, were provided for IN-F4106 and IN-QEK31. For IN-F4106, fetal body weight was decreased at a dose level that did not result in any toxicity to maternal animals, suggesting an increased sensitivity of the young.

In addition, effects on maternal and fetal body weight were observed at dose levels lower than those causing toxicity in the developmental toxicity study in rats with fluazaindolizine. For IN-QEK31, there were no adverse maternal or developmental effects at similar dose levels as those used in the developmental toxicity study with fluazaindolizine.

For metabolites IN-A5760, IN-QEK31, IN-REG72, IN-QZY47, IN-TMQ01, IN-TQD54, and IN-UJV12, the available information did not suggest higher toxicity than fluazaindolizine, although there was insufficient information to conclude that these metabolites were less toxic than fluazaindolizine. Metabolites IN-A5760, IN-QEK31, IN-REG72, IN-QZY47, IN-TMQ01, IN-TQD54, and IN-UJV12 were therefore considered to be of equal toxicity to fluazaindolizine for risk assessment purposes. The available evidence suggests that metabolites IN-F4106 and IN-VM862 are more toxic than fluazaindolizine. However, the toxicokinetic studies with fluazaindolizine showed that IN-F4106 is a significant metabolite detected in the liver and kidney of rats, and the repeat-dose dietary studies with fluazaindolizine identified IN-F4106 as a

metabolite in plasma of rats, mice, and dogs. These data suggest that the formation of IN-F4106 in laboratory animals dosed with fluazaindolizine could have contributed to the toxic effects noted in the fluazaindolizine database, tempering the concern for the lower points of departure observed in some studies with IN-F4106. Additionally, the points of departure for IN-F4106 converted to parent equivalents, on a molecular weight basis, are comparable to those for the parent compound. Therefore, using the reference doses for the parent compound for assessing risks from dietary exposure to IN-F4106 is considered to be protective of any potential toxic effects from exposure to IN-F4106. Metabolite IN-VM862 was not identified as a metabolite of the rat, mouse or dog or in plant matrices, but is a suspected environmental degradate that may be found in drinking water. Water modelling results indicated that IN-VM862 contributed very little (<0.5%) to the overall drinking water concentration. Given this information, the toxicological reference values selected for fluazaindolizine are considered protective of potential effects from IN-VM862.

A change to the manufacturing process for fluazaindolizine was implemented following the development of the toxicology database in order to improve process safety. As a result, additional acute toxicity and genotoxicity studies were conducted with a batch of test material produced with the revised manufacturing process in order to compare to the toxicity of batches produced via the two processes. These studies produced similar results to the studies using the test material from the original manufacturing process. Additional quantitative structure activity analysis and physiologically based pharmacokinetic modelling data were provided for various impurities produced by the two processes. Overall, a comparison of the impurity profiles between the various batches used in the toxicity studies, as well as a batch considered representative of the commercial production process, did not identify any toxicological concerns. Based on the collective information, it was concluded that the batches of fluazaindolizine obtained from either manufacturing process were considered toxicologically equivalent, and thus the toxicology studies conducted with the test material produced using the original manufacturing process were considered acceptable to support registration of the technical grade active ingredient.

The identification of select metabolites of fluazaindolizine is presented in Appendix I, Table 3. Results of the toxicology studies conducted on laboratory animals with end-use products of fluazaindolizine, technical fluazaindolizine, and its metabolites are summarized in Appendix I, Tables 4, 5 and 6 respectively. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 7.

3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.[5]

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies, including gavage developmental toxicity studies in rats and rabbits, and dietary 1-generation and 2-generation reproductive toxicity studies in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the developmental or reproductive toxicity studies. In the 1-generation rat reproductive toxicity study, no treatment-related effects were noted in offspring that were maintained on study up to weaning. There were numerous kidney pathology findings observed in adult F1 offspring, namely, dilation, discolouration, cysts, hyperplasia of transitional epithelium, pyelitis, pyelonephritis, and ulceration of the epithelial surface; these effects occurred in the presence of parental toxicity. In the 2-generation rat reproductive toxicity study, mucosal hyperplasia of kidneys, ureters, urinary bladders, and urethras, as well as cystitis of urinary bladders were observed in offspring at weaning; these effects also occurred in the presence of parental toxicity. In the developmental toxicity study in rats, short cervical ribs and decreased body weight were observed in fetuses, whereas in the developmental toxicity study in rabbits, fetal variations of sternebrae with thread-like attachment and small gallbladders were noted. These developmental effects occurred in the presence of maternal toxicity. A slight, equivocal increase in the number of abortions was also observed in the rabbit. These abortions occurred toward the end of the dosing period and at the same dose level that caused mortality, body weight loss, and renal pathology in maternal animals.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young as effects in the young are well-characterized and occurred in the presence of maternal toxicity. In the rabbit developmental toxicity study, a minimal increase in abortions occurred at the high-dose level following significant body weight loss. A similar pattern of body weight loss led to single incidences of abortion in other dose groups. Based on the overall weight of evidence, there was a low level of concern for the equivocal increase in abortions in rabbits. Therefore, on the basis of this information, the *Pest Control Products Act* factor (PCPA) factor was reduced to onefold.

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

3.2 Acute reference dose (ARfD)

To estimate acute dietary risk, the NOAEL of 125 mg/kg bw from the acute neurotoxicity study in rats was selected for risk assessment. At the LOAEL of 450 mg/kg bw, effects on motor activity were observed in males on the day of dosing, in the form of shorter duration of movement and decreased ambulatory activity counts as well as reduced habituation to the testing environment. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{125 \text{ mg/kg bw}}{100} = 1.3 \text{ mg/kg bw of fluazaindolizine}$$

3.3 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 17 mg/kg bw/day from the 1-year dietary toxicity study in the dog was selected. At the LOAEL of 36 mg/kg bw/day, there were decreases in body weight and bodyweight gain in females, increased weight of liver and adrenal gland in both sexes, histopathology of the liver in males (pigmented hepatocytes) and adrenal gland in females (corticomedullary pigmentation), as well as alterations in several clinical chemistry parameters suggestive of liver damage. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. The CAF is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{17 \text{ mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day of fluazaindolizine}$$

The ADI provides a margin of 600 to the dose level at which increased abortions were observed in the developmental toxicity study in rabbits.

The ADI provides a margin of 110 to the dose level at which decreased fetal body weights were observed in the developmental toxicity study in rats using the IN-F4106 metabolite.

Cancer assessment

There was no evidence of tumorigenicity; therefore, a cancer risk assessment is not necessary.

3.4 Occupational and residential risk assessment

3.4.1 Toxicological reference values

Short-, and intermediate-term dermal and inhalation

For short- and intermediate-term dermal and inhalation occupational exposures, the NOAEL of 20 mg/kg bw/day from the 90-day dietary toxicity study in dogs was selected for risk assessment. Limitations in the available short-term dermal toxicity study and the lack of a repeat-exposure inhalation toxicity study necessitated the use of an oral study for dermal and inhalation risk assessments. At the LOAEL of 59 mg/kg bw/day in the 90-day dog study, there were histopathology effects noted in the liver, spleen and Peyer's patch. Additionally at the LOAEL, altered clinical chemistry parameters, such as decreased cholesterol and albumin, and liver enzyme induction were observed.

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

Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). For the active ingredient fluazaindolizine, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected. The most relevant toxicology endpoints and assessment factors for acute and chronic oral aggregate exposure are the same as those selected for the ARfD (see Section 3.2) and ADI (see Section 3.3), respectively.

Occupational exposure to fluazaindolizine is expected to be via the dermal and inhalation routes for mixers, loaders and applicators, and through the dermal route for postapplication workers. The exposure duration is expected to be short- to intermediate-term.

3.4.1.1 Dermal absorption

An in vivo dermal absorption study in rats and in vitro dermal absorption study in rats and humans were reviewed. Together these studies are referred to as a "triple pack". For the in vivo study, the limitations were considered minor and not expected to affect the confidence of the dermal absorption value.

The coefficient of variation (CV) was <25% for all monitoring periods and for the low dose, a 1% dermal absorption value was obtained which includes skin bound residues. The vehicle used for this study was a blank formulation of the end-use product, which contains water as the primary diluent and is diluted with water prior to application in the field.

For the in vitro rat and human studies, the CVs were >25% for both low and high doses. In general, CVs greater than 25% in animals reduce the confidence in the study results and the triple pack approach. In humans, higher CVs (>25%) are expected given that there is higher variability in human subjects when compared to laboratory animals. Given that the receptor fluid used was ethanol, the rat and human in vitro absorption values of 21% and 5%, respectively, were considered to be conservative and likely to overestimate absorption of a water-based formulation. As per the OECD (2011) guidance notes on dermal absorption, the use of an organic solvent as a vehicle can jeopardize the integrity of the skin, which increases absorption. Specifically, ethanol can enhance solubility in the vehicle and the *stratum corneum* (OECD, 2011).

The use of the in vitro and in vivo data in the triple pack approach resulted in a ratio of animal in vitro to in vivo dermal absorption which was significantly greater than 1 ± 0.5 (calculated ratio was 21). Based on this, the in vitro rat dermal absorption value does not approximate the rat in vivo dermal absorption value and therefore the human in vitro dermal absorption value will not approximate the human in vivo dermal absorption value. This is largely based on the differences in vehicle and receptor fluid used in the in vivo and in vitro studies, respectively. Due to this, it was considered more appropriate to estimate the dermal absorption value from the rat in vivo study alone at the 144 hour time period (1%) for use in the risk assessment of fluazaindolizine.

3.4.2 Occupational exposure and risk

3.4.2.1 Mixer/loader/applicator exposure and risk assessment

Individuals have potential for exposure to Salibro Nematicide during mixing, loading and application. Dermal and inhalation exposure estimates for workers were generated from the Agricultural Handlers Exposure Task Force (AHETF) database.

Exposure to workers mixing, loading and applying Salibro Nematicide is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure was estimated using the maximum application rate of 2.24 kg a.i/ha for soil-directed applications and the adult bodyweight of 80 kg. The default area treated per day (ATPD) value for large field crops (360 ha/day) was used for tuberous and corm vegetables, which includes potatoes. For groundboom application to small field crops and chemigation application, the applicant provided maximum ATPD values of 40 ha/day and 182 ha/day, respectively. As these ATPD values are higher than default values, they were used for the risk assessment. The risk assessment is based on mixer/loader/applicator (M/L/A) using open cab groundboom application for pre-plant treatments (pre-plant incorporated, broadcast followed by soil incorporation or in-furrow) and mixer/loader (M/L) only for chemigation as there is no application involved.

The application rate for chemigation is based on the highest rate for fruiting vegetables, therefore, the resulting MOE will not underestimate the risks for all other crops. The exposure estimates are based on mixers/loaders/applicators wearing long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

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. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicology reference values (no observed adverse effects levels) to obtain the MOE; the target MOE is 100. Calculated MOEs were greater than the target MOE of 100 therefore, there are no health risks of concern.

Table 3.4.2.1.1 Mixer/loader/applicator dermal and inhalation exposure estimates and MOE

Exposure scenario	Total unit exposure (µg/kg a.i. handled)[1]	ATPD (ha/day)[2]	Rate (kg a.i./ha)	Daily exposure (mg/kg bw/day)[3]	MOE[4] Target MOE = 100
PPE: Single Layer and chemical-resistant gloves					
Open Mix/Load Liquid + Open Cab Groundboom Application – Tuberous and corm vegetables, including potatoes	3.149	360	2.24	0.032	630
Open Mix/Load Liquid + Open Cab Groundboom Application - Fruiting vegetables	3.149	40	2.24	0.004	5671
Open Mix/Load Liquid (Chemigation) – All crops	1.215	182	2.24	0.006	3230

ATPD = Area treated per day; MOE = Margin of exposure
[1] Total unit exposure values from AHETF. These were obtained by adjusting dermal unit exposure values for 1% dermal absorption then combining with inhalation unit exposure values.
[2] Default area treated per day for tuberous and corm vegetables; Area treated per day provided by applicant for the other crops
[3] Exposure = (Total Unit Exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[4] Based on NOAEL = 20 mg/kg bw/day; MOE = NOAEL/Exposure

3.4.2.2 Exposure and risk assessment for workers entering treated areas

When Salibro Nematicide is incorporated into the soil prior to planting, applied broadcast and then incorporated in the soil or applied in-furrow and then covered with soil, exposure to postapplication workers is expected to be minimal as any contact with the treated soil is expected to be negligible.

However, there is the potential for workers to be exposed to fluazaindolizine during and after chemigation application when it is applied through irrigation lines. Salibro Nematicide can be applied through an irrigation system which is set up as fixed, periodically moved, or self moving.

As there can be up to four (4) chemigation applications per season, irrigation lines may have to be moved throughout the field during or between applications, depending on the irrigation capacity of the farm. As such, the postapplication worker moving the irrigation lines may be exposed to residues on the irrigation pipes and treated soil around where the pipes are laid in the field. As Salibro Nematicide is typically applied early in the season, with no need for application to maturing crops, foliage will unlikely be present when Salibro Nematicide is applied via chemigation. In addition, it is not indicated on the label that this will be applied to transplants at planting, which further reduces the likelihood that foliage will be present during chemigation application.

Therefore, a postapplication dermal risk assessment for workers moving the irrigation lines and contacting treated soil was required. Dermal exposure was estimated by using a modified version of the dermal exposure equation for soil contact from the USEPA Risk Assessment Guidance for Superfund (RAGS) (USEPA, 2004). One of the key input values of the model: the adherence factor, or the amount of soil transferred to the skin over a given period of time (or event), was obtained from a study monitoring pipe laying activities in "wet" soil. Even though this study was not carried out in a commercial agricultural setting, this study and resulting adherence factor are still considered applicable to the proposed use of Salibro Nematicide when applied via chemigation. In the study, volunteers were given a plastic pipe and fittings, a trowel, and a plan of the desired piping layout. Activity proceeded for a fixed time interval of 15, 30, or 45 minutes. Individuals who completed the layout before the end of the time interval removed the pipe and began again. All subjects wore short sleeves and short pants.

The modified soil contact model is represented by the equation:

$$\text{Dermal Exposure (mg/kg bw/day)} = \frac{C_{soil} \times AF \times CF \times DA_{soil} \times SA \times Events}{BW}$$

The concentration of fluazaindolizine in soil (C_{soil}) on the day of application (mg a.i. /kg soil) was estimated using the maximum rate for soil application in field conditions (in other words, chemigation postplant for tuberous and corm vegetables and carrots; chemigation pre-/at-plant for cucurbit and fruiting vegetables) and the assumption that 100% of the applied fluazaindolizine was located within the uppermost 1 cm of soil. This is the same approach as that outlined in the USEPA Residential SOPs (USEPA, 2012, section 3.2.5). This is considered to be a conservative assumption for Salibro Nematicide as it needs to translocate through the soil to the full depth of the root to effectively control nematodes.

For the adherence factor (AF) of soil to skin (mg/cm^2-event), a value of 0.630 mg/cm^2-event for pipe layers in wet soil (geometric mean) from the RAGS guidance document (USEPA, 2004) was used. This value was reported per event and weighted for body part surface area. A conversion factor (CF) was applied to convert mg soil to kg soil (1×10^{-6} kg/mg).

The dermal absorption (DA_{soil}) of fluazaindolizine in soil was assumed to be equivalent to the dermal absorption from a liquid (1%). This may likely overestimate exposure as dermal absorption from solids is usually lower than that from liquids (PMRA Dermal Absorption Memo, 2012).

For the surface area (SA) of the parts of the body that could be exposed to fluazaindolizine in soil, a value of 3300 cm^2 for the surface area of hands, forearms and head from the RAGS guidance document (USEPA, 2004) was used (based on a worker wearing short-sleeved shirt and long pants). While this is an older value, it will be used as it is representative of adults of both sexes over the age of 18 years. The adult body surface areas have been updated and are reported in the USEPA Exposure Factors Handbook (2011); however, these are not combined for both sexes and are representative of males and females over the age of 21.

The events (number of exposure events per workday day) is assumed to be 1, as specifically recommended by USEPA RAGS guidance document. This recommendation is based on the assumption that after a period of work and exposure to soil, a "threshold" soil loading is achieved where no appreciable amount of soil continues to accumulate on the skin due to movement, abrasion, rubbing, etc. Given the conservatisms in the risk calculation already in place (for example, use of a liquid dermal absorption value for soil, using a high-end adherence factor, and the assumed concentration of fluazaindolizine in the soil), the use of 1 event, as recommended in the RAGS, would still result in a conservative risk assessment for this scenario. Body weight used was 80 kg.

Exposure estimates were compared to the toxicological reference values to obtain the margin of exposure (MOE); the target MOE is 100. Calculated MOEs were greater than the target MOE of 100 therefore, there are no health risks of concern.

Table 3.4.2.2.1 Postapplication dermal exposure estimates and MOE

Crops	Max appl. rate (kg a.i/ha)	Soil concentration[a] (mg a.i./kg soil)	Adherence factor[b] (mg soil/cm^2)	Surface area[c] (cm^2)	Dermal exposure[d] (mg/kg bw/day)	Dermal MOE[e] Target MOE = 100
Tuberous and corm vegetables, carrot, cucurbit vegetables	1.12	7.5	0.63	3300	1.940E-06	1.03E+07
Fruiting vegetables	2.24	14.9			3.881E-06	5.15E+06

[a] Volume of soil in a 1 ha surface area at 1cm depth is 1.0×10^8 cm^3. Assume a density of 1.5 g soil /cm^3 (typical soil density), then there is 1.5×10^8 g soil/ha. At the applied maximum rates of 1.12 kg a.i/ha (tuberous and corm vegetables; carrot and cucurbit vegetables) and 2.24 kg a.i/ha (fruiting vegetables); the concentration of fluazaindolizine in soil is 7.5 mg a.i/kg soil and 14.9 mg a.i/kg soil, respectively. By assuming all of the product is retained in the upper most 1 cm of soil the concentration is over estimated.
[b] USEPA superfund guidance document (USEPA, 2004).
[c] Surface area of exposed skin (head, hands, forearms). Value from USEPA RAGS guidance document (USEPA, 2004).
[d] Dermal exposure (mg/kg bw/day) = Refer to model described in text above.
[e] Based on a NOAEL of 20 mg/kg bw/day; MOE = NOAEL/Exposure

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk

As Salibro Nematicide is proposed as a commercial marketing class product, a residential handler risk assessment is not required.

3.4.3.2 Postapplication exposure and risk

Salibro Nematicide is not proposed for use in residential areas. As such, a postapplication residential risk assessment is not required.

3.4.3.3 Bystander exposure and risk

Bystander exposure is expected to 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, application equipment and sprayer settings.

3.5 Food residues exposure assessment

3.5.1 Concentrations in drinking water

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. Level 1 estimated environmental concentrations (EECs) are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. EECs of fluazaindolizine in drinking water sources (groundwater and surface water) were calculated using the Pesticide in Water Calculator (PWC) version 1.52. Groundwater EECs were calculated for several scenarios representing different regions of Canada by simulating leaching through a layered soil profile into shallow groundwater over time. All scenarios for the groundwater modelling were run for 100 years. Only the highest groundwater EECs from these scenarios are reported. EECs in surface water were calculated by simulating pesticide runoff and drift from a treated field into a small reservoir, and considered the subsequent degradation of fluazaindolizine within that waterbody. EECs for surface water were calculated based on a single standard scenario modelled for 50 years. The use pattern selected for the modelling was a single application of 2240 g a.i./ha in order to encompass both the highest single and yearly application rates. A uniform distribution of the pesticide within a soil layer of 0–10 cm for surface water and 0–15 cm for groundwater was assumed.

The modelling was conducted using a parent-daughter-granddaughter approach given the fluazaindolizine transformation pathway (Figure 1). The parent group (P) includes fluazaindolizine, IN-UGA22 and IN-REG72. From the parent group, the degradation pathway splits into two parts, which were modelled separately. One part consists of IN-QEK31 (defined as the first daughter compound, D1), which can be further transformed into IN-VM862 (defined

as the granddaughter GD1). The other part of the split includes IN-F4106 and IN-A5760, which were combined together as another daughter (D2) because they can be converted from one to the other. Major fate inputs for the P, D, and GD groups are summarized in Tables 3.5.1.1 and 3.5.1.2. Modelling was conducted both with and without IN-VM862 to understand its contribution to the overall EEC. Level 1 EECs, expressed as parent equivalent, are reported in Table 3.5.1.3.

Details of water modelling inputs and calculations are available upon request.

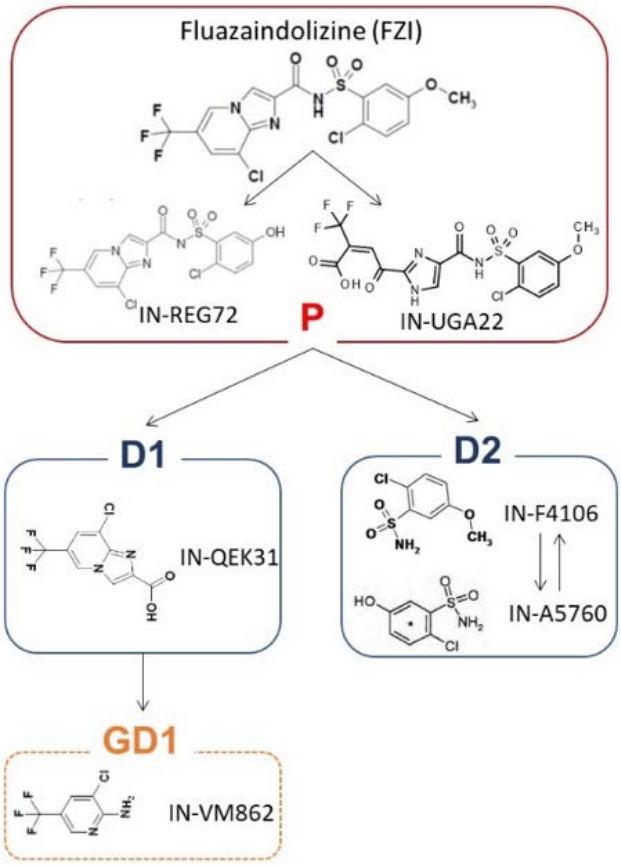

Figure 1: Components of the P-D-GD modelling

Table 3.5.1.1 Major fate inputs other than transformation parameters

Parameter	P	D1	GD1	D2	Unit
K_{oc} [a]	137	79	147	69	L/kg
Molecular Weight [b]	468	468	468	468	g/mol
Vapor Pressure (20 ºC)	1.59E-09	2.16E-10	0.00989	3.34E-07	Torr
Solubility (pH = 7) [c]	2.9E+03	1.45E+03	450	1.03E+04	mg/L

[a] Sorption studies were available for FZI, IN-A5760, IN-QEK31, IN-REG72, IN-VM862 and IN-F4106. K_d values derived from these studies significantly correlate with soil organic carbon for all the chemicals except IN-QEK31. K_{OC} was thus used for the modelling. In the absence of experimental data for IN-UGA22, KOCWIN(2.0) of EPISuite was used to estimate the K_{oc}.

[b] The molecular weight of P was used for D1, GD1 and D2 so that modelling results are expressed as parent mass equivalent concentrations.

Table 3.5.1.2 Transformation parameters

Test system	Half-life				Transformation faction		
	P	D1	GD1	D2	P to D1	D1 to GD1	P to D2
Phototransformation in sterile natural water [a]							
Irradiated sterile natural water	1.7	1.8	NA [b]	6.9	0.1	0 [b]	0.1
Biotransformation in aerobic soil [c]							
Sassafras	11.5	34.4	22.4	215.4	0.7	1.0	0.8
Nambsheim	34.2	12.1	29.3	68.4	0.7	1.0	0.6
Speyer 2.2	9.2	44.6	3.8	476.6	1.0	0.5	1.0
Thessaloniki	51.2	109.5	12.0	285.9	0.6	0.7	1.0
Graffignana	13.8	122.2	11.4	192.9	0.9	1.0	1.0
Lleida	52.2	35.7	17.7	101.4	0.7	0.8	0.8
Biotransformation in aerobic water/sediment (whole system)[d]							
Swiss Lake water-sediment	115.7	218.9	7.4	1.22E+08	0.3	1.0	0.4
Calwich Abbey water-sediment	262.1	94.0	4.8	157.9	0.7	0.9	0.7
Biotransformation in anaerobic water/sediment (whole system) [d]							
Swiss Lake water-sediment	51.5	3.9	677772	3.57E+08	0.4	0.9	0.2
Calwich Abbey water-sediment	23.5	6.72E+07	NA [b]	3.14E+10	0.024	0 [b]	0.1

[a] From a 10-d experiment with sterile natural water at pH 8 irradiated with summer equivalent light

[b] Transformation half-lives cannot be derived and transformation fractions of zero were used in the modelling due to non-detection of GD1 in these experiments.

[c] Based on experiments conducted with six natural soils. The other seven soils on which transformation tests were conducted were not included in the fitting because GD1 was not detected in those experiments. Due to the large variability in the transformation kinetics among the experiments, each of the six aerobic soil transformation datasets were used as the model input to calculate EECs for P, D1, GD1 and D2.

[d] Based on experiments using two sediment samples. Each of the two datasets were used as the model input to calculate EECs for P, D1, GD1 and D2.

Additional Note: No significant hydrolysis of FZI occurred at pH 7 over the 30-d experimental period, and therefore, hydrolysis was not considered in the modelling.

Table 3.5.1.3 EECs (in µg a.i./L) for the drinking water risk assessment of fluazaindolizine

Use pattern	Combined residue	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
		Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Overall[5]
One application of 2240 g a.i./ha	FZI+6 TPs[6]	1926	1924	60.7	11.3	8.2
	FZI+5 TPs[7]	1917	1915	60.5	11.3	8.2

1 90th percentile of daily concentrations

2 90th percentile of 365-day moving average concentrations

3 90th percentile of the highest 1-day average concentration from each year

[4] 90th percentile of yearly average concentrations
[5] Average of all yearly average concentrations
[6] Includes IN-VM862
[7] Does not include IN-VM862

3.5.2 Residues in plant and animal foodstuffs

The residue definition for enforcement in plant products and for risk assessment and enforcement animal commodities is fluazaindolizine. The residue definition for risk assessment in plant products is the sum of the posthydrolysis products, IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-RSU03, IN-UNS90, IN-UJV12, expressed as parent equivalents. The data gathering/enforcement analytical method is valid for the quantitation of fluazaindolizine residues in crop and livestock matrices. The residues of fluazaindolizine are stable in representative matrices from five commodity categories [high water (tomatoes), high oil (soybeans), high protein (dry pea seeds), high starch (wheat grain) and high acid content (oranges)] for up to 24 months, except for high water (34 months) when stored at -20 °C. Therefore, fluazaindolizine residues are considered stable in all frozen crop matrices and processed crop fractions for up to 24 months, except for high water commodities (34 months). Fluazaindolizine residues did not concentrate in any of the processed commodities for human consumption. Quantifiable residues are not expected to occur in poultry matrices with the current use pattern. Adequate feeding studies were carried out to assess the anticipated residues in ruminant matrices resulting from the current uses. Crop field trials conducted throughout Canada (and the United States) using an end-use product containing fluazaindolizine at approved rates in or on carrots, potatoes (Crop Subgroup1C), fruiting vegetables (Crop Group 8-09), and cucurbit vegetables (Crop Group 9) are sufficient to support the proposed maximum residue limits. Field accumulation studies (limited and extended) were conducted in various North American and European regions on several crops/crop groups. The data are adequate to recommend MRLs for selected field rotational crops at a 14-day plant-back interval. For all other crops, a plantback interval of 365 days must be followed.

3.5.3 Dietary risk assessment

Acute and chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.3.1 Acute dietary exposure results and characterization

The following criteria were applied to the acute analysis for fluazaindolizine based on the sum of the posthydrolysis products, IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-RSU03, IN-UNS90, IN-UJV12, expressed as parent equivalents (residue definition for dietary exposure assessment): 100% crop treated, default and experimental processing factors (where available), recommended MRLs in/on animal commodities, North American and/or European HAFT residue values from crop field trials and field accumulation trials. The acute dietary exposure from all supported fluazaindolizine food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 7% of the acute reference dose (ARfD), based on the 95th percentile (deterministic). Aggregate exposure from food and drinking water is considered acceptable.

The PMRA estimates that acute dietary exposure to fluazaindolizine equivalents from food and drinking water is 10% (0.126 mg/kg bw) of the ARfD for the total population. The highest exposure and risk estimate is for all infants at 30% (0.383 mg/kg bw) of the ARfD.

3.5.3.2 Chronic dietary exposure results and characterization

The following criteria were applied to the refined chronic non-cancer analysis for fluazaindolizine based on the sum of the posthydrolysis products, IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-RSU03, IN-UNS90, IN-UJV12, expressed as parent equivalents (residue definition for dietary exposure assessment): 100% crop treated, default and experimental processing factors (where available), recommended MRLs in/on animal commodities, North American and/or European median residue values from crop field trials and field accumulation trials. The chronic dietary exposure from all supported fluazaindolizine food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 2% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to fluazaindolizine equivalents from food and drinking water is 20% (0.040 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants at 74% (0.147 mg/kg bw/day) of the ADI.

3.5.4 Aggregate exposure and risk

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

3.5.5 Maximum residue limits

Table 3.5.5.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
Primary Crops	
0.2	Tuberous and corm vegetables (crop subgroup 1C)
0.15	Cucurbit vegetables (crop group 9)
0.07	Fruiting vegetables (crop group 8-09)
0.05	Carrot roots
Livestock Commodities	
0.01	Eggs, fat, meat, meat byproducts of cattle, goats, hogs, horses, poultry, and sheep, milk
Secondary Crops	
0.8	Legume vegetables, succulent or dried (crop group 6), oilseeds-revised (crop group 20)
0.02	Root vegetables, except sugar beet (crop subgroup 1B, except carrot roots)

MRL (ppm)	Food commodity
0.03	Bulb vegetables (crop group 3-07), stalk, stem, and leaf petioles (crop group 22)
0.015	Leaves of root and tuber vegetables (crop group 2), leafy vegetables (crop group 4-13), brassica head and stem vegetable (crop group 5-13)
0.01	Low growing berries (crop subgroup 13-07G), cereal grain (crop group 15)

Maximum Residue Limits (MRLs) are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides section of Canada.ca.

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 methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 2, 8 and 9.

3.6 Cumulative assessment

The *Pest Control Products Act* requires that Health Canada's PMRA consider the cumulative exposure to pest control products with a common mechanism of toxicity. Accordingly, an assessment of potential common mechanisms of toxicity with other pesticides was undertaken for fluazaindolizine.

Fluazaindolizine is a nematicide that belongs to the sulfonamide chemical class, although its pesticidal mode of action is not known. There is a group of herbicides commonly known as the triazolopyrimidine sulfonanilides that are structurally similar to fluazaindolizine. The triazolopyrimidine sulfonamides class of pesticides includes florasulam, cloransulam-methyl, flumetsulam, and pyroxsulam, which are registered for use in Canada, as well as diclosulam, penoxsulam, and metosulam, which are registered for use in the United States or Europe. With the exception of pyroxsulam, all members of this group of herbicides cause effects on the kidney in repeat-dose animal toxicity studies. The common areas of the kidney that have been shown to be a target include the renal tubules and collecting ducts of various species of animals. Some of the specific effects noted include inflammation, vacuolation, degeneration/regeneration and necrosis in the renal tubules, and hypertrophy and hyperplasia in the collecting ducts.

Fluazaindolizine shares structural similarities with triazolopyrimidine sulfonanilides, and toxicity studies conducted with fluazaindolizine consistently identified the kidney as a target organ across various species. Some of the specific renal effects noted in fluazaindolizine studies included infarctions, hypertrophy (tubular cells in the collecting ducts and medulla), hyperplasia (transitional cells, urothelial cells, and mucosal cells), fibrosis (interstitial cells), necrosis (papilla cells), dilation (renal pelvis and medullary tubules), and mineralization.

Although adequate data is not available to establish the key events in the pathway that lead to the effects in the specific regions of the kidney, there is sufficient information to demonstrate a consistent pattern of kidney effects across this structurally-related group of compounds. The possibility that fluazaindolizine acts through a similar mode of action as the triazolopyrimidine sulfonanilides herbicides could not be excluded. Based on the available information, it is plausible that fluazaindolizine, florasulam, cloransulam-methyl, flumetsulam, diclosulam, penoxsulam, and metosulam share a common mode of action for kidney toxicity, and thus were considered at this time to form a common assessment group. Therefore, a cumulative risk assessment was undertaken, which considered the following information:

- Toxicology reference values selected for these active ingredients by Health Canada, the United States Environmental Protection Agency (USEPA) and/or the European Food Safety Authority (EFSA) indicated relatively low toxicity (ADI of 0.05 to 1.0 mg/kg bw/day for all active ingredients).
- For florasulam, cloransulam-methyl and flumetsulam, which are registered for use in Canada, there are no domestic-class end-use products and the commercial-class products are registered for use on cereals, soybeans and field corn. For fluazaindolizine, there is one proposed commercial-class product for use on tuberous and corm vegetables, carrot, fruiting vegetables, and cucurbit vegetables. Therefore, there are no registered uses that could lead to residential exposure.
- Based on the use patterns, cumulative risk could result from co-exposure to fluazaindolizine, florasulam, cloransulam-methyl and flumetsulam through food and drinking water, and diclosulam, penoxsulam and metosulam through imported commodities.
- For the triazolopyrimidine sulfonanilide herbicides, low residue levels, mostly non-detectable or non-quantifiable, were found in the available crop field trials, consistent with early-season treatment and relatively low use rates of these herbicides (for example, florasulam is applied once early in the growing season with maximum application rates of 2.5–5 g a.i./ha).
- For the triazolopyrimidine sulfonanilide herbicides, single chemical dietary exposure assessments have been conducted by Health Canada, USEPA and EFSA, using conservative residue inputs (for example, maximum residue levels, 100% crop treated, default processing factors, conservative drinking water modelling). All assessments indicated low dietary exposure (less than 10% of the ADI, with exposure estimates <1% of the ADI for many of these herbicides).
- For fluazaindolizine, the estimated risks from chronic dietary exposure ranged from 14% to 74% of the ADI for the various sub-populations assessed. These risks would be reduced further (by approximately 1.5-fold) if using a point of departure for the common effect of kidney toxicity.

Based on the above, Health Canada has concluded that the cumulative risks from potential co-exposure to fluazaindolizine and the triazolopyrimidine sulfonalilides through food and drinking water are acceptable.

3.7 Health incident reports

Fluazaindolizine is a new active ingredient pending registration for use in Canada, and as of 4 May 2020, no human or domestic animal incident reports had been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Terrestrial environment:

Fluazaindolizine is expected to be stable to hydrolysis and phototransformation on soil.

Fluazaindolizine is biotransformed by microbial activity in soil, producing four major transformation products (TPs): IN-F4106, IN-QEK31, IN-A5760 and IN-VM862. Under laboratory conditions, fluazaindolizine is classified as non-persistent to persistent in aerobic soil, depending on the soil type. Degradation of fluazaindolizine is slower under anaerobic soil conditions, but follows the same pathway as for aerobic soil. Laboratory studies showed that IN-A5760 is non-persistent to moderately persistent, IN-F4106 is persistent, and IN-QEK31 is slightly persistent to persistent in various types of aerobic soils. Data on the biotransformation of IN-VM862 in soil were not available due to its volatility; however, as noted in the air section below, it is expected to exhibit lower volatility in the field. Carryover of fluazaindolizine residues to the following season is not expected as the field studies showed that <8.5% of the applied amount remained in soil after one year.

Fluazaindolizine and its TPs are expected to be mobile in soil based on their K_{oc} values, the criteria of Cohen et al. (1984), and their groundwater ubiquity scores, and were observed to reach depths of 70-90 cm in field studies. As such, a precautionary label statement to address the potential for fluazaindolizine to leach through soil is required.

Aquatic environment:

Fluazaindolizine is water-soluble. In aerobic and anaerobic aquatic biotransformation studies, <10% of applied fluazaindolizine partitioned to the sediment in test systems. Fluazaindolizine undergoes microbial biotransformation in both water and sediment phases. In water-sediment systems, fluazaindolizine is classified as non-persistent to moderately persistent, and biotransforms into three major TPs: IN-REG72, IN-A5760 and IN-QEK31. Data on the biotransformation of the major TPs in aquatic systems were not available.

Fluazaindolizine is expected to undergo rapid aqueous phototransformation, with representative half-lives (summer sunlight equivalents at 30 to 50°N) of 2.2, 2.5 and 3.3 days at pH 4, pH 9 and sterile natural water (pH 7.3), respectively. The aqueous phototransformation of fluazaindolizine produces several major TPs at various pH values (2-chloro-5-methoxybenzenesulfonic acid, IN-F4106, IN-UGA22, IN-QEK31, and an unidentified compound with a retention time of ~31.5 minutes).

Air:

Fluazaindolizine and its TPs, with the exception of IN-VM862, have low vapour pressures and low Henry's Law constants, which indicate a low potential for volatilization from moist soil and water. IN-VM862 has intermediate to high volatility based on its vapour pressure; however, IN-VM862 is very soluble in water, and it is not expected to be volatile from a water surface or moist soil based on the Henry's Law constant. IN-VM862 is therefore expected to exhibit lower volatility in the field in the presence of water, including soil moisture. Some binding of IN-VM862 to soil was observed during soil biotransformation studies using fluazaindolizine as the test compound. Long-range atmospheric transport is unlikely to occur.

A summary of the major TPs is provided in Appendix I, Table 10. The environmental fate parameters for fluazaindolizine and its TPs are provided in Appendix 1, Table 11.

4.2 Environmental risk characterization

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

Environmental toxicity data are summarized in Appendix I, Table 12. Toxicity endpoints used in risk assessments are adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). The magnitude of the uncertainty factor depends on the group of organisms being evaluated (for example, 10 for fish, 2 for aquatic invertebrates, 1 for bees and other beneficial arthropods). The difference in the value of the uncertainty factor reflects, in part, the ability of organisms at a certain trophic level (i.e., feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. For characterizing acute risk, acute toxicity values (for example, LC_{50}, LD_{50}, and EC_{50}) are divided by an uncertainty factor. When assessing chronic risk, a no observed effect concentration (NOEC) is used and an uncertainty factor is not applied.

Initially, a screening level risk assessment is performed to identify specific uses that do not pose a risk to non-target organisms, and groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the EEC by an appropriate toxicity value (RQ = EEC/toxicity endpoint), and is then compared to the level of concern (LOC). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to, or greater than the LOC, 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.

Environmental toxicology studies were conducted with fluazaindolizine, as well as several major TPs, depending on the organism. In addition, some studies were conducted with the end-use product, DPX-Q8U80 500 g/L SC, which has the same guarantee (500 g/L) as the proposed end-use product Salibro Nematicide. The toxicity endpoints and uncertainty factors used in the risk assessment are presented in Appendix I, Table 13.

4.2.1 Risks to terrestrial organisms

Fluazaindolizine is not applied as a foliar spray to crops. It is proposed for use via pre-plant soil incorporated, pre-plant broadcast application followed by soil incorporation, as an in-furrow soil treatment, or via chemigation (pre-plant, at plant or postplant). For optimum performance, fluazaindolizine is applied directly to the root zone of the plant. All applications must be immediately incorporated into the soil to a depth of at least 10 cm.

Terrestrial organisms, such as earthworms, bees and other beneficial arthropods, birds, wild mammals and terrestrial vascular plants may be exposed to fluazaindolizine through direct contact with spray or spray drift, contact with sprayed surfaces or from ingestion of contaminated food. A risk assessment of fluazaindolizine and its end-use product, Salibro Nematicide, was undertaken based on available toxicity data for earthworms, bees and other beneficial arthropods, birds, wild mammals, and terrestrial plants.

The screening level risk assessment for terrestrial organisms is shown in Appendix I, Table 14. At the screening level, the EEC for fluazaindolizine in soil was calculated based on a direct overspray, considering the maximum rate of one application of 2240 g a.i./ha. Soil EECs were converted from g a.i./ha to mg a.i./kg soil using the assumption that fluazaindolizine was homogeneously mixed in the top 15 cm soil layer with a soil bulk density of 1.5 g/cm^3. EECs for major TPs were conservatively calculated assuming 100% conversion of the parent on a molar basis.

To calculate the EEC on plant surfaces in the field after a direct spray, the maximum single application rate was considered. Non-target terrestrial organisms can also be exposed to fluazaindolizine via spray drift. The amount of spray drift depends on the type of equipment used, the size of the spray droplets, as well as the type of crop. To calculate off-field EECs, spray drift factors were applied to the in-field EECs. The spray drift factor is defined as the maximum percentage of spray drift deposition at one metre downwind from the point of application. For fluazaindolizine, application using a field sprayer with a medium spray droplets (as specified on the label), with a corresponding spray drift factor of 6%, was considered.

Earthworms

The chronic toxicity of fluazaindolizine, its TPs, and the end-use product, DPX-Q8U80 500 g/L SC, to earthworms (*Eisenia fetida*) were determined in laboratory studies. The results were compared to the screening level soil EECs. The resulting RQs (≤0.15) did not exceed the LOC of 1 (Appendix I, Table 14). As such, risks to earthworms from the use of fluazaindolizine are negligible.

Beneficial arthropods

Beneficial arthropods could be exposed to fluazaindolizine immediately after application in-field, as well as off-field via spray drift. Toxicity tests for beneficial arthropods were conducted with the end-use product, DPX-Q8U80 500 g/L SC. The screening level risk assessment for beneficial arthropods is shown in Appendix I, Table 14.

For ground-dwelling predatory arthropods (in other words, the predatory mite, *Hypoaspis aculeifer*), the soil EEC for fluazaindolizine (1.00 mg a.i./kg) was used to estimate exposure. The RQ (< 0.002) did not exceed the LOC. As such, risks to ground-dwelling arthropods from the use of fluazaindolizine are negligible.

For foliar-dwelling arthropods (in other words, the predatory mite, *Typhlodromus pyri*, and the parasitic arthropod, *Aphidius rhopalosiphi*), the maximum single application rate (2240 g a.i./ha) was used to estimate in-field exposure. No adverse effects on survival or reproduction were observed at the highest concentration tested (1000 g a.i./ha) in the toxicity studies for *T. pyri* and *A. rhopalosiphi*. The in-field RQs (<2.24) marginally exceeded the LOC of 2 because the maximum application rate exceeds the highest concentration tested in the toxicity tests. As noted above, fluazaindolizine is applied directly to the root zone of the plant and all applications must be immediately incorporated into the soil to a depth of at least 10 cm. As such, exposure of in-field foliar-dwelling arthropods would be limited. Given that the RQ is less than 2.24, that there were no adverse effects observed in the toxicity tests, and that exposure would be limited, risks to foliar-dwelling arthropods are considered to be negligible. These organisms may also be exposed to fluazaindolizine via spray drift off-field when applied with a field sprayer pre-plant. The off-field RQs (<0.13) did not exceed the LOC. As such, risks to off-field beneficial arthropods from the use of fluazaindolizine are negligible.

Bees

Foraging bees could be exposed to fluazaindolizine spray droplets during pre-plant application with a field sprayer or through the ingestion of pollen and nectar contaminated with fluazaindolizine (oral exposure). Additionally, bee brood may be exposed to fluazaindolizine if foraging bees bring contaminated pollen and nectar back to the hive. For the screening level risk assessment, it was conservatively assumed that fluazaindolizine is systemic, although it is not expected to move through plants to the pollen and nectar.

Contact exposure

In the screening level risk assessment, the estimated contact exposure for bees is compared to the toxicity endpoints (expressed in µg a.i./bee) derived from laboratory studies. As such, a conversion of the application rate from kg a.i./ha to µg a.i./bee is required. Contact toxicity studies are available for exposure of adult bees to fluazaindolizine, its end-use product (DPX-Q8U80 500 g/L SC), and its major TPs, IN-F4106 and IN-QEK31. The RQs (≤0.03) for contact exposure did not exceed the LOC of 0.4. As such, risks to adult bees from contact exposure to fluazaindolizine, its end-use product and TPs are negligible (Appendix I, Table 14).

Oral exposure

In the screening level risk assessment, the estimated oral exposure for bees is compared to toxicity endpoints (expressed in µg a.i./bee) derived from laboratory studies. As such, a conversion of the application rate from kg a.i./ha to µg a.i./bee is required. Oral exposure toxicity studies for adult and larval bees are available for fluazaindolizine, its end-use product DPX-Q8U80 500 g/L SC (toxicity study for adult bees only), and its major TPs, IN-F4106 and IN-QEK31.

As noted above, fluazaindolizine is not applied as a foliar spray to crops. Pre-plant and at-plant application is proposed at 1120 to 2240 g a.i./ha (the maximum seasonal rate). Postplant chemigation is used as a supplemental treatment, and is applied at a rate that is two to four times lower than the maximum rate (560 to 1120 g a.i./ha vs. 2240 g a.i./ha). For optimum performance, fluazaindolizine is applied directly to the root zone of the plant. All applications must be immediately incorporated into the soil to a depth of at least 10 cm. Fluazaindolizine is not systemic and is not expected to move through plants to the pollen and nectar.

In the submitted semi-field studies, fluazaindolizine applied at a rate of 1000 g a.i./ha as an in-furrow soil treatment at planting, or via drip irrigation at night during the bloom of lacy phacelia (*Phacelia tanacetifolia*), caused no adverse effects to honeybee colonies. No residues of fluazaindolizine or its TPs were detected in any of the nectar or pollen samples collected from treated plots. Given the above, oral exposure of bees to fluazaindolizine and its TPs is expected to be limited.

The screening level risk assessment evaluated risks to bees from oral exposure to fluazaindolizine applied as a soil treatment at the maximum single application rate (in other words, 2240 g a.i./ha). The RQs (≤0.13) for adult and larval bees exposed to fluazaindolizine and its TPs as a soil treatment were below the LOCs of 0.4 (acute) and 1 (chronic) (Appendix I, Table 14). As such, risks to bees from the use of fluazaindolizine as a soil treatment are negligible.

Terrestrial vertebrates

On an acute oral basis, fluazaindolizine is considered to be slightly toxic to practically non-toxic to birds, and slightly toxic to mammals. A screening level risk assessment was conducted to evaluate the acute and reproductive risk to birds and mammals from the use of fluazaindolizine.

To assess the risk to birds and mammals, the estimated concentration of fluazaindolizine on various food items was used to determine the amount of pesticide in the diet (the estimated daily exposure (EDE)). Exposure is dependent on the body weight of the organism, and the amount and type of food consumed. As such, a set of generic body weights was used to represent a range of species (20, 100, and 1000 g for birds and 15, 35, and 1000 g for mammals) and specialized feeding guilds (in other words, herbivore, frugivore, insectivore and granivore) were considered for each category of animal weights.

The screening level risk assessment evaluated a conservative exposure scenario based on:

- The maximum fluazaindolizine residue concentrations in food items;
- A diet that is composed entirely (100%) of a particular dietary item; and,
- The feeding guild assumed to have the highest exposure for each animal weight category.

If a concern was identified at the screening level (in other words, RQ > LOC), the risk was then further characterized.

Birds

The screening level risk assessment assumed that birds could be exposed to fluazaindolizine via the consumption of contaminated food items. Acute oral exposure and reproductive effects were evaluated. The RQs for acute oral exposure (≤0.91) were below the LOC of 1 for all bird size classes, indicating that risks from short term exposure to contaminated items are negligible.

The RQs for reproductive effects in all bird size classes exceeded the LOC of 1 when considering the on-field maximum residue concentrations on food items (RQs 1.80 to 3.57; Appendix I, Table 15).

To further characterize the reproductive risk for birds, the assessment was expanded to include all relevant food guilds. The concentrations of fluazaindolizine on food items were based on both on-field and off-field mean and maximum residue values. The RQs for reproductive effects in small and medium sized insectivorous birds still exceeded the LOC based on the on-field mean residue concentrations (RQs 2.46 and 1.92, respectively). Risks to birds off-field were negligible (RQs $\leq$ 0.15). Given that the on-field RQs marginally exceeded the LOC, the risk assessment from on-field exposure was further refined (Appendix I, Table 16).

The screening level risk assessment considered the no-observed effects dose (NOED) from the northern bobwhite reproductive study. Reproductive risks to small and medium birds on-field were further refined by considering the lowest-observed effects dose (LOED) from the bobwhite study. The LOED corresponded to a slight reduction in the number of 14-day old surviving hatchlings at the highest concentration tested (89% hatchling survival in the 1250 mg a.i./kg feed treatment compared to 96% in control). The LOED was determined to be 101.7 mg a.i./kg bw/day. When considering the LOED, the on-field RQs for small insectivorous birds (maximum and mean nomogram residues) and medium insectivorous birds (maximum nomogram residues only) marginally exceeded the LOC (RQs = 1.24 to 1.79) (Appendix I, Table 17).

For the assessment, it was assumed that 100% of the diet was composed of contaminated food items, and that residues of fluazaindolizine on insects were equivalent to those on sprayed plants with a similar surface area to volume ratio. Small and medium insectivorous birds may dig in the soil for insects; however, it is highly unlikely that they would consume a diet composed 100% of insects contaminated by fluazaindolizine over a long period of time. Feed reduction/aversion was observed in the dietary toxicity studies using the mallard and the zebra finch.

This indicates that birds may preferentially avoid fluazaindolizine treated food items in the wild, reducing potential exposure. Given this, the probability that adverse reproductive effects would occur following exposure to fluazaindolizine residues on food items is considered low, and risks to birds are considered negligible.

Wild mammals

The screening level risk assessment (Appendix I, Table 15) assumed that wild mammals could be exposed to fluazaindolizine via the consumption of contaminated food items. Acute oral exposure and reproductive effects were evaluated. The RQs for acute oral exposure (RQs of <1.12 to <2.16) marginally exceeded the LOC of 1 for all size classes when considering the on-field maximum residue concentrations on food items. The RQs for reproductive effects in all mammal size classes were below the LOC of 1 (RQs of 0.29 to 0.56), indicating that reproductive risks are negligible.

Since the LOCs for acute oral exposure were exceeded, the risk was further characterized by expanding the assessment to include all relevant food guilds and to consider both on-field and off-field mean and maximum residue values (Appendix I, Table 16). The acute oral RQs for small insectivorous mammals (RQ <1.12), and medium and large herbivores (RQs of <1.07 to <2.16) exceeded the LOC based on the maximum on-field residue concentrations. However, the RQs for these feeding guilds were below the LOC when considering the mean on-field residue concentrations (RQs of <0.35 to <0.77). Risks to wild mammals off-field were negligible (RQs <0.13).

It is considered unlikely that 100% of the diet of mammals would be composed of food items contaminated with fluazaindolizine. As noted above, fluazaindolizine is applied directly to the root zone of the plant for optimal performance, must immediately be soil incorporated after application, and is not systemic. As such, the concentration of fluazaindolizine in food items is expected to be limited. Risks to wild mammals are considered to be negligible given that the RQs based on mean on-field residue concentration and off-field exposure were below the LOC.

Terrestrial plants

The vegetative vigour and seedling emergence toxicity tests showed no adverse effects to plants at 2000 g a.i./ha, the highest application rate tested, with the exception of a 9% reduction in the shoot height of oat at 2000 g a.i./ha. The highest rate tested in these studies was below the maximum proposed annual application rate of 2240 g a.i./ha. The RQs of <1.12 for vegetative vigour and seedling emergence marginally exceeded the LOC of 1 given that the maximum proposed application rate exceeds the highest rate tested in the toxicity tests. The off-field RQs

(<0.07), considering 6% spray drift deposition at one metre downwind from the site of application, were below the LOC. Considering that limited adverse effects were observed at the highest rate tested, and that the LOC was not exceeded for off field drift, adverse effects to non-target terrestrial plants are not expected at the proposed application rate. The risks associated with the use of fluazaindolizine to non-target plants are acceptable.

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, amphibians and aquatic plants can be exposed to fluazaindolizine if spray drift or runoff enter an aquatic habitat. For the screening level risk assessment, EECs in surface water were calculated considering a direct overspray of fluazaindolizine at the maximum single application rate of 2240 g a.i./ha. EECs for major TPs were conservatively calculated assuming 100% conversion of the parent on a molar basis. Water bodies of two different depths were evaluated: an EEC in surface water of 15-cm depth was used to determine risk to amphibians while an EEC at 80-cm depth was used to evaluate risks to all other aquatic organisms.

Fluazaindolizine is classified as practically non-toxic to freshwater invertebrates, practically non-toxic to slightly toxic to marine invertebrates and freshwater/marine fish, and slightly toxic to freshwater/marine algae and freshwater vascular plants (Appendix I, Table 12). The toxicity of the end-use product differed from that of the technical product for freshwater invertebrates (slightly toxic) and freshwater algae (moderately toxic). Based on the available data, the major TPs have a similar toxicity to aquatic organisms as fluazaindolizine. No mortality or overt signs of toxicity were observed in the acute toxicity tests using the Eastern oyster, rainbow trout, bluegill sunfish or sheepshead minnow.

Risks to aquatic organisms from exposure to a direct overspray of fluazaindolizine at the maximum application rate are negligible (RQs $\leq$ 0.49; Appendix I, Table 18). Exposure of aquatic organisms to spray drift and runoff would be lower than for a direct overspray. As such, calculation of risks from spray drift or runoff were not required.

4.2.3 Environmental incident reports

Fluazaindolizine is a new active ingredient pending registration for use in Canada, and as of 4 May 2020, no environmental incident reports have been submitted to the PMRA.

5.0 Value

Fluazaindolizine is a new conventional active ingredient for the management of root-knot nematodes on vegetable crops in Canada. There are a limited number of products registered in Canada for the control or suppression of plant parasitic nematodes, including root-knot nematodes on vegetable crops. Fluazaindolizine is primarily active on parasitic root-knot nematodes.

The availability of Salibro Nematicide will provide Canadian vegetable growers with a new mode of action and a new nematicide for use on tuberous and corm vegetables (Crop Subgroup 1C), cucurbit vegetables (Crop Group 9), fruiting vegetables (Crop Group 8-09) and carrots to manage root-knot nematodes that cause significant economic losses to vegetable growers.

Efficacy data from 17 field trials and scientific rationales demonstrated that Salibro Nematicide can be expected to control or suppress root-knot nematodes on multiple vegetable crops. As no phytotoxicity or crop injury was reported in any of the submitted studies conducted at application rates equal to or greater than rates proposed for registration, application of Salibro Nematicide is not expected to result in crop injury.

Details of the supported uses are summarized in Appendix I, Table 20.

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, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, fluazaindolizine and its TPs were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that Reklemel Technical (containing fluazaindolizine) and its TPs do not meet all of the TSMP Track 1 criteria.

Please refer to Table 19 for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[7]

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

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

The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy*,[9] and taking into consideration the *Ozone-Depleting Substance Regulations*, 1998, of the *Canadian Environmental Protection Act* (substances designated under the *Montreal Protocol*).

The PMRA has reached the conclusion that Reklemel Technical (containing fluazaindolizine) does not contain any formulants or other contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. However, its end-use product, Salibro Nematicide, contains as a component, the preservative 1, 2-benzisothiazolin-3-one at significantly less than 0.1%, which contains low levels of polychlorinated dibenzodioxins and furans (TSMP Track 1). The use of this preservative in pest control products at a maximum of 0.1% was reassessed by the PMRA in 2012 and found to be acceptable because dioxin and furan levels are low and being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP. The Agency position at this time is that no further action is required.

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

7.0 Proposed regulatory decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the Pest Control Products Act, is proposing registration for the sale and use of Reklemel Technical Nematicide, and Salibro Nematicide, containing the technical grade active ingredient fluazaindolizine, to control root-knot nematodes in tuberous and corm vegetables (Crop Subgroup 1C), carrot, cucurbit vegetables (Crop Group 9) and fruiting vegetables (Crop Group 8-09).

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

Additional information being requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as postmarket information after registration.

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

9 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

List of abbreviations

↑	increased
↓	decreased
♀	female
♂	male
µg	microgram(s)
µM	micromolar
a.i.	active ingredient
abs	absolute
ACTH	adrenocorticotropic hormone
AD	administered dose
ADI	acceptable daily intake
AHETF	Agriculture Handler Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	applied radioactivity
ARfD	acute reference dose
atm	atmosphere
ATPD	Area Treated Per Day
AUC	area-under-the-curve
BAF	bioaccumulation Factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration Factor
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
C	carbon
CAS	Chemical Abstracts Service
CAF	composite assessment factor
CEPA	*Canadian Environmental Protection Act*
cm	centimetre(s)
cm^3	centimetre(s) cubed
CO_2	carbon dioxide
Cmax	maximal concentration
C_{stem}	concentration in stems
C_{soil}	concentration in soil
CYP450	cytochrome P450
d	day(s)
DACO	data code
DALA	days after last application
DFOP	double first order in parallel
DHT	dihydrotestosterone
DIR	directive
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight

E2	estradiol
EC_{50}	effective concentration on 50% of the population
ED_{50}	effective dose on 50% of the population
EDE	estimated dietary exposure
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
ELS	early-life stage
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate for 50% of the population
EU	European Union
F1	first generation
F2	second generation
fc	food consumption
fe	food efficiency
foc	fraction organic carbon
FIR	food ingestion rate
FZI	fluazaindolizine
g	gram(s)
GD	gestational day
GGT	gamma-glutamyl transpeptidase
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HCT	hematocrit
HDPE	high-density polyethylene
HGB	hemoglobin
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
IgM	immunoglobulin M
IM	[imidazo[1, 2-a]pyridine-2-^{14}C]fluazaindolizine ^{14}C radiolabel
IORE	indeterminate order rate equation
IP	imidazopyridine
IP	[imidazo[1, 2-a]pyridine-5,8a-^{14}C]fluazaindolizine ^{14}C radiolabel
IUPAC	International Union of Pure and Applied Chemistry
ILV	independent laboratory validation
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LH	luteinizing hormone
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern

LOEC	low observed effect concentration
LOED	lowest observed effect dose
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting
M/L/A	Mixer/loader/applicator
m/z	mass-to-charge ratio of an ion
mg	milligram
mL	millilitre
MA	motor activity
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
min(s)	minute(s)
MOE	margin of exposure
MRL	maximum residue limit
MRM	multiresidue method
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
NAFTA	North American Free Trade Agreement
NC	not calculated
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effects level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOER	no observed effect rate
NOI	notice of intent
NR	not reported
NZW	New Zealand white
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
P	parental generation
PBI	plantback interval
PBPK	physiologically based pharmacokinetic
PCPA	*Pest Control Products Act*
Ph	[phenyl-^{14}C(U)]fluazaindolizine ^{14}C radiolabel
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	Personal protective equipment
ppm	parts per million
PWC	pesticide in water calculator
QSAR	quantitative structure activity relationship
RAC	raw agricultural commodity
RAGS	USEPA Risk Assessment Guidance for Superfund
RBC	red blood cells

RD	residue definition
RDW	red cell distribution width
rel	relative
RQ	risk quotient
SC	suspension concentrate
SDH	sorbitol dehydrogenase
SFO	single first order
SRBC	sheep red blood cells
STMR	supervised trial mean residue
STMdR	supervised trial median residue
t_R	representative half-life
Tmax	time at maximum plasma concentration
T	testosterone
T3	tri-iodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
TRR	total radioactive residue
TSCF	transpiration stream concentration factor
TP	transformation product
TSMP	Toxic Substances Management Policy
UDPGT	uridine diphosphoglucuronyltransferase
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
vs.	versus
v/v	volume per volume dilution
WBC	white blood cells
wt	weight

Appendix I Tables and figures

Table 1 Chemical residue analysis

Matrix	Analyte	Method type	LOQ	Reference
Soil	Parent	HPLC-MS/MS	1.0 ppb	PMRA# 2957867 PMRA# 2957935 PMRA# 2958065
	IN-REG72			
	IN-VM862			
	IN-QEK31			
	IN-F4106			
	IN-A5760			
	IN-RYC33			
Water	Parent	HPLC-MS/MS	0.10 µg/L	PMRA# 2958050 PMRA# 2958106
	IN-REG72			
	IN-VM862			
	IN-QEK31			
	IN-F4106			
	IN-A5760			
	IN-RYC33			

Table 2 Residue analysis

Analytical methods	Matrices	Analytes	Method ID/ type	LOQ/Analyte	Reference
Livestock commodities					
Enforcement Method	Eggs; milk; cream; bovine muscle, fat, liver	Fluazaindolizine	DuPont-39226, Revision 1/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 2957968
Data-Gathering Method	Eggs; milk; bovine muscle, fat, liver	Fluazaindolizine	Charles River AV.225144.02[1]/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 2958048
ILV of Enforcement Method	Eggs; bovine liver and muscle	Fluazaindolizine	DuPont-39226, Revision 1/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 2958092
Radiovalidation	-	-	N/A	N/A	-

Analytical methods	Matrices	Analytes	Method ID/ type	LOQ/Analyte	Reference
Plant commodities					
Enforcement Method	Lime; dry pea seed; soybean; tomato	IN-A5760, IN-F4106, IN-QEK31, N-QZY47, IN-RSU03, IN-UJV12, IN-UNS90	DuPont-47054, Revision 2[2]/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 3136952 supersedes 2958119
ILV of Enforcement Method	Lime; dry peas seed; tomato	IN-A5760, IN-F4106, IN-QEK31, N-QZY47, IN-RSU03, IN-UJV12, IN-UNS90	DuPont-47054, Revision 1/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 2958105
Data-Gathering Method/Enforcement Method	Field corn stover; grape, orange; dry pea seed; soybean seed; tomato; wheat grain and straw	Fluazaindolizine, IN-A5760, IN-F4106, IN-QEK31, N-QZY47, IN-RSU03, IN-UJV12, IN-UNS90	DuPont-33861, Revision 3[3]/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 2957860; 2957944
Radiovalidation	Radish root; mature spinach; soybean seed and hay; wheat hay	Fluazaindolizine, IN-A5760, IN-F4106, IN-QEK31, N-QZY47, IN-RSU03, IN-UJV12, IN-UNS90	DuPont-33861, Revision 3; DuPont-47054, Revision 2/ HPLC-MS/MS	0.01 ppm for all matrices	PMRA# 2958171

[1]Method based on the enforcement method.
[2]Method proposed as enforcement method which involves hydrolysis step to convert free and conjugated metabolites of fluazaindolizine to seven core metabolites; therefore does not quantify fluazaindolizine per se.
[3]Method based on the enforcement method. Also subjected to independent method validation to assess its acceptability as a suitable enforcement method for the quantitation of the parent and the seven core metabolites posthydrolysis.

Table 3 Identification of select fluazaindolizine metabolites

Code name	Chemical name (IUPAC)
IN-A5760	2-Chloro-5-hydroxybenzenesulfonamide
IN-F4106	2-Chloro-5-methoxybenzenesulfonamide
IN-QEK31	8-Chloro-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid
IN-QZY47	3-[[(2-chloro-5-methoxyphenyl)sulfonyl]amino]-L-alanine hydrochloride
IN-REG72	8-chloro-N-[(2-chloro-5-hydroxyphenyl)sulfonyl]-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide
IN-RSU03 (racemate) **IN-TMQ01** (*R*-enantiomer in crops)	3-[[(2-chloro-5-methoxyphenyl)sulfonyl]amino]-2-hydroxypropanoic acid 3-[[(2-chloro-5-methoxyphenyl)sulfonyl]amino]-(2R)-hydroxypropanoic acid, potassium salt
IN-UNS90 (racemate) **IN-TQD54** (*R*-enantiomer in crops)	3-[[(2-Chloro-5-hydroxyphenyl)sulfonyl]amino]-2-hydroxypropanoic acid potassium salt 3-[[(2-chloro-5-hydroxyphenyl)sulfonyl]amino]-(2R)-hydroxypropanoic acid potassium salt
IN-UJV12	3-[[(2-Chloro-5-hydroxyphenyl)sulfonyl]amino]-L-alanine hydrochloride
IN-VM862	3-Chloro-5-(trifluoromethyl)pyridin-2-amine

Table 4 Toxicity profile of salibro nematicide containing fluazaindolizine

Study type/animal/PMRA#	Study results
Acute oral toxicity (up-and-down method) Sprague-Dawley rats (♀) PMRA# 2957793	Low acute toxicity LD_{50} > 2000 mg/kg bw (♀) Clinical signs of toxicity included irregular respiration
Acute dermal toxicity Sprague-Dawley rats PMRA# 2957794	Low acute toxicity LD_{50} > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity

Study type/animal/PMRA#	Study results
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA# 2957795	Low acute toxicity LC_{50} > 5.1 mg/L (♂/♀) No clinical signs of toxicity
Skin irritation NZW rabbits (♀) PMRA# 2957796	Minimally irritating MAS = 0.3 MIS = 0.6 at 72h
Eye irritation NZW rabbits (♀) PMRA# 2957797	Minimally irritating MAS = 1.1 MIS = 8.7 at 1h
Dermal sensitization (LLNA) CBA mice (♀) PMRA# 2957798	Negative

Table 5 Toxicity profile of technical fluazaindolizine

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

Study type/animal/PMRA#	Study results
Toxicokinetic studies	
Absorption, distribution, metabolism, elimination, pharmacokinetics following single or repeated gavage doses (low and high) Sprague-Dawley rats PMRA# 2957884	Single gavage dose administered at 10 mg/kg bw or 200 mg/kg bw using [Ph-^{14}C] DPX-Q8U80 or [IP-2-^{14}C] DPX-Q8U80; 14-day dosing with 10 mg/kg bw of unlabelled DPX-Q8U80 followed by single dose of [Ph-^{14}C] DPX-Q8U80; 4/sex/radiolabel, and /time-point for tissue distribution. Absorption: For both radiolabels, total absorption was 48–59% of the AD at the low-dose level, and 44–50% of the AD at the high-dose level, based on the radioactivity measured in bile, urine, cage wash, plasma, RBC and carcass.

Study type/animal/PMRA#	Study results
	Excretion: Excretion of radiolabel was slightly higher via feces (40–59% of AD) than urine (33–54% of AD) at 168h postdosing. At 48h after administration of a single low or high dose, 4.6–8.1% and 7.0–18% of the AD, respectively, was eliminated via the bile. Excretion was fairly rapid, with 93–99% of the AD eliminated within 48–72h after administration of the radiolabelled dose. Excretion was comparable between the high- and low-dose levels, the [IP-2-^{14}C] and [Ph-^{14}C] radiolabels, and the single- and repeat-dose regimens. Distribution: In single-dose experiments using the [IP-2-^{14}C] radiolabel, the concentration of radioactivity 168h post dosing was highest in the liver at the high- and low-dose levels in both sexes, except for high-dose ♀ where skin had the highest concentration. In single-dose experiments using the [Ph-^{14}C] radiolabel, the concentration of total radioactivity 168h post dosing was highest in pituitary in low-dose ♂, liver in low-dose ♀, and skin in high-dose ♂ and ♀. In repeat-dosing experiments using the [Ph-^{14}C] radiolabel, the concentration of radioactivity at 168h postdosing was highest in liver in both sexes. In single low-dose experiments using the [IP-2-^{14}C] radiolabel, the concentration of radioactivity at 1 and 6h postdosing was highest in plasma for both sexes. In single high-dose experiments using the [IP-2-^{14}C] radiolabel, the concentration of radioactivity at 8h was highest in the bladder of ♂, and in the plasma of ♀, while the highest concentrations at 24h were observed in the plasma of both sexes. In single low- or high-dose experiments using the [Ph-^{14}C] radiolabel, the concentration of radioactivity at 1 and 6h or 8 and 24h postdosing was highest in plasma in both sexes. Pharmacokinetics: In the plasma of animals that received a single dose of either radiolabel, Tmax was 0.25–0.63h at the low-dose level and 3–6h at the high-dose level. There was a six to eightfold increase in plasma Cmax compared to the 20-fold increase in the AD. In the RBC of animals that received a single dose of the either radiolabel, Tmax was determined to be 0.25–0.50h at the low-dose level and 1–10h at the high-dose level. There was a dose-proportional increase in RBC Cmax, except in ♀ with the [IP-2-^{14}C] radiolabel where there was a sevenfold increase compared to the 20-fold increase in the AD.

Study type/animal/PMRA#	Study results
	In the plasma and RBC of animals that received a single low or high dose of either radiolabel, the elimination half-lives were 7–13h. Comparison of the AUC for the low-dose and high-dose levels in both sexes and for both radiolabels indicates that absorption was relatively proportional to dose level. Metabolism: Unchanged DPX-Q8U80 was the most abundant component recovered from total excreted radioactivity (urine, feces, and cage wash) following a single low- or high-dose oral administration using either radiolabel. Metabolites IN-QEK31, IN-A5760 sulphate conjugate, and IN-UHD20 were also detected. In animals from the 14-day repeat-dosing experiment with DPX-Q8U80 followed by a single dose of the [Ph-^{14}C] radiolabel, unchanged DPX-Q8U80 was the most abundant component recovered from total excreted radioactivity (urine, feces, and cage wash), followed by IN-A5760 sulphate conjugate (5.5% of the AD in ♂) and IN-REG72 (1.6/0.2% of the AD (♂/♀). In the bile, unchanged DPX-Q8U80 was the most abundant component recovered following a single low- or high-dose oral administration of [IP-2-^{14}C] or [Ph-^{14}C]DPX-Q8U80. For the [IP-2-^{14}C] label, the most abundant metabolites were IN-QEK31 in low-dose animals, and IN-REG72 and IN-UHD20 glucuronide in ♂ and ♀, respectively, from the high-dose group. For the [Ph-^{14}C] label, the most abundant metabolites were IN-F4106 at the low-dose level, and IN-UHD20 and IN-F4106 in ♂ and ♀, respectively, from the high-dose group. In plasma, liver, and kidney samples collected 8h after high-dose oral administration of the [Ph-^{14}C] radiolabel, unchanged DPX-Q8U80 was the most abundant component recovered, with highest concentrations in plasma, followed by liver, and then kidney. Metabolite IN-F4106 was also detected in both sexes, with highest concentrations in kidney, followed by liver, and then plasma.
Metabolism rate and extent of elimination – pilot study Sprague-Dawley rats PMRA# 2957856	Supplemental Single gavage dose administration at 10 mg/kg bw using [Ph-^{14}C] DPX-Q8U80 or [IP-2-^{14}C] DPX-Q8U80; 2/sex/radiolabel. The majority of the AD was excreted via the feces (57–58% in ♂ and 46-49% in ♀) followed by the urine (25–36% in ♂ and 46% in ♀). The cage wash accounted for 6–13% and 5–8% of the AD in ♂ and ♀, respectively. Excretion was fairly rapid with the majority of the AD (93–97% in both sexes) recovered by 48–72h post dose. The

Study type/animal/PMRA#	Study results
	highest concentration of radioactivity was observed in the liver. Residues from either radiolabel were not eliminated in the exhaled breath. Limitations: small sample size
Metabolism rate and extent of elimination – pilot study CD1 mice PMRA# 2957858	Supplemental Single gavage dose administration at 10 mg/kg bw using [Ph-^{14}C] DPX-Q8U80 or [IP-2-^{14}C] DPX-Q8U80; 2/sex/radiolabel. Excretion was fairly rapid with the majority of the AD (92–95%) recovered in the first 24–48h postdose for ♂ and in the first 48h postdose in ♀. The highest concentration of radioactivity in tissues was observed in the liver. Residues from either radiolabel were not eliminated in the exhaled breath. Limitations: small sample size
Comparative metabolism of mouse, rat, rabbit, dog and human cryopreserved hepatocytes Hepatocytes from CD1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs, and humans PMRA# 2957849	Supplemental Radiolabelled compound (20 µM; [Ph-^{14}C] DPX-Q8U80 or [IP-5,8a-^{14}C] DPX-Q8U80) was incubated with cryopreserved hepatocytes. The amount of unchanged DPX-Q8U80 remaining after 120 mins of incubation was determined. Metabolism was observed in all the species tested with the highest rates observed in human hepatocytes while dog hepatocytes presented the lowest. Unchanged DPX-8U80 accounted for 86–91%, 91–96%, 93–96%, 96–98% and 73–76% of the total radioactivity recovered after 120 mins incubation with hepatocytes from mice, rats, rabbits, dogs and humans, respectively. Only two metabolites were formed at greater than 5%, relative to the total radioactivity recovered, in the various hepatocytes incubated with [Ph-^{14}C]DPX-Q8U80 or [IP-5,8a-^{14}C]DPX-Q8U80, namely IN-REG72, and IN-UHD20. Of these, IN-REG72 was the most prominent and it was the major metabolite detected in human samples. IN-UHD20 was the second most abundant metabolite formed and it was the most prominent in mouse hepatocyte incubations. Conclusion: DPX-Q8U80 was more rapidly metabolised in human-derived hepatocytes as compared to hepatocytes used from other species in this study. The primary in vitro biotransformation pathways of DPX-Q8U80 involved O-demethylation to form IN-

Study type/animal/PMRA#	Study results
	REG72, which in human hepatocytes was followed by sulphate conjugation. Direct hydroxylation of the phenyl ring of DPX-Q8U80 resulted in formation of the metabolite IN-UHD20 while hydrolysis of the amide bond produced metabolites IN-F4106 and IN-QEK31. Limitations: non-guideline study
Toxicokinetics – Repeat oral dose (14-day gavage) Assessed as part of preliminary screen for systemic toxicity Sprague-Dawley rats PMRA# 2958170	Supplemental Unlabelled DPX-Q8U80 was administered to 5 rats/sex/dose at dose levels of 0, 25, 300 or 1000/500 mg/kg bw/day for 14 days. The high-dose level of 1000 mg/kg bw/day was lowered to 500 mg/kg bw/day on day 8 due to bw loss. Concentrations of DPX-Q8U80 were determined in blood and fat of 3 ♀/dose. 25 mg/kg bw/day: Half-life of elimination from plasma and plasma Cmax recorded as 18h and 0.5h, respectively, after final dose. Steady state plasma concentrations were achieved by day 2 of dosing. 300 mg/kg bw/day: Half-life of elimination from plasma and plasma Cmax recorded as 19h and 5h, respectively, after final dose. Steady state plasma concentrations were achieved by day 2 of dosing. 1000/500 mg/kg bw/day: Toxicokinetic parameters not determined due to early unscheduled sacrifice of animals. Conclusion: Steady state plasma concentrations within the first few days of dosing were approximately equal at dose levels of 300 and 1000/500 mg/kg bw/day, suggesting saturation of absorption. Preferential partitioning into fat was not observed. Limitations: limited reporting; non-guideline study.
Acute toxicity studies	
Acute oral toxicity (up-and-down method) (conducted with various lots, consisting of test material from original and commercial production processes) Sprague-Dawley rats (♀)	Supplemental Moderate acute toxicity $LD_{50} \geq 940$ mg/kg bw (♀) Clinical signs of toxicity included mortality, hypoactivity, ↓ muscle tone, high posture, red stained nose, green oily fluid in jejunum, diffusely mottled and darkly discoloured lungs, laboured

Acute toxicity studies	
PMRA# 3049482, 2958177, 2957830	breathing, prostration, lack of righting reflex, piloerection Limitations: individual studies did not adhere to OECD guideline 425; collectively the studies provide sufficient information to determine an acute oral LD_{50} value.
Acute dermal toxicity Sprague-Dawley rats PMRA# 2957845	Low acute toxicity LD_{50} > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity
Acute dermal toxicity (conducted with test material from commercial production process) Sprague-Dawley rats (♀) PMRA# 2957832	Low acute toxicity LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity
Acute inhalation toxicity (nose-only) (conducted with test material from commercial production process) Sprague-Dawley rats PMRA# 2957836	Low acute toxicity LC_{50} > 5.3 mg/L (♂/♀) Clinical signs of toxicity included abnormal gait, laboured breathing, lung noises, high posture, discoloured skin, ataxia, and red nasal and ocular discharge
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA# 2957866	Low acute toxicity LC_{50} > 5.8 mg/L (♂/♀) Clinical signs of toxicity included laboured breathing
Eye irritation (conducted with test material from commercial production process) NZW rabbits (♀) PMRA# 3098864	Non-irritating MAS = 0 MIS = 2.7 (at 1h)

Acute toxicity studies	
Eye irritation NZW rabbits PMRA# 2957797	Mildly irritating MAS = 12.3 MIS = 19 (at 24h)
Skin irritation (conducted with test material from commercial production process) NZW rabbits (♀) PMRA# 2957833	Minimally irritating MAS = 0.33 MIS = 1.7 (at 1h)
Skin irritation NZW rabbits (♀) PMRA# 2957901	Non-irritating MAS = 0 MIS = 0
Dermal sensitization (Maximization test) Hartley guinea pigs (♂) PMRA# 2957892	Negative
Dermal sensitization (LLNA) (conducted with test material from commercial production process) CBA mice (♀) PMRA# 2957829	Supplemental No indication of a positive response as all stimulation index values were below 3.0. Limitation: validated vehicle not used
Short-term toxicity studies	
28-day oral toxicity (diet) CD1 mice PMRA# 2957851	NOAEL = 514/634 mg/kg bw/day (♂/♀) LOAEL = 1105/1286 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ RBC, ↓ HGB, ↓ HCT, ↑ reticulocytes, neutrophil infiltration in the gallbladder, renal basophilic tubules (♂/♀); ↓ bw/bwg, ↓ fe, ↓ total protein, ↓ albumin, ↓ globulin, hepatocellular hypertrophy (♂); ↓ total protein, ↓ albumin, ↓ globulin, dilation of the renal pelvis (♀)

Acute toxicity studies	
90-day oral toxicity (diet) CD1 mice PMRA# 2957861, 2957840	NOAEL = 146/157 mg/kg bw/day (♂/♀) LOAEL = 444/511 mg/kg bw/day (♂/♀) Effects at LOAEL: kidney hypertrophy, kidney infarctions, ↓ bilirubin (♂/♀); ↓ cholesterol, cytoplasmic basophilia in the liver, epithelium hypertrophy/hyperplasia in the gallbladder, eosinophilic crystals in the gallbladder, gallbladder hyalinosis (♂); ↓ ALT, ↑ reticulocytes, ↓ albumin, ↓ albumin/globulin ratio, ↑ spleen wt, inflammatory cell infiltration in the gallbladder (♀) DPX-Q8U80 levels in plasma ↑ with increasing dose levels, in a generally dose-proportional manner (slightly less than linear). Plasma concentrations of DPX-Q8U80 were higher in ♀ than in ♂, and were higher than those of metabolites. The most abundant metabolites in both sexes were IN-UHD20, followed by IN-REG72 and IN-QEK31.
14-day oral toxicity (gavage) – preliminary screen for systemic toxicity Sprague-Dawley rats PMRA# 2958170 Toxicokinetic and genotoxicity (induction of micronuclei) components of study summarized in other sections of table. β-oxidation and CYP450 activity determined from liver samples at sacrifice.	Supplemental NOAEL and LOAEL not established Effects at 300 mg/kg bw/day: ↑ hepatic β-oxidation (♂/♀); stomach erosion/ulcers, ↓ urine specific gravity, ↓ urine protein, ↑ urine volume, ↑ triglycerides, ↑ liver wt, ↑ kidney wt (♂) Effects at 1000/500 mg/kg bw/day (the dose of 1000 mg/kg bw/day was lowered to 500 mg/kg bw/day on day 8 due to bw loss): death, unscheduled sacrifice, bw loss, lethargy, head/nose swelling, ↓ RBC, ↓ HCT, ↓ reticulocytes, ↓ HGB, ↑ RDW, ↑ WBC, ↑ neutrophils, ↑ lymphocytes, ↑ monocytes, ↓ eosinophils, ↑ ALT, ↑ BUN, ↓ cholesterol, ↓ total protein, ↓ albumin, ↓ globulin, ↑ adrenal wt, ↓ heart wt, ↓ thymus wt, ↓ spleen wt, skin edema, stomach erosion/ulcers, nasal ulceration/inflammation, foreign material in nose, purulent exudate in nose, turbinate inflammation, turbinate ulcers/erosion, lymphoid depletion (thymus, spleen, lymph nodes), lymphoid necrosis in thymus, histiocytosis of lymph nodes, bone marrow atrophy, spleen congestion (♂/♀); hair loss, red discoloured skin, ↑ bilirubin, ↑ glucose, ↑ triglycerides, ↓ liver wt, ↓ kidney wt, ↓ epididymides wt, trachea inflammation/exudate, mesenteric inflammation/hemorrhage, testicular degeneration/atrophy, oligospermia, ↓ prostate and seminal vesicle secretion, ↓ pancreas zymogen (♂); polyuria, ↑ phosphorous, ↓ SDH, ↓ sodium, ↓ chloride, ↓ creatinine, ↓ calcium, ↓ ovary wt, ↑ rel liver wt, ↑ rel kidney wt, anestrus, corpora lutea necrosis, renal tubular hypertrophy, hepatocellular centrilobular degeneration, hepatocellular hypertrophy, ↑ hepatic

Acute toxicity studies	
	CYP450 and β-oxidation (♀) Limitations: limited reporting; non-guideline study.
90-day oral toxicity and neurotoxicity (diet) Sprague-Dawley rats PMRA# 2957875, 2957876	NOAEL = 84/97 mg/kg bw/day (♂/♀) LOAEL = 166/189 mg/kg bw/day (♂/♀) Effects at LOAEL: kidney transitional hyperplasia (♂/♀); ↓ spleen wt, ↑ urine volume, ↓ urine protein, ↓ urine specific gravity, kidney pyelonephritis (♂); ↓ cholesterol (♀) No evidence of neurotoxicity In the plasma, quantifiable concentrations of DPX-Q8U80 and metabolites IN-QEK31, IN-REG72, REG72-OH, and Q8U80-OH were observed at all dose levels. DPX-Q8U80 levels ↑ with dose level in a dose-proportional manner. Concentrations of DPX-Q8U80 were comparable between sexes. The most abundant metabolites were REG72-OH followed by Q8U80-OH. Metabolism of DPX-Q8U80 was more extensive in ♂ than in ♀.
28-day oral toxicity (diet) – Palatability study Beagle dogs PMRA# 2957859	Supplemental NOAEL and LOAEL not established Effects at ≥ 38/37 mg/kg bw/day: ↑ ALP (♂/♀); ↓ cholesterol (♀) Effects at 139 mg/kg bw/day: ↓ bw, ↓ fc, ↑ ALT, single cell necrosis and pigmented histiocytes in the liver (♀) Limitations: small sample size
90-day oral toxicity (diet) Beagle dogs PMRA# 2957862, 2957863, 2957864 Biochemical hepatic analysis from all animals: β-oxidation activity, UDPGT activity, total cytochrome P450 enzyme content, CYP1A, 2B, 2E, 3A, 4A activity.	NOAEL = 20/21 mg/kg bw/day (♂/♀) LOAEL = 59/61 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ platelets, ↓ albumin, ↓ cholesterol, ↑ AST, ↑ ALP, ↓ hepatic β-oxidation activity, ↑ hepatic CYP2E/3A/4A enzyme activity, ↑ hepatic UDPGT activity, ↑ total hepatic cytochrome P450 content, single cell necrosis in the liver (♂/♀); ↓ bw/bwg, ↓ fe, ↓ albumin to globulin ratio, ↑ chloride, ↑ rel liver/gallbladder wt, pigmented Kupffer cells, pigmented centrilobular hepatocytes, glycogen depletion in the liver, lymphoid depletion (in Peyer's patch) (♂); ↑ ALT, extramedullary hemopoiesis in the spleen (♀) DPX-Q8U80 levels in plasma ↑ with dose level in a generally dose-proportional manner (sub-linear at highest dose level). Plasma concentrations of DPX-Q8U80 were slightly higher in ♀

Acute toxicity studies	
	than in ♂, and were much higher than those of metabolites. The most abundant metabolite in both sexes was IN-QEK31, followed by IN-F4106.
12-month oral toxicity (diet) Beagle dogs PMRA# 2957966, 2957967	NOAEL = 20/17 mg/kg bw/day (♂/♀) LOAEL = 36/37 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ ALT, ↑ ALP, ↑ GGT, ↑ SDH, ↑ adrenal wt (♂/♀); ↓ bw/bwg, ↓ albumin, ↓ cholesterol, ↑ calcium, ↑ liver/gallbladder weight, pigmented hepatocytes (♂); ↓ total bilirubin, adrenal corticomedullary pigmentation (♀) DPX-Q8U80 levels in plasma ↑ with dose level in a generally dose-proportional manner (sub-linear at highest dose level). Plasma concentrations of DPX-Q8U80 were similar between sexes. DPX-Q8U80 levels were much higher than those of metabolites. The most abundant metabolite in both sexes was IN-QEK31, followed by IN-F4106.
28-day dermal toxicity Sprague-Dawley rats PMRA# 2957898	Supplemental No treatment-related findings up to 1000 mg/kg bw/day (♂/♀). Limitation: total body surface area covered with test compound ranged from 0.3 to 1.6%, well below the test guideline requirement of 10%.
Repeat-exposure inhalation toxicity – waiver rationale PMRA# 2957835	The request to waive the requirement for a repeat-exposure inhalation toxicity study was supported for the proposed uses on the basis of the low volatility and low acute inhalation toxicity of fluazaindolizine, as well as the magnitude of the margins of exposure obtained for the inhalation exposure scenarios when oral endpoints were used in the risk assessment.
Chronic toxicity/Oncogenicity studies	
18-month oncogenicity (diet) CD1 mice PMRA# 2957941, 2957841	NOAEL = 142/177 mg/kg bw/day (♂/♀) LOAEL = 436/534 mg/kg bw/day (♂/♀) Effects at LOAEL: parathyroid gland amyloidosis, pituitary gland cysts (♂/♀); amyloidosis (in jejunum, kidney, lacrimal gland, lymph node, spleen), eosinophilic inclusion in the liver, plasmacytosis in the lymph node, mononuclear cell infiltration in the pancreas, salivary gland atrophy, skin lymphoid hyperplasia (♂); ↑ spleen wt, ↑ kidney wt, discoloured and small kidneys, amyloidosis (in colon, pancreas, salivary gland), kidney abscess, kidney necrosis, acute inflammation of the lymph node (♀) DPX-Q8U80 levels in plasma ↑ with dose level in a generally

Acute toxicity studies	
	dose-proportional manner (slightly less than linear in ♀). Concentrations of DPX-Q8U80 were slightly higher in ♀ than in ♂, and were much higher than those of metabolites. The most abundant metabolites in both sexes was IN-UHD20, followed by IN-QEK31, IN-REG72 and IN-F4106. No evidence of tumourigenicity
24-month chronic toxicity/oncogenicity (diet) Sprague-Dawley rats PMRA# 2957939, 3082856, 2957842	**24-month sacrifice** NOAEL = 25/78 mg/kg bw/day (♂/♀) LOAEL = 76/254 mg/kg bw/day (♂/♀) Effects at LOAEL: kidney transitional cell hyperplasia (♂); ↓ bw/bwg, ↓ fe, ↑ rel kidney wt, kidney cysts, deformed papilla in the kidney, renal pelvis dilation, medullary tubule dilation in the kidney, kidney interstitial fibrosis, kidney urothelial cell hyperplasia, kidney papilla necrosis, nasal cavity eosinophilic globules, stomach squamous cell hyperplasia, irregular kidney surface, chronic progressive nephropathy, non-glandular edema in the stomach, glandular erosion/ulcer in the stomach, squamous metaplasia in the uterus/cervix, adrenal cortex hypertrophy (♀) **12-month sacrifice** NOAEL = 76/91 mg/kg bw/day (♂/♀) LOAEL = 237/281 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ urine osmolality, ↑ rel kidney wt, kidney urothelial cell hyperplasia (♂/♀); ↓ cholesterol, ↑ urine volume, kidney pelvis dilation, kidney transitional cell hyperplasia, kidney papilla necrosis (♂) DPX-Q8U80 levels in plasma ↑ with dose level in a generally dose-proportional manner. Plasma concentrations of DPX-Q8U80 were higher in ♀ than in ♂, and were much higher than those of metabolites. The most abundant metabolite in both sexes was IN-QEK31, followed by IN-F4106 and IN-UHD20. IN-REG72 was also detected at relatively high levels in ♂. No evidence of tumorigenicity
Developmental/Reproductive toxicity studies	
28-day oral toxicity and 1-generation reproductive toxicity (diet) Sprague-Dawley rats	**28-day study** NOAEL = 179/195 mg/kg bw/day (♂/♀) LOAEL = 361/369 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↓ fc/fe (week 1), ↓ cholesterol,

Acute toxicity studies	
PMRA# 2957850	hyperplasia of the transitional epithelium of the bladder mucosa (♂/♀); ↓ bw, ↓ protein, ↓ globulin, ↓ triglycerides, ↑ urinary volume, ↓ urinary protein (♂); ↓ phosphorus, ↑ triglycerides (♀) **Reproductive Toxicity Study** Parental NOAEL = 37/195 mg/kg bw/day (♂/♀) Parental LOAEL = 179/369 mg/kg bw/day (♂/♀) Effects at LOAEL: hyperplasia of transitional epithelium of the renal pelvis (♂); ↓ fc, renal pelvis dilation, pyelitis of the kidney, ulceration of the epithelial surface of the renal pelvis and renal papilla, kidney deformity/irregular shape, hyperplasia of transitional epithelium of the renal pelvis, pyelonephritis, hyperplasia of the transitional epithelium of the urinary bladder mucosa (♀) Reproductive NOAEL = 361/369 mg/kg bw/day (♂/♀) Reproductive LOAEL not established No treatment-related reproductive findings Pre-weaning Offspring NOAEL = 369 mg/kg bw/day (♂/♀) Pre-weaning Offspring LOAEL not established No treatment-related findings in offspring prior to weaning F1 Adult Offspring NOAEL = 199/204 mg/kg bw/day (♂/♀) F1 Adult Offspring LOAEL = 405/388 mg/kg bw/day (♂/♀) F1 adult offspring were dosed from PND 21 to PND 60 Effects at LOAEL: kidney discolouration, kidney dilation, renal cysts, hyperplasia of transitional epithelium of the renal pelvis, pyelitis of the kidney, pyelonephritis, ulceration of the epithelial surface of the renal pelvis or renal papilla (♂/♀); prostate inflammation (♂); ↓ bw/bwg, gross lesions of the kidney (discolouration, adhesion) (♀) No evidence of sensitivity of the young
2-generation reproductive toxicity (diet) Sprague-Dawley rats PMRA# 3088000	Parental NOAEL = 30/100 mg/kg bw/day (♂/♀) Parental LOAEL = 88/291 mg/kg bw/day (♂/♀) Effects at LOAEL: mucosal hyperplasia of kidney (F1) (♂); ↓ bw pre-mating (P, F1), ↓ bwg pre-mating (P, F1), ↓ fc pre-mating (P, F1), ↓ bw/bwg gestation (P, F1), ↓ bw lactation (P, F1), ↑ bwg lactation (P, F1), ↑ spleen wt (F1), kidney discolouration (F1),

Acute toxicity studies	
	dilation of ureters (F1), mucosal hyperplasia of kidney (F1), kidney dilation (P, F1), kidney deformity (F1), chronic progressive nephropathy (P, F1), erosion/ulcer of kidney (P, F1), hydronephrosis (P, F1), mucosal hyperplasia of kidney (P), interstitial inflammation of kidney (P), renal papillary necrosis (F1), pyelonephritis (F1), mucosal hyperplasia of urinary bladder (P, F1), hyperplasia of ureters (F1), inflammation of ureters (F1), inflammation of urethra (F1), mucosal hyperplasia of urethra (F1), cystitis of urinary bladder (F1), lymphoid aggregates in urinary bladder (F1) (♀) Offspring NOAEL = 39 mg/kg bw/day (♂/♀) Offspring LOAEL = 116 mg/kg bw/day (♂/♀) Effects at LOAEL: mucosal hyperplasia of kidneys, ureters, and urinary bladder (F2) (♂/♀); mucosal hyperplasia of urethra (F2), cystitis of urinary bladder (F2) (♀) Reproductive NOAEL = 265/291 mg/kg bw/day (♂/♀) Reproductive LOAEL not established No treatment-related findings No evidence of sensitivity of the young
Developmental toxicity (gavage) Sprague-Dawley rats PMRA# 2957999	Maternal NOAEL = 200 mg/kg bw/day Maternal LOAEL = 400 mg/kg bw/day Effects at LOAEL: slight bw loss (by GD 7), ↓ bw (GD 7-21), ↓ bwg, ↓ fc, ↓ gravid uterine wt, moderate dilation of the kidney Developmental NOAEL = 200 mg/kg bw/day Developmental LOAEL = 400 mg/kg bw/day Effects at LOAEL: ↑ short cervical ribs, ↓ fetal bw No evidence of sensitivity of the young No evidence of treatment-related malformations
Developmental toxicity (gavage) NZW rabbits PMRA# 2957873	Maternal NOAEL = 30 mg/kg bw/day Maternal LOAEL = 120 mg/kg bw/day Effects at LOAEL: equivocal ↑ abortions (3 litters versus 1 in controls; GD 25-26), 1 unscheduled sacrifice (GD 25), ↓ bwg (GD 10-13), bw loss (GD 13-20), ↓ fc (GD 13-20), small feces, ↓ defecation, soft stool, mucoid feces, kidney tubular degeneration and dilation, mononuclear infiltrate of the kidney

Acute toxicity studies	
	Developmental NOAEL = 30 mg/kg bw/day Developmental LOAEL = 120 mg/kg bw/day Effects at LOAEL: equivocal ↑ abortions, ↑ sternebrae with thread-like attachment (sternebrae number 4 attached to sternebrae number 5), ↑ small gallbladders No evidence of sensitivity of the young No evidence of treatment-related malformations
Genotoxicity studies	
Bacterial reverse mutation assay *S.* Typhimurium TA 1535, TA 100, TA 1537, TA 98 and *E. coli* WP2uvrA PMRA# 2957844	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay (conducted with test material from commercial production process) *S.* Typhimurium TA 1535, TA 100, TA 1537, TA 98 and *E. coli* WP2uvrA PMRA# 2957938	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay (conducted with test material from commercial production process) *S.* Typhimurium TA 1535, TA 100, TA 1537, TA 98 and *E. coli* WP2uvrA PMRA# 2957828	Negative ± metabolic activation Tested up to a limit concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes	Positive ± metabolic activation Tested up to cytotoxic and/or precipitating concentrations -S9 4h: Positive for structural aberrations at 600 µg/mL

Acute toxicity studies	
PMRA# 2957899	+S9 4h: Positive for structural aberrations at 400 and 425 µg/mL
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/HGPRT) cells PMRA# 2957900	Negative ± metabolic activation Tested up to cytotoxic and/or precipitating concentrations
In vivo micronucleus assay (gavage) CD1 mice PMRA# 2957963	Negative Clinical signs of toxicity included low posture, lethargy, eyelid ptosis, abnormal gait, tremors and hypersensitivity. Deaths occurred in ♀ at 1000 and 1500 mg/kg bw.
In vivo micronucleus assay (gavage) CD1 mice PMRA# 2958118	Negative No clinical signs of toxicity
In vivo micronucleus assay (gavage) (conducted with test material from commercial production process) CD1 mice PMRA# 2957831	Negative One ♂ at 750 mg/kg bw exhibited prostration and died. No other clinical signs of toxicity.
In vivo micronucleus assay - single and repeated oral dose (gavage) Assessed as part of 14-day preliminary screen for systemic toxicity Sprague Dawley rat PMRA# 2958170	Supplemental Based on the data presented, there was no evidence of induction of micronuclei under the conditions of this study, which involved testing up to the limit dose (single exposure) or dose levels causing significant toxicity (repeated dosing). Limitation: limited reporting; non-guideline study.
Neurotoxicity studies	
Acute oral neurotoxicity	NOAEL = 125/1750 mg/kg bw (♂/♀)

Acute toxicity studies	
(gavage) Sprague-Dawley rats PMRA# 2958015	LOAEL = 450 mg/kg bw/not established (♂/♀) Effects at LOAEL: ↓ fc (days 1–2), slight ↓ MA (duration and ambulation; day 1, sessions 1 and 2 only), slight ↓ MA habituation (day 1) (♂) No evidence of selective neurotoxicity
Other studies	
28-day immunotoxicity study (diet) Sprague-Dawley rats (♂) PMRA# 2958062	NOAEL = 393 mg/kg bw/day (♂) LOAEL not established No adverse treatment-related findings No treatment-related effect on anti-sRBC IgM antibody response No evidence of immune system dysregulation
3-day uterotrophic assay for detecting estrogenic activity (gavage) Sprague-Dawley rats (ovariectomized ♀) PMRA# 2957846	Supplemental Effects at 500 mg/kg bw/day: ↓ bw/bwg, ↓ fc, ↓ fe (♀) Effects in positive control: ↓ bw/bwg, ↓ fc, ↓ fe, ↑ conversion out of diestrus, ↑ uterine wt (wet and blotted), presence of uterine fluid (♀) No treatment-related effects indicative of estrogen agonism
15-day assay for detecting endocrine activity (gavage) Sprague-Dawley rats (♂) PMRA# 2957847	Supplemental Effects at ≥100 mg/kg bw/day: ↓ abs epididymis wt, ↓ abs testes wt, ↑ hepatic aromatase activity Effects at 500/350 mg/kg bw/day (dose of 500 mg/kg bw/day reduced to 350 mg/kg bw/day on day 10): death (1; day 12), dehydration, discharge, high posture (clinical signs starting day 9), ↓ bw/bwg, ↓ fc, ↓ fe, ↓ abs liver wt, ↓ prostate wt, ↓ seminal vesicle wt, oligospermia/germ cell debris in the epididymides, erosion/ulcer of the glandular stomach mucosa, eosinophils in the stomach mucosa, degeneration/atrophy of the seminiferous epithelium in the testes No clear effects on hormones assessed in the blood (DHT, LH, T, E2, T4, T3, and TSH) DPX-Q8U80 levels in plasma ↑ with dose level in a generally dose-proportional manner, except approaching the high-dose level

Acute toxicity studies	
	where the concentration-dose curve became less than linear. DPX-Q8U80 levels were much higher than those of metabolites. The most abundant metabolite was IN-QEK31, followed by IN-F4106 andIN-REG72. Limitation: non-guideline, small sample sizes, large inter- and intra-group variability in hormone data, exceedance of MTD at the high dose
H295R steroidogenesis assay (in vitro) Human adrenocortical carcinoma (H295R) cell PMRA# 2957889	Supplemental Incubation of H295R cells with DPX-Q8U80 caused statistically significant ↓ in T and E2 synthesis relative to the vehicle control only at the highest concentration of 100 µM. Positive controls showed expected responses. Under the tested conditions, DPX-Q8U80 was considered to be equivocal for the inhibition of steroid biosynthesis. Limitation: non-guideline

Table 6 Toxicity profile of metabolites and impurities of fluazaindolizine

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

Study type/animal/PMRA#	Study results
IN-A5760	
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958112	Negative ± metabolic activation Tested up to a limit concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958113	Positive Induction of structural and numerical chromosomal aberrations in the non-activated 4h exposure group at a cytotoxic concentration.

Study type/animal/PMRA#	Study results
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/HPRT) cells PMRA# 2958114	Negative ± metabolic activation Tested up to a limit concentration
In vivo micronucleus assay (gavage) CD1 mice PMRA# 2958165	Negative No clinical signs of toxicity Plasma analysis results showed that the test substance was present in the pooled plasma samples, indicating target cell exposure.
IN-F4106	
Acute oral toxicity (up-and-down method) Sprague-Dawley rats (♀) PMRA# 2957951	Low acute toxicity LD_{50} > 5000 mg/kg bw (♀) Clinical signs of toxicity included hypoactivity, irregular respiration, hunched posture, and ↓ fecal volume.
90-day oral toxicity (diet) Sprague-Dawley rats PMRA# 2958036, 2958037	NOAEL = 36/42 mg/kg bw/day (♂/♀) LOAEL = 149/165 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↓ fc/fe, ↑ WBC, ↑ lymphocytes, ↑ large unstained cells, ↑ bilirubin, ↑ BUN, ↑ cholesterol, ↓ creatinine, ↓ glucose, ↓ urine pH, ↑ liver wt, centrilobular hepatocellular hypertrophy, transitional cell hyperplasia of the urinary bladder mucosa (♂/♀); ↓ bw, ↑ eosinophils, ↑ reticulocytes, ↓ triglycerides, ↑ rel kidney wt, ↑ prostate wt (♂); ↑ total bile acids, ↑ urine volume, edema and inflammation of the urinary bladder (♀) There was a dose dependent ↑ in plasma concentrations of IN-F4106 and IN-A5760. The majority of the dose in urine was recovered as IN-A5760 (inclusive of its conjugates), suggesting that IN-F4106 undergoes extensive O-demethylation to form IN-A5760. Renal clearance was substantially faster for IN-A5760 conjugates than for IN-F4106.
Reproductive/ developmental toxicity screening study (diet) Sprague-Dawley rats PMRA# 2958094	Parental NOAEL = 47/45 mg/kg bw/day (♂/♀) Parental LOAEL = 179/173 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw/bwg, ↓ fc, ↑ rel liver wt, hepatocellular hypertrophy (♂/♀); ↑ rel kidney wt (♀) Reproductive NOAEL = 179/173 mg/kg bw/day (♂/♀) Reproductive LOAEL not established

Study type/animal/PMRA#	Study results
	No treatment-related findings Offspring NOAEL = 45 mg/kg bw/day (♂/♀) Offspring LOAEL = 173 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw on PND 0 and PND 4 (♂/♀) No evidence of sensitivity of the young
Developmental toxicity (gavage) Sprague-Dawley rats PMRA# 2958111	Maternal NOAEL = 67 mg/kg bw/day Maternal LOAEL = 200 mg/kg bw/day Effects at LOAEL: ↓ bw (GD 7-20), ↓ bwg (GD 6-20), ↓ fc Developmental NOAEL = 22 mg/kg bw/day Developmental LOAEL = 67 mg/kg bw/day Effects at LOAEL: ↓ fetal bw Evidence of sensitivity of the young No evidence of treatment-related malformations
2-generation reproductive toxicity (diet) Sprague-Dawley rats PMRA 2958095	Parental NOAEL = 35/40 mg/kg bw/day (♂/♀) Parental LOAEL = 111/122 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ pre-mating bw (P), ↓ pre-mating bwg (P, F1), ↓ pre-mating fc (P), ↓ pre-mating fe (P), ↑ rel kidney wt (P, F1) (♂/♀); ↓ pre-mating bw (F1), ↓ pre-mating fc (F1), ↑ rel liver wt (P, F1), ↑ adrenal wt (F1) (♂); ↓ pre-mating bw (F1), ↓ gestation bw/bwg (P, F1), ↓ pre-mating fc (F1), ↓ gestation fc (P, F1), ↑ rel liver wt (P, F1) (♀) Reproductive NOAEL = 111/122 mg/kg bw/day (♂/♀) Reproductive LOAEL not established No treatment-related reproductive findings Offspring NOAEL = 40 mg/kg bw/day (♀) Offspring LOAEL = 122 mg/kg bw/day (♀) Effects at LOAEL: ↓ bw (PND 21; F1, F2) No evidence of sensitivity of the young

Study type/animal/PMRA#	Study results
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958043	Negative ± metabolic activation Tested up to a limit concentration
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/ HGPRT) cells PMRA# 2958097	Negative ± metabolic activation Tested up to a limit concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958058	Positive Induction of structural chromosomal aberrations in the activated and non-activated 4h exposure group at cytotoxic concentrations
In vivo micronucleus assay (gavage) CD1 mice PMRA# 2958086	Negative No clinical signs of toxicity Cytotoxicity (↓ reticulocytes) in ♂ at 2000 mg/kg bw
IN-QEK31	
Acute oral toxicity (up-and-down method) Sprague-Dawley rats (♀) PMRA# 2958179	Slight acute toxicity LD_{50} > 1750 mg/kg bw (♀) Clinical signs of toxicity included abnormal redness in ears and paws, loss of righting reflex, abnormal gait, laboured breathing, coldness to touch, dehydration, ↓ fecal output, ptosis, abnormal posture (high), piloerection, hypoactivity, prostration, ↓ muscle tone.
90-day oral toxicity (diet) Sprague-Dawley rats PMRA# 2958038	NOAEL = 183/204 mg/kg bw/day (♂/♀) LOAEL = 784/820 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↓ fe, discolouration and dilation of the kidney, degeneration/regeneration of renal tubules, dilation of renal tubules and pelvis, transitional epithelium hyperplasia of the urinary bladder (♂/♀); ↓ bw, ↓ hindlimb grip strength, ↑ BUN, ↑

Study type/animal/PMRA#	Study results
	kidney wt, calculus/calculi in the urinary bladder, inflammation of the urinary bladder; concretions of urinary bladder (♂); ↑ triglycerides, ↓ monocytes, ↓ urine protein, ↓ liver wt, ↑ uterus wt, ↓ ovary wt, calculus/calculi and lesions in the kidney, irregular shape and course surface of the kidneys, transitional epithelium hyperplasia of the kidney (♀)
Reproductive/developmental toxicity screening study (diet) Sprague-Dawley rats PMRA# 2958096	Parental NOAEL = 228/223 mg/kg bw/day (♂/♀) Parental LOAEL = 864/838 mg/kg bw/day (♂/♀) Effects at LOAEL: microscopic findings in the kidneys (degeneration/regeneration of tubules, hyperplasia of transitional epithelium) and urinary bladder (hyperplasia of transitional epithelium and inflammation) (♂/♀); ↑ kidney wt, ↑ adrenal wt, dilatation of kidney tubules and pelvis, necrosis of papilla and concretions in kidney, microscopic findings in urinary bladder (degeneration/regeneration, infiltration of mast cells, concretions and hemorrhage) (♂); ↓ bw/bwg and fc (LD 0-4), ↓ thymus wt, hyperplasia of kidney epithelium in papillary tubules, ↑ white blood cells in renal papillary capillaries, lymphoid depletion in the thymus (♀) Reproductive NOAEL = 864/838 mg/kg bw/day (♂/♀) Reproductive LOAEL not established No treatment-related reproductive findings Offspring NOAEL = 223 mg/kg bw/day (♂/♀) Offspring LOAEL = 838 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw (PND 0 and PND 4) (♂/♀) No evidence of sensitivity of the young
Developmental toxicity (gavage) Sprague-Dawley rats PMRA# 2958107	Maternal NOAEL = 330 mg/kg bw/day Maternal LOAEL not established No adverse treatment-related findings Developmental NOAEL = 330 mg/kg bw/day Developmental LOAEL not established No adverse treatment-related findings No evidence of sensitivity of the young. No evidence of malformations

Study type/animal/PMRA#	Study results
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958056	Negative ± metabolic activation Tested up to a limit concentration
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/HPRT) cells PMRA# 2958059	Negative ± metabolic activation Tested up to a precipitating concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958057	Positive Induction of structural chromosomal aberrations in the activated and non-activated 4h exposure group (at a cytotoxic concentration for the non-activated condition).
In vivo micronucleus assay (gavage) CD1 mice PMRA# 2958100, 2957843	Negative Clinical signs of toxicity occurred at 2000 mg/kg bw in two ♂ and one ♀ which included ataxia, laboured breathing, dehydration, eyelid ptosis, clear ocular discharge, prostration, lethargy, and abnormal gait. These animals were sacrificed on day 2. All other animals from the 2000 mg/kg bw group were either found dead or sacrificed. Death was also observed at 1300 and 1600 mg/kg bw. Plasma analysis results showed that the test substance was present in the pooled plasma samples, indicating target cell exposure.
IN-QZY47	
Acute oral toxicity (up-and-own method) Sprague-Dawley rats (♀) PMRA# 2958121	Low acute toxicity LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity
7-day oral toxicity – dose range-finding (diet) Sprague-Dawley rats	Supplemental NOAEL and LOAEL not established Effects at 1077/899 mg/kg bw/day (♂/♀): ↑ BUN, ↑ liver wt,

Study type/animal/PMRA#	Study results
PMRA# 2958129	centrilobular hepatocellular hypertrophy (♂/♀); ↑ prothrombin time (♂); ↓ bw/bwg, ↓ fc, ↓ fe, ↑ bilirubin (♀) A less than dose proportional ↑ was observed in the plasma AUC 24h for IN-QZY47 absorption. A large amount of IN-QZY47 was either acetylated, metabolized and/or conjugated prior to urinary excretion. The most prominent metabolite in the urine appeared to the acetylated derivative of IN-QZY47.
28-day oral toxicity (diet) Sprague-Dawley rats PMRA# 2958168, 2958169	NOAEL = 220/235 mg/kg bw/day (♂/♀) LOAEL = 735/749 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↓ fc, ↑ neutrophils, ↑ cholesterol, ↑ bilirubin, ↑ rel kidney wt, ↑ liver wt, centrilobular hepatocellular hypertrophy (♂/♀); ↑ BUN, ↑ reticulocytes, ↑ ALT, ↑ prothrombin time, ↑ platelets, ↑ urine protein, ↑ prostate wt (♂); ↓ bw, ↓ fe, ↑ WBC, ↑ total bile acid, ↑ urinary volume (♀) A less than dose proportional ↑ was observed in the plasma AUC 24h for IN-QZY47, whereas a greater than dose proportional ↑ was observed in the plasma AUC 24h for IN-F4106 and IN-A5760.
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958101	Negative ± metabolic activation Tested up to a limit concentration Under the conditions of this study, IN-QZY47 showed a potential for mutagenicity with tester strain TA1535 both in the absence and presence of S9. However, this mutagenic potential was no longer observed when a highly purified sample was tested, and therefore, it was concluded that the test substance was negative in this in vitro bacterial mutagenicity test.
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/HPRT) cells PMRA# 2958108	Negative ± metabolic activation Tested up to a precipitating concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958104	Negative ± metabolic activation Tested up to a cytotoxic concentration

Study type/animal/PMRA#	Study results
In vivo unscheduled DNA synthesis (gavage) Primary culture of Sprague-Dawley rat hepatocytes PMRA# 2958109	Negative Tested up to a limit dose
IN-REG72	
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958098	Negative ± metabolic activation Tested up to a limit concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958099	Negative ± metabolic activation Tested up to a cytotoxic concentration
In vivo micronucleus assay (gavage) CD1 mice PMRA# 2958172	Negative No clinical signs of toxicity Plasma analysis results showed that the test substance was present in the pooled plasma samples, indicating target cell exposure.
IN-TMQ01	
Acute oral toxicity (up-and-down method) Sprague-Dawley rats (♀) PMRA# 2958120	Low acute toxicity LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity
7-day oral toxicity – dose range-finding (diet) Sprague-Dawley rats PMRA# 2958128	Supplemental NOAEL and LOAEL not established No treatment-related findings up to 1179/1075 mg/kg bw/day (♂/♀) A dose proportional ↑ plasma AUC 24h was observed for IN-TMQ01. Unchanged IN-TMQ01 was the major component found

Study type/animal/PMRA#	Study results
	in the urine. Known metabolites IN-F4106 and IN-UNS90 were minor components in the urine
28-day oral toxicity (diet) Sprague-Dawley rats PMRA# 2958166, 2958167	NOAEL = 847/219 mg/kg bw/day (♂/♀) LOAEL = not established/902 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ bw/bwg, ↑ fc, ↑ fe, ↑ hindlimb grip strength, ↑ forelimb grip strength, ↑ potassium, ↑ ALT, ↓ total bile acid, ↑ abs liver wt, ↑ kidney mineralization (♀) A less than dose proportional ↑ was observed in the plasma AUC 24h for IN-TMQ01, whereas a slightly more than dose proportional ↑ was observed in the plasma AUC 24h for IN-F4106, IN-A5760 was not detected in plasma. The main compound detected in plasma and urine was unchanged IN-TMQ01.
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958102	Negative ± metabolic activation Tested up to a limit concentration
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958103	Negative ± metabolic activation Tested up to a limit concentration
IN-TQD54	
Acute oral toxicity (up-and-down method) Sprague-Dawley rats (♀) PMRA# 2958122	Low acute toxicity LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958123	Negative ± metabolic activation Tested up to a limit concentration

Study type/animal/PMRA#	Study results
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958126	Negative ± metabolic activation Tested up to a limit concentration
IN-UJV12	
Acute oral toxicity (up-and-down method) Sprague-Dawley rats (♀) PMRA# 2958127	Low acute toxicity LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958125	Positive There was evidence of mutagenicity with tester strain TA1535 in the absence and presence of S9.
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958180	Negative ± metabolic activation Tested up to a limit concentration
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/HPRT) cells PMRA# 2958163	Negative ± metabolic activation Tested up to a limit concentration The results were equivocal in the absence of S9 activation; however, using a purer sample of the test substance, the result was negative in the absence of S9 activation.
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958124	Positive Induced structural chromosomal aberrations under the non-activated 22h test condition in the presence of cytotoxicity.

Study type/animal/PMRA#	Study results
In vivo micronucleus assay (gavage) Sprague-Dawley rats PMRA# 2958175; 2958176	Negative No clinical signs of toxicity Plasma analysis results showed that the test substance was present in the pooled plasma samples, indicating target cell exposure.
IN-VM862	
90-day oral toxicity (gavage) Sprague-Dawley rats PMRA# 2957838	NOAEL = 2 mg/kg bw/day (♂/♀) LOAEL = 10 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ neutrophils, ↑ total protein, ↑ albumin, ↑ cholesterol, ↑ adrenal wt, ↑ kidney wt, ↑ liver wt, lymphoid hyperplasia, hepatocellular hypertrophy (♂/♀); ↑ calcium, ↑ urine protein, kidney discolouration (♂); ↑ WBC, ↑ ALT, endometrial glands in uterus, capsulitis of lymph nodes (♀)
Bacterial reverse mutation assay *S.* Typhimurium (TA 1535, TA 100, TA 1537, TA 98) and *E. coli* (WP2uvrA) PMRA# 2958046	Negative ± metabolic activation Tested up to a cytotoxic concentration
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/HPRT) cells PMRA# 2958178	Negative ± metabolic activation Tested up to precipitating and cytotoxic concentrations
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA# 2958047	Negative ± metabolic activation Tested up to a cytotoxic concentration
Studies on impurities	
QSAR – Ames mutagenicity assessment (in silico) for fluazaindolizine and 5 impurities PMRA# 3051119	**Supplemental – Non-guideline** Fluazaindolizine and the 5 impurities analyzed were predicted as negative in the Ames test by Derek Nexus. Fluazaindolizine and the 5 impurities analyzed were predicted as negative but out of the applicability domain in the Ames test by OASIS TIMES Ames mutagenicity model and Ames mutagenicity S9 activated model.

Study type/animal/PMRA#	Study results
PBPK modelling for oral absorption (in silico) for fluazaindolizine and 2 impurities PMRA# 3051120	**Supplemental – Non-guideline** Both impurities were determined to be not likely absorbed to any appreciable extent due to their high molecular weights. Predicted oral absorption based on modeling was <1% in each case for the 2 impurities analyzed, and 41–75% for fluazaindolizine.

Table 7 Toxicology reference values for use in health risk assessment for fluazaindolizine

Exposure scenario	study	Point of departure and endpoint	CAF[1] or target MOE
Acute dietary general population	Acute neurotoxicity in rats	NOAEL = 125 mg/kg bw ↓ motor activity, ↓ habituation	100
ARfD = 1.3 mg/kg bw			
Repeated (chronic) dietary	1-year dietary toxicity in dogs	NOAEL = 17 mg/kg bw/day ↓ bw/bwg, pigmented hepatocytes	100
ADI = 0.2 mg/kg bw/day			
Short- and intermediate-term dermal[2] and inhalation[3]	90-day dietary toxicity in dogs	NOAEL = 20 mg/kg bw/day ↓ bw/bwg, pigmented Kupffer cells, pigmented centrilobular hepatocytes, glycogen depletion in the liver, lymphoid depletion (in Peyer's patch)	100
Aggregate	Due to the absence of residential uses, potential aggregation involves food and drinking water exposure only. Use of the ARfD and ADI in this scenario is appropriate.		
Cancer	No treatment-related tumours were observed, therefore a cancer risk assessment is not required		

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

Table 8 Integrated food residue chemistry summary

Nature of the residue in laying hen	PMRA# 2957852
Species and Numbers	5 laying hens per radiolabel (*Gallus gallus)*/Hy-Line Layer
Radiolabel position	[Ph-^{14}C]-Fluazaindolizine 0.95 MBq/mg [IP-2-^{14}C]-Fluazaindolizine: 0.98 MBq/mg
Average dose	[Ph-^{14}C]-Fluazaindolizine 13.1 ppm [IP-2-^{14}C]-Fluazaindolizine: 13.6 ppm
Treatment Regimen	Gelatin capsule once daily

Study period	14 consecutive days			
Collection time	Eggs: 2/day (morning and evening); Excreta: 1/day			
Tissues collected	Composite muscle and fat, whole liver			
Interval from last dose to sacrifice	6 hours			
Plateau of residues in eggs	The concentration of radioactivity plateaued in whole eggs within 9-13 days from the start of dosing with an average of 0.017 ppm.			
Extraction solvents	Acetonitrile:0.1 M ammonium formate, pH 7 (9:1, v/v)			
Matrices	**[Ph-U-^{14}C]-Fluazaindolizine**		**[IP-2-^{14}C]-Fluazaindolizine**	
	TRRs (ppm)	**% AD**	**TRRs (ppm)**	**% AD**
Excreta (Day 1 to 14)	-	85.9	-	83.8
Cage wash	-	8.1	-	9.1
Composite muscle	0.043	<0.1	0.047	<0.1
Composite fat	0.020	<0.1	0.027	<0.1
Liver	0.732	0.6	0.701	0.6
Whole eggs (Day 9 to 13)	0.017	<0.1	0.016	<0.1
Summary of major identified metabolites in hen matrices				
Radiolabel position	[Ph-U-^{14}C]-Fluazaindolizine and [IP-2-^{14}C]-Fluazaindolizine			
Metabolites identified	Major Metabolites			
Whole eggs	Fluazaindolizine; IN-RYC33			
Liver	Fluazaindolizine			
Composite muscle	Fluazaindolizine			
Composite fat	Fluazaindolizine			
Nature of the residue in laying hen			**PMRA# 2958071**	
Species and Numbers	5 laying hens (*Gallus gallus)*/Novogen Brown			
Radiolabel position	[IP-2-^{14}C]-IN-QEK31: 0.46 MBq/mg			
Average dose	[IP-2-^{14}C]-IN-QEK31: 9.96 ppm			
Treatment Regimen	Gelatin capsule once daily			
Study period	14 consecutive days			
Collection time	Eggs: 2/day (morning and evening); Excreta: 1/day			
Tissues collected	Composite muscle and fat, whole liver			
Interval from last dose to sacrifice	6 hours			
Plateau of residues in eggs	The concentration of radioactivity in whole eggs reached a maximum of 0.006 ppm within 5 days post first dose and fluctuated between 0.004–0.006 ppm, thereafter.			
Extraction solvents	Acetonitrile:0.1 M ammonium formate, pH 7 (9:1, v/v)			
Matrices	**[IP-2-^{14}C]-IN-QEK31**			
	TRRs (ppm)		**% AD**	
Excreta (Day 1–14)	N/A		93.2	
Cage wash	N/A		7.5	
Whole eggs	0.003		<0.1	
Liver	0.014		<0.1	
Composite muscle	<0.001		<0.1	

Composite fat	<0.001	<0.1
G.I. Tract Contents	N/A	0.2
Radioactive residues in composite whole egg, muscle and fat samples were <0.01 ppm and metabolite profiling of these tissues was not conducted.		
Summary of major identified metabolites in hen matrices		
Radiolabel position	[IP-2-^{14}C]-IN-QEK31	
Metabolites identified	Major Metabolites	
Liver	IN-QEK31	
Nature of the residue in lactating goat		**PMRA# 2957853**
Species and Numbers	Saanen/Toggenburg cross breed; two goats	
Radiolabel position	[Ph-^{14}C]-Fluazaindolizine: 0.88 MBq/mg [IP-2-^{14}C]-Fluazaindolizine: 1.14 MBq/mg	
Average dose	[Ph-^{14}C]-Fluazaindolizine : 12.2 ppm [IP-2-^{14}C]-Fluazaindolizine: 11.8 ppm	
Treatment Regimen	Once orally by gelatin capsule	
Study period	7 consecutive days	
Collection time	Milk: 2/day (morning and evening); Excreta: 1/day	
Tissues collected	Whole liver, both kidneys, composite muscle and fat	
Interval from last dose to sacrifice	6 hours	
Plateau of residues in milk	TRRs reached a plateau within 3 days in milk from the goats dosed with either [Ph-^{14}C]-Fluazaindolizine (0.05–0.06 ppm) or [IP-2-^{14}C]-Fluazaindolizine (0.04–0.05 ppm).	
Extraction solvents	Acetonitrile:0.1 M ammonium formate, pH 7 (9:1, v/v)	

Matrices	**[Ph-U-^{14}C]-Fluazaindolizine**		**[IP-2-^{14}C]-Fluazaindolizine**	
	TRRs (ppm)	**% AD**	**TRRs (ppm)**	**% AD**
Feces	N/A	50.6	N/A	52.3
Urine	N/A	32.9	N/A	21.3
Cage wash	N/A	3.3	N/A	1.5
G.I. tract contents	N/A	14.5	N/A	13.2
G.I. tract	N/A	2.9	N/A	2.7
Bile	2.149	2.9	3.397	4.8
Milk (Day 4–6)	0.057	0.1	0.047	<0.1
Liver	0.222	0.3	0.275	0.4
Kidney	0.358	0.5	0.357	0.5
Composite muscle	0.012	<0.1	0.011	<0.1
Composite fat	0.015–0.028	<0.1	0.009–0.014	<0.1

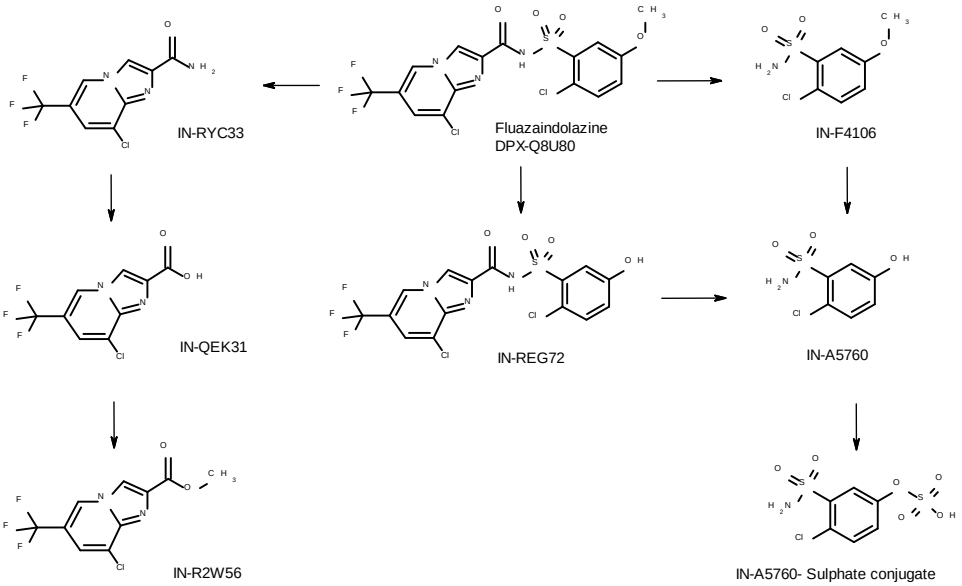
Summary of major identified metabolites in goat matrices	
Radiolabel position	[Ph-^{14}C]- and [IP-2-^{14}C]-Fluazaindolizine
Metabolites identified	Major metabolites
Milk	Fluazaindolizine
Liver	Fluazaindolizine; IN-QEK31; IN-REG72; IN-F4106
Kidney	Fluazaindolizine; IN-QEK31
Composite muscle	Fluazaindolizine; IN-F4106

Composite fat	Fluazaindolizine	
Nature of the residue in lactating goat		**PMRA# 2958040**
Species and Numbers	Saanen/Alpine cross breed; one goat	
Radiolabel position	[IP-2-^{14}C]-IN-QEK31: 0.62 MBq/mg	
Average dose	12.5 ppm in the diet	
Treatment Regimen	Once orally by gelatin capsule	
Study period	5 consecutive days	
Collection time	Milk: 2/day (morning and evening); Excreta: 1/day	
Tissues collected	Whole liver, both kidneys, composite muscle and fat	
Interval from last dose to sacrifice	6 hours	
Plateau of residues in milk	Radioactivity in milk reached plateau within 5 days post first dose 0.005 ppm.	
Extraction solvents	Acetonitrile: 0.1 M ammonium formate, pH 7 (9:1, v/v)	
Matrices	**[IP-2-^{14}C]-IN-QEK31**	
	TRRs (ppm)	**% AD**
Feces	N/A	14.4
Urine	N/A	57.1
Cage wash	N/A	1.7
Milk (Day 1–5)	0.168	2.1
Liver	0.035	<0.1
Kidneys	0.282	<0.1
Composite muscle	<0.001	<0.1
Composite fat	0.002–0.046	<0.1
G.I. Tract Contents	N/A	11.8
Summary of major identified metabolites in goat matrices		
Radiolabel position	[IP-2-^{14}C]-IN-QEK31	
Metabolites identified	Major metabolites	
Milk	IN-QEK31	
Liver	IN-QEK31	
Kidney	IN-QEK31	
Composite fat	IN-QEK31; IN-R2W56	
Nature of the residue in lactating goat		**PMRA# 2958061**
Species and Numbers	Saanen/Toggenburg cross breed; one goat	
Radiolabel position	[Ph-^{14}C]-IN-RSU03: 0.95 MBq/mg	
Average dose	10.9 ppm in diet	
Treatment Regimen	Once orally by gelatin capsule	
Study period	5 consecutive days	
Collection time	Milk: 2/day (morning and evening); Excreta: 1/day	
Tissues collected	Whole liver, both kidneys, composite muscle and fat	
Interval from last dose to sacrifice	6 hours	
Plateau of residues in milk	Radioactivity reached a plateau in milk within 3 days at 0.008 ppm.	
Extraction solvents	Acetonitrile: 0.1 M ammonium formate, pH 7 (9:1, v/v)	

Matrices	[Ph-^{14}C]-IN-RSU03	
	TRRs (ppm)	**% AD**
Feces	N/A	43.7
Urine	N/A	34.5
Cage wash	N/A	2.2
Milk (Day 1–5)	0.008	<0.1
Liver	0.021	<0.1
Kidney	0.220	<0.1
Composite muscle	0.002	<0.1
Composite fat	0.001–0.003	<0.1
G.I. Tract Contents	N/A	17.9
Summary of major identified metabolites in goat matrices		
Radiolabel position	[Ph-^{14}C]-IN-RSU03	
Metabolites identified	Major metabolites	
Milk	IN-F4106	
Liver	IN-RSU03	
Kidney	IN-RSU03	
Composite muscle	IN-RSU03; IN-F4106	
Composite fat	IN-RSU03; IN-F4106	
Nature of the residue in lactating goat		**PMRA# 2958093**
Species and Numbers	Saanen/Toggenburg cross breed; one goat	
Radiolabel position	[Ph-^{14}C]-IN-QZY47: 1.65 MBq/mg	
Average dose	10.1 ppm in diet	
Treatment Regimen	Once orally by gelatin capsule	
Study period	5 consecutive days	
Collection time	Milk: 2/day (morning and evening); Excreta: 1/day	
Tissues collected	Whole liver, both kidneys, composite muscle and fat	
Interval from last dose to sacrifice	6 hours	
Plateau of residues in milk	Radioactivity reached a plateau in milk within 1 day at 0.016 ppm.	
Extraction solvents	Acetonitrile:0.1 M ammonium formate, pH 7 (9:1, v/v)	
Matrices	**[Ph-^{14}C]-IN-QZY47**	
	TRRs (ppm)	**% AD**
Feces	N/A	7.2
Urine	N/A	75.1
Cage wash	N/A	1.4
Milk (Day 1-5)	0.018	0.2
Liver	0.354	<0.1
Kidney	0.824	<0.1
Composite muscle	0.057	<0.1
Composite fat	0.034–0.050	<0.1
G.I. Tract Contents	N/A	2.5
Summary of major identified metabolites in goat matrices		
Radiolabel position	[Ph-^{14}C]-IN-QZY47	

Metabolites identified	Major metabolites
Milk	IN-A5760 sulfate; IN-F4106
Liver	IN-A5760 glutathione; IN-A5760; IN-F4106
Kidney	IN-A5760-glucuronide; IN-F4106
Composite muscle	IN-F4106
Composite fat	IN-F4106; IN-A5760-glucuronide

Proposed metabolic scheme in livestock



Freezer storage stability in animal matrices			
Tested matrices	**Analyte**	**Storage interval (days)**	**Interval of demonstrated storage stability (days)**
Whole milk	Fluazaindolizine	125	206
Muscle		83	200
Liver		9	23
Kidney		134	250
Fat		93	255

LIVESTOCK FEEDING – Dairy cattle	**PMRA# 2958045**

Lactating dairy cows were administered fluazaindolizine via gelatin capsule at dose levels of 2.28 ppm, 6.68 ppm and 20.28 ppm for 28 consecutive days. Animals were sacrificed approximately 22–24 hours after the last dose. A depuration study was conducted using the 19.60 ppm feeding level and selected animals were sacrificed at 1, 2, and 5 days after the last dose. Residues of fluazaindolizine declined to <0.01 ppm in whole milk by Day-31 after the last administered dose (Day-28) of fluazaindolizine to dairy cattle. Residues of metabolites IN-A5760, IN-R2W56, IN-REG72, and IN-RYC33 were non-detectable in all milk and tissue samples.

Commodity / Collection day	Feeding level (ppm)	Highest residues (ppm)			Mean residues (ppm)		
		Fluazaindolizine	IN-F4106	IN-QEK31	Fluazaindolizine	IN-F4106	IN-QEK31
			As parent equivalents			As parent equivalents	
Whole milk/28	2.28	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
	6.68	0.022	<0.010	<0.010	0.020	<0.010	<0.010
	20.28	0.101	<0.010	<0.010	0.079	<0.010	<0.010
Composite fat/28	2.28	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
	6.68	0.022	<0.010	<0.010	0.020	<0.010	<0.010
	20.28	0.054	<0.010	<0.010	0.035	<0.010	<0.010
Composite muscle/28	2.28	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
	6.68	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
	20.28	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
Liver/28	2.28	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
	6.68	0.023	<0.010	<0.010	0.021	<0.010	<0.010
	20.28	0.078	<0.010	<0.010	0.061	<0.010	<0.010
Kidney/28	2.28	0.027	<0.010	<0.010	0.022	<0.010	<0.010
	6.68	0.096	<0.010	<0.010	0.091	<0.010	<0.010
	20.28	0.286	0.025	0.028	0.215	0.015	0.022

Another four dairy cows were divided into two groups (treatment; depuration) and dosed with IN-QEK31 at a single dose rate (19.46 ppm) for 28 consecutive days. The depuration study indicated that dairy cattle administered IN-QEK31 (18.5 ppm) had residues of IN-QEK31 <0.01 ppm in whole milk by Day-30. Residues of metabolites IN-A5760, IN-F4106, IN-R2W56, IN-REG72, and IN-RYC33 were non-detectable in all milk and tissue samples.

Commodity / Collection day	Feeding level (ppm)	IN-QEK31, expressed as parent equivalents	
		Highest residues (ppm)	Mean residues (ppm)
Whole milk/28	19.46	0.380	0.359
Liver/28		0.030	<0.025
Kidney/28		0.336	0.227
Composite muscle/28		<0.010	<0.010
Composite fat/28		<0.010	<0.010

Anticipated residues in animal matrices

Matrices	Residue definition	Dietary burden (ppm)	Anticipated residues of Fluazaindolizine (ppm)
Beef/Dairy Cattle			
Whole milk	Fluazaindolizine	0.23	0.001

Fat			0.001
Liver			0.001
Kidney			0.003
Muscle			0
Swine			
Fat	Fluazaindolizine	0.01	0
Liver			0
Kidney			0
Muscle			0

Anticipated residues in poultry matrices

A request to waive the feeding study was provided based on the low dietary burden. Therefore, the hen metabolism study was used to estimate the anticipated residues in the relevant poultry matrices.

Matrices	Residue definition	Dietary burden (ppm)	Hen metabolism feeding level (ppm)	Anticipated residues of Fluazaindolizine (ppm)
Whole eggs	Fluazaindolizine	0.01	13.6	9.6E-06
Fat				1.3E-05
Liver				5.0E-04
Composite muscle				3.4E-04

NATURE OF THE RESIDUE IN CARROTS		**PMRA# 2957871**
Radiolabel Position	[Ph-U-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine (specific activity: 0.92 MBq/mg)	
Treatment		
Test Crop	Carrots; *Daucus carota* cv. F1 Bangor	
Test Site	In individual pots in greenhouse	
Treatment	Two soil drench applications	
Total Rate	[Ph-U-^{14}C]-Fluazaindolizine and [IP-5,8a-^{14}C]-Fluazaindolizine: 2.0 kg a.i./ha	
Formulation	Suspension concentrate (SC) formulation of fluazaindolizine (guarantee: 67%)	
Preharvest intervals (days)	Carrot foliage	30 days after 1st application
	Immature carrot roots and foliage	43
	Mature carrot roots and foliage	63
Extraction solvent	Methanol:water (7:3, v/v)	

Matrices	PHI (days)	[Ph-^{14}C]-Fluazaindolizine	[IP-5,8a-^{14}C]-Fluazaindolizine
		TRR (ppm)	TRR (ppm)
Carrot tops	30 days after application one	4.435	3.170
	43	0.659	0.278
	63	1.174	0.382
Carrot roots	43	0.135	0.073
	63	0.104	0.068

Summary of major identified metabolites in carrot matrices			
Radiolabel position	[Ph-U-^{14}C]- and/or [IP-5,8a-^{14}C]-Fluazaindolizine		
Metabolites identified	Major Metabolites		
Carrot tops [PHI = 63d]	Fluazaindolizine; malonyl conjugate of IN-RSU03; IN-QEK31; IN-RSU03; IN-RYC33		
Carrot roots [PHI = 63d]	Fluazaindolizine; malonyl conjugate of IN-RSU03; IN-QEK31; IN-RSU03; malonyl conjugate of IN-QZY47 (IN-TUT81)		
NATURE OF THE RESIDUE IN POTATOES			**PMRA# 2958070**
Radiolabel Position	[Ph-U-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine (specific activity: 1.4 MBq/mg)		
Treatment			
Test Crop	Potatoes; *Solanum tuberosum* cv. Maris Bard		
Test Site	In individual pots in greenhouse		
Treatment	Two soil drench applications		
Total Rate	[Ph-U-^{14}C]-Fluazaindolizine and [IP-5,8a-^{14}C]-Fluazaindolizine: 2.0 kg a.i./ha		
Formulation	Suspension concentrate (SC) formulation of fluazaindolizine (guarantee: 40%)		
Preharvest intervals (days)	Immature potato foliage	15, 35	
	Mature potato foliage	70	
	Immature potato tubers	35	
	Mature potato tubers	70	
Extraction solvent	Methanol:water (7:3, v/v)		

Matrices	**PHI (days)**	**[Ph-^{14}C]-Fluazaindolizine**	**[IP-5,8a-^{14}C]-Fluazaindolizine**
		TRR (ppm)	**TRR (ppm)**
Potato foliage	15	0.277	0.072
	35	0.796	0.159
	70	5.052	0.775
Potato tubers	35	0.085	0.043
	70	0.126	0.069

Summary of major identified metabolites in potato matrices		
Radiolabel Position	[Ph-U-^{14}C]- and/or [IP-5,8a-^{14}C]-Fluazaindolizine	
Metabolites Identified	Major Metabolites	
Potato foliage [PHI = 70d]	IN-QEK31	
Potato tubers [PHI = 70d]	IN-QZY47; IN-QEK31; glucose conjugate of IN-RSU03; glucose conjugate of IN-UNS90	
NATURE OF THE RESIDUE IN TOMATOES		**PMRA# 2957870**
Radiolabel Position	[Ph-U-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine (specific activity: 0.9 MBq/mg)	
Treatment		
Test Crop	Tomatoes; *Lycopersicon esculentum* cv. Red Alert	
Test Site	In individual pots in greenhouse	
Treatment	Two soil drench applications	
Total Rate	[Ph-U-^{14}C]-Fluazaindolizine and [IP-5,8a-^{14}C]-Fluazaindolizine: 1.9 kg a.i./ha	
Formulation	Suspension concentrate (SC) formulation of fluazaindolizine (guarantee: 40%)	

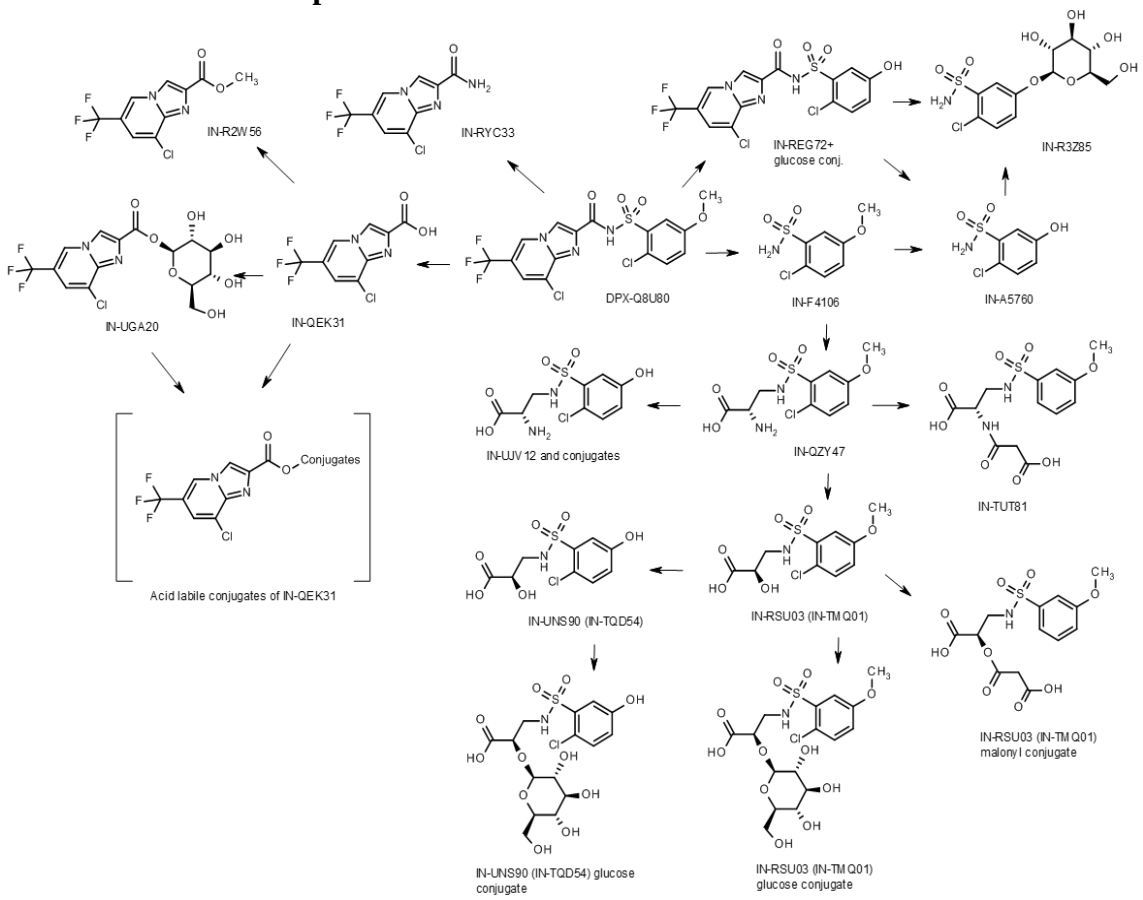
Preharvest intervals (days)	Tomato foliage	41, 50, 62		
	Tomato fruits	41 (early ripeness), 50 (medium ripeness), 62 (full ripeness)		
Extraction solvent	Methanol:water (7:3, v/v)			
Matrices	**PHI (days)**		**[Ph-^{14}C]-Fluazaindolizine**	**[IP-5,8a-^{14}C]-Fluazaindolizine**
			TRR (ppm)	**TRR (ppm)**
Tomato fruit	41		0.071	0.029
	50		0.079	0.029
	62		0.065	0.038
Tomato foliage	41		4.232	0.577
	50		5.743	0.918
	62		1.856	0.437
Summary of major identified metabolites in tomato matrices				
Radiolabel position	[Ph-U-^{14}C]- and/or [IP-5,8a-^{14}C]-Fluazaindolizine			
Metabolites identified	Major metabolites			
Tomato fruit [PHI = 62d]	IN-UGA20; IN-R3Z85; IN-A5760; glucose conjugate of IN-RSU03			
Tomato foliage [PHI = 62d]	IN-QEK31; IN-UGA20; glucose conjugate of IN-RSU03			
NATURE OF THE RESIDUE IN SOYBEANS				**PMRA# 2957872**
Radiolabel Position	[Ph-U-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine (specific activity: 1.4 MBq/mg)			
Treatment				
Test Crop	Soybeans, Glycine max: Elena			
Test Site	In individual pots in greenhouse			
Treatment	One soil drench application			
Total Rate	[Ph-U-^{14}C]-Fluazaindolizine and [IP-5,8a-^{14}C]-Fluazaindolizine: 1.0 kg a.i./ha			
Formulation	Suspension concentrate (SC) formulation of fluazaindolizine (guarantee: 40%)			
Preharvest intervals (days)	Soybean forage, hay, and seeds	48, 75, 112		
Extraction solvent	Methanol:water (7:3, v/v)			
Matrices	**PHI (days)**		**[Ph-^{14}C]-Fluazaindolizine**	**[IP-5,8a-^{14}C]-Fluazaindolizine**
			TRR (ppm)	**TRR (ppm)**
Soybean forage	48		0.435	0.764
Soybean hay	75		0.660	1.043
Soybean seed	112		0.271	2.018
Summary of major identified metabolites in soybean matrices				
Radiolabel position	[Ph-U-^{14}C]- and/or [IP-5,8a-^{14}C]-Fluazaindolizine			
Metabolites identified	Major Metabolites			
Soybean forage [PHI = 48d]	IN-TUT81; IN-QEK31; IN-UGA20			
Soybean hay [PHI = 75d]	IN-TUT81; IN-QEK31; IN-UGA20			
Soybean seeds [PHI = 112d]	Fluazaindolizine; IN-TUT81; IN-QEK31			

NATURE OF THE RESIDUE IN SUGARCANE			**PMRA# 2958039**
Radiolabel position	[Ph-U-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine (specific activity: 1.4 MBq/mg)		
Treatment			
Test crop	Sugarcane; *Saccharum officinarum* cv. NC0310		
Test site	In individual pots in greenhouse		
Treatment	One soil drench application		
Total rate	[Ph-U-^{14}C]-Fluazaindolizine and [IP-5,8a-^{14}C]-Fluazaindolizine: 1.0 kg a.i./ha		
Formulation	Suspension concentrate (SC) formulation of fluazaindolizine		
Preharvest intervals (days)	Immature sugarcane foliage (BBCH 32)	51	
	Mature sugarcane foliage and cane	231	
Extraction solvent	Methanol:water (7:3, v/v)		

Matrices	**PHI (days)**	**[Ph-^{14}C]-Fluazaindolizine**	**[IP-5,8a-^{14}C]-Fluazaindolizine**
		TRR (ppm)	**TRR (ppm)**
Sugarcane foliage	51	0.162	0.087
	231	0.069	0.121
Sugarcane cane	231	0.020	0.052

Summary of major identified metabolites in sugarcane matrices	
Radiolabel position	[Ph-U-^{14}C]- and/or [IP-5,8a-^{14}C]-Fluazaindolizine
Metabolites identified	Major Metabolites
Sugarcane cane [PHI = 231d]	IN-R3Z85; glucose conjugate of IN-RSU03; IN-QEK31; IN-UGA20
Sugarcane foliage [PHI = 231d]	IN-R2W56; IN-UNS90; glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03

Proposed metabolic scheme in plants



Freezer storage stability in plant matrices at -20 °C

Fluazaindolizine residues are stable in the five crop commodity categories (high water, high starch, high protein, high oil, and high acid) for at least 24 months, therefore, freezer storage stability can be assumed for all crops, including processed commodities. In dry commodities, residues of fluazaindolizine are stable for at least 23 months. There are acceptable freezer storage stability data in plant matrices to support the frozen storage intervals observed in the magnitude of the residue, processing and field accumulation trials. No correction to residues due to in-storage dissipation is required for crop field trial, processed and field accumulation samples.

Tested matrices	Category	Analyte	Tested intervals (months)	Demonstrated freezer storage stability (months)
Tomatoes	High water	Fluazaindolizine	0, 3, 6, 12, 18, 24, 34	34
Dry pea seed	High protein		0, 3, 6, 12, 18, 24	24
Wheat grain	High starch		0, 3, 6, 12, 18, 24	24
Soybean seed	High oil		0, 3, 6, 12, 18, 24, 33	24
Oranges	High acid		0, 3, 6, 12, 18, 24	24
Field corn stover	Dry		0, 3, 6, 12, 18, 24	24
Pea hay	Dry		0, 0.25, 1, 3, 6, 12, 18, 23	23

Crop field trials and residue decline on carrots	**PMRA# 2958068**

Eleven (11) field trials were conducted in the United States and Canada during the 2015–2016 growing seasons. Trials were conducted in North American Free Trade Agreement (NAFTA) growing region 1 (NS; 1 trial), 3 (FL; 1 trial), 5 (IA, OH, and ON; 3 trials, QC; 1 trial), 6 (TX; 1 trial), 10 (CA; 3 trials), and 11 (ID; 1 trial). The number and geographic distribution of trials exceed the requirements outlined in Health Canada's DIR2010-05. All trials were considered independent. Fluazaindolizine SC (500 g/L) was applied either once at 2.19–2.30 kg a.i./ha as an in-furrow spray at planting, or twice at 1.07–1.17 kg a.i./ha/application with a retreatment interval of 13–14 days as an in-furrow spray at planting followed by a soil directed spray over the top of the row for a seasonal application rate of 2.2–2.3 kg a.i./ha. Carrot samples were harvested at a minimum of 79 days (1 soil application) and 65 days (2 soil applications) following application. There was no clear trend of decline for residues of fluazaindolizine in carrots. Carrot samples were stored for a maximum of 6 months from harvest to analysis, which is covered by the freezer storage stability interval of 24 months for high starch commodities. Samples were analyzed using a validated analytical method.

Crop	**Total rate (kg a.i./ha)**	**PHI**	**(days)**	**Fluazaindolizine residue levels (ppm)**					
				n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
1 soil application at planting									
Mature carrots	2.19–2.30	**S2**	**79–145**	**11**	**<0.010**	**0.035**	**<0.010**	**0.013**	**0.008**
		S3	83–149	11	<0.010	0.023	<0.010	0.011	0.004
		S4	88–154	11	<0.010	0.035	<0.010	0.012	0.008
		S5	93–159	11	<0.010	0.027	<0.010	0.012	0.005
		S6	98–164	11	<0.010	0.012	<0.010	0.010	0.001
		S7	103–168	11	<0.010	0.013	<0.010	0.010	0.001
2 soil applications: 1 soil at planting followed by 1 soil at RTI of 14±1 days									
Mature carrots	2.20–2.30	S2	65–131	11	<0.010	0.017	<0.010	0.011	0.002
		S3	69–135	11	<0.010	0.012	<0.010	0.010	0.001
		S4	74–140	11	<0.010	0.027	<0.010	0.012	0.005
		S5	79–145	11	<0.010	0.022	<0.010	0.011	0.004
		S6	84–150	11	<0.010	0.011	<0.010	0.010	0
		S7	89–154	11	<0.010	<0.010	<0.010	<0.010	0

n = number of independent trials; For computation, values <LOQ are assumed to be at the LOQ.
Bolded input indicates interval used for MRL calculations.

Crop field trials and residue decline on potatoes	**PMRA# 2958069**

Twenty one (21) field trials were conducted in the United States and Canada during the 2015-2016 growing seasons. Trials were conducted in North American Free Trade Agreement (NAFTA) growing region 1 (PA and NY; 3 trials; NS and PI; 4 trials), 2 (NJ; 1 trial), 3 (FL; 1 trial), 5 (IL, MN, and ON; 3 trials; QC; 1 trial), 7 (SK; 1 trial), 10 (CA; 1 trial), 11 (CA, ID, and WA; 5 trials), and 14 (MB; 1 trial). Some of the potato trials were determined to be replicates, and as such, residues were averaged, which is reflected in the trial count. The number and geographic distribution of trials exceed the requirements outlined in Health Canada's DIR2010-05 with the exception of region 7A, where no trials were conducted. Fluazaindolizine SC (500 g/L) was applied either once at 2.15–2.32 kg a.i./ha as an in-furrow spray at planting, or twice at 1.09-1.18 kg a.i./ha/application with a retreatment interval of 13–14 days as an in-furrow spray at planting followed by a soil directed spray over the top of the row for a seasonal application rate of 2.2–2.3 kg a.i./ha. Potato samples were harvested at a minimum of 53 days (1 soil application) and 39 days (2 soil applications) following the last application. There was no clear trend of decline for residues of fluazaindolizine in potatoes. Potato samples were stored for a maximum of 16 months from harvest to analysis, which is covered by the freezer storage stability interval of 24 months for high starch commodities. Samples were analyzed using a validated analytical method.

Crop	**Total rate (kg a.i./ha)**	**Sampling interval**	**PHI (days)**	**Fluazaindolizine residue levels (ppm)**					
				n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
1 soil application at planting									
Potato tubers	2.15–2.32	S1	53–143	21	<0.010	0.104	0.017	0.027	0.024
		S2	58–147	21	<0.010	0.070	0.014	0.021	0.016
		S3	63–152	21	<0.010	0.089	0.012	0.021	0.020
		S4	68–157	21	<0.010	0.065	0.013	0.019	0.014
		S5	73–161	20	<0.010	0.073	0.012	0.020	0.018
		S6	**78–166**	**20**	**<0.010**	**0.160**	**0.011**	**0.025**	**0.034**
2 soil applications: 1 soil at planting followed by 1 soil application									
Potato tubers	2.20–2.30	S1	39–129	20	<0.010	0.039	0.012	0.016	0.008
		S2	44–133	20	<0.010	0.040	<0.010	0.016	0.009
		S3	49–138	20	<0.010	0.051	<0.010	0.015	0.010
		S4	54–143	20	<0.010	0.053	<0.010	0.015	0.011
		S5	59–147	19	<0.010	0.044	<0.010	0.016	0.009
		S6	64–152	19	<0.010	0.057	<0.010	0.017	0.013

n = number of independent trials; For computation, values <LOQ are assumed to be at the LOQ.
Bolded input indicates interval used for MRL calculations.

Crop field trials and residue decline on fruiting vegetables	PMRA# 2957997

Nine (9) trials were conducted with bell peppers in North American Free Trade Agreement (NAFTA) growing region 2 (GA; 1 trial), 3 (FL; 1 trial), 5 (IA and ON; 3 trials, QC; 1 trial), 6 (TX; 1 trial), and 10 (CA; 2 trials); nine (9) trials were conducted with non-bell peppers in regions 2 (GA; 1 trial), 5 (ON; 3 trials, QC; 2 trials), 8 (TX; 1 trial), and 10 (AZ and CA; 2 trials); and twenty (20) trials were conducted with tomatoes (small and large varieties) in region 1 (PA; 1 trial), 2 (GA; 2 trials), 3 (FL; 2 trials), 5 (IA, NE, ON, WI; 6 trials, QC; 2 trials), and 10 (AZ and CA; 7 trials). Some of the tomato and bell pepper trials were determined to be replicates, and as such, residues were averaged, which is reflected in the trial count. The number and geographic distribution of trials exceed the requirements outlined in Health Canada's DIR2010-05. Fluazaindolizine SC (500 g/L) was applied once at 1.12–1.13 kg a.i./ha at planting (drip/drench/spray) followed by 2 soil applications at 0.55–0.57 kg a.i./ha with a retreatment interval of 11-105 days, for a seasonal application rate of 2.22–2.25 kg a.i./ha. At a second treatment plot, four applications were made each at 0.55–0.57 kg a.i./ha/application for a total of 2.19–2.26 kg a.i./ha. Fruiting vegetable samples were harvested at a minimum of 0 to 1 day following 3 or 4 soil applications. Residues of fluazaindolizine declined to <LOQ in tomatoes, bell peppers, and nonbell peppers with increasing PHIs. Tomato and pepper samples were stored for a maximum of 23 months from harvest to analysis, which is covered by the freezer storage stability interval of 34 months for high water commodities. Samples were analyzed using a validated analytical method.

Crop	Total rate (kg a.i./ha)	Sampling interval	PHI (days)	Fluazaindolizine residue levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
3 soil applications: 1 soil at planting followed by 2 soil applications									
Tomatoes	2.23–2.25	**S1**	**0–1**	**20**	**<0.010**	**0.067**	**<0.010**	**0.013**	**0.013**
		S2	6–8	20	<0.010	0.013	<0.010	0.010	0.001
		S3	13–15	20	<0.010	<0.010	<0.010	<0.010	0
		S4	20–22	20	<0.010	<0.010	<0.010	<0.010	0
		S5	27–30	20	<0.010	<0.010	<0.010	<0.010	0
		S6	32–37	19	<0.010	<0.010	<0.010	<0.010	0
Bell peppers	2.22–2.25	**S1**	**1**	**9**	**<0.010**	**<0.018**	**<0.010**	**0.011**	**0.003**
		S2	6–8	9	<0.010	<0.010	<0.010	<0.010	0
		S3	13–16	9	<0.010	<0.010	<0.010	<0.010	0
		S4	21–23	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–30	9	<0.010	<0.010	<0.010	<0.010	0
		S6	35–37	9	<0.010	<0.010	<0.010	<0.010	0
Non-bell peppers	2.24	S1	1	9	<0.010	0.012	<0.010	0.010	0.001
		S2	6–7	9	<0.010	<0.010	<0.010	<0.010	0
		S3	14–15	9	<0.010	<0.010	<0.010	<0.010	0
		S4	20–22	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–29	9	<0.010	<0.010	<0.010	<0.010	0
		S6	31–35	8	<0.010	<0.010	<0.010	<0.010	0
4 soil applications									
Tomatoes	2.24–2.26	S1	0–1	20	<0.010	0.019	<0.010	<0.010	0.002
		S2	6–8	20	<0.010	0.025	<0.010	0.011	0.003
		S3	13–15	20	<0.010	<0.010	<0.010	<0.010	0
		S4	20–22	20	<0.010	<0.010	<0.010	<0.010	0
		S5	27–30	20	<0.010	<0.010	<0.010	<0.010	0
		S6	32–37	19	<0.010	<0.010	<0.010	<0.010	0

Bell peppers	2.19–2.25	S1	1	9	<0.010	0.011	<0.010	0.010	0
		S2	6–8	9	<0.010	0.010	<0.010	<0.010	0
		S3	13–16	9	<0.010	<0.010	<0.010	<0.010	0
		S4	21–23	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–30	9	<0.010	<0.010	<0.010	<0.010	0
		S6	35–37	9	<0.010	<0.010	<0.010	<0.010	0
Non-bell peppers	2.24	**S1**	**1**	**9**	**<0.010**	**0.027**	**<0.010**	**0.012**	**0.006**
		S2	6-7	9	<0.010	<0.010	<0.010	<0.010	0
		S3	14–15	9	<0.010	<0.010	<0.010	<0.010	0
		S4	20–22	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–29	9	<0.010	<0.010	<0.010	<0.010	0
		S6	31–35	9	<0.010	<0.010	<0.010	<0.010	0

n = number of independent trials; For computation, values <LOQ are assumed to be at the LOQ.
Bolded input indicates interval used for MRL calculations.

Crop field trials and residue decline on cucurbit vegetables **PMRA# 2957998**

Twenty-nine (29) field trials were conducted in the United States and Canada during the 2014-2015 growing seasons. Nine trials were conducted on cucumbers in North American Free Trade Agreement (NAFTA) growing region 2 (GA: 2 trials), 3 (FL; 1 trial), 5 (IA, IL, NE, ON and QC; 5 trials), and 6 (TX; 1 trial); 11 trials were conducted with muskmelons in region 2 (GA; 1 trial), 5 (IA, IL, ON and QC; 5 trials), 6 (TX; 1 trial), and 10 (AZ and CA; 4 trials); and 9 trials were conducted with summer squash varieties in Region 1 (PA; 1 trial), 2 (GA; 1 trial), 3 (FL; 1 trial), 5 (IA, NE, ON and QC; 4 trials), and 10 (CA; 2 trials). Some of the cucumber, muskmelon and summer squash trials were determined to be replicates, and as such residues were averaged, which is reflected in the trial count. The number and geographic distribution of trials exceed the requirements outlined in Health Canada's DIR2010-05. Fluazaindolizine SC (500 g/L) was applied once as a soil application (drip. drench, spray) at planting at 1.11 kg a.i./ha followed by 2 soil applications at 0.55–0.56 kg a.i./ha with retreatment interval of 27–91 days for a seasonal application rate of 2.22–2.26 kg a.i./ha. Fluazaindolizine SC (500 g/L) was also applied as 4 soil applications of 0.55–0.57 kg a.i./ha with a retreatment interval of 4–24 days for a seasonal application rate of 2.19–2.25 kg a.i./ha. Cucurbit samples were harvested at a minimum of 0 to 1 day following 3 or 4 soil applications. Residues of fluazaindolizine declined with increasing preharvest intervals. Cucumber, summer squash and muskmelon samples were stored for a maximum of 16 months from harvest to analysis, which is covered by the freezer storage stability interval of 34 months for high water commodities. Samples were analyzed using a validated analytical method.

Crop	Total rate (kg a.i./ha)	Sampling interval	PHI (days)		Fluazaindolizine residue levels (ppm)				
				n	LAFT	HAFT	Median	Mean	SDEV
3 soil applications: 1 soil at planting followed by 2 soil applications									
Cucumbers	2.22–2.26	**S1**	**1**	**9**	**<0.010**	**0.067**	**0.011**	**0.020**	**0.020**
		S2	6–8	9	<0.010	0.046	<0.010	0.014	0.012
		S3	14–16	9	<0.010	0.023	<0.010	0.011	0.004
		S4	21–23	8	<0.010	<0.010	<0.010	<0.010	0
		S5	28–30	8	<0.010	<0.010	<0.010	<0.010	0
		S6	34–37	7	<0.010	<0.010	<0.010	<0.010	0
Summer squash	2.24–2.26	**S1**	**0–1**	**9**	**<0.010**	**0.089**	**<0.010**	**0.021**	**0.026**
		S2	6–7	9	<0.010	0.041	<0.010	0.013	0.01
		S3	13–16	9	<0.010	0.022	<0.010	0.011	0.004

		S4	21–23	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–29	9	<0.010	<0.010	<0.010	<0.010	0
		S6	34–36	7	<0.010	<0.010	<0.010	<0.010	0
Muskmelons	2.22–2.25	S1	1–2	10	<0.010	0.014	<0.010	0.010	0.001
		S2	6–7	10	<0.010	<0.010	<0.010	<0.010	0
		S3	13–16	10	<0.010	<0.010	<0.010	<0.010	0
		S4	20–23	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–29	6	<0.010	<0.010	<0.010	<0.010	0
		S6	34–36	5	<0.010	<0.010	<0.010	<0.010	0
4 soil applications									
Cucumbers	2.19–2.25	S1	1	9	<0.010	0.054	<0.010	0.018	0.016
		S2	6–8	9	<0.010	0.046	<0.010	0.016	0.012
		S3	14–16	9	<0.010	0.028	<0.010	0.012	0.006
		S4	21–23	8	<0.010	<0.010	<0.010	<0.010	0
		S5	28–30	8	<0.010	<0.010	<0.010	<0.010	0
		S6	34–37	7	<0.010	<0.010	<0.010	<0.010	0
Summer squash	2.24–2.25	S1	0–1	9	<0.010	0.069	<0.010	0.021	0.022
		S2	6–7	9	<0.010	0.037	<0.010	0.013	0.009
		S3	13–16	9	<0.010	0.016	<0.010	0.011	0.002
		S4	21–23	9	<0.010	<0.010	<0.010	<0.010	0
		S5	28–29	9	<0.010	<0.010	<0.010	<0.010	0
		S6	34–36	7	<0.010	<0.010	<0.010	<0.010	0
Muskmelons	2.19–2.25	**S1**	**1–2**	**11**	**<0.010**	**0.039**	**<0.010**	**0.013**	**0.009**
		S2	6–7	11	<0.010	<0.010	<0.010	<0.010	0
		S3	13–16	11	<0.010	<0.010	<0.010	<0.010	0
		S4	20–23	10	<0.010	<0.010	<0.010	<0.010	0
		S5	28–29	7	<0.010	<0.010	<0.010	<0.010	0
		S6	34–36	5	<0.010	<0.010	<0.010	<0.010	0

n = number of independent trials; For computation, values <LOQ are assumed to be at the LOQ.
Bolded input indicates interval used for MRL calculations.

High-temperature hydrolysis study	**PMRA# 2957879**

The radiolabelled test compounds [Ph-U-^{14}C] and [IP-5,8a-^{14}C]-Fluazaindolizine were used for hydrolysis investigations with a concentration of approximately 10 µg/mL. When fluazaindolizine was subjected to high-temperature hydrolysis conditions (20 and 60 minutes), fluazaindolizine was observed to be hydrolytically stable as no other radiolabeled components were identified.

Processing	**Pasteurization**	**Baking/brewing/boiling**	**Sterilization**
Conditions	**pH 4/90 °C/20 min**	**pH 5/100 °C/60 min**	**pH 6/120 °C/20 min**
Major Identified Metabolites	Fluazaindolizine	Fluazaindolizine	Fluazaindolizine

Processed food and feed – Potatoes, tomatoes, soybeans, wheat, field corn, and strawberries	**PMRA# 2958008, 2958066, 2958067, 2958074, 2958075, 2958076**

Processing studies were conducted using Fluazaindolizine SC (500 g/L) applied at 11.3 kg a.i./ha (fivefold of maximum single seasonal use rate), and approximately 9 kg a.i./ha (fourfold of maximum single seasonal use rate), in/on potatoes, and tomatoes, respectively. Processing trials were also conducted in/on soybeans, wheat, field corn and strawberries at 4.5 kg a.i./ha (twofold of maximum single seasonal use rate) as rotational crops, however, residues of fluazaindolizine were not detected in the RACs of wheat, field corn and strawberries, and as such processing factors could not be determined. Residues of fluazaindolizine did not concentrate in processed commodities for human consumption. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.

RAC	**Processed fractions**	**HAFT [RAC] (ppm)**	**Median processing factor of Fluazaindolizine**	**Anticipated residues of Fluazaindolizine (ppm)**
Potatoes [CSG1C]	Dried flakes	0.160	0.16	0.026
	Chips		0.14	0.022
	French fries (unpeeled)		0.30	0.048
Tomatoes [CSG 8-09]	Paste	0.067	1.0	0.067
	Purée		1.0	0.067
	Dried		1.0	0.067
	Juice		1.0	0.067
Soybeans [CG 6]	Refined oil	0.750	0.56	0.417

Confined accumulation in rotational crops – Spinach, radish, wheat	**PMRA# 2957869**
Radiolabel Position	[Ph-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine:(specific activity: 0.7 MBq/mg)
Treatment	
Test Site	In individual pots in greenhouse
Soil Type	Sandy loam
Treatment	A single application to bare soil. Seeds of wheat, spinach and radish were subsequently sown into the aged soil and grown to maturity.
Plantback Interval (days)	30, 120, 300
Rate	[Ph-^{14}C]-Fluazaindolizine and [IP-5,8a-^{14}C]-Fluazaindolizine: 1.9 kg a.i./ha
Formulation	Suspension concentrate (SC) formulation of fluazaindolizine (guarantee: 40%)
Extraction solvents	Methanol:water (7:3; v/v)

Matrices	**PBI (days)**	**[Ph-^{14}C]-Fluazaindolizine**	**[IP-5,8a-^{14}C]-Fluazaindolizine**
		TRR (ppm)	**TRR (ppm)**
Wheat forage	30	1.165	0.411
	120	0.422	0.198
	300	0.396	0.609
Wheat hay	30	1.433	1.143
	120	0.334	0.377
	300	0.531	0.969

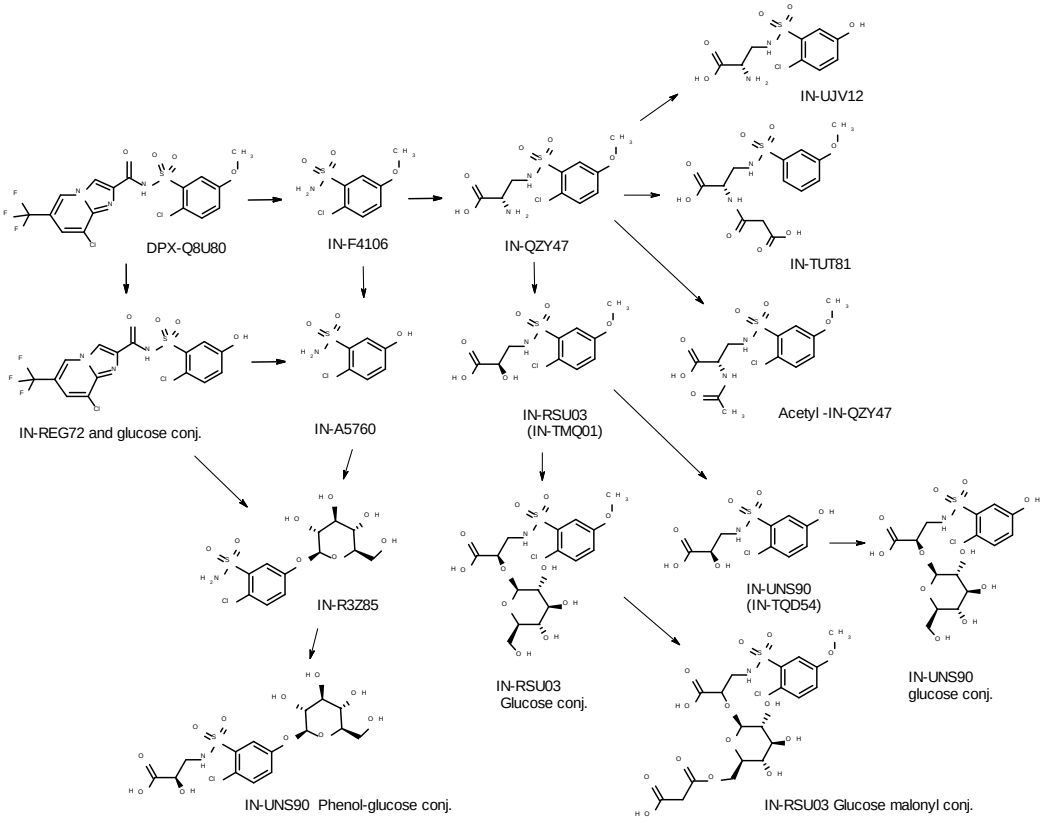
Wheat straw	30	6.873	3.547
	120	2.559	1.357
	300	2.741	4.073
Wheat grain	30	0.086	1.517
	120	0.055	0.521
	300	0.026	1.296
Immature spinach	30	0.254	0.116
	120	0.052	0.018
	300	0.087	0.167
Mature spinach	30	0.647	0.520
	120	0.095	0.043
	300	0.147	0.233
Immature radish foliage	30	0.342	0.329
	120	0.062	0.049
	300	0.056	0.092
Mature radish foliage	30	0.328	0.537
	120	0.054	0.064
	300	0.103	0.200
Mature radish roots	30	0.388	0.277
	120	0.131	0.037
	300	0.054	0.051

Summary of major identified metabolites in rotated crops

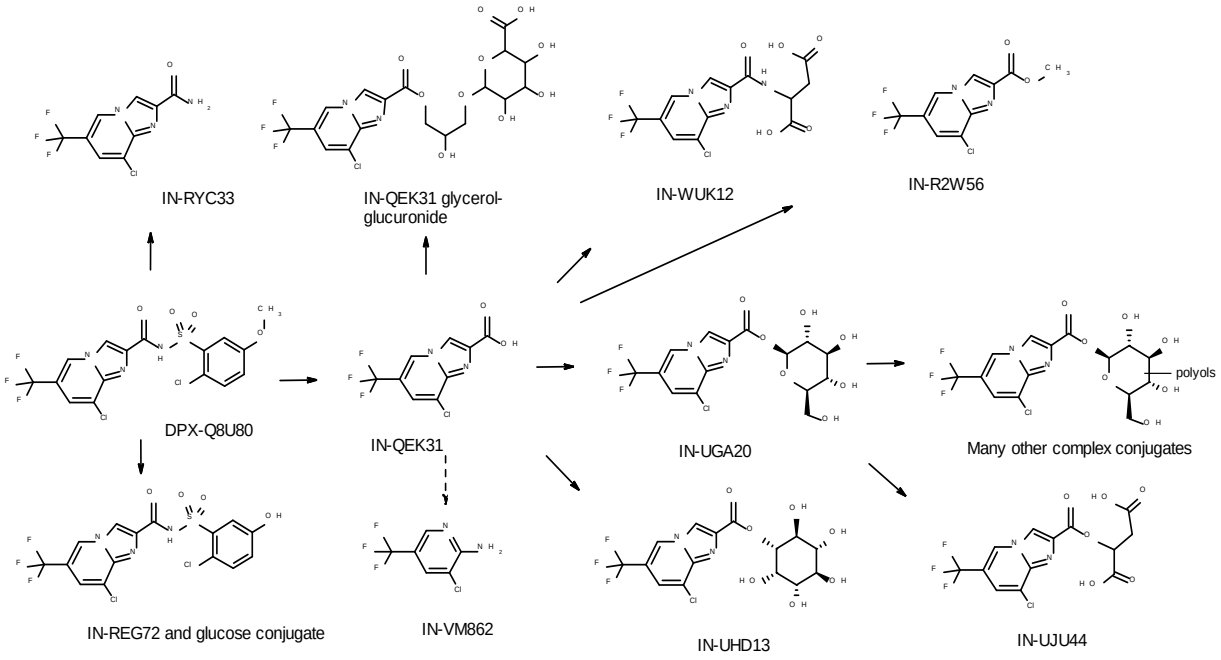
Radiolabel position	[Ph-^{14}C]- and [IP-5,8a-^{14}C]-Fluazaindolizine
Metabolites identified	Major metabolites

Plant-back Intervals (PBI)	1st Rotation (30 day PBI)	2nd Rotation (120 day PBI)	3rd Rotation (300 day PBI)
Immature spinach	Fluazaindolizine; IN-QEK31; IN-TUT81	Glycerol glucuronide conjugate of IN-QEK31; IN-QEK31; IN-TUT81	IN-QEK31; IN-TUT81
Mature spinach	Fluazaindolizine; IN-QEK31; IN-TUT81	Fluazaindolizine; IN-QEK31; IN-TUT81	IN-QEK31; IN-TUT81
Immature radish tops	Glucose conjugate of IN-RSU03; IN-QZY47; IN-QEK31; IN-UJU44	Glucose conjugate of IN-RSU03; IN-QZY47; IN-QEK31; IN-UJU44; glucose conjugate of IN-UNS90	Glucose conjugate of IN-RSU03; IN-QZY47; IN-QEK31; IN-UJU44
Mature radish tops	Fluazaindolizine; glucose conjugate of IN-RSU03; IN-QZY47; IN-QEK31; IN-UJU44; glucose conjugate of IN-UNS90	Glucose conjugate of IN-RSU03; IN-QZY47; IN-QEK31; IN-UJU44; glucose conjugate of IN-UNS90	Glucose conjugate of IN-RSU03; IN-QZY47; IN-QEK31; IN-UJU44; glucose conjugate of IN-UNS90
Mature radish roots	Fluazaindolizine; glucose conjugate of IN-RSU03; IN-QZY47; IN-TUT81; IN-UJU44; IN-UGA20	Fluazaindolizine; glucose conjugate of IN-RSU03; IN-QZY47; IN-TUT81; IN-UJU44	Glucose conjugate of IN-RSU03; IN-QZY47; IN-TUT81; IN-UJU44; IN-UGA20; IN-QEK31
Wheat grain	IN-QEK31	IN-QEK31	IN-QEK31
Wheat straw	IN-UNS90; glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03; IN-QEK31	IN-UNS90; glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03; IN-QEK31	IN-UNS90; glucose conjugate of IN-RSU03; an IN-QEK31
Wheat hay	IN-UNS90; glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03; IN-UGA20; IN-QEK31	Glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03; IN-QEK31	IN-UNS90; glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03; IN-QEK31; IN-QEK31 complex carbohydrate conjugate of IN-QEK31
Wheat forage	IN-UNS90; glucose conjugate of IN-UNS90; IN-QEK31	IN-UNS90; glucose conjugate of IN-UNS90; glucose conjugate of IN-RSU03; IN-QEK31	Glucose conjugate of IN-UNS90; IN-UNS90; IN-QEK31

Proposed metabolic scheme in rotational crops – [Ph-U-^{14}C]-Fluazaindolizine



[IP-5,8a-^{14}C]-Fluazaindolizine



Limited field accumulation - NAFTA	**PMRA# 2957918**

Limited field rotation trials (Tier 2) were conducted for six rotational crops (spinach/leaf lettuce, radish, wheat/sorghum, and soybeans), at three trial sites in the United States (NAFTA Regions 2, 5 and 10), where soil was treated with fluazaindolizine (500 g/L), and rotational crops were planted at three plant-back intervals. At each trial site, bare soil was treated with one dripline application at 1.25 kg a.i./ha (0.5-fold GAP) or with two dripline applications of 1.25 kg a.i./ha with a 60± 10 days retreatment interval for a total of 2.5 kg a.i./ha/season (1.1-fold GAP). Based on the principles of proportionality, residue data from trials conducted at 2.5 kg a.i./ha were scaled to the maximum seasonal application rate of 2.24 kg a.i./ha for primary crops and are reported herein. No adjuvants were used. Residues of fluazaindolizine decreased with increasing PBI, except for soybean hay where residues increased. In general, adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Although some samples were stored for periods outside the range of demonstrated storage stability, it is not expected to impact negatively the overall results of the study. Samples were analyzed using a validated analytical method.

Commodity	**PBI (days)**	**n**	**Scaled fluazaindolizine residue levels (ppm)**		
			LAFT	**HAFT**	**Mean**
Mature spinach/ lettuce	7–30	2	<0.010	<0.010	<0.010
	60–95	2	<0.010	<0.010	<0.010
	270–361	2	<0.010	<0.010	<0.010
Radish tops	7–30	2	<0.010	0.014	0.012
	60–95	2	<0.010	<0.010	<0.010
	270–368	2	<0.010	<0.010	<0.010
Radish roots	7–30	2	<0.010	0.015	0.012
	60–95	2	<0.010	0.012	0.012
	270–368	2	<0.010	<0.010	<0.010
Wheat/ sorghum forage	7–21	2	<0.010	<0.010	<0.010
	57–60	2	<0.010	<0.010	<0.010
	313–361	2	<0.010	<0.010	<0.010
Wheat hay	57	1	<0.010	<0.010	-
	313	1	<0.010	<0.010	-
Wheat/ sorghum grain	7–21	2	<0.010	<0.010	<0.010
	57–60	2	<0.010	<0.010	<0.010
	313–361	2	<0.010	<0.010	<0.010
Wheat/ sorghum straw/stover	7–21	2	<0.010	<0.010	<0.010
	57–60	2	<0.010	0.011	0.011
	313–361	2	<0.010	<0.010	<0.010
Soybean forage	7–17	2	<0.010	<0.010	<0.010
	63–252	2	<0.010	<0.010	<0.010
	303–361	2	<0.010	<0.010	<0.010
Soybean hay	7–17	2	<0.010	0.014	0.012
	63–252	2	<0.010	0.028	0.019
	303–361	2	<0.010	0.021	0.016
Soybean immature seed	7–17	2	<0.010	<0.010	<0.010
	63–252	2	<0.010	<0.010	<0.010
	303–361	2	<0.010	<0.010	<0.010
Dried soybean seed	7–17	2	<0.010	<0.010	<0.010
	63–252	2	<0.010	0.013	0.011
	303–361	2	<0.010	<0.010	<0.010

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ; n = number of independent field trials.

Limited field accumulation - EU	**PMRA# 2957917**

Limited field rotation trials (Tier 2) were conducted on four rotational crops (leaf lettuce, radish, wheat, and beans), at two trial sites, each in North and South Spain, where soil was treated with fluazaindolizine (DPX-Q8U80 500 g/L SC), and rotational crops were planted at three plant-back intervals. At each trial site, bare soil was treated with one dripline application at 1.25 kg a.i./ha (0.5-fold GAP) or with two dripline applications of 1.25 kg a.i./ha with a 60± 10 days retreatment interval for a total of 2.5 kg a.i./ha/season (1.1-fold GAP). Based on the principles of proportionality, residue data from trials conducted at 2.5 kg a.i./ha were scaled to the maximum seasonal application rate of 2.24 kg a.i./ha for primary crops and are reported herein. No adjuvants were used. A decline trend was not established as many of the residues were less than LOQ, with the exception of radish roots, wheat straw and bean hay, which declined by the third PBI. In general, adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Although some samples were stored for periods outside the range of demonstrated storage stability, it is not expected to impact negatively the overall results of the study. Samples were analyzed using a validated analytical method.

Commodity	**PBI (days)**	**n**	**Scaled fluazaindolizine residue levels (ppm)**		
			MIN	**MAX**	**MEAN**
Mature lettuce	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Radish tops	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Radish roots	7–30	2	<0.010	0.016	0.013
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	0.014	0.012
Wheat forage	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Wheat hay	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Wheat grain	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Wheat straw	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	0.013	0.011
	270–365	2	<0.010	<0.010	<0.010
Bean vines	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Bean hay	7–30	2	0.014	0.019	0.017
	60–270	2	0.011	0.012	0.011
	270–365	2	<0.010	0.013	0.012
Immature podded bean seed	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010
Dried bean seed	7–30	2	<0.010	<0.010	<0.010
	60–270	2	<0.010	<0.010	<0.010
	270–365	2	<0.010	<0.010	<0.010

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials.

Extended field accumulation - NAFTA **PMRA# 2957991**

Residue data (2014–2016) were submitted for eight rotational crops (strawberries, tomatoes, carrot, radish, celery, Swiss chard, broccoli, and leaf lettuce), at thirty trial sites in NAFTA Regions (2, 3, 5, and 10), where soil was treated with fluazaindolizine (500 g/L SC) and rotational crops were planted at three plant-back intervals. At each trial site, soil was treated with four applications of 1.12 kg a.i./ha with a 7-day retreatment interval for a total of 4.4–4.7 kg a.i./ha/season (twofold GAP). Based on the principles of proportionality, residue data were scaled to the maximum seasonal application rate of 2.24 kg a.i./ha for primary crops and are reported herein. Adjuvants were used at only 2 of the 30 trials. Crops were harvested at maturity and prepared for residue analysis. A decline trend was not established as many of the residues were less than LOQ, with the exception of celery which declined by the third PBI. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commodity	PBI (days)	n	Scaled fluazaindolizine residue levels (ppm)				
			LAFT	HAFT	Median	Mean	SDEV
Lettuce	7–9	5	<0.010	<0.010	<0.010	<0.010	0
	59–68	5	<0.010	<0.010	<0.010	<0.010	0
	203–378	5	<0.010	<0.010	<0.010	<0.010	0
Broccoli	7	5	<0.010	0.013	<0.010	0.011	0.001
	59–63	5	<0.010	<0.010	<0.010	<0.010	0
	271–369	5	<0.010	<0.010	<0.010	<0.010	0
Radish tops	6–28	2	<0.010	<0.010	-	<0.010	-
	65–68	2	<0.010	<0.010	-	<0.010	-
	365–379	2	<0.010	<0.010	-	<0.010	-
Radish roots	6–28	2	<0.010	<0.010	-	<0.010	-
	65–68	2	<0.010	<0.010	-	<0.010	-
	365–379	2	<0.010	<0.010	-	<0.010	-
Carrot tops	7	3	<0.010	<0.010	<0.010	<0.010	0
	60–63	3	<0.010	<0.010	<0.010	<0.010	0
	270–385	3	<0.010	<0.010	<0.010	<0.010	0
Carrot roots	7	3	<0.010	<0.010	<0.010	<0.010	0
	60–63	3	<0.010	<0.010	<0.010	<0.010	0
	270–385	3	<0.010	<0.010	<0.010	<0.010	0
Celery	7–26	4	<0.010	<0.010	<0.010	<0.010	0
	60–67	3	<0.010	0.020	<0.010	0.013	0.006
	363–378	3	<0.010	<0.010	<0.010	<0.010	0
Swiss chard	9	1	<0.010	<0.010	-	-	-
	67–68	2	<0.010	<0.010	-	<0.010	-
	226–366	2	<0.010	<0.010	-	<0.010	-
Strawberry	7–22	5	<0.010	<0.010	<0.010	<0.010	0
	59–63	5	<0.010	<0.010	<0.010	<0.010	0
	277–365	5	<0.010	<0.010	<0.010	<0.010	0
Tomato	7–12	5	<0.010	<0.010	<0.010	<0.010	0
	60–63	5	<0.010	<0.010	<0.010	<0.010	0
	260–369	5	<0.010	<0.010	<0.010	<0.010	0

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ; n = number of independent field trials.

Extended field accumulation - NAFTA	**PMRA# 2958031**

Residue data (2014–2016) were submitted for four rotational crops (dried peas, soybeans, field corn, and wheat), at five trial sites each in NAFTA Regions (2, 5, 6 and 11), where soil was treated with fluazaindolizine (500 g/L) and rotational crops were planted at three plant-back intervals. At each trial site, crops were treated with 4 applications of 1.12 kg a.i./ha/application at 7-day retreatment interval for a total rate of 4.4–4.5 kg a.i./ha/season (twofold GAP). Based on the principles of proportionality, residue data were scaled to the maximum seasonal application rate of 2.24 kg a.i./ha for primary crops and are reported herein. Adjuvants were used at only 7 trial sites out of 20. Crops were harvested at maturity and prepared for residue analysis. Quantifiable residues of fluazaindolizine declined with increasing plantback intervals, except for wheat straw, whereby residues increased at 60–64 days before decreasing by 365 days. In general, adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Although some samples were stored for periods outside the range of demonstrated storage stability, it is not expected to impact negatively the overall results of the study. Samples were analyzed using a validated analytical method.

Commodity	**PBI (days)**	**n**	**Scaled fluazaindolizine residue levels (ppm)**				
			LAFT	**HAFT**	**Median**	**Mean**	**SDEV**
Field pea vines	7–18	5	<0.010	0.083	<0.010	0.026	0.032
	60–116	5	<0.010	0.011	<0.010	0.010	0.000
	336–399	5	<0.010	<0.010	<0.010	<0.010	0
Field pea hay	7–18	5	0.019	0.403	0.032	0.109	0.165
	60–116	5	<0.010	0.055	0.021	0.025	0.019
	336–399	5	<0.010	0.019	<0.010	0.012	0.004
Immature podded field pea	7–18	5	<0.010	0.095	<0.010	0.027	0.038
	60–116	5	<0.010	<0.010	<0.010	<0.010	0.000
	336–399	5	<0.010	<0.010	<0.010	<0.010	0.000
Dry field pea seeds	7–18	5	<0.010	0.750	0.013	0.164	0.328
	60–81	4	<0.010	0.034	0.018	0.020	0.012
	336–399	5	<0.010	<0.010	<0.010	<0.010	0.000
Soybean forage	6–18	5	<0.010	0.017	<0.010	0.012	0.003
	60–64	5	<0.010	0.011	<0.010	0.010	0.001
	351–365	5	<0.010	<0.010	<0.010	<0.010	0
Soybean hay	6–18	5	<0.010	0.062	0.033	0.033	0.020
	60–64	5	<0.010	0.035	0.013	0.019	0.012
	351–365	5	<0.010	0.023	<0.010	0.013	0.006
Immature podded soybean	6–18	5	<0.010	<0.010	<0.010	<0.010	0.000
	60–64	5	<0.010	<0.010	<0.010	<0.010	0.000
	351–365	5	<0.010	<0.010	<0.010	<0.010	0.000
Soybean seeds	6–18	5	<0.010	0.012	<0.010	0.010	0.001
	60–64	5	<0.010	<0.010	<0.010	<0.010	0
	351–365	5	<0.010	<0.010	<0.010	<0.010	0
Field corn forage	7–18	5	<0.010	<0.010	<0.010	<0.010	0
	60–67	5	<0.010	<0.010	<0.010	<0.010	0
	317–365	5	<0.010	<0.010	<0.010	<0.010	0
Field corn stover	7–18	5	<0.010	<0.010	<0.010	<0.010	0
	60–67	5	<0.010	<0.010	<0.010	<0.010	0
	317–365	5	<0.010	<0.010	<0.010	<0.010	0
Field corn immature ears	7–18	5	<0.010	<0.010	<0.010	<0.010	0
	60–67	5	<0.010	<0.010	<0.010	<0.010	0
	317–365	5	<0.010	<0.010	<0.010	<0.010	0
Field corn grain	7–18	5	<0.010	<0.010	<0.010	<0.010	0
	60–67	5	<0.010	<0.010	<0.010	<0.010	0
	317–365	5	<0.010	<0.010	<0.010	<0.010	0

Wheat forage	6–11	5	<0.010	<0.010	<0.010	<0.010	0
	61–145	5	<0.010	<0.010	<0.010	<0.010	0
	345–375	5	<0.010	<0.010	<0.010	<0.010	0
Wheat grain	6–11	5	<0.010	<0.010	<0.010	<0.010	0
	61–145	5	<0.010	<0.010	<0.010	<0.010	0
	345–375	5	<0.010	<0.010	<0.010	<0.010	0
Wheat straw	6–11	5	<0.010	<0.010	<0.010	<0.010	0
	61–145	5	<0.010	0.055	<0.010	0.019	0.020
	345–375	5	<0.010	<0.010	<0.010	<0.010	0
Wheat hay	6–11	5	<0.010	<0.010	<0.010	<0.010	0
	61–145	5	<0.010	<0.010	<0.010	<0.010	0
	345–375	5	<0.010	<0.010	<0.010	<0.010	0

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials.

Extended field accumulation - EU **PMRA# 2958035**

Five rotational crop field trials, each including broccoli, lettuce, Swiss chard, celery, strawberry, tomato, and turnip, were conducted in Europe during the 2014–2015 growing seasons and rotational crops were planted at three plant-back intervals. Trials were conducted in the south of France (1 trial), north of Spain (2 trials), and south of Spain (2 trials). Two trials were conducted in plastic tunnels (protected environments), while the other trials were conducted in the field. At each trial site, four broadcast applications of a (500 g a.i./L) suspension concentrate (SC) formulation of fluazaindolizine were made to bare soil at 1.05–1.20 kg a.i./ha/application for a total rate of 4.29–4.55 kg a.i./ha (twofold GAP). Applications were made using ground equipment in spray volumes of 143–163 L/ha at retreatment intervals of 13–15 days. Based on the principles of proportionality, residue data were scaled to the maximum seasonal application rate of 2.24 kg a.i./ha for primary crops and are reported herein. No adjuvants were used at any trial. Samples were harvested at commercial maturity from each PBI at each trial. A decline trend was not established as many of the residues were less than LOQ, with the exception of turnip roots which declined by the third PBI. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commodity	PBI (days)	n	Scaled fluazaindolizine residue levels (ppm)				
			MIN	MAX	Median	Mean	SDEV
Broccoli	7–10	5	<0.010	<0.010	<0.010	<0.010	0
	60–270	5	<0.010	<0.010	<0.010	<0.010	0
	358–365	5	<0.010	<0.010	<0.010	<0.010	0
Mature lettuce	7–10	5	<0.010	<0.010	<0.010	<0.010	0
	60–270	5	<0.010	<0.010	<0.010	<0.010	0
	358–365	5	<0.010	<0.010	<0.010	<0.010	0
Turnip tops	7–10	5	<0.010	<0.010	<0.010	<0.010	0
	60–270	5	<0.010	<0.010	<0.010	<0.010	0
	358–365	5	<0.010	<0.010	<0.010	<0.010	0
Turnip roots	7–10	5	<0.010	<0.010	<0.010	<0.010	0
	60–270	5	<0.010	0.011	<0.010	0.010	0
	358–365	5	<0.010	<0.010	<0.010	<0.010	0
Celery	7–10	2	<0.010	0.014	-	<0.012	-
	60–270	2	<0.010	<0.010	-	<0.010	-
	358–365	2	<0.010	<0.010	-	<0.010	-
Swiss chard	7–10	3	<0.010	<0.010	<0.010	<0.010	0
	60–270	3	<0.010	<0.010	<0.010	<0.010	0
	358–365	3	<0.010	<0.010	<0.010	<0.010	0

Strawberry	7–10	5	<0.010	<0.010	<0.010	<0.010	0
	60–270	5	<0.010	<0.010	<0.010	<0.010	0
	358–365	5	<0.010	<0.010	<0.010	<0.010	0
Tomato	7–10	5	<0.010	<0.010	<0.010	<0.010	0
	60–270	5	<0.010	<0.010	<0.010	<0.010	0
	358–365	5	<0.010	<0.010	<0.010	<0.010	0

Values based on single sample per trial. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials.

Extended field accumulation - EU **PMRA# 2958030**

Five rotational crop field trials were conducted in the south of France (1 trial), north of Spain (2 trials), and south of Spain (2 trials) in/on dry peas, wheat, field corn, and oilseed rape during the 2014 growing season and rotational crops were planted at three plant-back intervals. Two of the trials were considered as dependent and as such values were averaged. At each trial site, four broadcast applications of a 500 g a.i./L suspension concentrate (SC) formulation of Fluazaindolizine was made to bare soil at 0.825 kg a.i./ha/application for a total rate of 3.0–3.4 kg a.i./ha (1.5-fold GAP). Applications were made using ground equipment in spray volumes of 143-160 L/ha at retreatment intervals of 14 days. Based on the principles of proportionality, residue data were scaled to the maximum seasonal application rate of 2.24 kg a.i./ha for primary crops and are reported herein. No adjuvants were used at any trial. Samples were harvested at commercial maturity. Quantifiable residues of fluazaindolizine declined with increasing plantback intervals. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commodity	PBI (days)	Scaled fluazaindolizine residue levels (ppm)					
		n	MIN	MAX	Median	Mean	SDEV
Field pea forage	7–10	4	<0.010	0.023	<0.010	0.013	0.007
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Field pea vines	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Field pea hay	7–10	4	0.016	0.129	0.034	0.053	0.052
	60–270	4	0.011	0.085	0.034	0.041	0.034
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Field pea seed	7–10	4	<0.010	0.059	0.026	0.030	0.021
	60–270	4	<0.010	0.057	0.015	0.024	0.022
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Canola forage	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Canola seed	7–10	4	<0.010	0.015	<0.010	<0.011	0.003
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Canola straw	7–10	4	<0.010	0.061	0.020	0.028	0.024
	60–270	4	<0.010	0.025	0.013	0.016	0.007
	358–365	4	<0.010	0.015	0.011	0.012	0.002
Field corn forage	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Field corn immature ears	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0

Field corn grain	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Field corn stover/fodder	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Wheat forage	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Wheat hay	7–10	4	<0.010	0.012	<0.010	0.011	0.001
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Wheat grain	7–10	4	<0.010	<0.010	<0.010	<0.010	0
	60–270	4	<0.010	<0.010	<0.010	<0.010	0
	358–365	4	<0.010	<0.010	<0.010	<0.010	0
Wheat stover/fodder	7–10	4	<0.010	0.109	0.011	0.035	0.049
	60–270	4	<0.010	0.031	<0.010	0.015	0.011
	358–365	4	<0.010	<0.010	<0.010	<0.010	0

Values based on individual samples/trial. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials.

Combined NAFTA and EU rotational crop data (Based on super crop groups)

Based on the OECD Guidance Document of Residues in Rotational Crops (ENV/JM/MONO (2018)), data from Tier 2 (limited) and Tier 3 (extensive) field rotational crop studies were combined based on the super crop group approach. Data from Tier 2 and Tier 3 studies were scaled to the maximum seasonal application rate for Canada (2.24 kg a.i./ha). Residues in edible and feed-relevant plant parts of rotational crops from the 1st rotation were selected to establish MRLs and for the estimation of dietary burden. Residues of fluazaindolizine in celery were highest from the 2nd rotation.

Crop Subgroup 1B, except sugar beet: Root Vegetables (except carrot)							
Representative crops	**PBI (days)**	**n**	**Residues of Fluazaindolizine (ppm)**				
			LAFT	**HAFT**	**Median**	**Mean**	**SD**
Radish; turnip; carrot roots	7–30	14	<0.010	0.016	<0.010	0.011	0.002
Crop Group 2: Leaves of Root and Tuber Vegetables							
Carrot; radish; turnip tops	7–30	14	<0.010	0.014	<0.010	0.010	0.001
Crop Group 3-07: Bulb Vegetables and Crop Group 22: Stalk, Stem, and Leaf Petioles							
Celery	60–67	6	<0.010	0.020	<0.010	0.012	0.004
Crop Group 4-13 and Crop Group 5-13 – Leafy Vegetables and Brassica Head and Stem Vegetables							
Lettuce/spinach; broccoli; Swiss chard	7–30	28	<0.010	0.013	<0.010	0.010	0.001
Crop Group 6: Legume Vegetables and Crop Group 20 (revised): Oilseeds							
Immature podded beans, peas and soybeans; dry bean, pea and soybean seeds; rapeseed	6–30	36	<0.010	0.750	<0.010	0.036	0.123
Commodities from Plant Parts of Legume Vegetables and Rapeseed Used as Animal Feed							
Bean, field pea vines; soybean and rapeseed forage	6–30	22	<0.010	0.083	<0.010	0.014	0.016
Bean, soybean and pea hay; rapeseed straw	6–30	22	<0.010	0.403	0.030	0.051	0.083

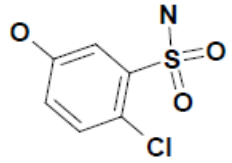
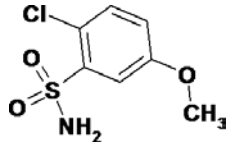
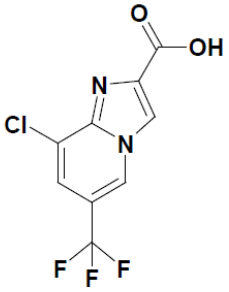
Crop Subgroup 13-07G: Low Growing Berries							
Strawberries	7–21	10	<0.010	<0.010	<0.010	<0.010	-
Crop Group 15: Cereal Grains							
Field corn; wheat; sorghum grain	6–30	22	<0.010	<0.010	<0.010	<0.010	-
Crop Group 16: Forage, Fodder, and Straw of Cereal Grains							
Field corn stover; wheat and sorghum straw and hay	6–30	34	<0.010	0.109	<0.010	0.015	0.018
Field corn; wheat; sorghum forage	6–30	22	<0.010	<0.010	<0.010	<0.010	-

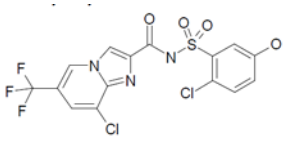
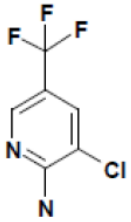
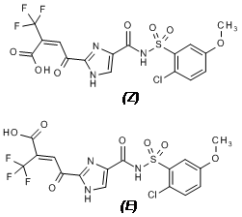
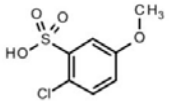
Table 9 Food residue chemistry overview of metabolism studies and risk assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (carrots, potatoes, soybeans, tomatoes, sugarcane)** **Rotational crops (radish, spinach, wheat)**	Fluazaindolizine
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (carrots, potatoes, soybeans, tomatoes, sugarcane)** **Rotational crops (radish, spinach, wheat)**	Sum of IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-UNS90, IN-UJV12, and IN-RSU03 (free and conjugated), expressed as parent equivalents.
METABOLIC PROFILE IN DIVERSE CROPS	Metabolic profiles of fluazaindolizine were similar in both the primary and rotational crops with variation in complex conjugation to endogenous plant constituents.
ANIMAL STUDIES	
ANIMALS	**Ruminant and Poultry**
RESIDUE DEFINITION FOR ENFORCEMENT	Fluazaindolizine
RESIDUE DEFINITION FOR RISK ASSESSMENT	Fluazaindolizine
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	Collectively, the goat, hen, and rat metabolism studies indicate that the metabolic profiles are comparable.
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND DRINKING WATER **RD_{DEA}: Sum of IN-A5760 + IN-F4106 + IN-QEK31 + IN-QZY47 + IN-RSU03 + IN-UJV12 + IN-UNS90** **(free and conjugated), expressed as parent equivalents**			
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Drinking Water**
Refined acute dietary exposure analysis, 95th percentile **ARfD = 1.3 mg/kg bw** **Estimated acute drinking water concentration = 1.926 ppm**	All infants	6.5	**29.5 (0.383 mg/kg)**
	Children 1–2 years	6.5	16.3
	Children 3–5 years	5.7	12.7
	Children 6–12 years	3.5	9.3
	Youth 13–19 years	2.2	7.8
	Adults 20–49 years	2.2	9.0
	Adults 50-99 years	1.9	7.9
	Total population	2.8	9.7 (0.126 mg/kg)
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food alone	**Food and drinking water**
Refined chronic non-cancer dietary exposure analysis **ADI = 0.2 mg/kg bw/day** **Estimated chronic drinking water concentration = 1.924 ppm**	All infants	0.8	**73.4 (0.147 mg/kg bw/day)**
	Children 1–2 years	1.3	28.0
	Children 3–5 years	1.0	22.8
	Children 6–12 years	0.7	16.9
	Youth 13–19 years	0.4	14.1
	Adults 20–49 years	0.4	19.7
	Adults 50-99 years	0.3	19.1
	Total population	0.5	19.9 (0.040 mg/kg bw/day)

Table 10 Major TPs of fluazaindolizine in the environment

TP	Maximum concentration[1]	comments
Major TPs		
IN-A5760  Only produced on Ph label	Aqueous phototransformation – not detected Aerobic soil – 16.1% AR Anaerobic soil – 15.2% AR Aerobic aquatic whole system – 10.36% AR Anaerobic aquatic whole system – 5.2% AR Terrestrial field studies – 0.91% of applied K_{oc} = 43.26 to 108.3 (mean 76.14)	Major TP for aerobic and anaerobic soil biotransformation, and aerobic aquatic systems. Minor TP in anaerobic aquatic systems and terrestrial field dissipation trials. High to very high soil mobility based on K_{oc} values.
IN-F4106  Only produced on Ph label	Aqueous phototransformation – 13.1% AR Aerobic soil – 86.0% AR Anaerobic soil – 65.5% AR Aerobic aquatic whole system – 4.01% AR Anaerobic aquatic whole system – 0.2% AR Terrestrial field studies – 27.38% of applied K_{oc} = 67.06 to 136.3 (mean 98.27)	Major TP for aqueous phototransformation, biotransformation in aerobic and anaerobic soils, and field dissipation trials. Minor TP in aerobic and anaerobic aquatic systems. High mobility in soil based on K_{oc} values.
IN-QEK31  Only produced on IP or IM labels	Aqueous phototransformation – 14.5% AR Aerobic soil – 79.0% AR Anaerobic soil – 62.9% AR Aerobic aquatic whole system – 9.9% AR Anaerobic aquatic whole system – 3.7% AR Terrestrial field studies – 20.62% of applied K_{oc} = 43.46 to 152.4 (mean 82.46)	Major TP for aqueous phototransformation, biotransformation in aerobic and anaerobic soils, field dissipation trials, and aerobic aquatic systems. Minor TP in anaerobic aquatic systems. Medium to very high mobility in soil based on K_{oc} values.

TP	Maximum concentration[1]	comments
IN-REG72  Produced on the IP, IM and Ph labels	Aqueous phototransformation – <2.5% AR Aerobic soil – 6.9% AR Anaerobic soil – 4.4% AR Aerobic aquatic whole system – 85.1% AR Anaerobic aquatic whole system –73.7% AR Terrestrial field studies – 2.11% of applied K_{oc} = 103.9 to 193.8 (mean 141.59)	Major TP in aerobic and anaerobic aquatic systems. Minor TP in aqueous phototransformation, aerobic and anaerobic soil biotransformation and field dissipation trials. Medium to high soil mobility based on K_{oc} values.
IN-VM862  Only produced on IP label	Aqueous phototransformation – 4.2% AR Aerobic soil – 20.6% AR Anaerobic soil – not detected Aerobic aquatic whole system – 2.3% AR Anaerobic aquatic whole system – 4.6% AR Terrestrial field studies – 8.76% of applied K_{oc} = 92.87 to 170.6 (mean 148.01)	Major TP for aerobic soil biotransformation. Minor TP in aqueous phototransformation, aerobic and anaerobic aquatic systems and field dissipation trials. Not detected in anaerobic soil. Medium to high soil mobility based on K_{oc}.
IN-UGA22  Produced on the IP and Ph labels	Aqueous phototransformation – 23.4% AR	Major TP in aqueous phototransformation. Not detected in other studies.
2-chloro-5-methoxybenzenesulfonic acid  Produced only on the Ph label	Aqueous phototransformation – 14.1% AR	Major TP in aqueous phototransformation. Not detected in other studies.

TP	Maximum concentration(1)	comments
Unidentified cluster of small polar compounds with a retention time of 2.3 minutes Produced on the IP and Ph labels	Aqueous phototransformation – 59.9% AR	Only identified for the aqueous phototransformation pathway and not detected in the dark samples. This group consists of multiple small polar compounds, likely small organic acids, which the study was unable to resolve or identify. There were 11 peaks in this region on the chromatogram.
Unidentified, retention time of 31.5 minutes Produced only on the Ph labels	Aqueous phototransformation – 10.5% AR	Major TP for aqueous phototransformation. Not detected for other degradation pathways.
IM label: [imidazo[1, 2-a]pyridine-2-^{14}C]fluazaindolizine ^{14}C radiolabel IP label: [imidazo[1, 2-a]pyridine-5,8a-^{14}C]fluazaindolizine ^{14}C radiolabel Ph label: [phenyl-^{14}C(U)]fluazaindolizine ^{14}C radiolabel (1)The maximum concentration is presented when the TP was produced on only one radiolabel (in other words, IP/IM or Ph). Mean maximum values are presented for IN-REG72, 2-chloro-5-methoxybenzenesulfonic acid, the unidentified cluster with a 2.3 minute retention time, and CO_2 because these TPs were produced by both forms of the radiolabels used in the studies.		

Table 11 Fate and behaviour of Fluazaindolizine in the environment

Property	Test substance	Medium	Value	Kinetic model	Major TPs(1)	Comments	PMRA#
Abiotic transformation							
Hydrolysis	Fluazaindolizine (IP and Ph labels)	Sterile aqueous solutions buffered at pH 4, 7 and 9	Stable	-	None	DPX-Q8U80, IN-F4106 and IN-QEK31 are stable to hydrolysis at 50 °C	2957879
	IN-F4106						2958055
	IN-QEK31						2958011

Property	Test substance	Medium	Value	Kinetic model	Major TPs[1]	Comments	PMRA#
Photo-transformation on soil	DPX-Q8U80	Sassafras soil (sandy loam, 1.2% OC, pH 6.3)	Irradiated DT_{50}: 16.6 days Dark DT_{50}: 18.8 days Phototransformation DT_{50}: 135.9 days	SFO	None	--	2957878
Photo-transformation in water	Fluazaindolizine	Sterile pH 4 ammonium acetate buffer, sterile pH 9 borate buffer, and sterile natural water (pH 7.3)	pH 4 DT_{50}=2.2 days pH 9 DT_{50}=2.5 days natural water DT_{50}=3.3 days	SFO model, natural summer sunlight equivalent at 30 to 50°N	2-chloro-5-methoxybenzenesulfonic acid, IN-F4106, IN-UGA22, IN-QEK31, and an unidentified compound with a retention time of ~31.5 mins	Concentrations of the TPs were decreasing at the end of the study.	2957937
Photo-transformation in air	--	--	--	--	--	Fluazaindolizine is not volatile. Phototransformation in air is not expected to be a significant pathway.	--
Biotransformation							
Bio-transformation in aerobic soil[2]	Fluazaindolizine (IP or IM, and Ph labels)	Tama (silty clay, 2.0% OC, pH 6.3)	t_R = 25.7 days DT_{50} = 14.4 days	IORE	IN-F4106, IN-QEK31	Non-persistent based on the DT_{50}	2957881
		Portervill e (sandy loam,	t_R = 240 days DT_{50} =	IORE	IN-F4106, IN-QEK31	Moderately persistent based on the	

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		0.6% OC, pH 6.5)	98.5 days			DT_{50}	
		Speyer (loamy sand, 1.7% OC, pH 5.7)	t_R = 5.72 days DT_{50} = 3.26 days	IORE	IN-F4106, IN-QEK31, IN-A5760, unextracted residues	Non-persistent based on the DT_{50}	
		Sassafras (sandy loam, 1.2% OC, pH 6.3)	t_R = 14.5 days DT_{50} = 11.6 days	IORE	IN-QEK31, IN-F4106, IN-VM862, CO_2, unextracted residues	Non-persistent based on the DT_{50}	2957882
		Nambsheim (sandy loam, 1.6% OC, pH 7.8)	t_R = 51.9 days DT_{50} = 39.9 days	IORE	IN-QEK31, IN-F4106, IN-VM862, CO_2, unextracted residues	Slightly persistent based on the DT_{50}	
		Speyer 2.2 (loamy sand, 1.7% OC, pH 5.8)	DT_{50} = 10.4 days	SFO	IN-QEK31, IN-VM862, IN-A5760, IN-F4106, CO_2	Non-persistent based on the DT_{50}	
		Thessaloniki (loam, 1.4% OC, pH 7.1)	t_R = 72.7 days DT_{50} = 58.8 days	DFOP	IN-QEK31, IN-F4106, unextracted residues	Moderately persistent based on the DT_{50}	2957934
		Graffignana (loam, 1.1% OC, pH 6.6)	DT_{50} = 19.2 days	SFO	IN-F4106, IN-QEK31, IN-VM862, unextracted residues, CO_2	Slightly persistent based on the DT_{50}	
		Lleida (silty clay	DT_{50} = 89.4 days	SFO	IN-QEK31, IN-F4106, unextracted	Moderately persistent based on the	

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		loam, 1.6% OC, pH 8.2)			residues	DT_{50}	
		Tama (clay loam, 3.7% OC, pH 7.1)	t_R = 157 days DT_{50} = 49.5 days	IORE	IN-QEK31, IN-F4106, CO_2, unextracted residues	Moderately persistent based on the DT_{50}	2958025
		Hidalgo (sandy clay loam, 0.4% OC, pH 8.2)	DT_{50} = 242 days	SFO	IN-F4106	Persistent based on the DT_{50}	
		Penn (loam, 1.2% OC, pH 6.5)	t_R = 70.9 days DT_{50} = 23.1 days	IORE	IN-QEK31, IN-F4106, unextracted residues	Slightly persistent based on the DT_{50}	
		Woodland (loam, 1.3% OC, pH 6.2)	t_R = 318 days DT_{50} = 46 days	DFOP	IN-QEK31, IN-F4106, unextracted residues	Moderately persistent based on the DT_{50}	
	IN-A5760	Nambsheim (sandy loam, 2.3% OC, pH 7.3)	t_R = 23.2 days DT_{50} = 4.77 days	IORE	Unextracted residues, CO_2	Non-persistent based on the DT_{50}	2958020
		Tama (clay loam, 3.7% OC, pH 7.1)	t_R = 137 days DT_{50} = 29.9 days	DFOP		Slightly persistent based on the DT_{50}	
		Penn (loam, 1.2% OC, pH	t_R = 77.4 days DT_{50} = 49.3 days	DFOP		Moderately persistent based on the DT_{50}	

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		6.5)					
		Woodland (loam, 1.3% OC, pH 6.2)	t_R = 278 days DT_{50} = 89.5 days	DFOP		Moderately persistent based on the DT_{50}	
		Sassafras (sandy loam, 1.1% OC, pH 5.2)	t_R = 389 days DT_{50} = 35.8 days	DFOP		Slightly persistent based on the DT_{50}	
	IN-F4106	Nambsheim (sandy loam, 1.5% OC, pH 7.7)	t_R = 355 days DT_{50} = 238 days	DFOP	Unextracted residues	Persistent based on the DT_{50}	2957886
		Tama (silty clay loam, 2.8% OC, pH 7.0)	DT_{50} = 384 days	SFO	Unextracted residues		
		Cajon (Porterville) (loam, 0.8% OC, pH 7.9)	DT_{50} = 507 days	SFO	Unextracted residues		
		Speyer (loamy sand, 1.5% OC, pH 6.4)	t_R = 7800 days DT_{50} = 232 days	IORE	Unextracted residues		
		Sassafras (sandy loam, 1.4% OC, pH	DT_{50} = 224 days	SFO	IN-A5760, unextracted residues		

Property	Test substance	Medium	Value	Kinetic model	Major TPs[1]	Comments	PMRA#
		5.3)					
	IN-QEK31	Tama (silty clay loam, 2.8% OC, pH 7.0)	t_R = 690 days DT_{50} = 281 days	DFOP	IN-VM862, unextracted residues	Persistent based on the DT_{50}	2957885
		Sassafras (sandy loam, 1.4% OC, pH 5.3)	t_R = 143 days DT_{50} = 32.4 days	DFOP	IN-VM862, unextracted residues, CO_2	Slightly persistent based on the DT_{50}	
		Nambsheim (sandy loam, 1.5% OC, pH 7.7)	t_R = 167 days DT_{50} = 43.5 days	IORE	IN-VM862, unextracted residues	Slightly persistent based on the DT_{50}	
		Portervill e (Cajon) (loam, 0.8% OC, pH 7.9)	DT_{50} = 1203 days	SFO	IN-VM862, unextracted residues	Persistent based on the DT_{50}	
		Speyer 2.2 (loamy sand, 1.5% OC, pH 6.4)	t_R = 284 days DT_{50} = 88.9 days	DFOP	IN-VM862, unextracted residues, CO_2	Moderately persistent based on the DT_{50}	
	IN-REG72[3]	Nambsheim (sandy loam, 1.5% OC, pH 7.7)	t_R = 126 days DT_{50} = 27.5 days	DFOP	Unextracted residues	Slightly persistent based on the DT_{50}	2957970
		Tama (silty clay	t_R = 134 days DT_{50} =	IORE	IN-A5760, unextracted residues	Slightly persistent based on the	

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		loam, 2.8% OC, pH 7.0)	30.7 days			DT_{50}	
		Cajon (Portervil le) (loam, 0.8% OC, pH 7.9)	t_R = 218 days DT_{50} = 80 days	DFOP	Unextracted residues	Moderately persistent based on the DT_{50}	
		Speyer (loamy sand, 1.5% OC, pH 6.4)	DT_{50} = 75.1 days	SFO	IN-A5760, unextracted residues	Moderately persistent based on the DT_{50}	
		Sassafras (sandy loam, 1.4% OC, pH 5.3)	DT_{50} = 118 days	SFO	IN-A5760, unextracted residues	Moderately persistent based on the DT_{50}	
Bio-transformation in anaerobic soil	Fluazaindolizine (IP and Ph label)	Sassafras (sandy loam, 2.6% OC, pH 5.9)	DT_{50} = 121 days	SFO	IN-F4106, IN-QEK31, IN-A5760, unextracted residues	Moderately persistent in anaerobic soil based on the DT_{50}	2957877
		Nambsheim (sandy loam, 1.5% OC, pH 7.7)	DT_{50} = 307 days	SFO	IN-F4106, IN-QEK31, unextracted residues	Persistent in anaerobic soil based on the DT_{50}	2957936
		Cajon (loam, 0.8% OC, pH 7.0)	DT_{50} = 1482 days	SFO	Unextracted residues		
		Greek (loam, 1.3%	DT_{50} = 247 days	SFO	IN-QEK31, IN-F4106, IN-A5760,		

Property	Test substance	Medium	Value	Kinetic model	Major TPs[1]	Comments	PMRA#
		OC, pH 7.3)			unextracted residues		
		Tama (silty clay loam, 2.8% OC, pH 7.0)	DT_{50} = 123 days	SFO	IN-QEK31, IN-F4106, IN-A5760	Moderately persistent in anaerobic soil based on the DT_{50}	
Bio-transformation in aerobic water-sediment systems	Fluazaindolizine	Swiss Lake (sand) Whole system Water phase Sediment phase	DT_{50} = 51.5 days DT_{50} = 47.7 days DT_{50} = 43.3 days	SFO SFO SFO	IN-REG72, IN-A5760, IN-QEK31[4]	Moderately persistent based on the DT_{50} in the whole system	2957883
		Calwich Abbey (silt loam) Whole system Water phase Sediment phase	DT_{50} = 20.6 days DT_{50} = 19.3 days DT_{50} = 41.4 days	SFO SFO SFO	IN-REG72, unextracted residues	Slightly persistent based on the DT_{50} in the whole system	
Bio-transformation in anaerobic water systems	Fluazaindolizine	Swiss Lake (sand) Whole system Water phase Sediment	DT_{50} = 22.4 days DT_{50} = 21.9 days t_R = 23.4 days	SFO SFO IORE	IN-REG72, unextracted residues	Slightly persistent based on the DT_{50} in the whole system	2957902

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		phase	DT_{50} = 6.55 days				
		Calwich Abbey (silt loam) Whole system Water phase Sediment phase	 DT_{50} = 11.4 days DT_{50} = 11 days t_R= 10.3 days DT_{50} = 7.4 days	 SFO SFO IORE	 IN-REG72, unextracted residues	 Non-persistent based on the DT_{50} in the whole system	
Mobility							
Adsorption / desorption in soil	Fluazaindolizine	Nambsheim (sandy loam,1.3 % OC, pH 7.7) Tama (silty clay loam, 2% OC, pH 6.2) Lleida (clay, 2% OC, pH 7.7) Portervill e (sandy loam, 0.6% OC, pH 6.5) Speyer (loamy sand, 1.7% OC, pH	Koc = 107 to 192	n/a	n/a	Moderate to high mobility	2957880
	IN-A5760		Koc = 43 to 108			High to very high mobility	2957964
	IN-F4106		Koc = 67 to 136			High mobility	2957915
	IN-QEK31		Koc = 43 to 152			Medium to very high mobility	2957914
	IN-REG72		Koc = 104 to 194			Medium to high mobility	2957943
	IN-VM862		Koc = 93 to 212			Medium to high mobility	2957942

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		5.9) Sassafras (sandy loam, 2.6% OC, pH 5.9)					
Soil leaching	Study not submitted, or required						
Volatilization	Fluazaindolizine and its TPs	Fluazaindolizine and its TPs, with the exception of IN-VM862, are considered non-volatile under field conditions. IN-VM862 has intermediate to high volatility based on its vapour pressure; however, IN-VM862 is very soluble in water, and it is not expected to be volatile from a water surface or moist soil based on the Henry's Law Constant. IN-VM862 is therefore expected to exhibit lower volatility in the field in the presence of water, including soil moisture. Some binding of IN-VM862 to soil was observed during soil biotransformation studies using fluazaindolizine as the test compound.					--
Field studies							
Field dissipation	DPX-Q8U80 500 g/L SC (EP)	Nambsheim, France: loam (0-50 cm), silt loam (50-90 cm)	DPX-Q8U80 DT_{50} = 26 days	DPX-Q8U80: IORE TPs: SFO	IN-F4106 DT_{50} = 541 days IN-QEK31 DT_{50} = 609 days	Fluazaindolizine is slightly persistent under field conditions, IN-F4106 and IN-QEK31 are persistent. All three chemicals were measured at a maximum depth of 70 to 90 cm (the deepest layer sampled).	2957929
		Alpicat, Spain: clay (0 to 50 cm),	DPX-Q8U80 DT_{50}=9.08 days	DPX-Q8U80: DFOP	IN-F4106 DT_{50} = 323 days	Fluazaindolizine is non-persistent under field	2957925

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		silty clay (50 to 90 cm)		TPs: SFO	IN-QEK31 DT_{50} = 526 days	conditions, IN-F4106 and IN-QEK31 are persistent. Fluazaindolizine and IN-QEK31 were measured at maximum depths of 70 to 90 cm (the deepest layer sampled). IN-F4106 was measured at a maximum depth of 30 to 50 cm.	
		Thessaloniki, Greece: loam (0 to 30 cm and 70 to 90 cm), sandy loam (30 to 70 cm)	DPX-Q8U80 DT_{50}=44.6 days	DPX-Q8U80: DFOP TPs: SFO	IN-F4106 DT_{50} = 217 days IN-QEK31 DT_{50} = 299 days	Fluazaindolizine is slightly persistent under field conditions, IN-F4106 and IN-QEK31 are persistent. All three chemicals were measured at a maximum depth of 70 to 90 cm (the deepest layer sampled).	2957927

Property	Test substance	Medium	Value	Kinetic model	Major TPs[(1)]	Comments	PMRA#
		New Jersey, USA: loam (0 to 90 cm)	DPX-Q8U80 DT_{50}=24.1 days	DPX-Q8U80 and IN-F4106: SFO IN-QEK31: DFOP	IN-F4106 DT_{50} = 139 days IN-QEK31 DT_{50} = 136 days	Fluazaindolizine is slightly persistent under field conditions, IN-F4106 and IN-QEK31 are moderately persistent. Fluazaindolizine and IN-QEK31 were measured at maximum depths of 70 to 90 cm (the deepest layer sampled). IN-F4106 was measured at a maximum depth of 30 to 50 cm.	2957911
		Branchton, Ontario: loam (0 to 90 cm)	DPX-Q8U80 DT_{50}=3.92 days	DPX-Q8U80: IORE, IN-F4106: SFO, IN-QEK31: DFOP	IN-F4106 DT_{50} = 338 days IN-QEK31 DT_{50} = 160 days	Fluazaindolizine is non-persistent under field conditions, IN-F4106 is persistent and IN-QEK31 is moderately persistent. Fluazaindolizine and IN-QEK31 were	2958026

Property	Test substance	Medium	Value	Kinetic model	Major TPs[1]	Comments	PMRA#
						measured at maximum depths of 70 to 90 cm (the deepest layer sampled). IN-F4106 was measured at a maximum depth of 50 to 70 cm.	
		Lombardia, Italy: loam (0 to 70 cm), silt loam (70 to 90 cm)	DPX-Q8U80 DT_{50} = 4.5 days	DPX-Q8U80: IORE TPs: SFO	IN-F4106 DT_{50} = 202 days IN-QEK31 DT_{50} = 152 days IN-VM862 DT_{50} not calculated as there were insufficient data available (amounts increased until day 300 and then decreased from 11.85 to 7.66% of applied).	Fluazaindolizine is non-persistent in soil under field conditions while IN-F4106 is persistent and IN-QEK31 is moderately persistent. All four chemicals were measured at maximum depths of 70 to 90 cm (the deepest layer sampled).	2957928

(1) Unextracted residues are presented as a major TP as they were formed at >10% AR; however, the composition is unknown and may represent a mixture of the parents and TPs.
(2) The 90% upper confidence level of the mean tR (aerobic biotransformation in soil) for fluazaindolizine, IN-A5760, IN-F4106, IN-QEK31 and IN-REG72 are 142, 243, 3230, 684 and 156 days, respectively.
(3) The IN-REG72 test item was labelled only on the phenyl ring. As such, TPs formed on the imidazopyridine ring (i.e., IN-QEK31 and IN-VM862) could not be measured.
(4) As the concentration of IN-QEK31 was increasing at the end of the study, and had reached 9.89% AR in the total system, it is considered a major TP.

Table 12 Toxicity to non-target species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Invertebrates					
Earthworm	28d-Contact	Fluazaindolizine	LC_{50}> 100 mg a.i./kg NOEC ≥ 100 mg a.i./kg	-	2957972
		DPX-Q8U80 500 g/L SC (end-use product)	LC_{50}> 411.5 mg a.i./kg NOEC = 205.8 mg a.i./kg	-	2957781
		IN-A5760	LC_{50} >400 mg/kg NOEC = 3.0 mg/kg	-	2957976
		IN-F4106	LC_{50} >100 mg/kg NOEC =50 mg/kg	-	2958003
		IN-QEK31	LC_{50} >100 mg/kg NOEC= 50 mg/kg	-	2958002
		IN-REG72[2]	LC_{50} >100 mg /kg NOEC ≥ 100 mg/kg	-	2957984
		IN-VM862	LC50 >100 mg/kg NOEC = 25 mg/kg	-	2957983
Honeybee *Apis mellifera* L.	48h-Oral	Fluazaindolizine	LD_{50} >19.62 µg a.i./bee NOED ≥ 19.62 µg a.i./bee	Practically non-toxic	2957994
	48h-Contact		LD_{50} >200 µg a.i./bee NOED ≥ 200 µg a.i./bee		
	10d-Oral		LD_{50} >4.76 µg a.i./bee/d NOED ≥ 4.76 µg a.i./bee/d	-	2957996
	72h-Larval		LD_{50} = 22.13 µg a.i./larva NOED = 4.70 µg a.i./larva	-	2958164
	120h-Larval		LD_{50} = 0.916 µg a.i./larva/d NOED = 0.375 µg a.i./larva/d	-	2957995
	22d-Larval		ED_{50} = 5.8 µg a.i./larva/d NOED = 2.6 µg a.i./larva/d	-	2958116
	48h-Oral	IN-F4106	LD_{50} = 15.8 µg/bee NOED = 13.6 µg/bee	Practially non-toxic	2958085
	48h-Contact		LD_{50} >100 µg/bee NOED ≥ 100 µg/bee		
	10d-Oral		LD_{50} >7.9 µg/bee/d NOED = 4.0 µg/bee/d	-	2958042
	120h-Larval		LD_{50} = 4.4 µg/larva/d NOED = 2.8 µg/larva/d	-	2958079

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
	48h-Oral	IN-QEK31	LD_{50} >110 µg/bee NOED ≥ 110 µg/bee	Practically non-toxic	2958081
	48h-Contact		LD_{50} >100 µg/bee NOED ≥ 100 µg/bee		
	10d-Oral		LD_{50} >18.0 µg/bee/d NOED ≥ 18.0 µg/bee/d	-	2958041
	120h-Larval		LD_{50} >25 µg/larva/d NOED = 0.3 µg/larva/d	-	2958077
	72h-Oral	DPX-Q8U80 500 g/L SC (EP)	LD_{50} = 120.8 µg a.i./bee NOED = 56.8 µg a.i./bee	Practically non-toxic	2957777
	48h-Contact		LD_{50} >200 µg a.i./bee NOED = 200 µg a.i./bee		
Bumblebee *Bombus terrestris* L.[3]	72h-Oral	Fluazaindolizine	LD_{50} >176 µg a.i./bee NOED ≥ 176 µg a.i./bee	Practically non-toxic	2958084
	48h-Contact		LD_{50} >200 µg a.i./bee NOED ≥ 200 µg a.i./bee		
	48h-Oral	IN-F4106	LD_{50} >67.4 µg/bee NOED ≥ 67.4 µg/bee		2958082
	48h-Contact		LD_{50} >100 µg/bee NOED ≥ 100 µg/bee		
	48h-Oral	IN-QEK31	LD_{50} >123 µg/bee NOED ≥ 123 µg/bee		2958083
	48h-Contact		LD_{50} >100 µg/bee NOED ≥ 100 µg/bee		
	72h-Oral	DPX-Q8U80 500 g/L SC (EP)	LD_{50} = 149.1 µg a.i./bee NOED = 43.8 µg a.i./bee		2957778
	48h-Contact		LD_{50} >200 µg a.i./bee NOED ≥ 200 µg a.i./bee		
Predatory arthropod – *T. pyri*	7d-Contact	DPX-Q8U80 500 g/L SC (EP)	LR_{50} > 1000 g a.i./ha NOER ≥ 1000 g a.i./ha	-	2958034
	7d-Contact		ER_{50} (reproduction) >1000 g a.i./ha NOER ≥ 1000 g a.i./ha	-	
Predatory arthropod – *H. aculeifer*	14d-Contact		LC_{50} >411.5 mg a.i./kg dry soil NOEC ≥ 411.5 mg a.i./kg dry soil	-	2957783
Parasitic arthropod *A. rhopalosiphi*	48h-Contact		LR_{50} > 1000 g a.i./ha NOER ≥ 1000 g a.i./ha	-	2958033

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Birds					
Bobwhite quail	Acute	Fluazaindolizine	LD_{50} > 2250 mg a.i./kg bw NOED = 486 mg a.i./kg bw	Practically non-toxic	2957891
		DPX-Q8U80 500 g/L SC (EP)	LD_{50}> 2250 mg a.i./kg bw LOED = 2250 mg a.i./kg bw		2957772
	5d-Dietary	Fluazaindolizine	LD_{50}> 1459 mg a.i./kg bw NOED ≥ 1459 mg a.i./kg bw	-	2957922
	21 week-Reproduction	Fluazaindolizine	NOED = 51.1 mg a.i./kg bw/d LOED = 101.7 mg a.i/kg bw/d	-	2957924
Mallard duck	Acute	Fluazaindolizine	NOED ≥ 2000 mg a.i./kg bw LD_{50}>2000 mg a.i./kg bw	Practically non-toxic	3051117
	5d-Dietary	Fluazaindolizine	LD_{50}>2288 mg a.i./kg bw/d NOED = 1547 mg a.i./kg bw/d	-	2957923
	21d-Reproduction	Fluazaindolizine	NOED ≥ 188.8 mg a.i./kg bw/d LOED> 188.8 mg a.i./kg bw/d	-	2957962
Zebra finch	8d-Dietary	Fluazaindolizine	NOED = 55 mg a.i./kg bw/d LC_{50} = 1414 mg a.i./kg feed[4]	Slightly toxic	2958117
Mammals					
Rat	Acute oral	Fluazaindolizine	LD_{50} ≥ 940 mg/kg bw (♀)	Slightly toxic	3049482 2958177 2957830
	Acute oral	DPX-Q8U80 500 g/L SC (EP)	LD_{50} ≥ 2000 mg/kg bw (♀)	Practically non-toxic	2957793
	28-day oral toxicity and 1-generation reproductive toxicity	Fluazaindolizine	NOAEL = 5000 ppm (361/369 mg/kg bw/day ♂/♀)	-	2957850

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
Vascular plants					
Vascular plant	21d-Seedling emergence (10 species)	DPX-Q8U80 500 g/L SC (EP)	ER_{25}/ ER_{50} > 2000 g a.i./ha	-	2957786
	21d-Vegetative vigour (10 species)		ER_{25}/ ER_{50} > 2000 g a.i./ha	-	2957785
Freshwater species					
Daphnia magna	48h-Acute	Fluazaindolizine	NOEC ≥ 120 mg a.i./L EC_{50} > 120 mg a.i./L	Practically non-toxic	2957897
		DPX-Q8U80 500 g/L SC (EP)	NOEC = 25.3 mg a.i./L EC_{50} = 43 mg a.i./L	Slightly toxic	2957775
		IN-QEK31	NOEC ≥ 125 mg/L EC_{50} > 125 mg/L	Practically non-toxic	2958161
		IN-F4106(2)	NOEC ≥ 10 mg/L EC_{50} > 10 mg/L	Slightly toxic to practically non-toxic	2957950
		IN-VM862(2)	EC_{50} = 13.4 mg/L NOEC = 6.65 mg/L	Slightly toxic	2957987
		IN-REG72	NOEC ≥ 100 mg/L EC_{50} > 100 mg/L	Practically non-toxic	2957988
	21d-Chronic	Fluazaindolizine	NOEC = 0.57 mg a.i./L	-	2957957
		IN-QEK31	NOEC ≥ 111 mg/L	-	2958089
		IN-F4106(2)	NOEC = 11.3 mg/L	-	2958090
Chironomus riparius(3)	48h-Acute	Fluazaindolizine	NOEC ≥ 110 mg a.i./L EC_{50} > 110 mg a.i./L	Practically non-toxic	2958162
	28d-Spiked water		NOEC ≥ 35 mg a.i./L EC_{50} > 35 mg a.i./L	-	2957960
	28d-Spiked sediment		NOEC ≥ 37 mg a.i./kg LC_{50} > 37 mg a.i./kg	-	2957955
Rainbow trout	96h-Acute	Fluazaindolizine	LC_{50} > 60 mg a.i./L	Slightly toxic to practically non-toxic	2957894
		DPX-Q8U80 500 g/L SC (EP)	LC_{50} > 99.4 mg a.i./L		2957774
		IN-QEK31	LC_{50} > 10.4 mg/L		2957947
		IN-F4106(2)	LC_{50} > 9.79 mg/L		2957948
	87d-Early life stage	Fluazaindolizine	NOEC ≥ 12 mg a.i./L	-	2958016
Bluegill sunfish	96h-Acute	Fluazaindolizine	LC_{50} > 58 mg a.i./L	Slightly toxic to practically non-toxic	2957895

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
Freshwater alga, *Pseudokirchneriella subcapitata*	72h-Growth inhibition	Fluazaindolizine	EC_{50} = 24 mg a.i./L NOEC = 12 mg a.i./L	Slightly toxic	2957896
		IN-VM862(2)	EC_{50} = 7.71 mg/L NOEC = 0.675 mg/L	Moderately toxic	2958009
	96h-Growth inhibition	Fluazaindolizine	EC_{50} = 38 mg a.i./L NOEC = 12 mg a.i./L	Slightly toxic	2957837
		DPX-Q8U80 500 g/L SC (EP)	EC_{50} = 9.79 mg a.i./L NOEC = 0.585 mg a.i./L	Moderately toxic	2957776
		IN-F4106(2)	EC_{50} > 8.96 mg/L NOEC = 5.19 mg/L	Moderately toxic	2957945
Freshwater plant, *Lemna gibba*	7d	Fluazaindolizine	EC_{50} = 16.2 mg a.i./L NOEC = 7.2 mg a.i./L	Slightly toxic	2957890
		DPX-Q8U80 500 g/L SC (EP)	EC_{50} = 14.8 mg a.i./L NOEC = 4.84 mg a.i./L	Slightly toxic	2957787
Marine species					
Saltwater mysid	96h-Acute	Fluazaindolizine	LC_{50} > 30 mg a.i./L NOEC = 16 mg a.i./L	Slightly toxic to practically non-toxic	2957958
Eastern oyster	96h-Acute	Fluazaindolizine	NOEC $\geq$ 10 mg a.i./L LC_{50} > 10 mg a.i./L	Slightly toxic to practically non-toxic	2957959
Sheepshead minnow	96h-Acute	Fluazaindolizine	NOEC $\geq$ 26 mg a.i./L LC_{50} > 26 mg a.i./L	Slightly toxic to practically non-toxic	2957893
	34d-ELS	Fluazaindolizine	NOEC = 0.75 mg a.i./L LOEC = 1.5 mg a.i./L	-	2958032
Marine alga, *Skeletonema costatum*	72h-Acute	Fluazaindolizine	EC_{50} = 34 mg a.i./L NOEC = 12 mg a.i./L	Slightly toxic	2957921

(1) USEPA classification, where applicable.
(2) Endpoints for minor TPs were not be carried forward into the risk assessment.
(3) The most sensitive endpoints for each taxa were used in the risk assessment. The honeybee endpoints were determined to be protective of bumblebees, and the *D.* magna endpoints were determined to be protective of chironomids because they were lower values.
(4) A LD_{50} for zebra finch could not be calculated due to feed aversion.

Table 13 Toxicity endpoints used in the risk assessment

Organism	Exposure	Test substance	Endpoint value	UF	Endpoint/UF
Terrestrial organisms					
Terrestrial invertebrates					
Earthworm	28d-Contact	Fluazaindolizine	NOEC ≥ 100 mg a.i./kg soil	1	≥ 100 mg a.i./kg soil
		DPX-Q8U80 500 g/L SC (end-use product)	NOEC = 205.8 mg a.i./kg soil	1	205.8 mg a.i./kg soil
		IN-A5760	NOEC = 3 mg/kg soil	1	3 mg/kg soil
		IN-F4106	NOEC = 50 mg/kg soil	1	50 mg/kg soil
		IN-QEK31	NOEC = 50 mg/kg soil	1	50 mg/kg soil
		IN-VM862	NOEC = 25 mg/kg soil	1	25 mg/kg soil
Honeybee	48h-Oral	Fluazaindolizine	LD_{50} > 19.62 µg a.i./bee	1	> 19.62 µg a.i./bee
		DPX-Q8U80 500 g/L SC (end-use product)	LD_{50} = 120.8 µg a.i./bee	1	120.8 µg a.i./bee
		IN-F4106	LD_{50} = 15.8 µg/bee	1	15.8 µg/bee
		IN-QEK31	LD_{50} > 110 µg/bee	1	> 110 µg/bee
	48h-Contact	Fluazaindolizine	LD_{50} > 200 µg a.i./bee	1	> 200 µg a.i./bee
		DPX-Q8U80 500 g/L SC (end-use product)	LD_{50} > 200 µg a.i./bee	1	> 200 µg a.i./bee
		IN-F4106	LD_{50} > 100 µg/bee	1	> 100 µg/bee
		IN-QEK31	LD_{50} > 100 µg/bee	1	> 100 µg/bee
	120h-Larval	Fluazaindolizine	LD_{50} = 0.916 µg a.i./larva/d	1	0.916 µg a.i./larva/d
		IN-F4106	LD_{50} = 4.4 µg a.i./larva/d	1	4.4 µg a.i./larva/d
		IN-QEK31	LD_{50} > 25 µg a.i./larva/d	1	> 25 µg a.i./larva/d
	10d-Oral	Fluazaindolizine	NOED ≥ 4.76 µg a.i./bee/d	1	≥ 4.76 µg a.i./bee/d
		IN-F4106	NOED = 4.0 µg a.i./bee/d	1	4.0 µg a.i./bee/d

Organism	Exposure	Test substance	Endpoint value	UF	Endpoint/UF
		IN-QEK31	NOED $\geq$ 18.0 µg a.i./bee/d	1	$\geq$ 18.0 µg a.i./bee/d
	22d-Larval	Fluazaindolizine	NOED = 2.6 µg a.i./larva/d	1	2.6 µg a.i./larva/d
Predatory arthropod – *T. pyri*	7d-Contact	DPX-Q8U80 500 g/L SC (end-use product)	LR_{50} > 1000 g a.i./ha	1	> 1000 g a.i./ha
Predatory arthropod – *H. aculeifer*	7d-Contact		LC_{50} > 411.5 mg a.i./kg dry soil	1	> 411.5 mg a.i./kg dry soil
Parasitic arthropod *A. rhopalosiphi*	48h-Contact		LR_{50} > 1000 g a.i./ha	1	> 1000 g a.i./ha
Birds					
Northern bobwhite quail	21 week - Reproduction	Fluazaindolizine	NOED = 51.1 mg a.i./kg bw/d LOED = 101.7 mg a.i./kg bw/d	1	51.1 mg a.i./kg bw/d 101.7 mg a.i./kg bw/d
Mallard duck	Acute oral(1)		LD_{50} > 2000 mg a.i./kg bw	10	> 2000 mg a.i./kg bw
Mammals					
Rat	Acute	Fluazaindolizine	$LD_{50} \geq$ 940 mg/kg bw	10	$\geq$ 94 mg/kg bw
	28-day oral toxicity and 1-generation reproductive toxicity (diet)		NOAEL = 361 mg a.i./kg bw	1	361 mg a.i./kg bw/d
Vascular plants					
Vascular plant	21d-Seedling emergence (10 species)	DPX-Q8U80 500 g/L SC (end-use products)	ER_{25} > 2000 g a.i./ha	1	> 2000 g a.i./ha
	21d-Vegetative vigour (10 species)		ER_{25} > 2000 g a.i./ha	1	> 2000 g a.i./ha

Organism	Exposure	Test substance	Endpoint value	UF	Endpoint/UF
Freshwater organisms					
Daphnia magna	48h-Acute	Fluazaindolizine	EC_{50} > 120 mg a.i./L	2	> 60 mg a.i./L
		DPX-Q8U80 500 g/L SC (EP)	EC_{50} = 43 mg a.i./L	2	21.5 mg a.i./L
		IN-QEK31	EC_{50} > 125 mg/L	2	> 62.5 mg/L
		IN-REG72	EC_{50} > 100 mg/L	2	> 50 mg/L
	21d-Chronic	Fluazaindolizine	NOEC = 0.57 mg a.i./L	1	0.57 mg a.i./L
		IN-QEK31	NOEC $\geq$ 111 mg/L	1	$\geq$ 111 mg/L
Rainbow trout[(2)]	96h-Acute	Fluazaindolizine	LC_{50} > 60 mg a.i./L	10	> 6 mg a.i./L
		DPX-Q8U80 500 g/L SC (end-use products)	LC_{50} > 99.4 mg a.i./L	10	> 9.94 mg a.i./L
		IN-QEK31	LC_{50} > 10.4 mg/L	10	> 1.04 mg/L
	87d-ELS	Fluazaindolizine	NOEC $\geq$ 12 mg a.i./L	1	$\geq$ 12 mg a.i./L
Freshwater alga, *Pseudokirchneriella subcapitata*	72h-growth inhibition	Fluazaindolizine	EC_{50} = 24 mg a.i./L	2	12 mg a.i./L
	96h-growth inhibition	DPX-Q8U80 500 g/L SC (end-use product)	EC_{50} = 9.79 mg a.i./L	2	4.90 mg/L
Freshwater plant, *Lemna gibba*	7d	Fluazaindolizine	EC_{50} = 16.2 mg a.i./L	2	8.1 mg a.i./L
		DPX-Q8U80 500 g/L SC (end-use product)	EC_{50} = 14.8 mg a.i./L	2	7.4 mg a.i./L
Marine species					
Saltwater mysid	96h-Acute	Fluazaindolizine	LC_{50} > 30 mg a.i./L	2	> 15 mg a.i./L
Eastern oyster	96h-Acute	Fluazaindolizine	LC_{50} > 10 mg a.i./L	2	> 5 mg a.i./L
Sheepshead minnow	96h-Acute	Fluazaindolizine	LC_{50} > 26 mg a.i./L	10	> 2.6 mg a.i./L
	34d-ELS	Fluazaindolizine	NOEC = 0.75 mg a.i./L	1	0.75 mg a.i./L

Organism	Exposure	Test substance	Endpoint value	UF	Endpoint/UF
Marine alga, *Skeletonema costatum*	72h-Acute	Fluazaindolizine	EC_{50} = 34 mg a.i./L	2	17 mg a.i./L

ELS – early life stage

(1) The most sensitive avian acute oral endpoint was used in the screening level risk assessment, rather than the endpoint from the dietary studies, as it is a more conservative exposure scenario (direct exposure via capsule).

(2) Rainbow trout to be used as a surrogate for amphibians.

Table 14 Screening level risk assessment for non-target terrestrial species

Organism	Exposure	Test substance	EEC	Endpoint/UF	RQ	LOC	LOC exceeded?
Terrestrial organisms							
Terrestrial invertebrates							
Earthworm	28d-Contact	Fluazaindolizine	1.00 mg a.i./kg soil(1)	≥ 100 mg a.i./kg soil	≥ 0.01	1	No
		DPX-Q8U80 500 g/L SC (EP)	1.00 mg a.i./kg soil(1)	205.8 mg a.i./kg soil	0.01	1	No
		IN-A5760	0.44 mg/kg soil(1)	3 mg/kg soil	0.15	1	No
		IN-F4106	0.47 mg/kg soil(1)	50 mg/kg soil	0.01	1	No
		IN-QEK31	0.57 mg/kg soil(1)	50 mg/kg soil	0.01	1	No
		IN-VM862	0.42 mg/kg soil(1)	25 mg/kg soil	0.02	1	No
Honeybees	Acute contact – individual survival (adults)	Fluazaindolizine	5.38 µg a.i./bee(2)	> 200 µg a.i./bee	< 0.03	0.4	No
		DPX-Q8U80 500 g/L SC	5.38 µg a.i./bee(2)	> 200 µg a.i./bee	< 0.03	0.4	No
		IN-F4106	2.53 µg /bee(2)	> 100 µg/bee	< 0.03	0.4	No
		IN-QEK31	3.06 µg/bee(2)	> 100 µg/bee	< 0.03	0.4	No
	Acute oral exposure (soil incorporated) – individual	Fluazaindolizine	0.29 µg a.i./bee(3)	> 19.62 µg a.i./bee	< 0.01	0.4	No
		DPX-Q8U80 500 g/L SC	0.29 µg a.i./bee(3)	120.8 µg a.i./bee	0.00	0.4	No
		IN-F4106	0.08 µg/bee(3)	15.8 µg/bee	0.00	0.4	No

Organism	Exposure	Test substance	EEC	Endpoint/UF	RQ	LOC	LOC exceeded?
	survival (adults)	IN-QEK31	0.10 µg/bee[3]	> 110 µg/bee	< 0.00	0.4	No
	Acute oral (soil incorporated) – larval surival	Fluazaindolizine	0.12 µg a.i./larva/d[3]	0.916 µg a.i./larva/d	0.13	0.4	No
		IN-F4106	0.03 µg/larva/d[3]	4.4 µg/larva/d	0.01	0.4	No
		IN-QEK31	0.04 µg/larva/d[3]	> 25 µg/larva/d	< 0.00	0.4	No
	Chronic oral exposure (soil incorporated) – individual survival (adults)	Fluazaindolizine	0.29 µg a.i./bee/d[3]	≥ 4.76 µg a.i./bee/d	≤ 0.06	1	No
		IN-F4106	0.08 µg/bee/d[4]	4.0 µg/bee/d	0.02	1	No
		IN-QEK31	0.10 µg/bee/d[5]	≥ 18.0 µg/bee/d	≤ 0.01	1	No
	Chronic oral (soil incorporated) – larval survival (repeated exposure)	Fluazaindolizine	0.12 µg a.i./larva/d[3]	2.6 µg a.i./larva/d	0.05	1	No
Predatory arthropod – *T. pyri*	Contact: in-field	DPX-Q8U80 500 g/L SC (end-use product)	2240 g a.i./ha[6]	> 1000 g a.i./ha	**< 2.24**	2[8]	**Yes**
	Contact: off-field (6% spray drift)		134.4 g a.i./ha[7]	> 1000 g a.i./ha	< 0.13	2[8]	No
Predatory arthropod – *H. aculeifer*	Contact		1.00 mg a.i./kg dry soil[1]	> 411.5 mg a.i./kg dry soil	< 0.002	1	No
Parasitic arthropod *A. rhopalosiphi*	Contact: in-field		2240 g a.i./ha[6]	> 1000 g a.i./ha	**< 2.24**	1[9]	**Yes**
	Contact: off-field (6% spray drift)		134.4 g a.i./ha[7]	> 1000 g a.i./ha	< 0.13	1[9]	No

Organism	Exposure	Test substance	EEC	Endpoint/UF	RQ	LOC	LOC exceeded ?
Vascular plants							
Vascular plants	21d-Seedling emergence (10 species): in-field	DPX-Q8U80 500 g/L SC (end-use product)	2240 g a.i./ha(6)	> 2000 g a.i./ha	< **1.12**	1	**Yes**
	21d-Vegetative vigour (10 species): in-field		2240 g a.i./ha(6)	> 2000 g a.i./ha	< **1.12**	1	**Yes**
	21d-Seedling emergence or vegetative vigour (10 species): off-field		134.4 g a.i./ha(6)	> 2000 g a.i./ha	< 0.07	1	No

The EECs for the major TPs were conservatively calculated assuming 100% conversion of the parent on a molar basis.

(1) EEC in soil is the maximum single application rate of 2240 g a.i./ha, assuming a soil bulk density of 1.5 g/cm^3 and soil depth of 15 cm.

(2) EEC for bees (Contact) = Application rate (kg a.i./ha)*2.4 µg a.i./bee

(3) EEC for bees (oral exposure - soil incorporated) was calculated as the Brigg's EEC × food consumptions rate. The food consumption rates for larvae and adult worker bees were 0.124 g/day and 0.292 g/day, respectively. The Briggs EEC for fluazaindolizine (0.993 µg a.i./g plant**)** is calculated as follows:

Equation 1. $C_{stem} = \left[10^{(0.95 * Log\ Kow - 2.05)} + 0.82\right] * TSCF * \left[\frac{\rho}{\theta + \rho * Koc * foc}\right] * C_{soil}$

Where:

C_{stem}	= concentration in stems (μg a.i./g plant)	= 1.00 mg a.i./kg (soil EEC)
C_{soil}	= concentration in soil (μg a.i./g soil)	= 0.01
f_{oc}	= fraction of organic carbon in soil	= 0.2 cm^3/cm^3
θ	= soil-water content by volume (cm^3/cm^3)	= 1.5 g dw/cm^3
ρ	= soil bulk density (g-dw/cm^3)	= 2.24(3)
log K_{ow}	= log octanol-water partitioning	= 147.8 (mean value based on submitted adsorption/ desorption
K_{oc}		
TSCF		

Organism	Exposure	Test substance	EEC	Endpoint/UF	RQ	LOC	LOC exceeded?
			coefficient = soil organic carbon-water partitioning coefficient (cm^3/g OC or L/kg OC) =Transpiration Stream Concentration Factor		studies = calculated by Equation 2 below		

Equation 2. $TSCF = -0.0648 * (Log\ Kow)^2 + 0.241 * Log\ Kow + 0.5822$

Log K_{ow} at pH 4 used in the calculation as the log K_{ow} values for fluazaindolizine at pH 7 and 9 are negative, resulting in lower estimated concentrations in plant stems

(4)Brigg's EEC for IN-F4106 of 1.18 µg a.i./g plant calculated using a soil EEC of 2.11 mg/g soil, log K_{ow} of 0.73, and mean K_{oc} of 98.27. Only one K_{ow} at 20°C for IN-F4106 is available.

(5) Brigg's EEC for IN-QEK31 of 1.10 µg a.i./g plant was calculated using a soil EEC of 1.77 mg/g soil, log K_{ow} of 0.58, and K_{oc} of 82.46. The log K_{ow} at pH 4 was used as the log K_{ow} values for IN-QEK31 at pH 7 and 9 are negative, resulting in lower estimated concentrations in plant stems

(6) The maximum single application rate of fluazaindolizine (based on Salibro Nematicide).

(7) The maximum single application rate, accounting for 6% spray drift deposition from application with a field sprayer and ASAE medium droplet size.

(8) A LOC of 2 is used for spray applications on glass plates for *T. pyri* and *A. rhopalosiphi*, based on an extensive empirical comparison of the risk quotients and known acceptable effects from field and semi-field studies for the two indicator species. Significant ecological effects of pest control products on non-target arthropod populations are not expected at a risk quotient of 2 or less. A LOC of 1 is used for other beneficial arthropod species, given the LOC of 2 was only validated for spray applications on glass plates with *T. pyri* and *A. rhopalosiphi*.

(9) A LOC of 1 is used for a refined risk assessment for *T. pyri* and *A. rhopalosiphi*.

Table 15 Screening level risk assessment for birds and mammals

Organism	Toxicity (mg a.i./kg bw/d)	Feeding guild (food item)	EDE (mg a.i./kg bw)(1)	RQ	LOC	LOC exceeded?
Small bird (0.02 kg)						
Acute	> 200.0	Insectivore	182.3	< 0.91	1	No
Reproduction	51.10	Insectivore	182.3	**3.57**	1	**Yes**
Medium sized bird (0.1 kg)						
Acute	> 200.0	Insectivore	142.3	< 0.71	1	No
Reproduction	51.10	Insectivore	142.3	**2.78**	1	**Yes**
Large sized bird (1 kg)						
Acute	> 200.0	Herbivore (short grass)	91.91	< 0.46	1	No
Reproduction	51.10	Herbivore (short grass)	91.91	**1.80**	1	**Yes**
Small Mammal (0.015 kg)						

Organism	Toxicity (mg a.i./kg bw/d)	Feeding guild (food item)	EDE (mg a.i./kg bw)(1)	RQ	LOC	LOC exceeded?
Acute	94.00	Insectivore	104.9	**1.12**	1	**Yes**
Reproduction	361.0	Insectivore	104.9	0.29	1	No
Medium sized Mammal (0.035 kg)						
Acute	94.00	Herbivore (short grass)	203.4	**2.16**	1	**Yes**
Reproduction	361.0	Herbivore (short grass)	203.4	0.56	1	No
Large sized Mammal (1 kg)						
Acute	94.00	Herbivore (short grass)	108.7	**1.16**	1	**Yes**
Reproduction	361.0	Herbivore (short grass)	108.7	0.30	1	No

(1) EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398(bw in g) $^{0.850}$

All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(bw in g) $^{0.651}$.

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(bw in g) $^{0.822}$

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 16 Refined risk assessment for birds and mammals

Exposure type	Toxicity (mg a.i./kg bw/d)	Food guild	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field		On-field		Off-field	
			EDE	RQ	EDE	RQ	EDE	RQ	EDE	RQ
Small bird (0.02 kg)										
Reproduction	51.10	Insectivore (small insects)	182.33	**3.57**	10.94	0.21	125.89	**2.46**	7.55	0.15
		Granivore	28.22	0.55	1.69	0.03	13.46	0.26	0.81	0.02
		Frugivore	56.43	**1.10**	3.39	0.07	26.92	0.53	1.61	0.03
Medium sized bird (0.1 kg)										
Reproduction	51.10	Insectivore (small insects)	142.29	**2.78**	8.54	0.17	98.25	**1.92**	5.89	0.12
		Granivore	22.02	0.43	1.32	0.03	10.50	0.21	0.63	0.01
		Frugivore	44.04	0.86	2.64	0.05	21.00	0.41	1.26	0.02

Exposure type	Toxicity (mg a.i./kg bw/d)	Food guild	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field		On-field		Off-field	
			EDE	RQ	EDE	RQ	EDE	RQ	EDE	RQ
Large sized bird (1 kg)										
Reproduction	51.10	Insectivore	41.54	0.81	2.49	0.05	28.68	0.56	1.72	0.03
		Granivore (grain and seeds)	6.43	0.13	0.39	0.01	3.07	0.06	0.18	0.00
		Frugivore (fruit)	12.86	0.25	0.77	0.02	6.13	0.12	0.37	0.01
		Herbivore (short grass)	91.91	**1.80**	5.51	0.11	32.64	0.64	1.96	0.04
		Herbivore (long grass)	56.12	**1.10**	3.37	0.07	18.32	0.36	1.10	0.02
		Herbivore (broadleaf plants)	85.04	**1.66**	5.10	0.10	28.11	0.55	1.69	0.03
Small mammal (0.015 kg)										
Acute	94.00	Insectivore (small insects)	104.87	**1.12**	6.29	0.07	72.41	0.77	4.34	0.05
		Granivore	16.23	0.17	0.97	0.01	7.74	0.08	0.46	0.00
		Frugivore	32.46	0.35	1.95	0.02	15.48	0.16	0.93	0.01
Medium sized mammal (0.035 kg)										
Acute	94.00	Insectivore (small insects)	91.93	0.98	5.52	0.06	63.48	0.68	3.81	0.04
		Granivore	14.23	0.15	0.85	0.01	6.79	0.07	0.41	0.00
		Frugivore	28.45	0.30	1.71	0.02	13.57	0.14	0.81	0.01
		Herbivore (short grass)	203.39	**2.16**	12.20	0.13	72.23	0.77	4.33	0.05
		Herbivore (long grass)	124.19	**1.32**	7.45	0.08	40.55	0.43	2.43	0.03
		Herbivore (forage crops)	188.18	**2.00**	11.29	0.12	62.21	0.66	3.73	0.04
Large sized mammal (1 kg)										
Acute	94.00	Insectivore (large insects)	49.12	0.52	2.95	0.03	33.92	0.36	2.04	0.02

Exposure type	Toxicity (mg a.i./kg bw/d)	Food guild	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field		On-field		Off-field	
			EDE	RQ	EDE	RQ	EDE	RQ	EDE	RQ
		Granivore	7.60	0.08	0.46	0.00	3.63	0.04	0.22	0.00
		Frugivore	15.20	0.16	0.91	0.01	7.25	0.08	0.44	0.00
		Herbivore (short grass)	108.68	**1.16**	6.52	0.07	38.60	0.41	2.32	0.02
		Herbivore (long grass)	66.36	0.71	3.98	0.04	21.67	0.23	1.30	0.01
		Herbivore (forage crops)	100.55	**1.07**	6.03	0.06	33.24	0.35	1.99	0.02
		Herbivore (leafy foliage)	49.12	0.52	2.95	0.03	33.92	0.36	2.04	0.02

Table 17 Further refinement of the risk assessment for reproductive risks to birds considering LOED

Exposure type	Toxicity (mg a.i./kg bw/d)	Food guild	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field		On-field		Off-field	
			EDE	RQ	EDE	RQ	EDE	RQ	EDE	RQ
Small bird (0.02 kg)										
Reproduction	101.70	Insectivore	182.33	**1.79**	10.94	0.11	125.89	**1.24**	7.55	0.07
		Granivore (grain and seeds)	28.22	0.28	1.69	0.02	13.46	0.13	0.81	0.01
		Frugivore (fruit)	56.43	0.55	3.39	0.03	26.92	0.26	1.61	0.02
Medium sized bird (0.1 kg)										
Reproduction	101.70	Insectivore	142.29	**1.40**	8.54	0.08	98.25	0.97	5.89	0.06
		Granivore (grain and seeds)	22.02	0.22	1.32	0.01	10.50	0.10	0.63	0.01
		Frugivore (fruit)	44.04	0.43	2.64	0.03	21.00	0.21	1.26	0.01

Exposure type	Toxicity (mg a.i./kg bw/d)	Food guild	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field		On-field		Off-field	
			EDE	RQ	EDE	RQ	EDE	RQ	EDE	RQ
Large sized bird (1 kg)										
Reproduction	101.70	Insectivore	41.54	0.41	2.49	0.02	28.68	0.28	1.72	0.02
		Granivore (grain and seeds)	6.43	0.06	0.39	0.00	3.07	0.03	0.18	0.00
		Frugivore (fruit)	12.86	0.13	0.77	0.01	6.13	0.06	0.37	0.00
		Herbivore (short grass)	91.91	0.90	5.51	0.05	32.64	0.32	1.96	0.02
		Herbivore (long grass)	56.12	0.55	3.37	0.03	18.32	0.18	1.10	0.01
		Herbivore (forage crops)	85.04	0.84	5.10	0.05	28.11	0.28	1.69	0.02

Table 18 Screening level risk assessment for non-target aquatic species

Organism	Exposure	Test substance	EEC[(1)]	Endpoint/UF	RQ[(2)]	LOC of 1 exceeded?
Freshwater organisms						
Daphnia magna	48h-Acute	Fluazaindolizine	0.28 mg a.i./L	> 60 mg a.i./L	< 0.00	No
		DPX-Q8U80 500 g/L SC (EP)	0.28 mg a.i./L	21.5 mg a.i./L	0.01	No
		IN-QEK31	0.50 mg/L	> 62.5 mg/L	< 0.01	No
		IN-REG72	0.29 mg/L	> 50 mg/L	< 0.01	No
	21d-Chronic	Fluazaindolizine	0.28 mg a.i./L	0.57 mg a.i./L	0.49	No
		IN-QEK31	0.50 mg/L	$\geq$ 111 mg/L	$\leq$ 0.00	No
Rainbow trout	96h-Acute	Fluazaindolizine	0.28 mg a.i./L	> 6 mg a.i./L	< 0.05	No

Organism	Exposure	Test substance	EEC[1]	Endpoint/UF	RQ[2]	LOC of 1 exceeded?
		DPX-Q8U80 500 g/L SC (EP)	0.28 mg a.i./L	> 9.94 mg a.i./L	< 0.03	No
		IN-QEK31	0.50 mg/L	> 1.04 mg/L	< 0.48	No
	87d-ELS	Fluazaindolizine	0.28 mg a.i./L	≥ 12 mg a.i./L	≤ 0.02	No
Amphibians (rainbow trout surrogate)	96h-Acute	Fluazaindolizine	1.49 mg a.i./L	> 6 mg a.i./L	< 0.25	No
	87d-ELS	Fluazaindolizine	1.49 mg a.i./L	≥ 12 mg a.i./L	≤ 0.12	No
Freshwater alga, *Pseudokirchneriella subcapitata*	72h-growth inhibition	Fluazaindolizine	0.28 mg a.i./L	12 mg a.i./L	0.02	No
	96h-growth inhibition	DPX-Q8U80 500 g/L SC (EP)	0.28 mg a.i./L	4.90 mg a.i./L	0.06	No
Freshwater plant, *Lemna gibba*	7d	Fluazaindolizine	0.28 mg a.i./L	8.1 mg a.i./L	0.03	No
		DPX-Q8U80 500 g/L SC (EP)	0.28 mg a.i./L	7.4 mg a.i./L	0.04	No
Marine species						
Saltwater mysid	96h-Acute	Fluazaindolizine	0.28 mg a.i./L	>15 mg a.i./L	< 0.02	No
Eastern oyster	96h-Acute	Fluazaindolizine	0.28 mg a.i./L	> 5 mg a.i./L	< 0.06	No
Sheepshead minnow	96h-Acute	Fluazaindolizine	0.28 mg a.i./L	> 2.6 mg a.i./L	< 0.11	No
	34d-ELS	Fluazaindolizine	0.28 mg a.i./L	0.75 mg a.i./L	0.37	No
Marine alga, *Skeletonema costatum*	72h-Acute	Fluazaindolizine	0.28 mg a.i./L	17 mg a.i./L	0.02	No
UF – Uncertainty factor						

Organism	Exposure	Test substance	EEC(1)	Endpoint/UF	RQ(2)	LOC of 1 exceeded?

(1) A direct overspray to a 80-cm deep water body was used to evaluate risks to all organisms except amphibians, where a 15-cm deep water body was considered. The EECs for major TPs were conservatively calculated assuming 100% conversion of the parent on a molar basis.
(2) RQ = EEC/(endpoint/UF)

Table 19 Toxic substances management policy considerations

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Fluazaindolizine endpoints	TP endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes for one of the 14 available DT_{50} values in aerobic soil. The DT_{50} values in aerobic soil range from 3.26 to 242 days; however, 13 of the 14 available DT_{50} values are < 100 days. DT_{50} values in anaerobic soil range from 121 to 1482 days.	IN-A5760: 4.77 to 89.5 days - No IN-F4106: 224 to 507 days – Yes, for all five available DT_{50} values IN-QEK31: 32 to 1203 days – Yes, for two of the five available DT_{50} values IN-REG72: 28 to 118 days – No IN-VM862 – DT_{50} not available
	Water	Half-life ≥ 182 days	No, DT_{50} values in aerobic and anaerobic aquatic whole systems are ≤ 52 days.	Not reported
	Sediment	Half-life ≥ 365 days		Not reported
	Air	Half-life ≥ 2 days or evidence of atmospheric long range transport to remote regions such as the Arctic	No, volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (2.04×10^{-7} Pa) and Henry's Law constant ($< 4.27 \times 10^{-11}$ atm m^3/mol).	No, volatilisation is not an important route of dissipation for the TPs (with the exception of IN-VM862, see below). Long-range atmospheric transport is unlikely to occur based on the vapour pressures (≤ 4.45×10^{-5} Pa) and Henry's law constants (≤ 1.20×10^{-10} atm m^3/mol). IN-VM862 has intermediate to high volatility based on its vapour pressure (1.319 Pa); however, it is very soluble in water (range of 0.33 g/L in distilled water to 0.45 g/L at pH

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Fluazaindolizine endpoints	TP endpoints
			9), and it is non-volatile from a water surface or moist soil based on its Henry's law constants ($\leq 8.74 \times 10^{-6}$ at pH 4 to 9). IN-VM862 is therefore expected to exhibit lower volatility in the field in the presence of water, including soil moisture. Some binding of IN-VM862 to soil was observed during the soil biotransformation studies using fluazaindolizine as the test compound.
Bioaccumulation[4]	Log $K_{ow} \geq 5$	$\leq$ 2.24	$\leq$ 1.84
	BCF $\geq$ 5000	The bioaccumulation potential of fluazaindolizine and its TPs is expected to be low since the log K_{ow} values are $\leq$ 2.24.	
	BAF $\geq$ 5000		
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.	No, do not meet TSMP Track 1 criteria.

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, 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 TPs meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Bioaccumulation Factors (BAF) are preferred over Bioconcentration Factors (BCF); in the absence of BAF or BCF data, the octanol-water partition coefficient (log K_{ow}) may be used.

Table 20 List of supported uses

Supported use claims for Salibro Nematicide
Crop: Tuberous and corm vegetables (Crop Subgroup 1C)[1] **Pest:** Root-knot nematode (*Meloidogyne* spp.) **Claims:** Suppression at the low rate and control at the high rate **Application instructions:** • 2.24–4.48 L product/ha applied by pre-plant incorporated or broadcast followed by soil incorporation, or by in-furrow application; and/or, • 1.12–2.24 L product/ha applied by postplant chemigation as supplemental in-season chemigation following a pre-plant or at plant application of Salibro Nematicide or fumigant. A maximum of two applications per year (no more than 4.48 L/ha per year) is allowed with a minimum of 14 days re-application interval.

Crop: Carrot **Pest:** Root-knot nematode (*Meloidogyne* spp.) **Claims:** Suppression at the low rate and control at the high rate **Application instructions:** • 2.24–4.48 L product/ha applied by pre-plant incorporated or broadcast followed by soil incorporation; and/or, • 1.12–2.24 L product/ha applied by postplant chemigation as supplemental in-season chemigation following a pre-plant or at plant application of Salibro or fumigant. A maximum of two applications per year (no more than 4.48 L/ha per year) is allowed with a minimum of 14 days re-application interval.
Crop: Cucurbit vegetables (Crop Group 9)[2] **Pest:** Root-knot nematode (*Meloidogyne* spp.) **Claim:** Suppression only **Application instructions**: • 1.12–2.24 L product/ha applied by pre-plant incorporated or broadcast followed by soil incorporation, or by pre-plant or at-plant chemigation application; and/or, • 0.56–1.12 L product/ha applied by postplant chemigation applications as supplemental in-season chemigation following a pre-plant or at plant application of Salibro or fumigant. A maximum of four applications per year (no more than 4.48 L/ha per year) is allowed with a minimum of 14 days re-application interval.
Crop: Fruiting vegetables (Crop Group 8-09)[3] **Pest:** Root-knot nematode (*Meloidogyne* spp.) **Claims:** Suppression at the low rate and control at the high rate **Application instructions**: • 2.24–4.48 L product/ha applied by pre-plant incorporated or broadcast followed by soil incorporation; and/or, • 1.12–2.24 L product/ha applied by postplant chemigation applications as supplemental in-season chemigation following a pre-plant or at plant application of Salibro or fumigant. A maximum of three applications per year (no more than 4.48 L/ha per year) is allowed with a minimum of 14 days re-application interval.

[1] **Crop subgroup 1C**: Arrowroot, chayote root, Chinese artichoke, Jerusalem artichoke, edible canna, chufa, dasheen, ginger, potato, sweet potato, and true yam.
[2] **Crop Group 9**: Chayote, Chinese waxgourd, citron melon, cucumber, gherkin, edible gourd (hyotan, cucuzza, hechima and Chinese okra), *Momordica* spp. (balsam apple, balsam pear, bitter melon and Chinese cucumber), muskmelon (true cantaloupe, cantaloupe, casaba, crenshaw melon, golden pershaw melon, honeydew melon, honey balls, mango melon, Persian melon, pineapple melon, Santa Claus melon and snake melon), pumpkin, summer squash (crookneck squash, scallop squash, straightneck squash, vegetable marrow and zucchini), winter squash (butternut squash, calabaza, hubbard squash, acorn squash and spaghetti squash) and watermelon.

[3] **Crop Group 8-09**: African eggplant, currant tomato, eggplant, garden huckleberry, goji berry, ground cherry, martynia, okra, pea eggplant, pepino, bell pepper, non-bell pepper, scarlet eggplant, sunberry, tomatillo and tomato.

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

Fluazaindolizine is an active ingredient that is concurrently being registered in Canada and the United States for use on various crops. The MRLs proposed for fluazaindolizine in Canada are the same as corresponding tolerances to be promulgated in the United States, except for poultry commodities, in accordance with Table 1, for which differences in MRLs/tolerances are due to different regulatory requirements.

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

Currently, there are no Codex MRLs[10] listed for fluazaindolizine in or on any commodity on the Codex Alimentarius Pesticide Index website.

Table 1 compares the MRL proposed for fluazaindolizine in Canada with corresponding American tolerances and Codex MRL.

Table 1 Comparison of Canadian MRL, American tolerance and codex MRL (where different)

Food commodity	Canadian MRL (ppm)	American tolerance (ppm)
Eggs, fat, meat and meat byproducts of poultry	0.01	Not established

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.

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

References

A. List of studies/Information submitted by registrant

1.0 Chemistry

PMRA Document Number	Reference
2957839	2018, Analytical method and validation for the determination of impurities in fluazaindolizine (DPX-Q8U80) technical grade material, DACO: 2.13.4, Document K, IIA 4.2.3 CBI
2957903	2014, DPX-Q8U80: Laboratory study of storage stability and corrosion characteristics, DACO: 2.14.14, Document K, IIA 2.17.1 CBI
2957906	2013, DPX-Q8U80: Determination of pH of 1% (w/v) aqueous solution/suspension, DACO: 2.14.15, Document K, IIA 2.16 CBI
2957907	2013, DPX-Q8U80: Determination of relative density, DACO: 2.14.6, Document K, IIA 2.2 CBI
2957909	2013, DPX-Q8U80: Determination of color, odor and physical state, DACO: 2.14.1, 2.14.2, 2.14.3, Document K, IIA 2.4.1, IIA 2.4.2 CBI
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2.0 Human and Animal Health

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4.0 Value

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